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Authors:	C. R. McMillin, B. J. Warner, J. R. McKendree and L. Stamper
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DEVELOPMENT OF A PORTABLE ULTRAVIOLET METHOD FOR THE ANALYSIS OF POLYCHLORINATED BIPHENYLS IN SOIL

Prepared by

Carl R. McMillin, Beverly J. Warner
Jesse R. McKendree, and Leonard Stamper

Contract No. RP1263-13

Prepared for

Electric Power Research Institute
3412 Hillview Agency
Palo Alto, California 94304

EPRI Project Officer

Ralph T. Komai
Coal Combustion Systems Division

MONSANTO RESEARCH CORPORATION
DAYTON LABORATORY
Dayton, Ohio 45407

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ABSTRACT

The need exists for a rapid field method for analyzing polychlorinated biphenyls (PCBs) in soil samples. A method has been developed for this purpose that consists of the extraction of PCBs from soil using hexane, the removal of interferents using an alumina column, and the analysis of the sample using ultraviolet absorption. The method was evaluated using five different soil types. Background ultraviolet absorption from the soils averaged an equivalent PCB concentration of 15 ppm, with a range of 10 ppm to 19 ppm. The analysis of spiked soils showed a recovery of 92% ± 3% of the PCB that was spiked.

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SECTION 1

INTRODUCTION

BACKGROUND

Under federal regulations for polychlorinated biphenyls (PCBs), the continued use of PCB capacitors, askarel transformers, and PCB-transformers is allowed. Such equipment can rupture while in use, and the uncontrolled discharge must be cleaned up to below 50 ppm PCB. Currently, there is no available low cost portable technique to analyze the level of contamination of soil. Samples must be sent for analysis to a laboratory where the potential waiting time for results can approach one week. Delays in site clean-up can present problems in control of the contaminated area and public relations.

A technique is needed for the rapid quantification of PCBs at the incident site in the field. The technique must be rapid, accurate, portable, and easily used by personnel having no special chemical training.

PROGRAM OBJECTIVE

The objective of this program was to prepare an inexpensive portable chemical test kit utilizing ultraviolet (UV) spectroscopy for the rapid, accurate quantification of PCBs in soil. The elements of this kit would be designed to be readily usable by untrained personnel. The purpose of this report is to summarize the results of this program.

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SECTION 2

DATA SUMMARY AND ANALYSES

PREPARING SPIKED SOILS

During the development work, both individually spiked soil samples and a large master batch of PCB-spiked soil was used. For many of the tests for method development, individually spiked soil samples were used. These were prepared in the following manner.

For the master batch, a sample of humis rich garden soil was homogenized by mixing in a Roto-vap with hexane. The PCB sample in hexane was added to the soil mixture, and the resulting sample was dried. Aliquots of this soil were then used in the experiments.

For the individually spiked samples, a 10-gram sample of air-dried soil was weighed into a 40-mL Teflon® septum-lined screw-capped vial. A 1-mL aliquot of a 541 µg/mL Aroclor 1254 in hexane standard was pipetted onto the soil sample. The sample was allowed to stand uncapped prior to analysis until all of the hexane had evaporated.

SELECTION OF A WAVELENGTH FOR PCB QUANTITATION

As shown in Figures 1, 2, and 3, all three Aroclor formulations (1242,1254, and 1260) absorb in the 200-to 300-nm range. A wavelength of 280 nm was selected because all three Aroclors can be measured at concentrations of 5 to 50 ppm in that region. In addition, three pesticides, endrin, lindance, and methoxychlor, were analyzed by UV (Figure 4) and found to absorb strongly in the 230-to 260-nm range. Herbicides and pesticides are potential contaminants at sites where soil analyses for PCBs may be desired.

LINEARITY OF THE AROCLORS

The analytical linearity of the three commercially available Aroclors (1242, 1254, and 1260) was investigated. Figures 5, 6, and 7 show the UV absorbance of Aroclors 1242, 1254, and 1260 in hexane, respectively, as a function of concentration in hexane. Figure 8 shows this relationship for all three Aroclors on one graph. No problems in linearity for the analysis of PCBs using ultraviolet detection were encountered between one and greater

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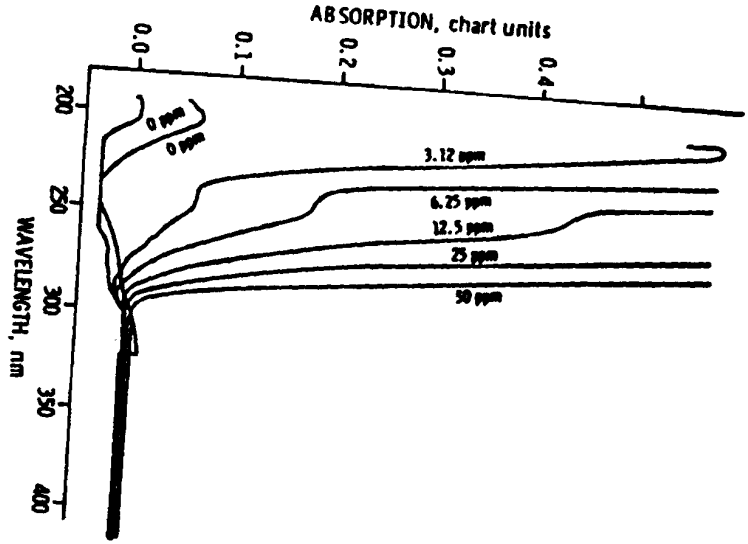

Figure 1. UV absorption spectra for Aroclor 1242 in hexane (range 1.0).

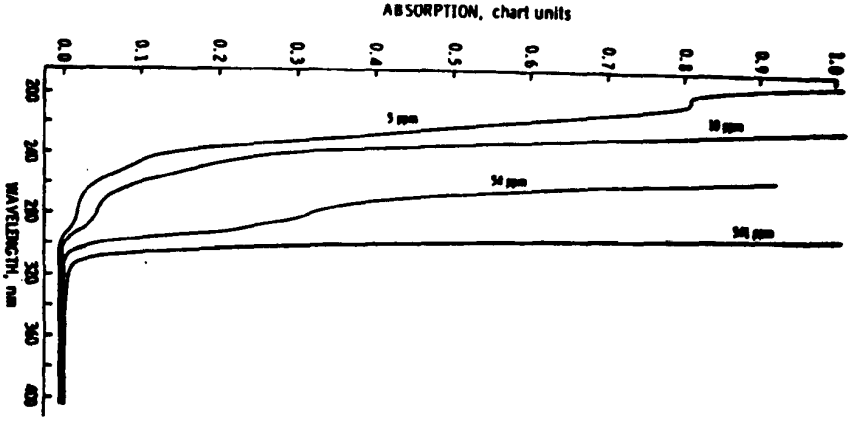

Figure 2. UV absorption spectra for Aroclor 1254 in hexane (range 1.0).

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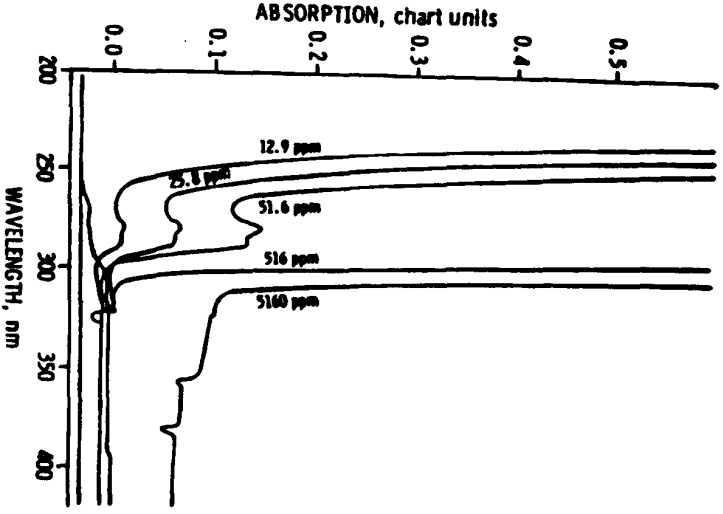

Figure 3. UV absorption spectra for Aroclor 1260 in hexane (range 1.0).

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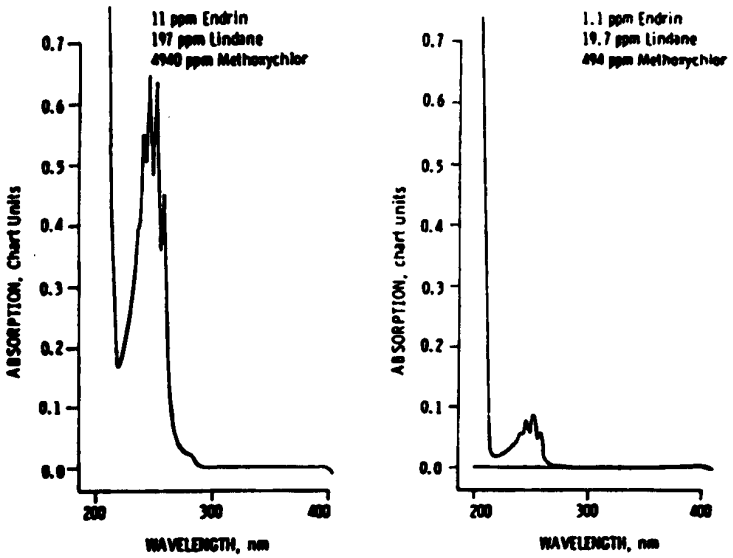

Figure 4. UV absorption spectra for mixtures of endrin, lindane, and methoxychlor.

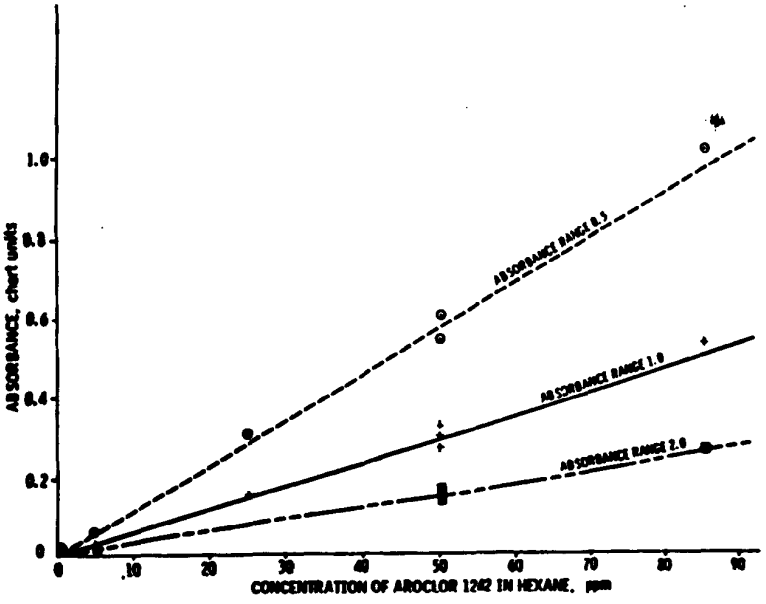

Figure 5. UV absorbance at 280 nm of Aroclor 1242 in hexane as a function of Aroclor concentration.

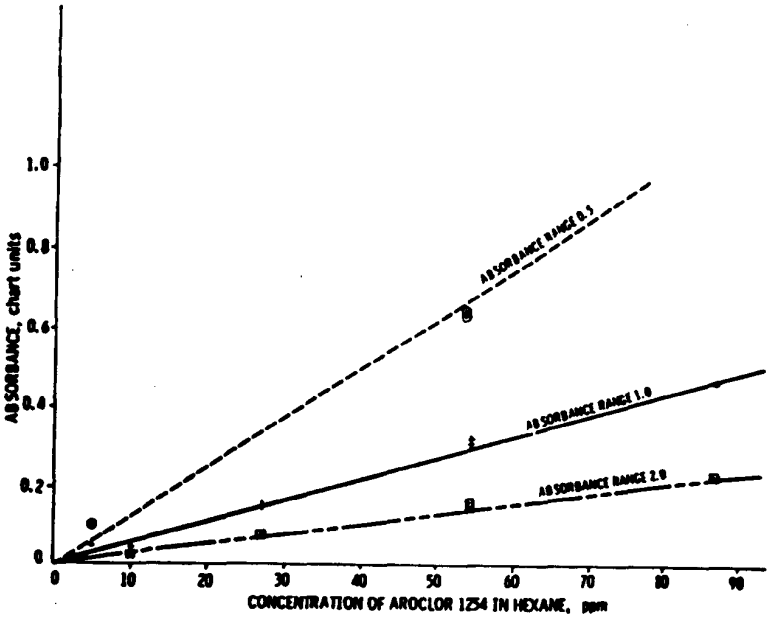

Figure 6. UV absorbance at 280 nm of Aroclor 1254 in hexane as a function of Aroclor concentration.

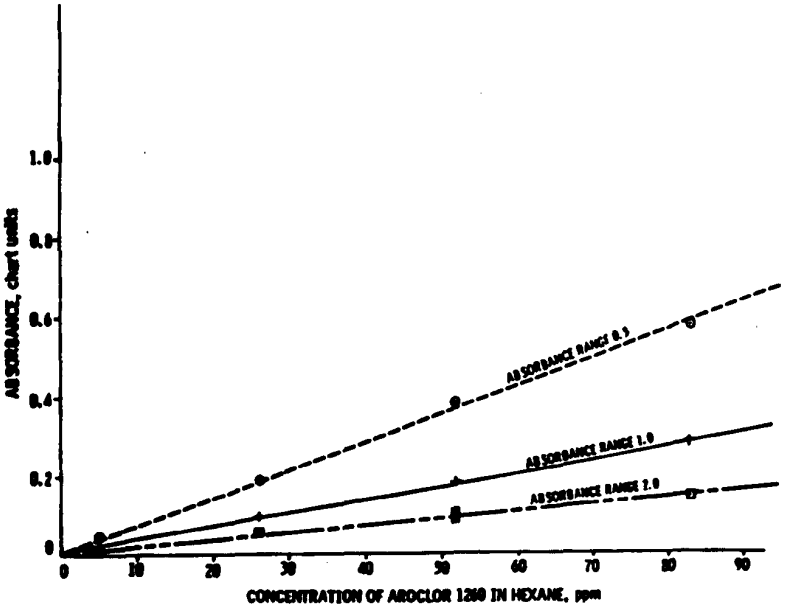

Figure 7. UV absorbance at 280 nm of Aroclor 1260 in hexane as a function of Aroclor concentration.

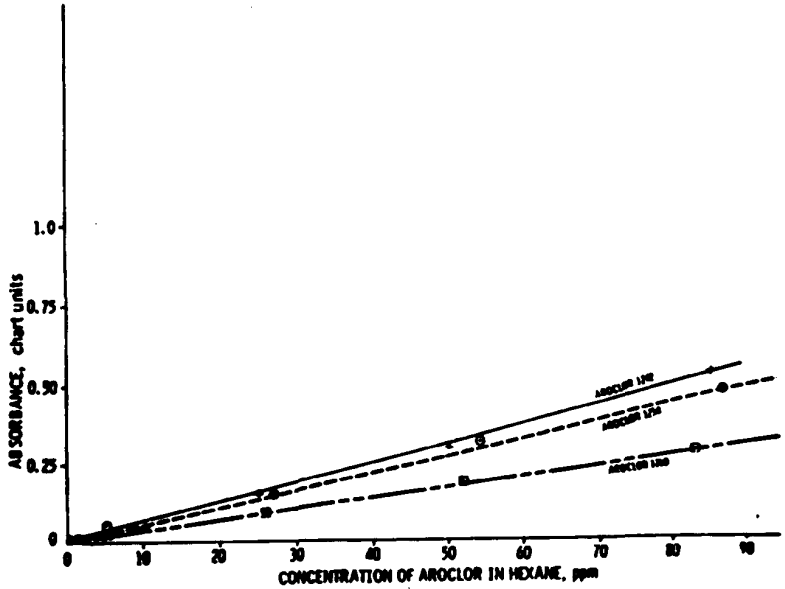

Figure 8. UV absorbance at 280 nm of Arclors 1242, 1254, and 1260 (individual) in hexane as a function of Aroclor concentration.

than 500 ppm of PCBs. Although concentration is linear with respect to absorbance, the individual Aroclor formulations absorb somewhat differently for the same relative concentration. It is thus necessary to have prior knowledge of which PCBs or mixtures of PCBs may be present in order to accurately determine their concentration directly from these analytical curves. Subsequent results, shown in Figure 9, indicate that mixtures of Aroclors (total concentration) also are linear vs. absorbance. Figures 10 and 11 show the linear response for the UV absorbance of Aroclors 1242 and 1260 respectively, in acetonitrile.

If the identity of the PCBs is unknown, a scan of the wavelengths between 260 nm and 290 nm will enable Aroclor 1260 to be identified due to the absorption minimum at 269 nm. As seen in Figure 8, this is significant because the absorption of Aroclor 1260 differs the most from the other PCBs. In the absence of the 268-nm absorption minimum, the use of an average of the Aroclor 1242 and the Aroclor 1254 calibration curves could be used giving an error that is insignificant compared to the inherent error in the overall method (e.g. percent recovery variability). Alternately, the method can be used assuming that the least sensitive PCB is present to give a maximum possible PCB concentration in the soil.

CLEAN-UP MATERIALS

Several packing materials were investigated to determine which materials would be suitable for removing interferences from the soil. Florisil, silica gel, charcoal, a C_{18}-Bonapak resin, and alumina were studied.

Florisil, silca gel, charcoal, and the C_{18}-packing were not found to be suitable. When a clean soil extract (analyzed by gas chromatography/mass spectrometry and found to contain less than 0.1 ppm of any PCB, pesticide, herbicide, or identifiable extractable organic) was passed through a small chromatographic column packed with any of these four packings, a UV response greater than that of a 50-ppm Aroclor standard was obtained. Only alumina (deactivated 5% with deionized water) provided sufficient cleanup of the blank soil extract. Subsequent studies were conducted using hand-packed micro-columns of 5% (W/V) deactivated alumina.

Four replicate samples (5 mL each) of a 54.1-ppm Aroclor 1254 standard were run through an alumina clean-up column followed by three 5-ml hexane rinses. The concentration of each extract was measured using both GC/EC and UV to determine the volume of eluant necessary to rinse the PCBs from the column. Results are shown in Table 1. It can be seen that virtually all of the PCBs were recovered in the first two 5-mL rinses.

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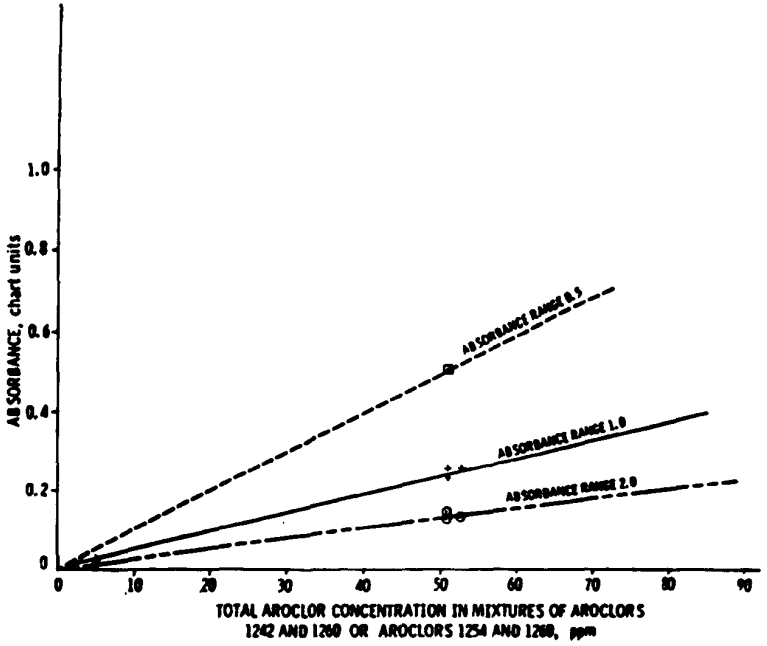

Figure 9. UV absorbance at 280 nm of mixtures of Aroclors 1242, 1254, and 1260 (individual) in hexane as a function of Aroclor concentration.

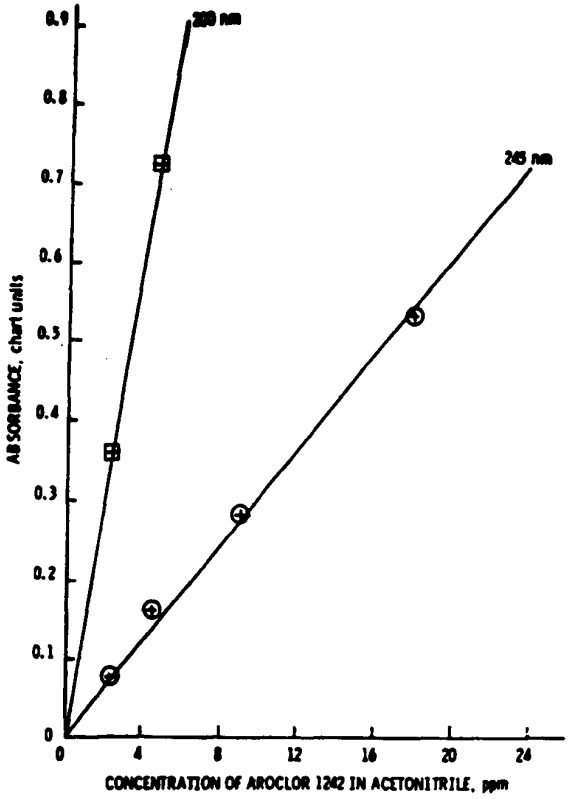

Figure 10. UV absorbance at 200 nm and at 245 nm Aroclor 1242 in acetonitrile as a function of Aroclor concentration.

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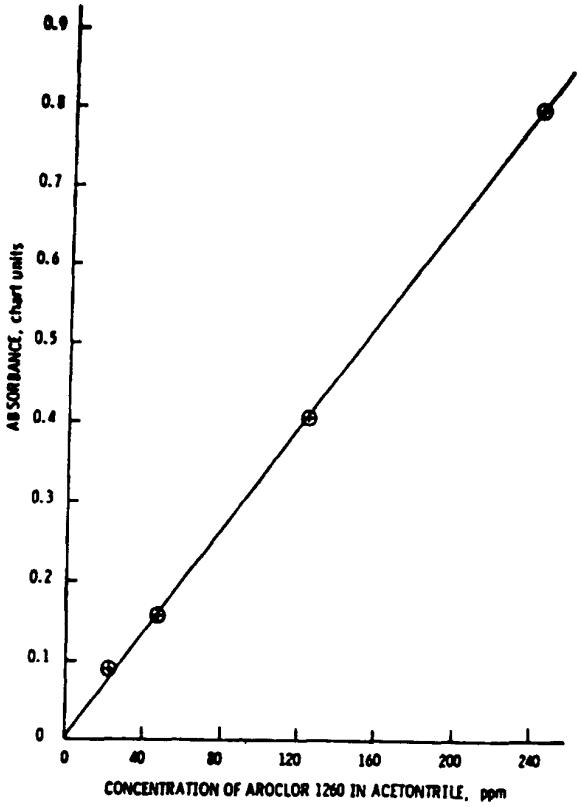

Figure 11. UV absorbance at 280 nm of Aroclor 1260 in acetonitrile as a function of Aroclor concentration.

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TABLE 1. RESULTS OF ALUMINA CLEAN-UP COLUMN

Sample No.	Fraction	GC/EC Fraction recovery, %	GC/EC Total recovery, %	UV Fraction recovery, %	UV Total recovery, %
1	5-mL Sample	0		0	
	First 5-mL rinse	47	77	68	96
	Second 5-mL rinse	30		28	
	Third 5-mL rinse	0		0	
2	5-mL Sample	47		41	
	First 5-mL rinse	78	137	61	111
	Second 5-mL rinse	12		9	
	Third 5-mL rinse	0		0	
3	5-mL Sample	35		50	
	First 5-mL rinse	53	92	59	111
	Second 5-mL rinse	4		2	
	Third 5-mL rinse	0		0	
4	5-mL Sample	39		75	
	First 5-mL rinse	62	103	85	179
	Second 5-mL rinse	2		13	
	Third 5-mL rinse	0		6	

Fraction	Average recovery, % GC/EC	UV
5-mL Sample	30	41
First 5-mL rinse	60	68
Second 5-mL rinse	12	13
Third 5-mL rinse	0	1
TOTAL	102	123

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SELECTION OF EXTRACTION SOLVENT

Several extraction solvents were tried in an attempt to reproducibly remove the Aroclors from the soil. These included hexane, acetonitrile, methanol, benzene, ethyl ether, chloroform, methylene chloride, tetrahydrofuran and the use of sodium sulfate with hexane.

Ten-gram samples of soil were spiked with 541 µg of Aroclor 1254 (54.1 µg/g. Duplicate analyses with each solvent were performed after extracting the sample with 20 mL of solvent. The extraction consisted of manually shaking the sample and then placing the sample in an ultrasonic bath for 8 minutes with manual agitation every minute. The extract was decanted and saved. A second extraction was performed using an additional 10 mL of solvent, with ultrasonication for 2 minutes and manual agitation every 30 seconds. The two extracts were combined and analyzed by electron capture gas chromatography. Results are shown in Table 2.

Wetting the soil with a polar solvent (acetone or dimethyl sulfoxide) prior to extraction with a nonpolar solvent (hexane) also was investigated. Acetone removed so many interferences from the soil that the extract was completely opaque in the UV region (280 nm). Dimethyl sulfoxide yielded "recoveries" of 144 to 189% on triplicate samples, after correction by subtracting an unspiked soil blank. Hexane was shown to be a relatively good extraction solvent for PCBs while not extracting a great number of potentially interfering compounds from the soil.

EFFECTS OF VARYING THE EXTRACTION TECHNIQUE

The effects of hand agitation and ultrasonication on recovery were investigated in an attempt to find the fastest method for reproducibly removing the Aroclors from the soil using hexane as an extraction solvent.

In one experiment, 10-gram samples of soil were spiked with 541 µg (54.1 µg/g) of Aroclor 1254. Then, 20-mL of hexane was added to each sample, and each was hand-agitated for 8 minutes. The resultant extract was decanted and analyzed by UV spectroscopy. A second aliquot of hexane, 5 mL, was added to the soil and shaken for one minute. It was decanted and saved. A third aliquot, 5 mL, was added and shaken for one minute. This extract was combined with the second aliquot and analyzed by UV. Results are provided in Table 3.

Ultrasonication was studied as a means of removing the Aroclors from soil. Ten-gram samples spiked with 541 µg of Aroclor 1254 (54.1 µg/g) were extracted using 15-mL aliquots of hexane and placed in an ultrasonic bath for varying times. The resulting extracts were analyzed by UV and a high degree of variability was noted as shown in Table 4.

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TABLE 2. RESULTS OF VARIOUS EXTRACTION SOLVENTS

Solvent	Recovery, %
Acetonitrile	96
Acetonitrile	75
Benzene	76
Benzene	72
Ethyl ether	76
Ethyl ether	90
Hexane	75
Hexane	64
Hexane + $NaSO_4$	72
Hexane + $NaSO_4$	74
Methanol	76
Methanol	70
Tetrahydrofuran	104
Tetrahydrofuran	90
Methylene chloride[a]	-[b]
Methylene chloride[a]	-[b]
Chloroform[a]	-[b]
Chloroform[a]	-[b]

[a]Could not be analyzed by GC/EC; was analyzed by UV.

[b]Opaque to UV at 280 nm after soil extraction.

TABLE 3. RECOVERY IN SAMPLES EXTRACTED BY HAND-AGITATION

Sample No.	Extract	Extract recovery, %	Total recovery, %
1	20-mL Extract	33	33
2	20-mL Original extract	44	53
	Two 5-mL subsequent extracts	9	
3	20-mL Original extract	30	41
	Two 5-ml subsequent extracts	11	
4	20-mL Original extract	24	34
	One 5-mL subsequent extract[a]	10	

[a]Sample performed to examine effect of using only one subsequent extraction.

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TABLE 4. RECOVERY IN SAMPLES EXTRACTED BY ULTRASONICATION

Sample No.	Extraction time, min	Recovery, %
1	1	120
2	5	72
3	10	24
4	20	120

The same experiment was repeated by first mixing the spiked soil with 10% (W/V) distilled water (1 mL per 10g sample). The results also were highly variable as shown in Table 5.

Four additional samples were analyzed (without water additions) to determined whether shaking manually for 10 minutes and then placing the samples in an ultrasonic bath for 10 minutes would significantly improve the extraction efficiency and reproducibility over the 10-minute ultrasonic extraction. Results are shown in Table 6.

Six spiked soil samples (54.1 µg/g Aroclor 1254) were analyzed in the following mannaer to evaluate the reproducibility of the combined hand-agitation/ultrasonication method. Twenty milliliters of hexane was added to each sample; it was shaken for 8 minutes and ultrasonicated for 8 minutes. The extract was decanted and analyzed by UV. Two subsequent 5-mL aliquots of hexane were added to the soil; each was shaken for one minute and placed in an ultrasonic bath for one minute. The resultant extracts were combined and analyzed by UV. The results from the original and combined subsequent analyses summarized in Table 7. Reproducibility was still found to be a problem.

TABLE 5. EFFECTS OF 10% WATER ADDITION TO SOIL SAMPLES EXTRACTED BY ULTRASONICATION

Sample No.	Extraction time, min	Recovery, %
1	1	48
2	5	12
3	10	84
4	20	132

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TABLE 6. RECOVERY FROM SAMPLES SUBJECTED TO MANUAL AGITATION AND ULTRASONICATION

Sample No.	Extraction time, min		Recovery, %
	Manual	Ultrasonic	
1	10	10	60
2	10	10	170
3	0	10	100
4	0	10	100

TABLE 7. REPRODUCIBILITY IN RECOVERY FROM COMBINED MANUAL EXTRACTION/ULTRASONICATION

Sample No.	Extract	Extract recovery, %	Total recovery, %
1	20-mL Original extract	56	84
	Two 5-mL subsequent extracts	28	
2	20-mL Original extract	59	81
	Two 5-mL subsequent extracts	22	
3	20-mL Original extract	41	54
	Two 5-mL subsequent extracts	13	
4	20-mL Original extract	41	52
	Two 5-mL subsequent extracts	11	
5	20-mL Original extracts	30	-
	Two 5-mL subsequent extracts[a]		
6	20-mL Original extract	96	113
	Two 5-mL subsequent extracts	17	

[a]Sample lost.

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SECTION 3

COMMENTS ON PRELIMINARY AND FINAL METHODS FOR PCBs IN SOIL

CRITICAL REVIEW OF THE PRELIMINARY METHOD

Although the preliminary method of hexane extraction of PCBs from soil with ultrasonic enhancement followed by 5% water deactivated alumina cleanup and UV detection showed promise, reproducbility was a major problem. At that point, the preliminary method was written and circulated among various MRC researchers for comments. The significant points of concern were as follows:

- The preliminary method contained several steps in which extracts were combined and an aliquot was taken for subsequent processing. The method was revised to start with a smaller soil sample (from 10 grams to 2 grams) such that all processing steps could use the entire extract. This eliminated the need for combining fractions and taking aliquots and also resulted in increasing the ratio of hexane-to-soil from 2 mL of hexane per gram soil to 6 mL hexane per gram soil.

- The amount and activity of the deactivated alumina used in the method could have been a significant source of variability. Regular alumina (activated by heating to 400°C for 4 hours) is a good sorbent for PCBs and is sometimes used to remove PCB interferences from samples for other analyses. After deactivation with 5% water, the alumina passes PCBs in hexane but retains many other interferences. Discussions with the method development technician indicated that deactivated alumina on hand from another project was used to dry pack one of two types of columns requiring approximately 3 grams or 4 grams of alumina, respectively. Freshly prepared deactivated alumina was specified in the method. For the cleanup column, the 11 mm x 85 mm column was selected with 2.00 grams of alumina.

- Acetonitrile is used in the method to clean the alumina immediately prior to hexane. Because acetonitrile and hexane are not miscible, this might create a problem with wetting the alumina with hexane. In one experiment, a small quantity of acetone, an intermediate solvent miscible with both acetonitrile and hexane, was run through the column between the acetonitrile and the hexane. Unfortunately, small traces

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of acetone remaining on the alumina and eluting with the hexane had a high enough UV extinction coefficient to interfere with sample analyses.

The final method resulting from the above comments (given in the Appendix) was then evaluated to determine if it was accurate and reproducible.

PRELIMINARY EVALUATION OF THE FINAL METHOD

Samples were prepared by spiking 2.00 grams of soil with a known amount of Aroclor 1260 in hexane. The blanks were spiked with an equal volume of hexane solvent. The hexane was allowed to evaporate. Alumina cleanup columns were made by placing 2.00 grams of 5% water-deactivated alumina in 11 mm x 85 mm columns.

Each sample was first extracted by adding 4 mL of hexane, manually shaking ten times, and sonicating for 2 minutes. This shaking/sonicating was repeated five times. The extract was decanted and started through the alumina column. The sample was then extracted twice more by adding 4 mL of hexane, manually shaking six times, sonicating for 30 seconds, and repeating the shaking/sonicating sequence four times. The second and third extracts were placed sequentially on the alumina cleanup column. The first 10 mL eluting from the alumina column was collected in a volumetric flask (includes most of the third extract) for UV analysis at 281 nm.

The results of the analysis of one sample and blank are given in Table 8. Results for three additional samples and three additional blanks analyzed 15 days later are shown in Table 9. These tests indicate that the problems in recovery reproducibility encountered earlier have been resolved by the changes incorporated in the final methcd.

EVALUATION OF FINAL METHOD UING A VARIETY OF SOIL TYPES

Any method for analyzing PCBs in soil must be useful with a variety of soil types. During the methods development phase of this work, it was assumed that PCBs would be most difficult to extract from a humis-rich black soil. This type of soil also would be expected to contain the potentially most interfering aromatic organic compounds. Because the method was developed with this type of soil, the method was expected to handle soil types with high sand or clay content. A series of tests were conducted to confirm that the PCBs could be recovered from a variety of soil types in a consistent manner and to determine the range of ultraviolet absorbing background interfences that would be encountered in soil analyses not removed by the alumina clean-up column.

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TABLE 8. STANDARD CURVE AND TEST RESULTS FOR A SAMPLE USING REDUCED SOIL SAMPLE SIZE

Sample identification	Absorbance	Concentration of Aroclor 1260, µg/g
Standard 1	0.0590	9.6 (Known)
Standard 2	0.1110	19.2 (Known)
Standard 3	0.2049	38.4 (Known)
Standard 4	0.3505	67.2 (Known)
Standard 5	0.5088	96.0 (Known)
Blank	0.0650	10
Sample Spike 1	0.2860	54

Amount spiked: 48 µg/g
Recovery: 92%

TABLE 9. PRELIMINARY EVALUATION OF THE FINAL METHOD

Sample identification	Absorbance	Concentration of Aroclor 1260, µg/g
Standard 1	0.0590	9.6 (Known)
Standard 2	0.0175	19.2 (Known)
Standard 3	0.2026	38.4 (Known)
Standard 4	0.3522	67.2 (Known)
Standard 5	0.5006	96.0 (Known)
Blank 1	0.0790	14
Blank 2	0.1153	21
Blank 3	0.0957	17
Sample spike 1	0.3610	69
Sample spike 2	0.3305	63
Sample spike 3	0.3278	62

Amount spiked: 48 µg/g
Average blank value: 17 µg/g
Average analyzed value: 65 µg/g
Average recovery: 99%

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Monsanto Agricultural and Nutritional Products Company (MANPC) maintains a supply of standard, well characterized soils for its research and development programs. Samples of four soils were obtained (gratis) from MANPC. A general description of the soil types used is shown in Table 10; specific-analyzed characteristics of these soils are shown in Table 11.

Each soil blank was analyzed in triplicate using the method shown in the Appendix. These tests were conducted to determine the range of concentration of ultraviolet absorbing species that would be extracted from the soil and not removed by the clean-up procedure. The results of these tests are shown in Table 12. The potentially interfering background absorption extracted from the four soils was found to vary from an equivalent PCB concentration of 15 ppm to 19 ppm. Preliminary tests with the garden soil used for methods development (Tables 8 and 9 showed background absorption equivalent to 10 ppm and 19 ppm. Considering the wide range of soil types tested, the background absorption was found to be relatively consistent from one soil type to another.

A potential reproducibility problem within soil type blanks was encountered, but probably involved familiarity with the method because it did not occur in the analysis of the spiked samples.

The four soil types were spiked with 48 ppm of Aroclor 1260 and analyzed in triplicate with the final method shown in the Appendix. These tests were conducted to determine if some soil (e.g., high organic content) adsorbed the PCBs more strongly than others; this feature would reduce the recovery of the spiked PCBs. The results of these analyses, presented in Table, show that the percent recovery of the spike varied from soil to soil from 89% to 95%. Preliminary tests of the method (Tables 8 and 9) showed recoveries of 92% and 99% with the garden soil. Clearly, this method is capable of reproducibility extracting the PCBs from the soils. The variability within triplicate analyses also is reasonable. The grand average for recovery of the Aroclor 1260 spikes from the four soil types was 92% ± 3%.

The method in its present form could be used in the field to determine the extent of clean-up required after a spill or it could easily be put into kit form.

Further areas of potential improvement for the method could include a detailed analysis of the shaking and ultrasonic agitation in the method to reduce operator time (e.g., it may be possible to eliminate some of the manual shaking). A layered alumina column could be evaluated to determine if a combination of acidic, neutral, and basic aluminas would reduce the soil background. GC/MS might be used to identify the interfering species so that specific modification to the clean-up procedure would be made to remove these interferences.

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TABLE 10. GENERAL DESCRIPTIONS OF SOIL TYPES[a]

SPINKS LOAMY SAND - Spinks series is a member of the sandy, mixed, mesic family of Psammentic Hapludalfs.

Drainage and Permeability - Well drained; surface runoff ranges from slow to medium; permeability is moderately rapid.

Use and Vegetation - Generally used for growing hay and pasture, with small part in corn, wheat, soybeans, and orchards; large part of steeper areas is in forest or permanent pastures; native vegetation was forest, dominantly oaks and hickories.

Distributation and Extent - Southern Michigan and northwestern Ohio; series is of moderate extent.

Setting - In moraines, till, plains, outwash plains, and beach ridges within lake plains of Wisconsin age; dominant slopes from 2 to 18 percent, ranging from 0 to 40 percent.

DRUMMER SILTY CLAY LOAM - Drummer series is fine-silty, mixed, mesic Typic Haplaquolls.

Drainage and Permeability - Poorly drained; surface runoff is slow or ponded; permability is moderate.

Use and Vegetation - Largely cropped to corn and soybeans; some small grain and meadow also grown; native vegetation was probably marsh grasses and sedges.

Distribution and Extent - Northern and eastern Illinois; extent is moderate.

Setting - Occur on nearly level parts and in depressions of till and outwash pleins; slopes range from 0 to 2 percent; formed in 40 to 60 inches of loess or waterlaid silty material and underlying stratified outwash and glacial drift.

(continued)

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TABLE 10 (continued)

DUPO SILT LOAM - Dupo series is member of course-silty over clayey, mixed, nonacid, mesic family of Aquic Udifluvents.

Drainage and Permeability - Somewhat poorly drained; surface runoff is slow; permeability is moderately slow to slow.

Use and Vegetation - Mainly cultivated to corn, soybeans, and small grains; native vegetation was probably mixed deciduous hardwoods and sedges or grasses.

Distribution and Extent - Central and southern Illinois; extent is small.

Setting - On floodplains on slope gradients less than 2 percent; formed in 20 to 40 inches of recent light colored silty alluvium overlying dark colored silty clay or clay.

HODGE FINE SAND - Hodge series is mixed, mesic Typic Udipsamments.

Drainage and Permeability - Somewhat excessively drained; runoff is slow; permeability is rapid; Hodge soils are frequently flooded where not protected by levees.

Use and Vegetation - Commonly cropped to corn, wheat, soybeans and hay; native vegetation is mostly cottonwood and oak trees with some interspersed tall grasses.

Distribution and Extent - Mainly along the Missouri River in Missouri and possibly along major streams in Iowa and Nebraska; extent is moderate.

Setting - On nearly level to gently undulating floodplains; slope gradients dominantly less than 2 percent but range to 5 percent in some pedons; formed in calcareous sandy alluvial sediments.

[a]Information from National Cooperative Soil Survey, U.S.A.

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TABLE 11. SPECIFIC CHARACTERISTICS OF SOILS USED FOR EVALUATION

	Spinks loamy sand	Drummer silty clay loam	Dupo silt loam	Hodge fine sand
Composition %				
Organic matter	2.4	3.4	1.2	0.3
Sand	75.1	2.4	4.6	61.2
Silt	17.8	68.8	84.2	28.0
Clay	4.8	25.3	10.0	10.8
Other characteristics				
pH	4.7	6.2	8.1	7.2
CEC, meq/100 g	11.3	24.6	10.4	7.3
Bulk density, g/cc	1.41	1.16	1.13	1.4
One-third bar, %	17.9	28.8	23.9	8.9

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TABLE 12. ANALYTICAL RESULTS FOR FOUR SOIL TYPES

Parameter	Aroclor 1260 concentration, ppm	Absorption at 281 nm[a]	
		Background	Spiked samples
Standard curves	9.6	0.038	0.041
	19.2	0.090	0.091
	38.4	0.182	0.184
	67.2	0.341	0.346
	96.0	0.528	0.534

(continued)

TABLE 12 (continued)

Parameters	Absorption at 281 nm	Equivalent Aroclor 1260 conc., ppm
Spinks background	0.052	8.6
	0.182	36.5
	0.023	8.1
Average		17.7
Drummer background	0.062	15.0
	0.099	21.6
	0.022	8.0
Average		14.9
Dupo background	0.047	12.5
	0.186	37.1
	(0.130 rerun)	
	0.019	7.5
Average		19.0
Hodge background	0.076	17.6
	0.056	13.9
	0.070	16.5
Average		16.0

(continued)

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TABLE 12 (continued)

Parameters	Absorption at 281 nm	Total equivalent Aroclor 1260 concentration, ppm	Concentration less average background, ppm	Percent recovery
Spinks with 48-ppm spike	0.282	62.9	45.2	94
	0.234	59.9	42.2	88
	0.208	58.2	40.5	84
Average				89
Drummer with 48-ppm spike	0.251	60.9	46.0	96
	0.229	59.6	44.7	93
	0.255	61.2	46.3	97
Average				95
Dupo with 48-ppm spike	0.292	63.5	44.2	92
	0.271	62.2	43.2	90
	0.270	62.2	43.2	90
Average				91
Hodge with 48-ppm spike	0.278	62.6	46.6	97
	0.271	62.2	46.2	96
	0.225	59.3	43.2	90
Average				94
Overall mean recovery of spike from four soils				92

[d]Standard curve was generated on two different days.

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APPENDIX

PORTABLE ULTRAVIOLET TEST METHOD FOR POLYCHLORINATED BIPHENYLS IN SOIL

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PORTABLE ULTRAVIOLET TEST METHOD FOR POLYCHLORINATED BIPHENYLS IN SOIL

1. Scope and Application

1.1 This method covers the qualitative and semi-quantitative determination of polychlorinated biphenyls (PCBs) in soil samples by the ultraviolet absorbance spectrophotometric analysis of hexane soil extracts.

1.2 The method is designed for the rapid field determination of whether PCBs occur in test soils at levels greater than the 50 parts per million (ppm) specified in many spill clean-up operations.

1.3 The method detection limit (MDL), defined as the minimum concentration of a substance that can be measured and reported with 99% confidence that the value is above zero, was calculated to be 4.5 ppm for Aroclor 1260 from replicate analyses with this method.

1.4 Different PCBs have ultraviolet extinction coefficients that vary by a factor of almost two. Aroclor 1260 differs the most in 281-nm absorption from Arclors 1254 and 1242. However, it can be differentiated from Arclors 1254 and 1242 by an absorption minimum that occurs at 268 nm for Aroclor 1260. In cases where the identity of the PCBs present is unknown (or mixed), standards of the least-UV-absorbing PCB (Aroclor 1260) should be used to calculate the maximum possible PCB concentration for the sample.

2. Summary of the Method

Approximately 2-g samples of soil are extracted three times by 4-mL portions of hexane. The hexane extracts are passed in series through an alumina column to minimize potential interferants and collected in a volumetric flask for analysis via ultraviolet absorbance spectrophotometry at a wavelength of 281 nm.

3. Interferences

3.1 Ultraviolet (UV) absorption at 281 nm is generally due to the presence of aromatic compounds. Extraction of soil samples with hexane removes not only any PCBs present, but also many other UV-absorbing compounds. Although the alumina column retains many of these compounds while passing the PCBs, some species elute with the PCBs and give a background signal from "clean" soils.

3.2 In five different soil types analysed, the UV-absorbing background interferences ranged from an equivalent PCB concentration of 10 ppm to 19 ppm, with an average equivalent concentration of 16 ppm.

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4. Safety

Although PCBs have a low acute toxicity and have not been found to be carcinogenic by standard National Cancer Institute bioassays, they are regulated as carcinogens. All appropriate precautions should be taken by personnel conducting analyses to follow OSHA regulations and to avoid contact with PCBs or PCB-containing samples or extracts.

5. Apparatus and Materials

5.1 Extraction Tubes -- Corning, 16 mm x 100 mm, Pyrex® culture tubes with Teflon-lined screw cap (Fisher 9825-16 or equivalent).

5.2 Volumetric Flasks -- 10 mL.

5.3 Volumetric Pipettes or Solvent Dispenser -- Capable of 4 mL volumes.

5.4 Clean-up Columns -- 11 mm x 85 mm.

5.5 Sonicator -- Branson, Bronsonic Model 32 sonic bath or equivalent.

5.6 Laboratory Analytical Balance -- 0.0001-g sensitivity for preparation of standards.

5.7 Field Balance -- 0.1-g sensitivity for weighing 2-g samples of soils.

5.8 Ultraviolet Spectrophotometer -- Capable of analyses at 281 nm.

6. Reagents

6.1 Aroclor 1260 -- Chem Service Stock No. PLZ-130 or equivalant and other PCB standards as required.

6.2 Hexane -- Fisher, HPLC-grade or equivalent.

6.3 Acetonitrile -- Burdick and Jackson, UV quality or equivalent.

6.4 Alumina -- Bio-Rad, neutral, AG® 7, 100 to 200 mesh or equivalent.

6.5 Standard Solutions -- Stock standard solutions may be prepared by addition of weighed quantities of Aroclor 1260 to hexane in volumetric flasks, or they may be purchased as certified solutions.

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6.6 Secondary Dilution Standards -- Using stock standard solutions, prepare secondary dilution standards in hexane such that the standards will bracket the expected concentration of PCB in the hexane extracts of the soil samples.

7. Calibration

7.1 Prepare calibration standards at a minimum of four concentration levels, bracketing the expected concentration of PCB in the final hexane extract.

7.2 Determine the absorbance of each solution using an ultraviolet spectrophometer at a wavelength of 281 nm.

7.3 Prepare the calibration curve by plotting PCB concentration versus ultraviolet absorbance.

7.4 Determine the least-squares-fit of data points to the best straight line plot.

8. Quality Control

8.1 Each new analyst should analyze a number of blank and spiked soils to become familiar with the method prior to the analysis of field samples.

8.2 An ongoing program of performance checks is recommended to assure that results are within the accuracy and precision limits expected for the method.

9. Sample Collection, Preservation, and Handling

Soil samples for PCB analyses are not expected to degrade significantly under any normal sample collection or storage conditions.

10. Sample Extraction and Ultraviolet Spectrophotometry

10.1 Approximately 2 g of soil is placed in a Pyrex culture tube supplied with a Teflon-lined screw cap. Each sample is extracted three times with 4-mL portions of hexane.

10.2 For the first extraction, the hexane soil mixture is manually shaken ten times followed by sonication for 2 minutes. This process is repeated four more times for a total of 50 shakes and 10 minutes of sonication and then the hexane extract is decanted onto the alumina column (see 10.3). For the second and third extractions, the mixtures are manually shaken six times followed by sonication for 30 seconds. This shaking/sonication process is repeated three more times for a total of 24 shakes and 2-minute sonication for both the second and third extractions. These

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hexane extracts are passed sequentially through the alumina column to remove potential ultraviolet-absorbing interferants. The first 10 mL eluting from the alumina column is collected in a volumetric flask for analysis.

10.3 The 11 mm x 85 mm alumina columns are prepared by filling them with 2 g of alumina (Bio-Rad , neutral AG 7, 100 to 200 mesh) that has been activated by heating for 4 hours at 400°C, deactivated by the addition of 5% (w/w) water. The columns are further conditiond in the field by washing with 3 mL of acetonitrile and then with 3 mL of hexane immediately prior to use.

10.4 The hexane extracts from the alumina columns are analyzed for absorbancy using an ultraviolet spectrophotometer at a wavelength of 201 nm.

10.5 A Corning 16 mm x 100 mm ultraviolet cell (Fisher 9825-16 or equivalent) is used for the analyses.

11. Calculations

11.1 The concentration of PCB is obtained by direct interpolation from the calibration curve.

11.2 When blanks, duplicates, or spiked samples are used, all data obtained with the sample results should be reported.

12. Method Performance

12.1 The method detection limit (MDL) is defined as the maximum concentration of a substance that can be measured and reported with 99% confidence that the value is above zero.

12.2 An MDL may be computed from the variability of replicate analyses conducted near the detection limits of a method. This is accomplished by multiplying the standard deviation of replicate analyses times the Student's t-value appropriate for a 99% confidece level with n-1 degrees of freedom.

12.3 A worst case MDL was computed using triplicate analyses from four different soil types spiked at 40 ppm with Aroclor 1260. The average analyzed value for the 12 analyses was 61.2 ppm with a standard deviation of 1.65 ppm. The Student's t-value at the 99% confidence level for 12 replicate analyses (11 degrees of freedom) of 2.73 times the 1.65 ppm standard deviation gives a computed MDL of 4.5 ppm (2.73 x 1.65 ppm) for Aroclor 1260.

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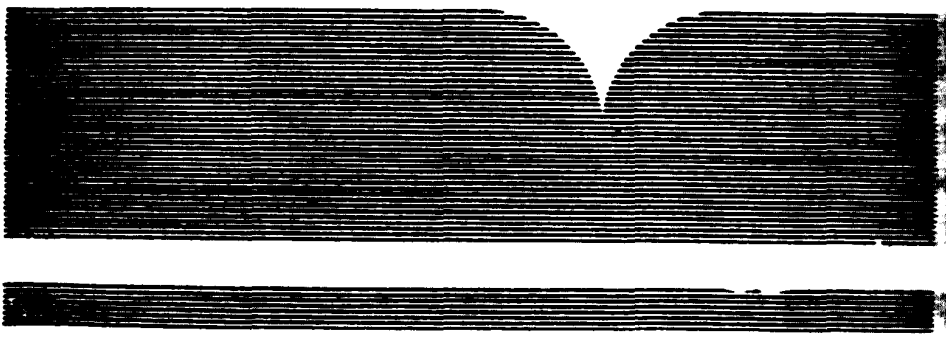
Advances in Exposure, Health and Environmental Effects Studies of PCBs

ICAIR Life Systems, Inc.
Cleveland, Ohio

13 May 1982



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ADVANCES IN EXPOSURE, HEALTH AND ENVIRONMENTAL EFFECTS STUDIES OF PCBs

SYMPOSIUM PROCEEDINGS

May 12-13, 1982

Prepared Under Contract No. 68-01-6554
Project 1247
ICAIR Work Assignment No.: 30

by

ICAIR
Life Systems, Inc.
Cleveland, OH 44122

for

Office of Toxic Substances
Health and Environmental Review Division
U.S. Environmental Protection Agency
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Analytical Methodologies;
Exposure Studies: Environmental Residues and Bioaccumulation;
Exposure Studies: Industrial Processes;
Health Effects: Epidemiology;
Health Effects: Laboratory Studies;
Environmental Effects; and
Risk Assessment

Each contributed paper includes a significant bibliography of cited and related scientific literature references for those seeking greater detail.

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ADVANCES IN EXPOSURE, HEALTH AND ENVIRONMENTAL EFFECTS STUDIES OF PCBs

Symposium Proceedings

May 12-13, 1982

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by

ICAIR
Life Systems, Inc.
Cleveland, OH 44122

for

Office of Toxic Substances
Health and Environmental Review Division
U.S. Environmental Protection Agency
Washington, DC 20460

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DISCLAIMER

Although this Proceedings Document reports the presentations and discussion that occurred in the PCB Symposium funded by the United States Environmental Protection Agency through Contract No. 68-01-6554 with Life Systems, Inc., the contents of the Proceedings are the independent views of scientists not associated with EPA. Consequently, the Proceedings Document has not been subjected to the Agency's peer review process. It does not necessarily reflect the views of the Agency and no official endorsement should be inferred.

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FOREWORD

Almost anyone who is likely to open this book will know the basic facts about polychlorinated biphenyls (PCBs): first described in the late 19th century, they have been produced on an industrial scale since about 1930. In the subsequent 40 years they have been used extensively in a variety of applications because of their chemical and thermal stability and good dielectric properties. Since the different commercial PCB products are not simple entities but families of compounds, the picture is complicated because individual components of these mixtures differ in their chemical, physical and biological properties.

The initial concern about chlorinated aromatic compounds originated from reports around 1940 of chloracne and liver changes in workers who came in contact with these materials during production or handling. Worldwide attention was not given to PCBs, however, until 1966 when the journal, New Scientist, reported on Soren Jensen's finding of PCBs in pike from Swedish lakes, in the human brain and in an eagle which was found dead in the Stockholm area. During the years that followed, PCBs were found in environmental samples in several parts of the world. It became evident that these persistent and bioaccumulating compounds were ubiquitously distributed; biological material from polar regions and other uninhabited and remote areas contained traces of PCBs.

The U.S. manufacturers responded to these findings by limiting sales of PCBs to uses in enclosed systems only. The presence of PCBs in some isolated environmental samples from Sweden might have remained an analytical curiosity for some time had not Rachael Carson's book, "Silent Spring", alerted environmental scientists - and the general public - some years before to the possible danger of organochlorine compounds.

In 1968 accidental ingestion of PCBs through contaminated rice oil revealed a number of toxic effects of PCBs in a group of Japanese people. This incident also established placental transfer of these compounds and persistance in the milk of contaminated mothers. Comparable effects were observed in the 1979 PCBs poisoning incident in Taiwan.

In the early 1970s, it was also shown that humans were directly exposed to PCBs from such diverse sources as food packaging materials and carbonless copying paper. The same time period also saw the beginning of intensive scientific efforts to understand the route of exposure and the fate and effects of PCBs.

Long term exposures at low levels were studied and the phenomena of bioaccumulation and food-chain magnification were also investigated. Prior to studies with PCBs, little was known on photochemical behavior and metabolic patterns of chloroaromatic compounds.

PCBs production and import is either forbidden or limited in most industrialized countries. However, most of the total PCBs produced to date are either still in service or found in dumps and land fills. To avoid further environmental contamination, safe methods for ultimate disposal have to be found.

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The PCBs problem will not disappear overnight. There may be emotional reaction and unfounded fear concerning PCBs, but there is also the possibility of real environmental problems with potentially hazardous consequences. We must look at the facts, evaluate them and conduct investigations in areas where additional scientific research is required. A scientifically sound basis for prudent political decisions must be developed. The U.S. Environmental Protection Agency and Life Systems, Inc. are to be commended for organizing this important Symposium.

O. Hutzinger
University of Bayreuth
Bayreuth, Germany

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We wish to gratefully acknowledge the administrative services of the following individuals responsible for the program organization, execution, and subsequent preparation of these proceedings: Dr. Irwin Baumel, Dr. William Farland and Mr. H. Glenn Williams of the Office of Pesticides and Toxic Substances, and Mr. Michael Kamgas, Ms. Cynthia Patrick, Dr. Roy Reuter, Mr. Greg Schiefer, Ms. Patricia Sweeney and Ms. Cynthia Wesley of ICAIR.

Special appreciation is extended to the symposium participants for the excellent quality of the presentations, the professional manner in which the sessions were conducted, and the stimulating nature of the discussions.

It was the combined efforts of all these individuals which ensured the success of this symposium and the resultant contribution of knowledge to the scientific community.

R. J. Davenport
B. K. Bernard

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CHAPTER 1

INTRODUCTION

This publication is a compilation of data presented and discussed during the symposium entitled, "Recent Advances in Exposure, Health and Environmental Effects Studies of PCBs," held May 12-13, 1982 in Bethesda, Maryland. The symposium was organized specifically as an information update for the Environmental Protection Agency's (EPA's) Polychlorinated Biphenyls (PCBs) Program. In more general terms, the symposium provided an opportunity for the exchange of information between PCBs researchers from academia, government agencies, industry and independent research institutions.

The PCBs Program was implemented by the Office of Pesticides and Toxic Substances (OPTS) to carry out the specific requirements of Section 6(e) of the Toxic Substances Control Act (TSCA). Section 6(e) mandates the promulgation of rules by the EPA for the disposal and marking of PCBs, and establishes a timetable for controlling the use of PCBs, and for eliminating the manufacture, processing and distribution of PCBs in commerce.

As part of the continuing update process for acquiring relevant data for the PCBs Program, the OPTS requested that a two-day symposium be undertaken which would provide a forum for a full and free discussion of scientific issues related to PCBs.

Symposium Scope and Objectives

The data presented in the symposium was limited to that which has become available since 1978, including both published data and data from studies that are still in progress. No formal consideration was given the EPA's past or potential regulatory activities concerning PCBs.

The following objectives were established for the symposium:

1. To review, discuss and interpret PCBs scientific data published since 1978 and preliminary PCBs data from ongoing work.

2. To provide for an exchange of views between scientists who are knowledgeable about exposure, health and environmental effects, and human health studies associated with PCBs.

3. To identify research gaps and areas of agreement and controversy.

Symposium Participants

The following individuals participated as the Chairperson, as Speakers or as Discussion Leaders:

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Chairperson:

Dr. Otto Hutzinger*
University of Amsterdam
The Netherlands

Authors:

Dr. Seymour Priess
Jrill, Priess, Hays, Loomis & Schaffer, Inc.
Arlington, VA 22209

Dr. Robert Moolenaar
Dow Chemical Company
Midland, MI 48640

Dr. William Gaffey
Monsanto Company
St. Louis, MO 63167

Dr. Ido Pallizzari
Research Triangle Institute
Research Triangle Park, NC 27706

Mr. Kent Hodges
Dow Chemical Company
Midland, MI 48640

Dr. Stephen Safe
Texas A & M University
College Station, TX 77843

Mr. Richard Hunter
U.S. Army Corps of Engineers
Tulsa, OK 74121

Dr. Mary Jo Vodicnik
Medical College of Wisconsin
Milwaukee, WI 53226

Dr. Robert James†
Ecology and Environment, Inc.
Buffalo, NY 14255

Discussion Leaders:

Dr. Raymond Harbison
University of Arkansas for Medical Sciences
Little Rock, AK 72205

Dr. Mark Melancon
Medical College of Wisconsin
Milwaukee, WI 53226

Dr. Robert Kaley
Monsanto Company
St. Louis, MO 63167

Dr. Mary Wolff
Mount Sinai School of Medicine
New York, NY 10029

Dr. Renate Kimbrough‡
Center for Disease Control
Chamblee, GA 30341

---

*Now at University of Bayreuth, Bayreuth, Federal Republic of Germany.
†Now at University of Arkansas, Division of Toxicology, Little Rock, AR 72205.
‡Now at Center for Environmental Health, Atlanta, GA 30333.

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Organization of Symposium

In order to achieve the above symposium objectives, the symposium was divided into seven sessions. The session topics, in order of presentation were as follows:

Analytical Methodologies
Exposure Studies: Environmental Residues and Bioaccumulation
Exposure Studies: Industrial Processes
Health Effects: Epidemiology
Health Effects: Laboratory Studies
Environmental Effects
Risk Assessment

Each session consisted of the presentation of papers by one to three speakers, followed by a discussion period. During the discussion period, a dialogue was established between the speakers and the symposium attendees. Questions were answered, and data and the interpretations of data were exchanged.

Each Discussion Leader moderated the discussion period for one or two sessions. Following the symposium, the Discussion Leaders prepared summaries of the discussions from their notes and transcripts made during the symposium.

The chapters that follow are arranged in the order of the seven sessions. Each chapter contains the papers that were presented and the discussion summary, prepared by the Discussion Leader.

The last chapter (Chapter 9) is a summary of the accomplishments and results of the work presented and discussed during the symposium. Although written from the technological viewpoint of a single participant (the symposium Chairperson, Dr. Otto Hutzinger), it provides a needed interpretation of the many facts, recent technical advances and identified data gaps that were presented and discussed during this two-day period.

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CHAPTER 2

ANALYTICAL METHODOLOGIES

This chapter reviews certain analytical advances in PCBs detection, identification, and quantification. High resolution gas chromatography is covered in detail, with specific references to capillary column development and supporting 'phase' methodologies, detector systems, and the comparative advantages and limitations of each combination. Problems associated with instrument calibration are generally caused by the nonavailability or lack of primary PCBs standards, and the possibility of using secondary standards such as well-defined commercial PCBs mixtures. The application of these newer methods to environmental, biological, and process stream samples are discussed.

The discussion summary is a review of the advantages and limitations of the various methodologies. Topics include procedures for analysis of PCBs contaminants, validation methodology, limits of detection, PCBs pattern recognition, and the cost/benefit ratio of packed versus capillary column gas chromatography.

RECENT ADVANCES IN THE ANALYSIS OF POLYCHLORINATED BIPHENYLS IN ENVIRONMENTAL AND BIOLOGICAL MEDIA

E. D. Pellizzari, M. A. Moseley, S. D. Cooper, J. W. Harry, B. Demian

Analytical and Chemical Sciences
Research Triangle Institute
Research Triangle Park, NC 27709

M. D. Mullin

U.S. Environmental Protection Agency
Large Lakes Research Station
Grosse Ile, MI 48138

INTRODUCTION

Polychlorinated biphenyls (PCBs), terphenyls (PCTs) and quadphenyls (PCQs) had been manufactured as commercial mixtures [Aroclors® (US), Clophen® (Germany), and Kanoclor® (Japan)] for more than four decades before they were banned in the US in 1976. Because of their long-term heavy usage as dielectric fluids, in transformers and capacitors, in hydraulic fluids, fire retardants, etc., and their persistence, PCBs have permeated into practically every environmental medium throughout the world (Hutzinger et al. 1974). Because of their ubiquity PCBs have received considerable attention in recent years in the area of analytical measurements and toxicology.

Since environmental pollution by PCBs first became apparent, a plethora of purification procedures, gas chromatographic systems, detectors and methods for quantifying gas chromatographic responses has been reported to determine the contamination of environmental and biological samples (Hutzinger et al. 1974, Sherma 1975, Chau and Sampson 1975, Lao et al. 1976, Krull 1977, Brinkman et al. 1978, Pomerantz et al. 1978, Stalling et al. 1979a,b, Sherma

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1981, Albro et al. 1979). However, until recent advances in analytical instrumentation, most of the conventional methodology yielded only semi-quantitative data with virtually no qualitative or quantitative information on the isomer composition for PCBs in the sample. The analytical problems are complicated by the fact that there are 209 individual chlorinated biphenyl isomers (Ballschmitter and Zell 1980) spanning 10 homologous series (1 to 10 chlorines per biphenyl). A commercial mixture (e.g., Aroclor) itself may contain as many as 60 chlorobiphenyl isomers representing several homologs (Ballschmitter and Zell 1980).

The conventional quantification method is based upon packed column gas chromatography (GC) and reports the PCB content in environmental and biological samples by referring it to a particular Aroclor mixture (e.g., Aroclor 1242, 1254 or 1260). The GC detector is first calibrated using commercial Aroclor mixtures, and then the appropriate commercial Aroclor profile is matched to the sample profile. Using the Webb-McCall technique or a variation of it the total PCB content is calculated (Webb and McCall 1973). This approach, however, is potentially subject to considerable error.

Environmental contamination may be derived from Aroclor mixtures or from incidentally generated chlorobiphenyls whose profiles do not resemble Aroclor patterns (Pittaway et al. 1981). In either case, the conventional quantification method is inadequate. As time passes, the "Aroclor patterns" undergo alteration in the environment since selective weathering and biotransformation and bioaccumulation in living organisms perturb these patterns. The problem of Aroclor pattern dissimilarity will be further aggravated as PCB monitoring continues into the future.

The quantification problem is further exacerbated by production of chlorobiphenyl isomers in chemical process streams, incineration, etc., via chemical or pyrolysis reactions which are not the same as the chemical reactions once used for the manufacture of Aroclors (Pittaway et al. 1981). There is no reason to believe that incidental generation produces any fixed pattern of chlorobiphenyl isomers which the analyst can use to identify and quantify chlorobiphenyls based upon pattern recognition from the packed column gas chromatogram. Thus, the qualitative and quantitative analysis of PCBs in environmental and biological samples and in samples from process streams involves the difficult issue of having to detect, identify and quantify each individual isomer.

The accuracy of PCB determination in environmental, biological and process stream samples is, in addition to the reasons given above, also related to the degree of variability in the analytical response of each chlorobiphenyl isomer to the detector employed (Hutzinger et al. 1974, Boe and Egase 1979, Albro et al. 1981, Safe et al. 1975).

Recent theoretical and experimental studies have indicated that the biological properties of chlorobiphenyl isomers are significantly influenced by the number and biphenyl ring position of the chlorine atoms (McKinney and Singh 1981, Poland and Glover 1977, Matthews et al. 1978, Kimbrough 1980). Because the toxicological properties vary considerably among isomers (McKinney and Singh 1981, Poland and Glover 1977), more sophisticated methods capable of yielding information about the chemical composition at the isomeric level are

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required in order to precisely investigate and assess the toxicological consequences of PCB pollution. Obviously, the ideal analytical procedure is one which identifies and measures each individual chlorobiphenyl isomer.

This chapter examines the most recent advances which strive to meet the objective of individual chlorobiphenyl isomer identification and quantification. The areas discussed are: (a) high resolution gas chromatography; (b) detection systems; (c) availability of chlorobiphenyl isomer standards; and (d) application of state-of-the-art methods to the analysis of environmental and biological samples. It is beyond the scope of this paper to include sampling techniques and isolation and purification methods. These have been adequately reviewed elsewhere.

HIGH RESOLUTION GAS CHROMATOGRAPHIC TECHNOLOGY

In order to analyse for 209 individual chlorobiphenyl isomers the use of high resolution chromatographic techniques is mandatory. In this respect, GC currently is far superior to high resolution thin-layer and high resolution liquid chromatography for PCB analysis. The relative merits of packed columns (low resolution) versus capillary columns (high resolution) GC analysis of PCBs have been succinctly reported by Mullin and Pilkiw (1981). Their work provided the impetus for further research into the determination of an optimum capillary column(s) for the analysis of individual isomers of PCBs, polybrominated biphenyls, pesticides and other halogenated hydrocarbons in biological and environmental samples.

Development of Capillary Columns

Moseley and Pellizzari have recently reported on extensive investigation into five variables which affect capillary performance for the analysis of PCBs (Moseley and Pellizzari 1982a,b, Pellizzari et al. 1981). These variables are: (a) material of construction; (b) pretreatment/deactivation procedures; (c) stationary phase type; (d) stationary phase film thickness; and (e) capillary dimensions. Evaluation criteria employed were: (a) separation number (TZ) between 2,2',4',5-tetrachlorobiphenyl and 2,2',4,4',6,6'-hexachlorobiphenyl; (b) resolution between 2,2',5,5'-tetrachlorobiphenyl and 2,2',4',5-tetrachlorobiphenyl; (c) height equivalent to an effective theoretical plate (HETP) for 2,2',4',5-tetrachlorobiphenyl; (d) adsorption characteristics; (e) thermal stability; and (f) general performance on an Aroclor 1242/1260 mixture (1:1, w/w).

Capillaries were made from pyrex and soft glass, quartz, vitreous silica and fused silica materials (Moseley and Pellizzari 1982a,b, Pellizzari et al. 1981). The objective of this facet of the study was to determine the most suitable material for construction, pretreatment/deactivation, and amenability to coating of a thin, uniform, stable film of stationary phase. It was recognized early in this work that these variables were not independent of each other. Except for C-87, all stationary phases evaluated could be coated on the flexible silica capillaries (Pellizzari et al. 1981). Preference for the silica capillaries was attributed to their flexible nature facilitating their assembly into GCs even by the novice. Thus, a major impediment to the use of capillaries by the analytical community had been removed.

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Many pretreatment/deactivation procedures were investigated since the raw construction material was not suitable for directly coating with stationary phase (Moseley and Pellizzari 1982a,b, Pellizzari et al. 1981). The procedures were: (a) barium carbonate treatment; (b) Carbowax 20M; (c) Superox-4; (d) HCl etching; (e) persilylation; and (f) thermally induced polysiloxane (SE-52 or OV-101) bonding. The preferred methods were polysiloxane deactivation on silica and pyrex and persilylation on pyrex (Moseley and Pellizzari 1982b, Pellizzari et al. 1981).

Although glass capillaries coated with C-87 stationary phase provide excellent resolution of individual chlorobiphenyl isomers, use of C-87 currently is limited by two factors - its temperature stability (~220°C) and the current inability to successfully coat a uniform film on silica. Because of the upper temperature limit the C-87 phase coated capillaries are inadequate for the analysis of PCTs, PCQs, PBBs and sample extracts which are very "dirty" (e.g., fish). For these reasons alternate stationary phases were sought.

The current literature reports several different phases used in capillary GC for analysis of PCBs (Albro et al. 1981, Mullin and Filkins 1981, Krupcik et al. 1976, Krupcik et al. 1980, Albro et al. 1977, Stalling et al. 1978, Trunstre et al. 1981); however, until our research there was not a concerted effort to systematically evaluate phases (Moseley and Pellizzari 1982a,b, Pellizzari et al. 1981). Using the previously mentioned criteria a matrix designed study was executed in concert and while making a comparison of phase selectivity (McReynolds' constants) to guide the overall investigation toward the "optimum" phase. Among the phases evaluated were C-87, SE-54, SP-2100, QF-1, SE-52, OV-101, Dexsil 410, Apiezon M and Apiezon L. Early results predicted (from McReynolds' constants) that Apiezon M would most closely mimic the excellent separation pattern of C-87 (Pellizzari et al. 1981). In fact, this correspondence was experimentally demonstrated (Moseley and Pellizzari 1982a). Several advantages of Apiezon M were recognized and will be discussed later. Finally, a complementary stationary phase to Apiezon M was sought so that one phase could serve as a primary analytical column and the other a reference column. SE-54 coated capillaries provided a significantly different resolution pattern compared to Apiezon M and SE-54 was also selected in our research (Moseley and Pellizzari 1982a,b).

It has long been recognized that the thinner the stationary film thickness the higher the mass transfer coefficient. The sample capacity, however, decreases. Thus, research was performed to determine a film thickness which had a very high mass transfer coefficient (as measured by HETP), adequate sample capacity for the detection system to be employed, and stability to long periods of usage (Moseley and Pellizzari 1982a,b, Pellizzari et al. 1981). Stability (to solvent and thermal shock) could, of course, be imparted by immobilizing the film on the silica surface by a crosslinking/surface bonding reaction (Moseley and Pellizzari 1982b).

Two methods were reported which immobilized phases to silica (Moseley and Pellizzari 1982b). One utilized a thermal technique (SE-52), the second a dicumyl peroxide reaction (SE-54). The first method easily produced the desired 0.025 µ film capillaries for use with electron capture (EC) and negative ion chemical ionization (NICI) mass spectrometric (MS) detection of

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PCBs. These capillaries exhibited a bleed of 0.7 pA (flame ionization detection) at 320°C. The second method yielded thicker films (0.1 μ) for higher capacity for use with electron impact MS.

An Apiezon H phase immobilized to silica has not been reported.

The results of these investigations which specifically focused on resolution of PCBs indicated that a silica capillary, polysiloxane deactivated, 0.2-mm ID x 50-m in length, coated with Apeizon H (0.025 μ film) or SE-54 (0.025-μ film) is preferred (Mooseley and Pellizzari 1982a,b. Pellizzari et al. 1981). An Apiezon H coated silica capillary allows the elution of PCBs to occur approximately 30-40°C lower than other stationary phases (Mooseley and Pellizzari 1982a,b, Pellizzari et al. 1981) and is thermally stable to ~285°C.

Comparison of Packed and Capillary Column Profiles

The inherent differences between low and high resolution gas chromatographic columns are exemplified by Figures 1 and 2. Figure 1 compares the profiles for a standard mixture of Aroclor 1242/1260. Figure 2 depicts the profiles for a stack (stationary source) sample (Mullin 1981). Both high resolution analyses were performed on SE-54 fused silica capillaries.

It is evident in Figure 2 that the low resolution profile does not readily resemble a commercial Aroclor mixture. Thus, it would be highly inaccurate to quantify the low resolution profile using a commercial Aroclor standard for instrument calibration and the Webb-McCall method (Webb and McCall 1973).

Several examples demonstrating the performance of Apiezon H silica capillaries will be discussed later in this chapter.

DETECTION SYSTEMS

Modes of Detection

Use of several types of detectors has been reported over the years in the analysis of PCBs. However, only a few have made significant recent advances that are noteworthy. These are electron capture, negative ion chemical ionization mass spectrometry (NICI-MS) and selected ion monitoring (SIM), a variant of electron impact mass spectrometry.

Electron Capture Detection

The electron capture detector continues to be one of the most sensitive and hence valuable selective detectors for PCB detection. It is only recently, however, that its full potential has been realized and incorporated into commercial systems.

From a quantitative standpoint, one of the limitations of the electron capture detector in past has been nonlinearity of response. Until the mid-1970s the ECD in use had a linear dynamic range of approximately 50-100. Several papers have dealt with determining the proper function which would give a linear relationship with concentration (Pellizzari 1974, Wentworth and

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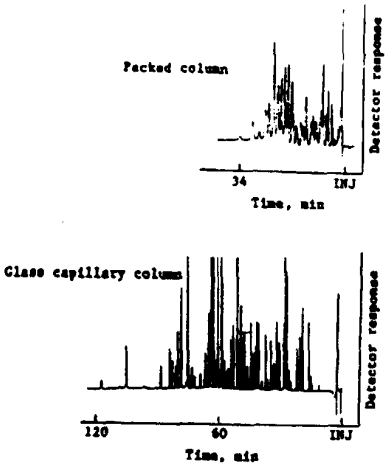

Figure 1. Chromatograms of Aroclor 1242/1260.
Top - packed column, bottom - capillary.

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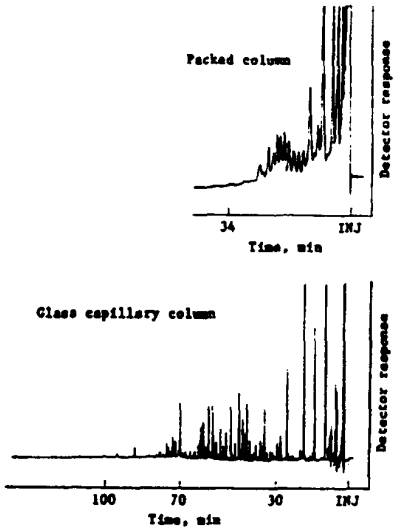

Figure 2. Chromatograms of stack sample.
Top - packed column, bottom - capillary.

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Chen 1979). It has been suggested that the response was logarithmic by analogy to light absorption (Wentworth and Chen 1979). However, when the ECD was operated in the pulse sampling mode the reactions occurred primarily in the field free period, so that the analogy was not considered very appropriate (Wentworth and Chen 1979).

Once a valid kinetic model for the electron capture processes for thermal reactions was derived by Wentworth et al. (1979) and the research in atmospheric pressure ionization mass spectrometry gave direct evidence on negative and positive ion formation (under ECD conditions), the solution to electron capture detector nonlinearity was in hand. Attention was focused on the ECD's concentration dependence which has been of great concern to analytical chemistry. Analysis of the kinetic model was carried out by numerical solution of differential equations which alleviated some of the early mathematical assumptions.

As a result of the experimental work on electron capture mechanisms, subsequent reports appeared in the literature describing an alternate method of linearization of response (Maggs et al. 1971, Patterson et al. 1976). The fundamental principle was based upon modulating the frequency of pulsing the detector electrodes so that the plasma current was maintained constant. This function is given by

$$E_q = \frac{F-F_o}{F_o}$$

where F_o = the frequency giving the base current in the absence of capturing species
F = the frequency giving the base current in the presence of a capturing species

Initially there were reports of a "break" in linearity, but with improved instrument design parameters this problem was eliminated (Patterson et al. 1976). Thus, the modern ECD utilizes modulated pulsed frequency to achieve a dynamic range of approximately four orders of magnitude, an improvement which is necessary for the analysis of PCBs in environmental and biological samples.

A second limitation was the ECD cell volume. This problem did not surface until analysts began investigating the use of high resolution capillary columns (Pellizzari 1974). The original cell volumes of 1-4-mL were adequate when used with packed columns whose flows were high and chromatographic peak shape and efficiency were preserved. A few isolated reports appeared in the literature addressing improved cell design, in particular low volume cells, for use with capillaries. ECD cell volumes between 250 and 500-uL utilizing a coaxial design still required a scavenger gas after the capillary column to reduce the residence time in the ECD cell and preserve the ultra-high theoretical plates which were attainable by capillaries (Pellizzari 1974). However, it was only recently that commercial GC systems became routinely available with ECDs compatible with capillary flow rates.

With these two parallel developments it is now feasible to perform elegant quantitative electron capture detection of PCBs.

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Negative Ion Chemical Ionization Mass Spectrometry

This detection method is a variant of positive ion chemical ionization mass spectrometry. The associated electronics to regulate, focus and pass negative ions to an appropriately polarized electron multiplier were developed in the mid-1970s; however, it was not until recently that ion source and reagent gas conditions were investigated for optimizing PCB analysis (Pellizzari et al. 1981).

NICI-MS is uniquely suited to measuring trace quantities of polyhalogenated chemicals in environmental samples because of its high sensitivity for these chemicals and its virtual transparency to otherwise potentially interfering molecules (Knehl et al. 1980). It also provides, in addition to sensitivity, molecular ion information and thus a verification of the structural entity being measured, a highly desirable feature when examining complex environmental and biological samples.

NICI-MS is very closely analogous to electron capture detection in that the ion forming reactions are common to both. The ion forming reactions that are important for polychlorinated molecules have been described (Knehl et al. 1980). They include: (a) the resident capture of thermal electrons; (b) chloride attachment; (c) deprotonation; and (d) oxygen exchange. Because NICI-MS is a novel technique, the operating parameters which optimize the technique preferentially to one of the above mechanisms for PCB analysis have recently been studied in our laboratory.

Investigations in this laboratory have centered on the use of high resolution gas chromatography in combination with NICI-MS while elucidating and characterizing instrumental parameters suitable for PCB analyses (Pellizzari et al. 1981). These investigations have included: (a) examining the performance of two different ion source designs; (b) the effect of source pressure on sensitivity and spectral signature; and (c) the effect of various reagent gases on sensitivity and fragmentation of PCB isomers. Compared to conventional electron impact MS, less information about the structure of the compound is obtained. Thus, the specific aim of the investigations was to study several moderating and reagent gases to enhance: (1) the formation of molecular anions of the individual chlorobiphenyl isomers; or (2) their dissociation to yield chloride 35 and 37 isotopic anions (Pellizzari et al. 1981).

Reagent gas studies were conducted with methane, oxygen/nitrogen, nitrous oxide/nitrogen, nitrous oxide/methane, difluorodichloromethane, and tetrafluoromethane. This variety of reagent gases was necessary because a major problem encountered in NICI-MS analysis of PCBs had been the lack of molecular weight information obtained for the lower molecular weight PCBs (C_1-C_6) under methane moderated electron capture conditions. Since the lower molecular weight PCBs undergo dissociative electron capture to form Cl^- ions under these conditions, use of a reagent gas which chemically reacts with individual chlorobiphenyl isomers rather than just moderating electron energy led to the observation of useful molecular weight information in the spectral signature.

Field et al., (Smit and Field 1980) had observed that a mixture of nitrous oxide and methane produced abundant OH^- ions under negative ion

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conditions. The hydroxide ions were observed to react with a wide variety of compounds by proton abstraction to form $(M-H)^-$ ions. Therefore, this reagent gas mixture was studied in our laboratory as a likely candidate to provide molecular weight information for individual chlorobiphenyl isomers.

Experiments were conducted with an LKB 2091 magnetic sector instrument with a relatively open source design. Figures 1-7 depict mass spectra of monochlorobiphenyl, trichlorobiphenyl, hexachlorobiphenyl, octachlorobiphenyl, and decachlorobiphenyl obtained under H_2O/CH_4 NICI conditions. Nitrous oxide was introduced through a reagent gas inlet (5×10^{-5} Torr as measured at the Penning gauge) and methane (3×10^{-5} Torr) was passed into the ion source via a GC make-up line and separator. Based on calculations made for positive ion methane CI the actual source pressure exerted by both reagent gases was 0.2-0.3 Torr. The MS system was optimized for m/z 17 (OH^-). A 2-μL injection (~100-pg) of a standard solution of PCBs was made with a 5:1 split ratio. As indicated in Figure 3 the spectrum of 2-chlorobiphenyl exhibited $(M-H)^-$ ions. The $M^{\pm}$ peak at m/z 188 is no larger than expected from ^{13}C isotope abundance. In addition, very low intensity ions were found for the $(M-H+O)^-$ ion at m/z 203, $(M-H+H_2O)^-$ ion at m/z 231, and $(M-H+NO)^-$ ion at m/z 217.

The high mass region for trichlorobiphenyl (> m/z 40, Figure 4) mass spectrum was dominated by the $(M-H)^-$ ions at m/z 253, 257, and 259. The $M^{\pm}$ intensity was greater than predicted on the basis of ^{13}C isotope abundance (24% vs. 13%) suggesting that some stabilization of $M^{\pm}$ as occurring. Also, $(M-Cl)^-$ ions were evident at m/z 221 and 223.

For hexachlorobiphenyl (Figure 5) the $(M-H)^-$ ions at m/z 357, 359, 361, and 363 were present. Also, substantial abundance of $M^{\pm}$ ions was observed (53% observed vs. 13% calculated as ^{13}C). Ion clusters for the loss of one chlorine (m/z 323) and two chlorines (m/z 288) from the parent molecule were detected. An interesting ion cluster formed by the loss of chlorine and the addition of oxygen $(M-19)^-$ was observed (m/z 338).

The mass spectrum of octachlorobiphenyl (Figure 6) exhibited negligible hydrogen abstraction but was certainly dominated by $M^{\pm}$ ions. Since there are only two hydrogens available for abstraction on this PCB homolog, this result was unexpected.

Decachlorobiphenyl (Figure 7) with no hydrogens available for abstraction yields a spectrum that is due to electron capture (formation of $M^{\pm}$) and Cl^-.

The above observations for H_2O/CH_4 reagent gas indicate that verification of the molecular weight of the chlorobiphenyl isomer can be achieved in high resolution GC NICI-MS. Furthermore, the homogeneity of gas chromatographic peaks in complex mixture analysis can be established since non-PCB substances or nonhomologous PCB isomers can be distinguished. NICI-MS will thus provide molecular weight information, which has been one of the strong suits claimed for EI-MS.

Another moderating gas typically used in NICI-MS is methane. Experiments in our laboratories on the effects of source pressure on sensitivity indicated that as the methane pressure increased so also did sensitivity. As a compromise between maximum sensitivity and excessive pressure, a reagent gas pres-

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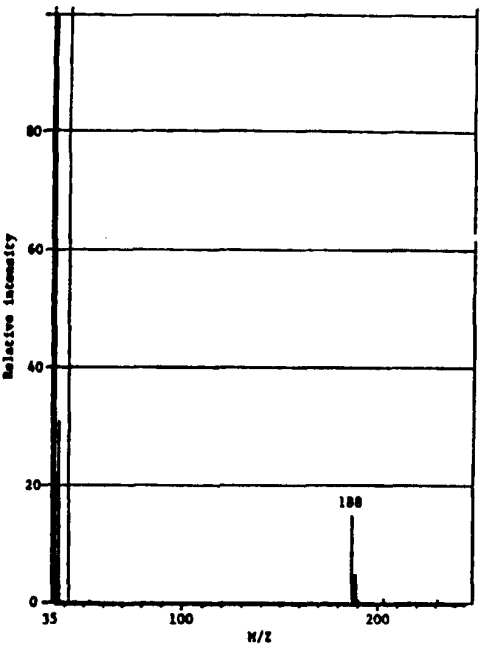

Figure 3. H_2O/CH_4 NICI mass spectrum of monochlorobiphenyl.

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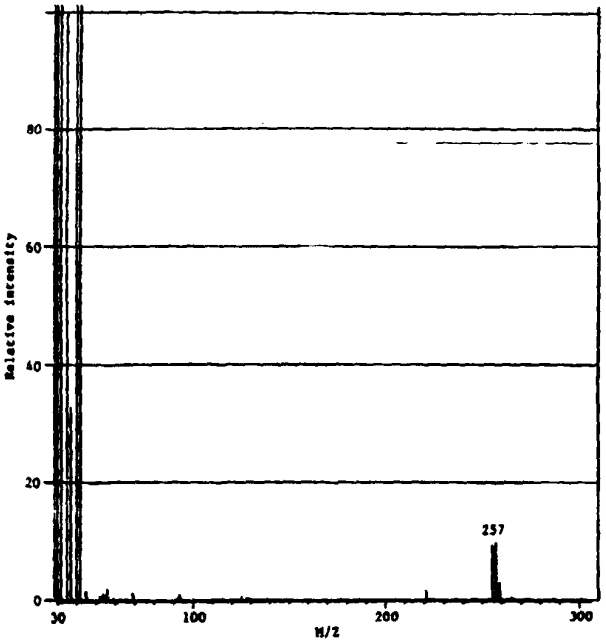

Figure 4. H_2O/CH_4 NICI mass spectrum of trichlorobiphenyl.

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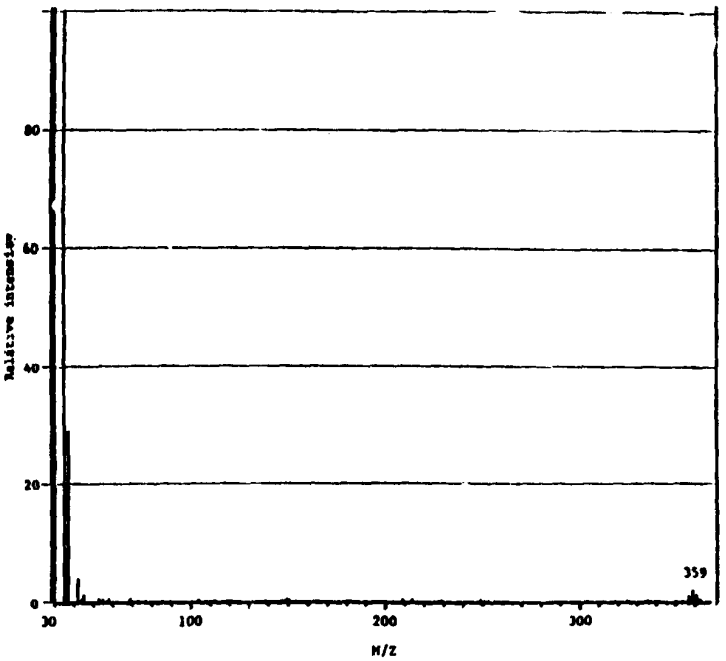

Figure 5. H_2O/CH_4 NICI mass spectrum of hexachlorobiphenyl.

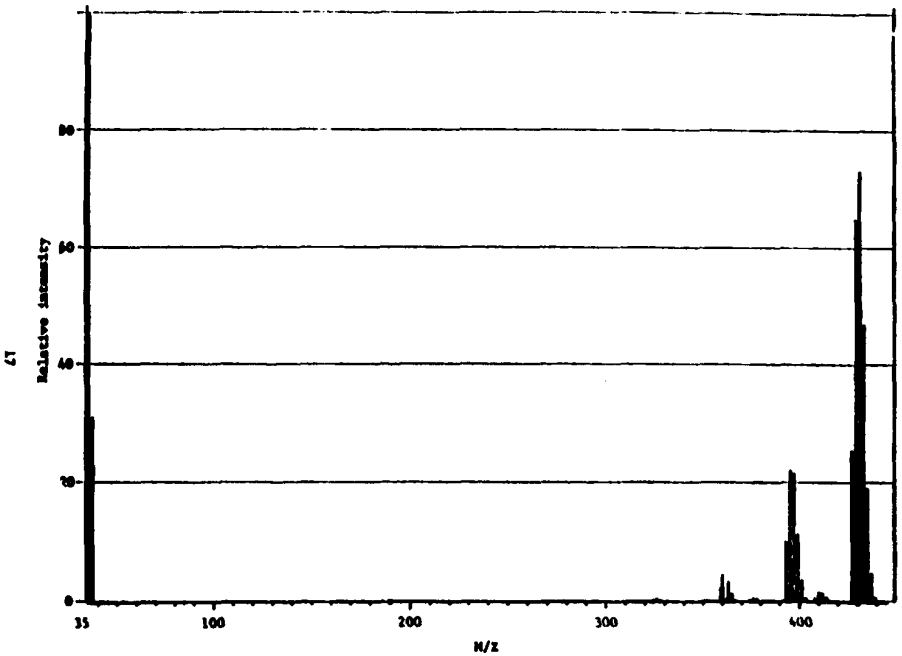

Figure 6. N_2O/CH_4 NICI mass spectrum of octachlorobiphenyl.

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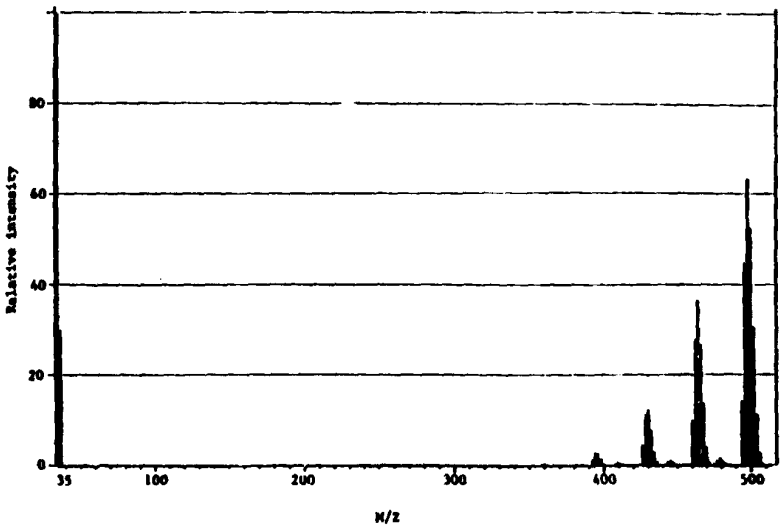

Figure 7. N_2O/CH_4 NICI mass spectrum of decachlorobiphenyl.

sure of 4×10^{-5} Torr is normally employed (measured at diffusion pump throat, actual source pressure may be higher).

Of the reagent and moderating gases studied, methane provides one of the more sensitive modes of operation. However, the principal mechanism of reaction is dissociative electron capture leading to m/z 35 and 37 which can be used for quantification.

The chemical thermodynamics in NICI-MS is also affected by the physical design of the GC/MS source where the CI takes place. The experiments conducted with a relatively open and closed source designs gave parallel results. The principal feature of the open source was that it was less subject to filament carbonization and its sensitivity was maintained stable for a few weeks. Considerable absolute differences in the limits of detection were observed between two different instrument makes. One system was clearly capable of detecting in the high femtogram region, while the other required two orders of magnitude more PCB material.

Thus, the advantages of both sensitivity and molecular weight information can be realized with NICI-MS. The recent studies have provided a basis for choosing the appropriate operating parameters for analysis of PCBs.

Selected Ion Monitoring Utilizing EI-MS

Electron impact mass spectrometry has been a very popular analytical tool, in addition to ECD, as a GC detector for PCBs. The use of the conventional scanning mode suffers from an inadequate limit of detection for chlorobiphenyl isomers. The limits of detection may differ between EI-MS and ECD by as much as three orders of magnitude (Pellizzari 1981). For this reason, EI-MS per se has not been widely successful unless there are large quantities of PCBs present in environmental and biological samples.

There have been reports, however, of a specialized application of EI-MS. Selected ion monitoring (SIM) had been primarily developed for drug analysis, but recently it has been applied to verifying and quantifying PCBs (Tindall and Wininger 1980, Martelli et al. 1981, Albro and Parker 1980, Erickson and Pellizzari 1979). Improved limits of detection are realized.

Another variant of EI-MS is limited mass scanning (LMS). The use of SIM (programmed mode) and LMS permits the spectrometer to spend more time transmitting through the analyzer to the electron multiplier ions of interest to yield lower limits of detection (Tindall and Wininger 1980). Both of these techniques are under computer control and are also available to the analyst when operating in the NICI-MS mode.

Pulsed Positive Ion Negative Ion Chemical Ionization (PPINICI) Mass Spectrometry

During the past few years PPINICI has been developed: rapid switching between positive and negative CI (1KHz) allows simultaneous information to be acquired (Pellizzari and Mooney 1981). Little research has been performed on its optimization and application to PCB analysis.

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Combination of High Resolution Gas Chromatography and Ultrasensitive Detection

Figures 1 and 2 depict the combination of state-of-the-art high resolution chromatography and electron capture detection. It is clearly evident from these profiles that modern EC detectors are designed to preserve the high resolution which capillary columns are now capable of delivering.

The direct coupling of high resolution GC capillaries with the ion source of mass spectrometers has also been successfully accomplished. The flexible nature of silica capillaries has greatly facilitated this accomplishment, since most MS systems are not well engineered to accept the rigid glass capillaries.

Figure 8 depicts an example of analysis of an Aroclor 1016/1254/1260 mixture (2.5:2.0:1.0 w/w/w) utilizing an Apiezon H phase coated (0.025-u film), FSD silica capillary and NICI-MS detection. Table 1 lists the operating conditions which were optimized for dissociative electron capture (i.e., enhancement of m/z 35 and 37). The mass chromatogram (m/z 35) exemplifies the close similarity between the proportional response for individual chlorobiphenyl isomers under methane NICI conditions and those obtained with ECD. An expanded version of this chromatogram is given in Figures 9-11. Chromatographic peaks 3, 33, and 103 are the internal standards, 1,2-dichloronaphthalene, 1,2,3,4-tetrachloronaphthalene, and octochloronaphthalene, respectively. The chromatographic peaks depicted in Figures 9-11 indicate ideal symmetry and thus the chromatography was preserved. The peak residence times are generally 7-8s. Because the ECD and NICI-MS profiles are superimposable, the numbering scheme shown in Figures 9-11 was standardized for our characterization research and for our cross-referencing and verification efforts. The identity of several of the peaks will be discussed below.

Another means of representing NICI-MS information is depicted by Figures 12 and 13. The top tracing is the one shown in Figure 8 but it is considerably reduced. The remaining profiles in Figure 12 are mass chromatograms for m/z 188 (Cl_1), 222 (Cl_2), 256 (Cl_3), 292 (Cl_4), and 326 (Cl_5) representing the five homologous series. It is important to note that under methane NICI conditions, the intensity of molecular anions for Cl_1-Cl_4 is very weak to nonexistent. It is more appropriate to use M_2O/CH_4 for detecting which chromatographic peak belongs to a homolog. Figure 13 shows mass chromatograms for m/z 360 (Cl_6), 394 (Cl_7), 428 (Cl_8), 462 (Cl_9), and 496 (Cl_{10} not detected) representing the remaining homologous series. In this case all of the chlorobiphenyl isomers were detected in the Aroclor mixture.

Variation of Detector Responses

A common problem with ECD, NICI-MS and EI-MS (SIM, LMS) as detectors is the large variation which is observed between the individual chlorobiphenyl isomers, both within and between homologous series (Mutzinger et al. 1974, Boe and Egaas 1979, Albro et al. 1981, Safe et al. 1975). The relative response factors (RRF_i) for a few individual chlorobiphenyl isomers obtained with high resolution GC-ECD [(GC)^2-ECD] have been reported. A majority of the isomers have been analyzed in our laboratory and the RRF_i compared (Table 2). The RRF_i was calculated as follows:

MONS 026061

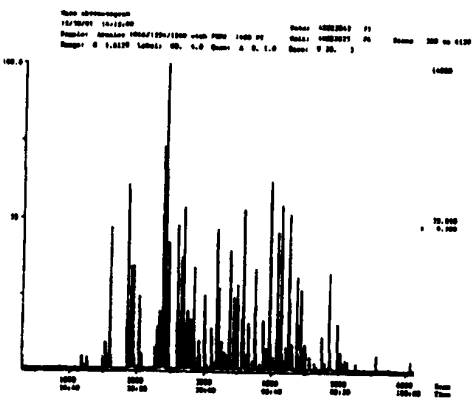

Figure 8. Mass chromatogram (m/z 35) of Aroclor 1016/1254/1260 obtained by CH_4 NICI-MS.

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Table 1. $(GC)^2$/NICI-MS Operating Conditions (Finnigan 4021)

Parameter	Condition
GC	
Capillary	Fused silica
ID	0.23 mm
Length	45 m
Deactivation	Polysiloxane
Stationary phase	Apiezon H
Film thickness	0.025 μ
He carrier	0.6 mL/min (32 cm/sec)
Splitless/split	40 sec; 10:1
Temperature	100°C/0.1 min → 260°C @1.5°C/min
MS	
Reagent gas	CH_4
Forepressure	0.2 torr
High vacuum pressure	4.2×10^{-5} torr
Manifold temperature	120°C
Ionizer temperature	260°C
Emission current	0.5 mA
Electron energy	70 eV
Scan cycle	1.0 sec
Scan range	30-700 daltons

MONS 026063

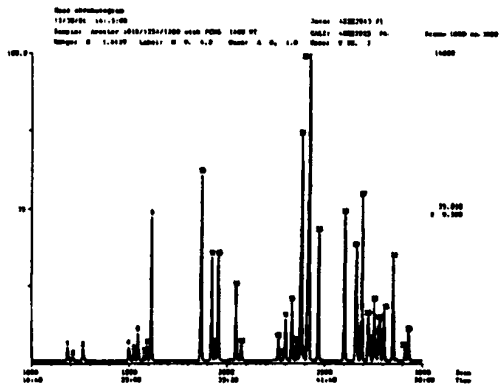

Figure 9. Mass chromatogram (m/z 35) of Aroclor 1016/1254/1260 obtained by CH_4 NICI-MS (Figure 8 expanded).

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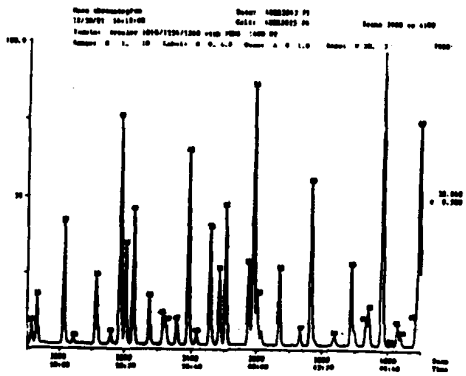

Figure 10. Mass chromatogram (m/z 35) of Aroclor 1016/1254/1260 obtained by CH_4 NICI-MS (Figure 8 expanded--middle portion).

MONS 026065

ASSESSMENT OF CARCINOGENIC RISKS FROM PCBs IN FOOD

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Kenny S. Crump, Ph.D.
Marjory D. Masterman, B.S.
SCIENCE RESEARCH SYSTEMS, INC.

Box 7356
Ruston, LA 71272

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1. Chemical Properties

Polychlorinated biphenyls (PCBs) are a family of compounds produced by the total or partial chlorination of biphenyl. There are ten possible hydrogen bonds which can accommodate chlorine substitution in a biphenyl molecule. A specific chlorobiphenyl molecule may be referred to by naming the positions of the chlorine atoms according to the diagram in Figure 1 (National Institute for Occupational Safety and Health (NIOSH), 1977). In naming a particular molecule, the lowest possible numbers are assigned and the ring with the fewest chlorine substitutions is assigned primed numbers. See Figure 2 for examples of the naming convention.

When two compounds have the same number of chlorine substituents on the biphenyl molecule but the substitutions occur in different locations, the two compounds are called isomers. The class of chlorobiphenyls consisting of one type of isomers is referred to using a prefix denoting the number of chlorine substituents, e.g. pentachlorobiphenyls. There are ten possible chlorobiphenyls and 209 possible individual isomers. The term PCBs is used to refer to a complex mixture of different chlorobiphenyls and their isomers (Nisbet, 1976a).

The synthesis of a pure sample of a specific chlorobiphenyl in the laboratory is quite difficult because the chlorination process of biphenyl naturally forms mixtures of many PCBs. Because some chlorine substitution patterns are more likely than others, some isomers are more likely to occur than others and this in turn causes some of the

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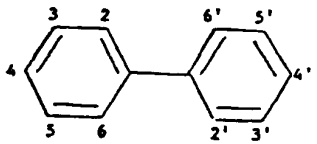
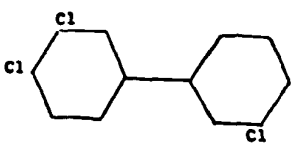
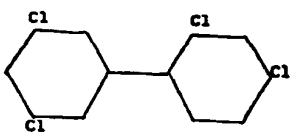


Figure 1: Biphenyl molecule and ring numbering system



3,3',4-trichlorobiphenyl



2',3,4',5-tetrachlorobiphenyl

Figure 2: Examples of the numbering system for chlorobiphenyls

chlorobiphenyls to be more abundant than others. For example, a chlorobiphenyl completely chlorinated on one ring and unchlorinated on the other is not likely to appear (Environmental Protection Agency (EPA), 1976).

PCBs are produced commercially by the chlorination of biphenyl with anhydrous chlorine in the presence of a catalyst, usually iron filings or ferric chloride (EPA, 1976). The chlorination process is terminated at a particular step in order to produce a mixture of chlorinated biphenyls with an average percentage of chlorine. These crude isomeric mixtures are further refined to remove color, traces of hydrogen and the catalyst by a distillation process (EPA, 1976). PCB products made by Monsanto are called by the trade name "Aroclor". Varying kinds of Aroclors are designated by a four-digit number, e.g. Aroclor 1254 or Aroclor 1242. The first two digits refer to the fact that biphenyl is made up of twelve carbon atoms, and the second two digits refer to the approximate percent by weight of chlorine in the mixture. Thus, Aroclor 1254, a mixture of chlorinated biphenyls, would contain by weight, 54% chlorine and 46% carbon, hydrogen and trace elements. Aroclor 1254 would not always contain the exact same amount of a particular compound since commercial mixtures will vary from batch to batch, but the relative amounts of the ten isomer classes will stay the same from batch to batch.

One exception to the usual Aroclor nomenclature is Aroclor 1016, which was introduced in 1971 to gradually replace Aroclor 1242. Aroclor 1016 is comprised mainly of tri- and tetrachlorobiphenyl compounds and contains 41% chlorine by weight. It differs from Aroclor 1242 in that

the latter contains a greater percentage of the more highly chlorinated compounds (NIOSH, 1977).

In Japan other PCB products were marketed under the trade names "Santotherm" and "Kanechors" 300, 400, 500, and 600. In Germany PCB products were marketed under the trade name "Clophens" A50 and A60, and in France under the names "Phenoclors" and "Pyralenes" (NIOSH, 1977).

Studies of the commercial preparations with PCBs have turned up two interesting facts. First, about half of the 209 possible isomers do not occur in the commercial mixtures. In fact, Aroclor 1248 contains less than 50 separable isomers. Second, trace contaminants such as polychloro naphthalenes and polychloro dibenzofurans (PCDF) have been found in some samples of PCBs. The contamination may occur during the manufacturing process (NIOSH, 1977).

PCBs have several physical and chemical properties of both industrial and environmental interest. Even through the basic properties of the different commercial PCB mixtures depend on the particular mixture of chlorobiphenyls in the specific preparations, the mixtures are enough alike that the Aroclors can be used as a basis for discussion of these properties (EPA, 1976). Commercial PCB mixtures can be mobile oils, viscous liquids, sticky resins or crystalline solids at room temperature. Their color ranges from clear to yellow to yellow-green to black. A more complete listing of physical properties is given in EPA (1976), p. 40.

Chemically, PCBs are very stable organic compounds, exhibiting a high heat capacity, low electrical conductivity, a resistance to oxidation, low vapor pressure and excellent dielectric properties.

PCBs are quite stable to long heating and those PCB liquids with four or more chlorine atoms are non-flammable as are their vapors. Although PCBs are not very soluble in water, with this solubility decreasing with increasing clorine content, PCBs are quite soluble in hydrocarbon solvents, lipids and in oils. Also the adsorption rate of PCBs onto plastic, glass, dust particles, silt and sand is high. Because of these "attractive" chemical properties, industry has made extensive use of PCBs, mostly in "closed" or "semi-closed" systems such as electrical transformers and capacitors, and in heat transfer systems (EPA, 1976).

When it became evident in the late 1960's that PCBs had become an environmental pollutant, Monsanto Co. voluntarily phased out production of Aroclors 1232, 1248, 1260, 1262 and 1268 in 1971. Monsanto also began selling PCBs for use in "closed" electrical systems only and, as of 1975, was producing only Aroclors 1221, 1016, 1242 and 1254 (Nisbet, 1976a).

2. Food and Environmental Contamination

The particular combination of physical and chemical properties in chlorobiphenyls that led to such a widespread usage of PCBs in industry is also an important factor in the process of PCBs becoming environmental pollutants (EPA, 1976). Some of the more significant properties include low solubility in water, high solubility in lipids and high specific gravity. To determine the impact of PCBs as environmental pollutants and food contaminants, it is necessary to determine first how they are released into the environment and, secondly, how they are dispersed throughout the environment.

2.1 Routes of Contamination and Environmental Distribution

There are basically three ways that PCBs can be released into the environment. First, there is intentional disposal of PCBs and products containing PCBs, mostly into dumps and landfills. Second, there is disposal into water, including losses of industrial fluids and deliberate dumping of industrial wastes. Third, PCBs are released into the air, including vaporization from plasticized products, releases from incomplete burning in dumps or incinerators, and releases from burning scrap products (Nisbet, 1976b).

There are two major methods of transport once the PCBs are in the environment. PCBs are transported aerially in the form of a vapor or because they are trapped on airborne dust particles (EPA, 1976), and eventually return to earth in rain or dustfall. PCBs are transported through water in several ways including the movement of sediment containing PCBs, dumping sewage sludge in the ocean and direct leaks from coastal industries (Nisbet, 1976b). Due to the low solubility of PCBs in water and/or the high specific gravity of PCBs, most of the PCBs discharged into the water will either be absorbed into the sediment at the bottom of the body of water or evaporate into the air. The latter possibility is evidenced by a co-evaporation study on Aroclor solutions, and since each Aroclor is made up of different isomers of several chlorobiphenyls, the vapor pressure or solubility of a particular Aroclor really represents an average over its various isomeric components (EPA, 1976). The former possibility is evidenced in a study of drainage basins in the United States and Puerto Rico where it was apparent that bottom sediments contained much higher concentrations of PCBs than did overlying water (EPA, 1976),

presumably because of the high specific gravity and low solubility in water of PCBs (Dennis, 1976).

PCBs are available for introduction into food chains through the above methods of release into the environment. The PCBs are taken in by biota directly, through absorption, or indirectly, through a food chain. That biological magnification can occur has been observed in the wide ranging accumulation of PCBs within the biota, where extremely large loads are found in the highest members of the food chain (EPA, 1976). It has been demonstrated in the laboratory that fish can accumulate PCBs to concentrations as much as 274,000 times the concentration of PCBs in water (Nisbet, 1976a).

Food may be contaminated by PCBs also through machine leaks, such as heat transfer equipment leaking during pasteurization, contamination of packaging materials (recycled paper) and contamination of animal feed which leads to contamination of meat and poultry. Mothers' milk has also been found to contain PCBs.

Polychlorinated biphenyls are very persistent in the environment. The more highly chlorinated biphenyls are more resistant to degradation, resulting in a "differential persistence" of PCBs. The selective degradation of PCBs has an effect on which of the Aroclors are most persistent in air, water, fish, and in humans. Most of the PCBs found in dry

fallout and in the air resemble Aroclor 1254 (Nisbet, 1976c). In a study done by the U.S. Department of Interior's Geological Survey on PCBs contained in whole water samples and in bottom sediments in the major drainage basins of the United States and Puerto Rico for 1971-1974, the predominant PCB detected was Aroclor 1254 (Dennis, 1976). In other studies though, combinations of PCBs are reported: in samples of both bottom and suspended sediment taken from the upper Chesapeake Bay Aroclors 1254, 1262, 1242 and 1248 were found (Munson, et al., 1976).

A study by Sanborn et al. (1976) on the green sunfish demonstrated that in fish a main difference in metabolism comes between trichlorobiphenyls and tetrachlorobiphenyls, with a relatively efficient storage of tetrachlorobiphenyls. This is also evident in data from the 1970 National Pesticide Residue Monitoring Program in which substantial fractions of Aroclor 1248 occurred in fish taken from the Ohio and Hudson Rivers (Walker, 1976). McDermott, et al. (1976) found that Aroclors 1254 and 1242 were present in Dover sole taken near discharge points of southern California wastewater plants in the ratio of 2:1 while the ratio in the wastewater was about 3:8. This last example would imply that other factors such as the sediment load or solubility of a particular PCB are involved in determining the levels of PCBs in fish. Another factor is the phenomenon of bioaccumulation, the concentration of PCBs in the tissues at much higher levels than in the surrounding water. This is due primarily to the fact that PCBs are highly soluble in lipids and not very soluble in water.

In humans there is differential storage of the more highly chlorinated biphenyls, and the less chlorinated isomers are either metabolized or excreted. Results of studies on residues in human

adipose tissue indicate that the chlorobiphenyl compounds most often found were the penta-, hexa-, and heptachlorobiphenyl compounds, in amounts most comparable to those prevalent in Aroclors 1254 and 1260 (Kutz and Strassman, 1976). But human food monitoring indicates that most humans are exposed to PCBs through diet, and that most PCBs in human food are in fish. This would apparently contradict the fact that substantial quantities of tetrachlorobiphenyls are found in fish. What apparently happens is that humans may be exposed to these less highly chlorinated biphenyls but do not retain them (Nisbet, 1976c).

2.2 Levels in Food from the FDA Total Diet Program

In the FDA Total Diet Program (Johnson and Manske, 1977), a market basket of food representing the basic 2-week diet of a 16-to-19-year-old male is collected in each of several geographic areas. The various foods are prepared in the manner in which they would normally be eaten and are then analyzed for the presence of various substances including PCBs. The lowest concentration at which it is possible to quantify the level of PCBs present is .05 ppm. Levels detected below this level are recorded as "trace". The results of these studies pertaining to PCBs for the fiscal years 71-76 are summarized in Table 1.

Table 1: Total Diet Studies-American teenage male

	Percent of composites containing PCB's								
	Food class composites								
Fiscal Year	Dairy products	Meat, fish & poultry	Grain & cereal products	Potatoes	Legume vegetables	Root vegetables	Garden fruits	Oils, fats & shortening	Sugars and adjuncts
1971		47	13						
1972	6	46	6		6	3	3	17	6
1973	10	33	17	3				3	
1974		43							3
1975 (1st half)		40							
1976		15*							

* Manske (1979), personal communication

Source: Jelinek and Corneliussen (1976)

(No entries signify zeros)

Table 2: Estimates of daily PCB intakes
(Total Diet Study-teenage male)

	Average daily intake of PCB's[a]	
Fiscal year	Total diet (µg/day)	Meat-fish-poultry food class (µg/day)
1971	15.0	9.5
1972	12.6	9.1
1973	13.1	8.7
1974	8.8	8.8
1975 (1st half)	8.7	8.7
1976	3.3*	3.3*

[a]Lower limit of quantitative reporting = 0.05 ppm with analytical method employed.

* Manske (1979), personal communication

Source: Jelinek and Corneliussen (1976)

The only food class in which PCBs were detected in 1975 or 1976 was meat, fish and poultry and all of the positive observations were trace values. It is likely that these positive finds are all due to PCBs in fish samples.

Jelinek and Corneliussen (1976) estimated the microgram per day intake of PCBs based upon the FDA Total Diet Program. These values which are listed in Table 2, must be viewed as only very crude estimates since, in order to obtain them, numerical values had to be assigned to trace observations. For those levels which were reported as trace, the decision was made to consider them to be at one-half the quantitative lower level of detection, i.e., .025 ppm (Nisbet, 1976a).

2.3 Levels in Fish

Based upon the FDA Total Diet Study (Johnson and Manaka, 1977), it appears that, for the U. S. population as a whole, the most significant exposure to PCBs from food is through fish. It does not seem possible to evaluate adequately at this time the overall distribution of exposures to PCBs through eating fish. The distribution of total fish consumption and consumption of tuna can be calculated from the Seafood Consumption Study (National Marine Fisheries Service, 1976), but the distribution of consumption of other species is not available. Moreover, the concentration of PCBs in fish is highly variable, both between species and within a single species. Fish caught further offshore tend to have smaller amounts of PCBs than estuarine fish, and

fresh water fish caught in areas of high PCB pollution tend to have the highest concentrations of PCBs.

Butler and Schutzmann (1978) reported on PCB residues in juvenile estuarine fish as part of the National Pesticide Monitoring Program. This report is based upon 1524 analyses collected in 144 estuaries nationwide during the period 1972 to 1976. The annual incidence of PCB residues and the average residue discovered are given in Table 3. These data indicate a possible gradual decline in both the maximum residues observed and average concentrations. This is likely due to the general curtailment in production and use of these compounds. It appears from Table 3, however, that PCBs will continue to contaminate estuarine fish for many years to come. Table 4 indicates the geographical distribution of PCB residues in estuarine fish. We note that average concentrations vary widely from state to state. Although these data are indicative of geographical distribution and time trends of PCB concentrations, they only represent a lower bound to concentrations of PCBs in fish caught in these waters for human consumption. This is because the fish sampled were generally no more than one year old. Fish caught for human consumption are usually older and consequently more heavily contaminated with PCBs.

Walker (1976) summarized the PCB levels in freshwater fish as determined by the National Fish and Wildlife Monitoring Program.

> Geographically, the higher concentrations appear to be associated with certain river systems having industrial activity . . . . PCB residues expressed as Aroclor 1254 were found in five major river systems in the Atlantic coastal region, with residues exceeding 5 mg/kg. Four of these stations had residues exceeding 10 mg/kg during the last 5 years. Fish in four of the Great Lakes stations had PCB concentrations exceeding the 5 mg/kg level and all stations reported concentrations

Table 3: Annual incidence of ΣDDT, PCB, and dieldrin residues in juvenile whole fish samples, 1972-76

		Residues, μg/kg								
		DDT			PCBs			Dieldrin		
Year	No. of Samples	% Positive	Maximum Residue	Average Residue[1]	% Positive	Maximum Residue	Average Residue[1]	% Positive	Maximum Residue	Geometric X
1972	187	48	1425	62	34	4903	540	7	140	21
1973	483	34	667	58	12	3363	479	6	140	30
1974	380	46	1640	42	29	2078	320	8	145	12
1975	284	34	4082	89	20	2639	460	1	15	14
1976	192	36	2588	88	22	1258	351	0	—	—

[1]Arithmetic average of the geometric means of positive samples from each coastal area.

Source: Butler and Schutzmann (1978)

Table 4: Frequency and average concentration of PCB residues in juvenile estuarine fish by coastal area, 1972-76

Coastal Area	Frequency of Residues, %	Coastal Area	Average Concentration, μg/kg[1]
Connecticut	87	Washington state	1674
Rhode Island	75	Delaware	780
New York	63	Virginia	439
Delaware	51	Virgin Islands	379
Virginia	38	Rhode Island	330
Maryland	36	Connecticut	323
Puerto Rico	32	Georgia	323
California	31	Maryland	306
Florida	26	New York	262
Texas	24	Louisiana	256
Alabama	23	Puerto Rico	245
Virgin Islands	18	Hawaii	244
Washington state	17	North Carolina	242
Hawaii	14	California	239
Oregon	10	Oregon	182
North Carolina	9	South Carolina	182
Georgia	3	Alabama	163
Louisiana	2	Texas	135
South Carolina	1	Florida	83
Alaska	0		
Mississippi	0		

NOTE: Comparisons are limited in that the number of samples, number of sampling stations, periods (years) of sampling, and species of fish differ for each coastal area.

[1]Arithmetic average of geometric means of positive samples in all collection years.

Source: Butler and Schutzmann (1978)

> exceeding 0.5 mg/kg. In the Mississippi River system, the Allegheny and Ohio were the hot spots, with seven out of the eight stations reporting residue concentrations in excess of 5 mg/kg. Thirty-one of thirty-five stations in this river system reported residues in excess of .15 mg/kg in the 1970-73 sampling programs. The highest residues, often exceeding 10 mg/kg were found in the Allegheny, Kanasha, Cumberland, Tennessee, and Ohio Rivers along with stations on the Mississippi River at Memphis, Tennessee, and the Missouri River at Herman, Missouri. Other monitoring stations that were found to have residue levels exceeding 5 mg/kg during the sampling periods 1970-73 included: the Williamette River on the Columbia system; the Rouge River in the Pacific coastal drainage; the Sacramento River in California; the Chena River tributary of the Yukon in Alaska; and the Rio Grande, Alabama, and Mississippi Rivers in the Gulf States region. Only in two sample periods of 1972-73 and in the current monitoring samples, which are still yet to be fully analyzed, has there been a downward trend, but this occurs only in those samples where residues are not being detected. The stations where high residues have been noted in the past still remain relatively contaminated with PCB. Unlike the decline of DDT in Great Lakes fishes, PCB concentrations do not show significant changes and may trend upward in salmonids, ...

An analysis of PCB levels in fresh-water fish in New York State from 1971 through 1975 by the New York State Department of Environmental Conservation (Spagnoli and Skinner, 1977) indicated that Hudson River fish contained the highest known PCB concentrations within the United States. Levels in individual fish were often found to exceed 100 ppm. The highest individual concentration recorded was 559.25 ppm in a large eel.

Lake Michigan is another body of water that has a high level of contamination by PCBs. Table 5 shows data from a three-year study of two species of Lake Michigan fish by the U. S. Fish and Wildlife Service Laboratory (Humphrey, 1977). As shown, the PCB levels in lake trout rose during the three year period and levels in Coho salmon did not change appreciably.

Table 5: PCB contamination in whole fish*

Species & Location	Collection Year	Length (inches)	Sample Size	Mean PCB Value (ppm)
Lake Trout near South Haven	1972	20 - 28	9	12.86 ± 4.75
	1973	20 - 28	30	18.93 ± 2.08
	1974	20 - 28	30	22.91 ± 3.75
Coho Salmon near Ludington	1972	20 - 32	10	10.93 ± 2.12
	1973	20 - 32	29	12.17 ± 0.77
	1974	20 - 32	30	10.45 ± 0.92

*Data from the Great Lakes Fishery Laboratory, U.S. Bureau of Sport Fisheries and Wildlife.

Source: Humphrey (1977)

2.4 Human Exposure from Consuming Lake Michigan Sport Fish

A two year study (1973-1974) was made under an FDA contract (Humphrey, 1977) of persons who regularly consumed PCB-contaminated Lake Michigan sport fish and randomly selected persons who did not consume such fish. A total of 180 adults participated in the study including 91 who consumed more fish than recommended by the Michigan Department of Public Health (no more than one meal per week or 24 pounds per year), 31 who consumed less than 6 pounds per year, another group who consumed an intermediate amount, and 19 fish eaters who consumed fish primarily from Lake St. Clair which are not as heavily contaminated with PCBs as fish from Lake Michigan. A medical record, a dietary record, and blood specimens were obtained for all participants. Summaries of mean PCB levels of participants arranged by city of residence and level of fish consumption is shown in Table 6. In 1973 those who annually consumed 24 or more pounds of sport fish from Lake Michigan had a mean blood PCB level of 0.073 ppm; persons annually eating 6 pounds or less had a mean level of 0.020 ppm; persons eating no fish had averaged 0.017 ppm; and persons eating 24 or more pounds from Lake St. Clair (who resided in Algonac) had an average blood level of .023 ppm. A comparison of PCB blood levels in persons in the group with highest consumption of Lake Michigan fish to PCB levels in those who ate no fish revealed a highly significant difference in mean PCB levels ($p << .001$). A similar comparison between persons who occasionally ate Lake Michigan fish (1-6 pounds per year) with those who ate no fish also indicated a highly significant difference ($p << .002$). The level of PCBs found in the blood of participants did not change significantly from year to year, nor did it diminish

Table 6: Year to year comparison of mean PCB blood levels for consumers of Lake Michigan fish

City	Mean Total PCB Value (ppm) 1973			Mean Total PCB Value (ppm) 1974		
	Participant Group			Participant Group		
	Control	Inter-mediate	Exposed	Control	Inter-mediate	Exposed
Traverse City	0.017	0.026	0.060	0.019	0.036	0.061
Manistee	0.025	0.068	0.109	0.028	0.029	0.120
Ludington	0.021	0.048	0.062	0.024	0.058	0.055
South Haven	0.028	0.036	0.083			
Algonac	-	0.024	0.023			
Group Mean First 3 Cities	0.020	0.044	0.073	0.023	0.041	0.075

Source: Humphrey (1977)

significantly when fish consumption was eliminated for up to nine months. PCB levels measured during the study in cooked Lake Michigan fish are exhibited in Table 7. A comparison with Table 5 reveals that levels in cooked fish appear to be only 1/6 to 1/4 the levels in raw fish. The quantity of PCB ingested from eating Lake Michigan fish averaged 46.5 mg/year and ranged from 14.17 to 114.31 mg/year for the 91 participants eating more than 24 pounds per year. Within this same heavily exposed group, the PCB dose averaged 1.7 ug/kg/day (micrograms PCB per kilogram body weight per day) and ranged from .490 to 3.940 ug/kg/day.

One participant in the study gave birth to a child in January of 1979. A milk specimen from this individual contained 4 ppm PCB (fat basis--the specimen had 2% fat content), whereas a blood specimen collected at the same time contained .053 ppm total PCB.

As a group, the exposed participants had no health problems or medical conditions that could be correlated with PCB blood levels, exposure to Lake Michigan fish, or known symptoms of PCB poisoning.

2.5 PCB Levels in Human Milk

Savage (1979) reported on levels of PCBs in human milk sampled from 1038 individuals residing in 44 different states. Of the 1038 samples, PCBs were detected in all but 9 samples. Trace values were separated for 720 samples and the concentrations in the other 309 samples ranged from a low of 0.3 ppm (fat basis) to 16.92 ppm (fat basis). Eighty-one or 7.8% of the samples contained residues in excess of 2.5 ppm (fat basis) which was the temporary tolerance set by FDA for PCB levels in commercial milk.

Table 7: PCB levels in cooked Lake Michigan fish

LOCATION	FISH SPECIES								
	LAKE TROUT			SALMON			OTHERS*		
	PCB 1254 (ppm)			PCB 1254 (ppm)			PCB 1254 (ppm)		
	1973	1974	1973-74	1973	1974	1973-74	1973	1974	1973-74
Traverse City:									
Mean	2.80	2.22	2.52	2.78	3.49	3.28	1.43	1.11	1.25
No. Samples	11	10	21	3	7	10	6	8	14
Manistee:									
Mean	2.85	2.40	2.60	3.74	2.20	2.86	0.98	0.59	0.78
No. Samples	5	6	11	3	4	7	2	2	4
Ludington:									
Mean	3.36	4.02	3.58	2.50	2.65	2.55	1.06	0.86	0.99
No. Samples	6	3	9	7	4	11	3	1	4
South Haven:									
Mean	4.11			2.51			1.17		
No. Samples	6			6			2		

*Includes: Pike, Whitefish, Smelt, Chubs, Menominee and Perch

Source: Humphrey (1977)

To estimate the average concentration of PCBs in human milk, we took natural logarithms of the reported concentrations in whole milk. Estimates $\hat{\mu}$ and $\hat{\sigma}^2$ of the mean and variance of the log-concentration of PCBs in whole milk were calculated using the method of Cohen (1961) for estimating the mean and variance of a normal distribution from censored data. We then estimated the mean concentration of PCBs in whole human milk to be $\exp(\hat{\mu} + \hat{\sigma}^2/2) = \exp(-3.4124 + .6337/2) = .0453$ ppm. Since the average percent lipid content in the 309 samples was calculated as 4.497% we estimated the average concentration of PCBs in human milk to be .0453/.04497 = 1.007 ppm (fat basis). By way of contrast, the temporary tolerance set by FDA for infant and junior food is 0.2 ppm. Based upon our use of the log-normal distribution for PCB concentration in whole milk samples, we estimate that approximately 95% of the 1038 human milk samples had PCB concentrations in excess of 0.2 ppm (fat basis). We likewise estimate that the percent of human milk samples having more than 2.5 ppm, 5.0 ppm, 10 ppm is 7%, 1%, .05%, respectively. It would be difficult to estimate precisely the proportion of PCB contamination of human milk that is due to PCBs in food, but most of the contamination is likely due to dietary exposure.

The single measurement of 4 ppm (fat basis) of PCB in human milk of a consumer of Lake Michigan fish in the FDA study (Humphrey, 1977) indicates that consumers of PCB contaminated sport fish may have significantly higher levels of PCBs in their milk than women in general. To corroborate this single measurement, we considered comparisons of PCB levels in human blood plasma and milk made by Polishuk, et al. (1977) in a study involving 29 Israeli women. Average PCB levels measured were .0193 ± .0126 ppm in plasma, and .0442 ± .0412 ppm in whole

milk. Consequently, the concentration of PCBs in whole milk was .0442/.019 = 2.33 times the average concentration in plasma. If this ratio holds for the most heavily exposed group of fish eaters then the average concentration of PCBs in whole milk of humans who consume PCBs from fish at the same level as this heavily exposed group should be about (.073)(2.33) = .170 ppm. If further, we assume the average lipid content of whole milk is 4.497% (Savage, 1979), then the average concentration of PCBs in milk from these heavily exposed individuals should be about .170/.04497 = 3.78 ppm (fat basis). The level of uncertainty associated with this calculated value if fairly high. However, it does agree nicely with the value of 4 ppm measured in the single sample obtained in the FDA study (Humphrey, 1977).

Since high consumers of Lake Michigan fish were purposefully recruited for the study, it is not possible to estimate from the study the number of people in Michigan who consume such high levels of contaminated fish. However, based upon the information in the study, it seems reasonable to assume there is a sizable population of women who consume fairly high levels of PCB contaminated sport fish and who consequently have PCB levels in milk which average about four times (= 4 ppm vs. 1 ppm) the levels in the general population.

3. Carcinogenic Effects

3.1 Human Data

In the early part of 1968 the accidental contamination of edible rice-bran oil led to an epidemic poisoning of the Japanese families who consumed this oil. The disease later became known as Yusho or rice-oil disease. The contamination of the rice-oil was due to a leak in a heat-exchange unit while the oil was being heated to remove some of its odorous components (NIOSH, 1977). The chief symptoms of Yusho disease were chloracne and eye discharges while other symptoms

included discoloration of the skin, headaches, fatigue, abdominal pain, menstrual changes and liver disturbances. Babies born to mothers who consumed the rice-oil were small-for-date and had temporary skin discoloration. The first symptoms of Yusho disease were registered on June 7, 1968 and 1291 cases had been reported as of May, 1975 (NIOSH, 1977).

The concentration of PCBs in the oil varied according to date of production and method of shipment. For canned oil produced on February 5, 1968, the PCB concentration ranged from 2000 to 3000 ppm, while the bottled oil produced on February 10, 1968 contained 134 ppm and only a trace was detected in samples of oil produced after February 19, 1968 (Cordle, et al., 1978). The main contaminant of the rice-oil was Kanechlor 400, but one important "minor" contaminant was polychlorinated dibenzofuran, present at about 1/200 the concentration of PCBs in the rice-oil (NIOSH, 1977).

An analysis of 146 of the total 1291 reported cases of Yusho disease was done in 1971. It was estimated that the lowest dose producing overt effects was 0.5 g (Cordle, et al., 1978) while the average ingestion producing these same symptoms was 2.0 g and the average volume consumed was 800 ml (NIOSH, 1977). But the question arises as to whether the effects noted are due in fact to the PCBs alone. The ratio of PCBs to PCDFs in the Yusho oil (containing "used" Kanechlor 400) was 200:1 whereas the ratio of PCBs to PCDFs in "unused" (unheated) Kanechlor 400 is 50,000:1. Thus with respect to PCBs the ratio of PCDFs in Yusho oil to PCDFs in rice-oil is 250:1. Also, the toxicity of PCDFs ranges from 200 to 500 times that of PCBs (Cordle, et al., 1978). Thus for equal amounts of rice-oil and pure Kanechlor 400, the

toxicity of the rice-oil would range from 2 to 3.5 times that expected from its PCB content alone.

Because of the uncertainty about the confounding of effects between PCBs and PCDFs, it is difficult to determine from the Yusho data exactly what effect(s) exposure to PCBs alone could have on humans. Careful records of the 1291 Yusho patients have been kept in an effort to determine possible long term effects. At least 9 out of the 29 deaths that occurred as of May, 1975, were attributed to malignant neoplasms (NIOSH, 1977), but a causal relationship between PCBs and cancer can necessarily be inferred because of the high concentration of PCDF in the oil. The Yusho study, nevertheless, had two important results: first, the information established that PCBs can be transferred from mother to fetus and from mother to child through breast feeding, and second, highly chlorinated PCB compounds are excreted more slowly from the body than the less chlorinated ones (NIOSH, 1977).

In a study of chemical workers (Zahn, et al., 1976, 1977), two malignant melanomas were diagnosed in 31 workers heavily exposed to Arochlor 1254 (and also exposed to other chemicals that could possibly cause cancer). It was estimated that .04 malignant melanomas would have been expected from this group of individuals. Among 41 other workers also, but less heavily, exposed to Aroclor 1254, one additional melanoma was diagnosed.

3.2 Data from Lifetime Animal Feeding Experiments

There have been a number of studies on neoplastic effects resulting from feeding PCBs to experimental rats or mice (Ito, 1973, Linder, et al., 1974, Kimbrough, et al., 1973, 1974, 1975, Calandra, 1976, NCI, 1978). Although each of these studies provides some evidence that

PCBs induce neoplastic lesions in rodents, only three of these experiments were of sufficient duration to be classified as lifetime feeding experiments. These three long-term experiments will be summarized below.

3.2.1 The Experiment of Kimbrough et al. (1975) on the Effect of Aroclor 1260 on Female Sherman Rats

Four hundred weanling Sherman strain COES female rats 21-26 days old were divided randomly into two groups of 200 animals each. One group was maintained as controls and the animals in the other group were fed ad libitum a diet containing 100 ppm Aroclor 1260. Exposure was continued until 6 weeks prior to the termination of the experiment. When the animals were 23 months old all surviving animals were sacrificed and autopsied. A total of 184 dosed rats and 173 controls survived to the end of the experiment. Pathologic findings are summarized in Table 5.

Of the three studies discussed in this section, this study provides the most convincing evidence of the carcinogenicity of PCBs. This study involved a relatively large number of animals and the increased incidence of hepatocellular carcinomas in the treated group is highly significant. Following are excerpts from the analysis of this study in the Criteria Document for PCBs (Nisbet, 1976a).

> This was a well-designed and well-conducted study, deviating from recommended protocols in only one respect: its limitation to female rats. . . . Two other limitations may be noted: (a) the rats were not exposed prior to weaning, although the authors . . . had indicated the rats exposed to PCB's during gestation and nursing showed early liver changes at much lower dietary levels; (b) the rats were killed at 23 months, relatively early in comparison to the 26-30 month expected life span. Each of these design features of the experiment, although common practice in carcinogenesis bioassays, is likely to have reduced its sensitivity in demonstrating carcinogenic effects. . . .

Table 8: Incidence and type of liver lesions and tumors of other organs examined histologically

Organ or tissue	Type of lesion	Incidence	
		Controls	Experimental
Liver	Hepatocellular carcinoma	1/173	26/184
	Neoplastic nodule	0/173	144/184
	Foci or areas of cytoplasmic alteration	25/173	182/184
Thyroid gland	Parafollicular cell tumor	37/163	15/166
Adrenal gland	Pheochromocytoma	1/173	1/167
Pituitary gland	Chromophobe adenoma	41/153	25/139
	Carcinoma	0/153	1/139
Uterus	Endometrial polyp	15/149	25/163
	Adenocarcinoma	0/149	2/163
	Sarcoma of endometrial stroma	3/149	7/163
Urinary bladder	Transitional cell papilloma	1/167	0/169
Mammary gland	Fibroadenoma	17/173*	13/184*
	Adenocarcinoma	5/173*	1/184*
Salivary gland	Fibrosarcoma	1/173*	0/184*
Lung	Adenoma	2/173	2/184
Adipose tissue	Lipoma	0/173*	2/184*
Brain	Glioma	0/173	2/184
Ovary	Granulosa theca cell tumor	5/149	0/163
	Papillary adenoma	1/149	2/163
Hematopoietic system	Granulocytic leukemia	1/173	0/184
	Lymphoma	0/173	2/184
Kidney	Hemangioma	0/173	1/184
Thymus	Thymoma	1/173*	0/184*
Parathyroid gland	Adenoma	0/173	2/184
Skin	Fibroma	0/173*	1/184*

* Incidence based on gross detection with microscopic confirmation.

Source: Kimbrough, et al.. (1975)

3.2.2 The National Cancer Institute (1978) Bioassay of the Carcinogenic Effect of Aroclor 1254 in Fisher 344 Rats

Groups of 24 Fisher 344 rats of each sex were administered Aroclor 1254 at one of three doses, either 25, 50, or 100 ppm ad libitum for 104-105 weeks. Matched controls consisted of groups of 24 untreated rats of each sex. All animals were 53 ± 2 days of age when placed on study. All surviving animals were sacrificed 104-105 weeks after the animals were placed on study. It was concluded that "under the conditions of this bioassay, Aroclor 1254 was not carcinogenic in Fisher 344 rats; however, a high incidence of hepatocellular proliferative lesions in both male and female rats was related to the administretion of the chemical. In addition, the carcionmas of the gastrointestinal tract may be associated with the administration of Araclor 1254 in both males and females." The observed incidences of leukemias, lymphomas, and hepatecellular carcinomas are listed in Table 9.

Although Aroclor 1254 was not shown to be carcinogenic in Fischer 344 rats by the NCI Bioassay, it must be kept in mind that this was a relatively small experiment utilizing only 24 animals per dose group. The usual number of animals per group for an NCI bioassay appears to be 50. This study was part of a larger study designed to assess the combined affects of a group of chemicals which is likely the reason this biosssay is smaller than most. Overlooking for the moment the fact that the protocols were different and different Aroclors were tested, the results of the NCI bioassay and the Kimbrough study are not all that inconsistent. A χ^2-test that the risk of hepatocellular carcinoma at 100 ppm was the same for Kimbrough study as for the female rats in the NCI study was barely significant at the .05 level. The corresponding

Table 9: Incidences of leukemias and hepatocellular carcinomas in rats from NCI (1978) Bioassay of Aroclor 1254. Data is reported as no. animals with condition/no. animals examined for condition.

Dose (ppm)	Leukemias		Hepatocellular Carcinomas	
	Male	Female	Male	Female
0	3/24	4/24	0/24	0/24
25	2/24	6/24	0/24	0/24
50	5/24	5/24	1/24	0/24
100	8/24	4/24	2/24	0/24

χ^2-test applied to the Kimbrough study and the male rats in the NCI study was not significant ($p > 0.3$). Thus, because this experiment involved relatively few animals, it is simultaneously consistent with both no carcinogenic effect as well as an affect approaching that observed in the Kimbrough (1975) study.

3.2.3 Industrial Bio-Test Experiment with Charles River Rats

This experiment was described in an unpublished report (Industrial Bio-Test Laboratories, 1971) and a brief summary of results was presented at the National Conference on Polychlorinated Biphenyls (Calandra, 1976). The following comments on the experiment are taken from the EPA Criteria Document on PCBs (Nisbet, 1976a). One thousand Charles River strain albino rats were divided into 10 treatment groups. One hundred rats (50 male and 50 female) served as controls and 100 rats (50 male and 50 female) were included in each of nine exposed groups which were fed diets containing 1, 10, and 100 ppm of Aroclors 1242, 1254 and 1260 respectively. Dosage started when the animals were about 4-6 weeks old and continued for 24 months. The liver slides from this study have been examined twice by the original pathologist, once in the original report (Industrial Bio-Test Laboratories, 1971) and in a later report (Monsanto, 1975). The diagnoses in these two examinations were markedly different. For example, in the animals dosed at 100 ppm the earlier examination diagnosed one hepatoma and two animals with nodular hyperplasia, whereas the later examination diagnosed eleven animals with hepatomas and twenty-eight animals with nodular hyperplasia. A summary of the results of the latter pathological examination as given by Nisbet (1976a) is listed in Table 10.

Table 10: Liver pathology reported in Industrial Bio-Test rat experiment: 1975 re-diagnosis

Dose rate (ppm):	Control	Aroclor 1242			Aroclor 1254			Aroclor 1260		
		1	10	100	1	10	100	1	10	100
No. of animals	23	31	30	20	31	26	27	25	23	27
Vacuolar change	1	7	8	9	8	10	13	5	6	10
Focal hypertrophy	0	2	3	8	3	5	13	3	10	11
Nodular hyperplasia	1	0	2	8	0	3	13	0	9	7
Hepatoma	0	0	0	2	0	0	4	0	0	5
Ductular hyperplasia	5	3	3	3	6	3	4	6	5	14
Cholangio-hepatoma	0	0	0	1	0	0	2	0	0	2
Hepatocellular necrosis	1	1	1	0	3	1	2	4	2	6

Source: Nisbet (1976a)

For some reason that was not explained, there was unusually high mortality among the rats in the experiment. The numbers of rats were further reduced by interim sacrifices during the course of the experiment. For example, only 6-21 animals out of the initial 100 in each treatment/sex subgroup fed 100 ppm survived to the terminal sacrifice. Even so, the re-diagnosis of the liver pathology (Table 10) indicates a significant tumorigenic effect. The incidence of nodular hyperplasia is significantly elevated in the group fed 10 ppm Aroclor 1260 over the incidence in the control group ($p << .005$, Fisher's exact test). There are a total of 9 hepatomas in the groups fed 100 ppm of one of the three Aroclors, but none in the groups fed lesser concentrations of PCBs.

3.3 Synergistic Effects

The synergistic effects of PCBs acting in conjunction with other chemicals may be quite significant in some instances, although quantitative estimates of these effects at environmental levels of exposure would be quite tenuous.

Ito et al. (1973) reported on experiments in which groups of 12-30 dd male mice were exposed to various levels of PCBs (Kanechlors KC-300, KC-400, KC-500 at 100-500 ppm in the diet) alone or in combination with one of three isomers of BHC (hexachlorocyclohexane β-BHC, δ-BHC, γ-BHC at 50-250 ppm in the diet). In the groups exposed to PCBs alone, only the group exposed to 500 ppm KC-500 developed hepatocellular carcinomas (5 animals out of 12 exposed). In the groups exposed to BHC alone, only the group exposed to 250 ppm α-BHC developed hepatocellular carcinomas (8 animals out of 30). However, carcinomas

were induced within 24 weeks by joint feeding of PCBs and BHC at levels below those which had no effect when fed independently. The combinations of 100 ppm α-BHC and 250 ppm KC-500 produced 1 hepatocellular carcinoma in 25 animals; 50 ppm α-BHC and 250 ppm KC-500 produced 2 hepatocellular carcinomas in 30 animals, 250 ppm each of β-BHC and KC-500 produced 6 hepatocellular carcinomas in 29 animals. The authors concluded that PCBs promoted the induction of tumors by α-BHC and β-BHC.

Other experiments have produced negative and even antagonistic results. In an experiment with mice (Uchiyama, et al., 1974), PCBs (KC-400) fed in the diet did not appear to accelerate the development of cervical carcinoma induced by methylcholanthrene. In another study in rats (Makiura, 1974), feeding with PCBs for 24 weeks appeared to inhibit the induction of hepatocellular carcinoma by three other carcinogens.

VCM (vinyl chloride) is a known human liver carcinogen and is also a mutagen, but both its carcinogenicity and mutagenicity appear to depend on metabolism in the liver to an active metabolite (Rannug, et al., 1974). The mutagenicity of VCM has been demonstrated only in the presence of liver microsomal preparations, including those stimulated by PCBs (Nisbet, 1976a). This strongly suggests that there may be a synergistic effect between PCBs and VCM in the production of tumors.

4. Quantification of Carcinogenic Risk

4.1 Calculation of Virtually Safe Doses from Different Mathematical Models

To illustrate the computation of virtually safe doses (VSDs) by extrapolation of the results of animal experiments to low dose levels,

we have selected the three data sets listed in Table 11. To this data we have applied three dose response models and related extrapolation procedures; the probit model (Mantel, et al., 1975).

$$P(d) = C + (1-C)\int_{-\infty}^{a+b\text{Log}_{10}d} (2\pi)^{-1/2}\exp(-y^2/2)dy \qquad [1]$$

the one-stage or one-hit model (Crump et al., 1977)

$$P(d) = 1-\exp\{-(q_0 + q_1 d)\}, \qquad q_0, q_1 \geq 0, \qquad [2]$$

and the multistage model (Crump, et al., 1977)

$$P(d) = 1-\exp\{-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)\}, \quad q_0, \ldots, q_k \geq 0 \qquad [3]$$

The gamma multihit model (Rai and Van Ryzin, 1978) was also considered. This model requires at least two positive experimental doses and could not be applied to the first two data sets. When applied to the third data set, the computer algorithm for computing the estimates failed to converge (Van Ryzin, personal communication).

For each of these models, P(d) represents the probability of a particular tumorignic response in a single animal fed a test substance at a dose-rate d during the course of a lifetime feeding experiment. A discussion of these models and their theoretical rationale is given in the Appendix.

The results of applying these extrapolation procedures to the data sets in Table 11 are summarized in Table 12. In this table are computed maximum likelihood (best-fit) estimates of the dose required to produce extra risks over background risk of 10^{-8}, 10^{-6}, 10^{-5}, respectively. Lower 95% confidence bounds for each of these doses are also computed from the various models. Maximum estimates are not recorded for the method based upon the probit model since this method was not designed to fit data. As explained in the Appendix, the

Table 11: Data sets used for calculating virtually safe doses in Table 12.

Data Set #1--Kimbrough et al. (1975) rat study with Aroclor 1260--Hepatocellular carcinomas

Dietary level (ppm)	No. of animals	No. animals with Hepatocellulor carcinomas
0.	173	1
100	184	26

Data Set #2--Kimbrough et al. (1975) rat study with Aroclor 1260--Liver neoplastic nodules

Dietary level (ppm)	No. of animals	No. animals with Neoplastic Nodules
0	173	0
100	184	144

Data Set #3--Industrial Bio-Test rat experiment with Aroclor 1260--Liver neoplastic nodules

Dietary level (ppm)	No. of animals	No. animals with Neoplastic Nodules
0	23	1
1	25	0
10	23	9
100	27	7

Table 12: Virtually Safe Doses computed from data in Table 11

Data Set	Analytic Method	Maximum likelihood estimates of dose in ppb. corresponding to extra risk of			Virtually safe doses (lower 95% confidence bounds for dose) in ppb. corresponding to extra risk of		
		10^{-8}	10^{-6}	10^{-5}	10^{-8}	10^{-6}	10^{-5}
I	Probit				1.96	14.2	43.6
I	One-Hit and Multistage	.0069	.686	6.86	.0051	.511	5.11
II	Probit				.025	.180	.552
II	One-Hit and Multistage	.00063	.063	.634	.00055	.0551	.551
III	Probit				.178	1.29	3.97
III	One-Hit	.0046	.465	4.65	.00235	.235	2.35
III	Multistage	.0046	.465	4.65	.00205	.205	2.05

parameter b appearing in this model is set equal to unity regardless of the data. This designation precludes the model from providing an adequate fit to most data sets. Likewise, the gamma multihit model is applied only to data set III since this model cannot be applied to data containing only one experimental dose.

These models yield quite different values for the lower confidence bounds on dose. These divergent results are predicted by and, to some extent, explained by the discussion in the Appendix. The probit procedure will typically estimate virtually safe doses larger than those predicted by the multistage models for extra risks below about 10^{-3}. Virtually safe doses based upon the multistage model are identical with those based upon the one-hit model when there is only one positive experimental dose. This is illustrated with data sets I and II. The multistage procedure also yields virtually the same values as the one-hit model for data set III since introduction of the parameters q_2, q_3, etc. into the model cannot improve the fit to this data. However, as explained in the Appendix, the multistage can yield higher values for the VSD than the one-hit model whenever the data exhibit upward curvature and are inconsistent with the one-hit model.

To compare with the VSDs in Table 12, we estimate from Table 2, that the average consumption of PCBs in the United States in 1976 was about 3.3 μg/day ÷ 1557 gm/day = 2.1 ppb of PCB, assuming an average daily food intake of 1557 grams.

4.2 Estimates of Risk from PCBs in Diets of U.S. Adults

Next we shall estimate levels of risk for the general U.S. population and for the population of consumers of fresh water fish. The

risks from consuming human milk in infancy present some special difficulties and will be dealt with separately. The data of Kimbrough et al. (1975) on the increased incidence of hepatocellular carcinomas in rats fed Aroclor 1260 provides the most convincing evidence of carcinogenicity of PCBs. Our estimates of risks to human populations will therefore be based upon this data. The fact that only one dose level of PCBs was used in this experiment means that the one hit is the only one of the models discussed previously that can be utilized. The Mantel et al. (1975) procedure based upon the probit model [1] is an operational procedure for calculating a virtually safe dose. Since the parameter b in the model is not chosen based upon the data, the method should not be used to calculate "best" estimates (e.g., maximum likelihood estimates) or risk at a given dose. Except for the one-hit model the other models require at least two positive experimental doses for their utilization.

In Table 13 are exhibited lifetime risks of cancer based upon extrapolating the Kimbrough data from the experimental doses to PCB exposure levels in humans. This process involved two steps. First, exposure levels in humans were converted to equivalent exposure levels in rats. Results are given for two methods for making this conversion: 1) on a ppm of PCBs in total diet basis and 2) on a mg intake of PCBs per kg body weight per day basis. The next step is to calculate the extra risk of hepatocellular carcinoma at this dose based upon a one-hit model fit to the animal data. The risks exhibited in Table 13 are based upon the one-hit model which fits the animal data best. Upper confidence bounds on these risks are not listed but an upper 95% confidence bound is given by multiplying all corresponding risks in the table by 1.5.

The estimates of dose from the total diet study (Table 2) are tenuous. The estimates for the years 1975 and 1976 are based upon 8 and 3, respectively, trace findings of PCBs in 20 samples from the meat, fish, and poultry food class and no findings at all in samples from other food classes. The PCB levels in Table 2 were estimated by assuming that .025 ppm PCB (1/2 of .05 ppm, the lower limit of PCB quantification) were present in all food samples in which trace amounts of PCBs were found (Nisbet, 1976a).

In computing the risk estimates, no allowance was made for the composition of PCBs in food to which humans are exposed being different from the composition of Aroclor 1260 used in the experiment. As indicated in an earlier section, however, it appears that the higher clorinated biphenyls predominate in the environment and consequently the composition of PCBs in food should not be too different from Aroclor 1260. Also, no allowance was made for the fact that PCB levels in human adipose tissue are likely much greater than corresponding levels in rats for a given level of dietary exposure.

The risk estimates are computed for a hypothetical human population exposed throughout their lifetime to current levels of PCBs in food. In actuality, PCB levels appear to be decreasing.

Based upon the estimates in Table 13 the expected number of extra cases of hepatocellular carcinoma per year resulting from a nationwide exposure at the dietary level detected in the 1976 Total Diet Study (3.3 µg/day) would range between 220,000,000/(238,000 × 70) = 11.1 cases/year and 220,000,000/(764,000 × 70) = 4.1 cases/year.

Using the assumptions of a one-hit model, figures on total catch of Lake Michigan fish (Humphrey, 1977) and estimates of PCB levels in

Lake Michigan fish, we can estimate the total expect number of hepatocellular carcinomas among residents of Michigan from consuming PCBs in Lake Michigan fish. From Table 2 in Humphrey (1977) we estimate that in 1974, Michigan sport fishermen caught 4,065,930 lbs. of lake trout, 6,979,500 lbs. of salmon, and 2,930,220 of other sport fish from Lake Michigan. From Table 7 it is estimated that cooked portions of these fish contained an average of 3.28 ppm, 2.88 ppm, and 1.0 ppm PCBs, respectively. Assuming that 1/3 of the total of weight of these fish were injested by humans, it follows that a total of approximately $[4,065,930 \times 3.28 + 6,979,500 \times 2.88 + 2,930,220 \times 1.16] \times 10^{-6} \times .333 = 12.28$ lbs. of PCBs were injested by humans from eating these fish. Since, according to Table 12 injesting 127 µg/day of PCB ($127 \times 10^{-6} \times 365 \times 70 = 3.2$ gm in a lifetime) would produce on the average about 1/8,000 tumors, 12.28 lbs. = 5575 gms of PCBs would produce $(1/6000) \times (5575/3.2) = .22$ hepatocellular carcinomas/year.

4.3 Estimates of Risk to Breast-Fed Infants

The population of infants whose diet during early life consists wholly or at least in large part of human milk has a much higher exposure to PCBs through food than the general population. As estimated in Section 2.5, human milk in the United States contains an average of 1 ppm (fat basis) PCBs with 7% of the samples containing more than 2.5 ppm (fat basis) PCBs. Further, it was estimated that there is a population of consumers of fresh water fish whose milk samples could contain on the average four times the levels in the general population.

Risks from exposures at such an early age are difficult to quantify. Studies on similar exposure patterns in animals have apparently not been done.

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There are a number of animal studies in which various acute effects were detected with 1-10 ppm exposure to PCBs in food. Linder et al. (1974) exposed rats for two generations to 1, 5, 20 and 100 ppm PCBs. Significant increases in liver weights were observed in 21-day-old F_1 male weanlings at the 1 ppm level of Aroclor 1254 and in either sex of F_1 and F_2 weanlings at 5 ppm or higher levels of both Aroclor 1254 and 1260. It must be kept in mind, however, that because of biomagnification, concentrations of PCBs in milk may have been much greater than the levels in feed. Rhesus monkeys are considerably more sensitive to PCBs than rodents: Rhesus monkeys fed 3 ppm PCBs all died after 8 months (McNulty, 1976). Female Rhesus monkeys given 2.5 and 5.0 ppm Aroclor 1248 in their diets developed facial edema, swollen eyelids, erythema, loss of hair and acne within two months (Barsotti, 1976). Following 6 months of PCB exposure the female monkeys were bred to control males. There was a significant reproductive effect of the PCB in the diet as shown in Table 14. The six infant monkeys were permitted to nurse their mothers for 4 months. The mothers' milk contained 0.15-0.40 ppm of PCBs (whole milk basis). Within 2 months focal areas of hyperpigmentation, swollen lips and eyelids, loss of eyelashes, and acne form lesions of the face developed. Within four months, 3 of the 6 infants died due to PCB intoxication. From the data of Savage (1979) it is estimated that approximately 3% of human milk samples in the United States have PCB levels in excess of .15 ppm (whole milk basis).

Any estimates of carcinogenic risk from exposures to PCBs in human milk on the basis of existing animal data must be regarded as extremely tenuous. Not only does one have to contend with the

Table 14: Modification in reproduction in primates that were exposed to Aroclor 1248 in the diet

	Control	2.5 ppm	5.0 ppm
Total impregnated (no./no. animals)	12/12	8/8	6/8
Resorptions or abortions (no./no. animals)	0/12	3/8	4/8
Stillborn (no./no. animals)	0/12	0/8	1/8
Normal births (no./no. animals)	12/12	5/8	1/8

Source: Allen and Norback (1976)

uncertainties of extrapolation from high doses in animals to low doses in humans, it is also necessary to make assumptions regarding the effect of a time-varying dosage. The effect of dosages early in life on carcinogenicity could be much different from equivalent doses later in life.

To illustrate what such an effect might be, we shall calculate some hypothetical risks of hepatocellular carcinoma by relating the cancer incidence observed in the Kimbrough et al. (1975) study to human PCB exposure levels in human milk. The calculation will be based upon the multistage model of cancer. Peto (1977b) indicates that this model may be particularly applicable to carcinomas. The model is capable of explaining observed high rates of increase of cancer with age without having to specifically posit an aging mechanism. In applying the model we must decide which stages PCBs might effect and the nature of the effect. Let us assume in the absence of evidence to the contrary, that PCBs affect only the first stage and that the effect is to increase the rate at which cells pass through this stage by an amount proportional to the quantity of PCBs present in the diet at the time. This assumption is a "worst case" assumption because with the particular multistage model we have in mind, cells pass through the stages in a prescribed order on their way to becoming cancerous. Consequently, exposures at infancy will have the greatest overall effect if they act upon the first stage.

With such a model, it can be argued that when exposure to PCBs is at a level D from birth to an age which represents an age-fraction f of the normal life span, with no exposure for the remainder of the lifetime, then the extra life-time risk of hepatocellular carcinoma

over risk at zero dose should be approximately of the form

$$P(D,f) = 1-\exp[-\beta D[1-(1-f)^k]] \qquad [5]$$

where k is the number of states in the multistage model. We estimate $\beta = .147 \times 10^{-2}$ from the Kimbrough et al. (1975) data by taking $f = 1$ and $D = 100$ ppm. This method of estimating β should tend to underestimate the carcinogenic risk since the rats in this experiment were exposed only after weaning and prior to 21.5 months of age, and were sacrificed at 23 months of age. With β estimated in this fashion we can now calculate theoretical extra lifetime risks of hepatocellular carcinoma from [5] for different values of D, f and k. The results of some such calculations are tabulated in Table 14.

These estimates are based upon unverifiable assumptions and should be regarded as hypothetical. They do illustrate, however, the carcinogenic effect that might result from doses of a carcinogen applied early in life, such as PCBs in human milk. Some of the assumptions made in constructing these estimates were conservative in that other assumptions which are equally reasonable would predict even higher cancer risks. For example, if we had converted dose from rats to humans on a mg/kg/day basis rather than on a ppm basis, the estimated risks would likely be greater. Cells in infants are going through mitosis much more often than cells in adults which might imply that they are at a greater risk per unit time from a carcinogenic insult than cells in adults. However, this possibility was not reflected in the model.

It should perhaps be pointed out that with this model (as well as possibly in real life), even though carcinogenic dose is very early

in life, a cancer eventually resulting from this dose can occur at any age.

The risks tabulated in Table 15 are perhaps more useful for comparative purposes rather than in an absolute sense. By comparing these values with those in Table 13, it appears that the subpopulation of breast-fed infants could be at much higher levels of risk of hepatocellular carcinoma from PCBs than the U.S. population in general.

Table 15: Theoretical extra lifetime risks of hepatocellular carcinoma in breast-fed infants based upon Kimbrough et al. (1975) rat data.

A k-stage model of cancer is assumed with dose effecting the first stage only (Equation [5]). Conversion of dose from rats to humans is by assuming ppm of PCB in rat diet is equivalent to ppm (fat basis) in human milk.

	Extra risk to infant in general population (D = 1.0 ppm)		Extra risk to offspring of consumers of more than 24 lbs./year of Lake Michigan sport fish (D = 4.0 ppm)	
	Age at Weaning		Age at Weaning	
K	6 months (f=1/140)	12 months (f=1/70)	6 months f=1/140)	12 months f=1/70)
1	1/95000	1/48000	1/24,000	1/12,000
3	1/32000	1/16000	1/8000	1/4000
5	1/19000	1/9800	1/4800	1/2500

Table 13: Estimates of lifetime extra risk to humans of hepatocellular carcinoma based upon applying a one-hit model [2] to the Kimbrough et al. (1975) rat study.

Human PCB Dosage	Risks calculated from converting human dose to animal dose on the basis of ppm in diet	mg/kg/day
8.7 ug/day (1975 Total Diet Study, Table 2)	1/123,000	1/288,000
3.3 ug/day (1976 Total Diet Study, Table 2)	1/328,000	1/764,000
127 ug/day (Avg. intake of people consuming more than 24 lbs./yr. Lake Michigan fish, Humphrey (1977)	1/8,000	1/20,000

APPENDIX

...IEW AND EVALUATION OF METHODS OF DETERMINING RISKS FROM CHRONIC LOW-LEVEL CARCINOGENIC INSULT

Basic Principles and Considerations

To aid in determining a proper regulatory action regarding ...nogen that is present in man's environment, whether it be ...additive, industrial polutant, or otherwise, it is helpful ...have some knowledge about the number of extra cancers ...e likely to be caused by the presence of the carcinogen ...environment. It is also helpful to have some knowledge ...likely change in number of extra cancers that would ...ny some projected increase or decrease in the level of exposure occuring either as a result of regulatory action ...tion. This kind of information is usually impossible to ...directly from human data. For this reason it is often ...ary to use data from animal feeding experiments to estimate ...isk. This procedure invalves two difficult steps, 1) re... the animal risk at high doses to doses very near to zero ... relating the animal risk to risk in humans.

Typically, animal experiments use on the order of 100 ...s at each experimental dose. If a particular experimental ...auses a lifetime increase in cancer risk of 1/10, this

crease can be measured with a small degree of accuracy using
) animals. But if the increased cancer risk is less than 1/100
is increase will often not even be detectable by an animal
eding experiment. For example, if the true risk is 1/100 it
uld require that over 400 animals be tested at that dose in
der to be 99% sure of detecting any carcinogenic response at
l (i.e., for there to be a probability of .99 that at least one
imal gets cancer). If background or spontaneous carcinogenesis
present even larger numbers of animals will be required. On
e other hand, the extra human risk that we may want to esti-
te resulting from environmental exposure is usually (and hope-
lly) much smaller than 1/100 for any given chemical, perhaps
the order of 1/1,000,000. It is clear that it would not be
ctical to conduct an experiment with enough animals to measure
rectly an increase in risk this small.

For these reasons the procedure has been developed of
nducting lifetime animal feeding experiments using, in addition
a control dose of zero, several doses at which the projected
tra cancer risk may be 1/10 or larger. This high dose data is
en used to estimate the extra risk at a dose where the extra
sk may be no larger than, say, 1/1,000,000. An equally import-
nt variant to this problem is the calculation of the so-called
afe' dose, that is, a dose for which there is some measure of
tatistical assurance that the extra risk at that dose is no
re than, say, 1/1,000,000. These problems are often referred
collectively in the literature as the "low dose extrapolation
oblem."

Importance of the Mathematical Model

Performing a low-dose extrapolation involves the choice of a mathematical function to model the dose-carcinogenic response relationship and the choice of statistical procedures to apply to the mathematical function. The choice for this mathematical function turns out to be extremely crucial to the outcome of low dose risk estimation. If the assumed relationship between tumor occurrence and dose does not apply in the regions to which the extrapolation is being made, a serious overestimate of the 'safe' dose may result (Mantel and Bryan, 1961, p. 458). Chand and Eng (1974) compared five standard dose response models and observed that they could differ by many orders of magnitude at low dose levels for which extra risks are on the order of 1/100,000,000.

It might be supposed that it should be possible to discriminate among the various potential dose response functions on the basis of experimental data but, unfortunately, two different dose response functions can often fit experimental data equally well but still differ by several orders of magnitude at very low doses. Moreover, even if a particular dose response function were to give a significantly better fit to data than several others this would still not furnish assurance that this function would necessarily correlate in any way with the true dose response at very low doses where it is not feasible to measure the true extra risk directly. As a consequence of the great disparity of dose response functions at low doses it is imperative that the dose response function be selected, neither arbitrarily nor solely on the basis of how well it can be made to

experimental data, but, insofar as is possible, it should reflect known or at least plausible information regarding the biological mechanisms through which a chemical induces or promotes cancer.

What Shape Should be Expected for the Dose Response Curve at Low Doses?

Tumors of so many different types arise in such a diversity of different tissues, their etiology is so little understood, and the agents that cause tumors affect a subject in such diverse ways, that it might seem that no general conclusions can be drawn. However, for a certain broad class of "directly-acting" chemical carcinogens the range of uncertainty associated with the shape of the dose response curve at low doses can be greatly narrowed. As used in this paper, the term "directly-acting carcinogen" encompasses (Guess, Crump and Peto, 1977) carcinogenic agents for which either the agent itself or a metabolite acts directly at the cellular level and produces a hereditable change which eventually leads to the formation of a tumor. Carcinogens which are carcinogenic by reason of their mutagenicity should fall into the category of "directly-acting carcinogens." Accordingly, carcinogens which test positively using the Ames mutagenicity screening test for carcinogenicity are very likely to be directly-acting. (See McCann and Ames, 1976). In a recent study (McCann, Choi, Yamasaki and Ames, 1975) in which about 300 carcinogens and non-carcinogens were tested using the Ames Test, 90% (157 out of 175) of the carcinogens were mutagenic including almost all of the

known human carcinogens. This indicates that the class of directly-acting carcinogens may encompass most of the known carcinogens.

A partial solution to the low-dose extrapolation problem for the case of directly-acting chemical carcinogens has been given in Peto (1977), Crump, Hoel, Langley and Peto (1976), and Guess, et al. (1976). The key result is that, at least as long as background carcinogenesis is present, we should expect the dose response curve not to be absolutely flat at zero dose. What this means is simply that when risk is plotted against dose response on ordinary linear scales, the tangent line to the dose response curve at zero dose should have a positive slope. When a dose response function has this property we will say it is linear at low dose. This simple property can have far-reaching consequences on low-dose extrapolation. For example, consider the two potential dose response functions 1) $0.1(\frac{99}{999}\, d + \frac{900}{999}\, d^2)$ and 2) $.1d^2$ for the dose interval $0 \leq d \leq 3$. Both of the curves give a risk of 1/10 at a dose of $d = 1$ and are practically indistinguishable at higher doses. However, at a dose of $d = 1/1{,}000$ 1) predicts a risk of 1/100,000 and 2) predicts a risk of 1/10,000,000, a difference of two orders of magnitude. We note also that 1) has a tangent line with a positive slope at $d = 0$ whereas 2) does not.

One explanation of why the dose response function should be linear at low dose when background is present may be found in Crump, et al. (1976) and Peto (1977) and will be briefly outlined here. When background carcinogenesis is present, the cellular mechanism through which the test agent produces cancer should

already be operative in producing background tumors. When this is true the effect of the test agent is to add to an already ongoing process. The result of this additive effect is illustrated in Figure 1. The dose response curve is for all tumors produced through the mechanism through which the test agent acts. Background carcinogenesis is allowed for in the Figure by an effective background dose d_o. We see that, in this case, the added risk caused by a dose d of the test agent should be expected to increase approximately linearly near d = 0 (i.e., the tangent line at d = 0 will have a positive slope). Implicitly assumed by the way Figure 1 is drawn is the fact that an added dose of a carcinogen acting through this mechanism does not produce a smaller risk. If background carcinogenesis is allowed for as in Figure 1 by positing an effective background dose d_o which is estimated from the data then the wide range of risks obtained using different models effectively disappears (Peto, 1977). We note that the existence of a tangent line with a positive slope at zero dose does not, in itself, imply any lower bound for extra risk at low doses since the slope of the tangent line could possibly be very small.

The evidence given above for a positive slope to the dose response function at zero dose applies particularly to the case in which background carcinogenesis is operative. This does not imply that we expect the dose response curve not to be linear at low dose in the absence of background carcinogenesis. For example, the multistage models of cancer (Armitage and Doll, 1961) are a fairly broad class of models in which it is assumed that

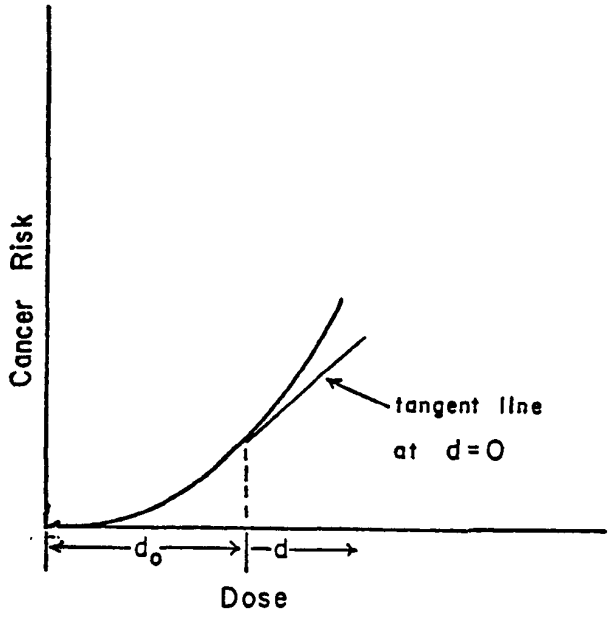


Figure 1. Illustration of why the dose response curve should be linear at low dose in the presence of background carcinogenesis. d_o is the effective background dose and d is the dose of the carcinogen of interest.

a number of events are required to occur at the cellular level to initiate cancer. Although all models in this class are linear at low dose provided background carcinogenesis is present, a sizable subclass of them are linear at low dose in the absence of background carcinogenesis (Crump, et al., 1976).

Watson (1977) has recently proposed a more specialized model for cancer induction and promotion based upon reversible epigenetic cellular changes. Watson concludes that his model supports the low-dose-linearity hypothesis and states "as suggested by a different argument of Crump, et al. . . . , it is reasonable to assess the risk due to an additional carcinogen at low constant dosage by a linear relation."

The evidence for low-dose-linearity given above applies mainly to directly-acting carcinogens. An indirectly acting carcinogen might be one which causes some gross physiological change such as suppression of ovulation which could predispose the subject to cancer. For such carcinogens the shape of the dose response curve at low dose is highly speculative. There could possibly be a threshold dose below which the agent has no carcinogenic effect at all on an individual. However even if a threshold mechanism is operative, there is likely to be considerable variation in individual thresholds in a large population. Consequently the dose response curve for the entire population could still exhibit a linear trend at risks as low as 1/1,000,000 or lower.

The effects of metabolic activation and detoxification upon carcinogenic dose response have been recently considered by

Cornfield (1977) through a kinetic model that encompasses free toxic substance, metabolite, deactivator, and the interactions of these substances. Only a steady state situation is studied in that variation over time of the concentrations of these agents is not considered. The model predicts a threshold dose below which there is no carcinogenic risk under the assumption that the deactivator is 100% efficient in deactivating the carcinogen. However, in a naturally occurring process it is likely that deactivation would not be perfect and would be less than 100% effective in always combining with 100% of the carcinogen before an amount of the active metabolite reaches a cancer target site. Any of a number of modifications to the model to allow for non-perfect deactivation would rule out a threshold and would lead directly to a model for which carcinogenic response varies linearly with dose at low doses. Cornfield's own modification of perfect deactivation, that of allowing the deactivating reaction to be reversible, leads, as Cornfield points out, to a model which is linear at low dose. This occurs regardless of how slowly the reverse reaction takes place, as long as the possibility is not eliminated entirely. Furthermore, even in the extremely unlikely case of perfect deactivation, an otherwise realistic model should still imply low-dose-linearity since the theoretical time required for perfect deactivation would not be zero and would likely be infinite.

For most, perhaps all, carcinogens, the mechanisms through which cancer is produced is not sufficiently understood so that the shape of the carcinogenic response curve can be theoretically

predicted with certainty. As pointed out earlier, neither can experiments of sufficient size be conducted that would permit direct experimental investigation of the dose response curve at low dose. We have noted that there are plausible arguments that the dose response curve is linear at low dose for many carcinogens. On the other hand, this author knows of no serious proposal of a mechanism that would lead to a more conservative dose response relationship such as the risk varying approximately as the square root of dose at low dose. In view of these uncertainties it would seem reasonable to base estimates of added risk of cancer upon a mathematical model that encompasses low-dose-linearity unless, of course, the mechanism through which the carcinogen operates is sufficiently understood so that low-dose-linearity can be conclusively ruled out. Once the principle of low-dose-linearity is accepted the problem of estimation of risks at low dose is nearly solved. This is because the disagreement between the upper statistical confidence bounds on risk at low doses based upon a model that incorporates low-dose-linearity and one that does not is typically several orders of magnitude whereas the corresponding disagreement between two reasonable models both of which incorporate low-dose-linearity is usually much less than this.

Specific Methods for Low Dose Risk Estimation

A. Mantel-Bryan

The Mantel-Bryan procedure (Mantel and Bryan, 1961 and Mantel, Bohidar, Brown, Ciminera and Tukey, 1975) has been selected by the Food and Drug Administration as part of their procedures for evaluating assays for carcinogenic residues in edible products of animals. Before the Mantel-Bryan procedure

itself is discussed, the "Sensitivity of Method" (SOM) document (Federal Register, Vol. 42, No. 35 - Tuesday, Feb. 22, 1977, p. 10412) will be reviewed briefly so that the role of the Mantel-Bryan procedure in official FDA policy can be understood and appreciated.

The so-called Delaney clause of Section 409 of the Federal Food, Drug and Cosmetic Act of 1958 prohibited the approval of any food additive that "is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of safety of food additivies, to induce cancer in man or animal . . . . This language was interpreted as forbidding FDA to approve the use of a carcinogenic substance as a feed additive for food-producing animals whether or not the compounds might leave any residues in the edible products of the animals. However, in 1962 Congress modified this prohibition as part of the Drug Amendments of 1962. Section 409(c)(3)(A) now reads in part:

> . . . [N]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additivies, to induce cancer in man or animal, except that this proviso shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the Secretary finds (i) that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (ii) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (f) and (g)) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal . . .

Originally, the FDA applied this so-called "DES proviso" on a case-by-case basis without published criteria. However the FDA on February 22, 1977 published the "Sensitivity of Method" document which established objective criteria for acceptance of an assay method for detecting residues of a carcinogenic feed additive and for establishing post-administration withdrawal periods for these additives. Thus the document furnished an operational definition of the no-residue requirement of the DES proviso. This operational definition involves the application of the Mantel-Bryan procedure to animal experimental dose response data. The test-animal species/strains to be utilized are to have "the greatest possible susceptibility to the test compound" while at the same time being "appropriate models for man." (Federal Register, vol. 42, 1977, p. 10418). The Mantel-Bryan procedure is applied to the animal test data to determine residue level, designated S_o, corresponding to a risk of 1,000,000 in test animals (i.e., S_o is the "safe" dose level determined by the Mantel-Bryan procedure). The level S_o is released as a fraction of the total diet (i.e., parts per million). This level is adjusted to account for the respective portions of the human diet that is represented by the various food products containing residues of the carcinogen being tested, transfer from animals to man being made on a fraction of animal diet basis. The resulting dose level S_m is "the level of total residues of carcinogenic concern that can be operationally defined as satisfying the no-residue requirement of the act for specific tissues" (Federal Register, Vol. 42, 1977, p. 10418).

The dose level S_m thus represents the upper bound to the lowest limit of reliable measurement that an approved assay method must satisfy.

The Mantel-Bryan procedure is thus an integral part of the "Sensitivity of Method" document. The procedure as originally set forth (Mantel and Bryan, 1961) and "improved" (Mantel, et al, 1975) is for the purpose of conservatively choosing a "safe" dose of a carcinogen, a "safe" dose being defined as one for which it can be expected that, with a given level of statistical assurance (e.g., 99%), the true dose producing a preassigned "safe" level (e.g., 1/1,000,000) of risk will lie above the "safe" dose. In the Mantel-Bryan procedure the mathematical model used for the dose response model is the probit function

$$P(d) = C + (1-C) \int_{-\infty}^{a+b\text{Log}_{10}d} (2\pi)^{-1/2} \exp\{-x^2/2\}\, dx \qquad [A1]$$

where d represents the dose of the carcinogen and P(d) represents the probability of a cancerous response in an animal subjected to a dose d. The parameters in the model are an intercept parameter a, a probit slope parameter b, and C, which represents the probability of a response in untreated animals. The parameter b is not estimated from the data but rather is arbitrarily set equal to 1. This choice is stated as being conservative (Mantel and Bryan, 1961), the argument for this being that typical dose data exhibit a probit slope in the experimentally observable region above 1% incidence that is greater than one. In Mantel and Schneiderman (1975) it was observed that a set of DES data (Gass, G. H., Coats, D., Graham, N., 1964, C3H females) exhibited

a probit slope of 1/2, but the general use of a probit slope of b=1 was still suggested. A slope of b=1 was adopted in the SOM document unless the experimental data exhibit a smaller slope, in which case the smaller value would be used.

With the probit slope parameter fixed at b=1 the remaining parameters, a and C, are estimated from the data and then adjusted so as to produce a higher level of risk as a given dose that corresponds to a upper 99% statistical limit on the true risk at a given dose. The value 99% is the one used in the SOM document but the choice is arbitrary. The safe dose is then determined to be the one producing a given low risk (e.g., 1/1,000,000) based upon the adjusted values of a and C. The risk value of 1/1,000,000 was also adopted in the SOM document.

As pointed out in Mantel, et al. (1975), the Mantel-Bryan procedure rewards larger and better experiments in that the more evidence there is of safety, the higher the calculated safe dose will be. However this advantage should be shared by any extrapolation method that uses reasonable statistical procedures.

Some have considered the Mantel-Bryan procedure as adopted in the SOM document to be too conservative (Federal Register, Vol. 42, 1977, p. 10419) in that it involves three conservative choices (99% statistical assurance, lifetime risk of 1/1,000,000, and probit slope set equal to 1) and that any one of these assumptions alone could provide adequate protection to the public. The first two of these choices are regulatory decisions that would have to be made with any extrapolation procedure. However, the arbitrary selection for the slope parameter seems to be peculiar

to the Mantel-Bryan procedure. To investigate its effect upon the extrapolation procedure a typical fit is presented in Figure 2 (from Crump, 1977b) of the Mantel-Bryan probit curve [A1] to experimental carcinogenicity data when the probit slope parameter is fixed at b = 1. As can be readily seen the probit curve typically provides a very poor fit, curving downward even when the trend of the data is toward an increasingly upward curvature. This typically bad fit to data of the probit curve raises serious questions regarding the validity of statistical procedures associated with the Mantel-Bryan method. (See Salsburg, 1977 and Crump, 1977b.)

On the other hand, the Mantel-Bryan procedure utilizing the choice b = 1 was put forth as conservative procedure and it gives that appearance in Figure 1 since the probit curve appears to lie far above the trend of the data at the lowest doses. However as mentioned earlier and also pointed out by Mantel (Mantel and Bryan, 1961, p. 458) a procedure may, while appearing conservative at experimental dose levels, at the same time seriously overestimate the "safe" dose (i.e., be seriously anticonservative) if the assumed dose response relationship does not apply at the low risk levels to which extrapolation is being made. Thus, before the degree of conservation can be evaluated for any procedure, the properties of the dose response curve at very low doses must be evaluated.

As described earlier, there are strong arguments that indicate the dose response curve should be 'linear at low dose' (see p.50 for the definition of this concept) particularly for

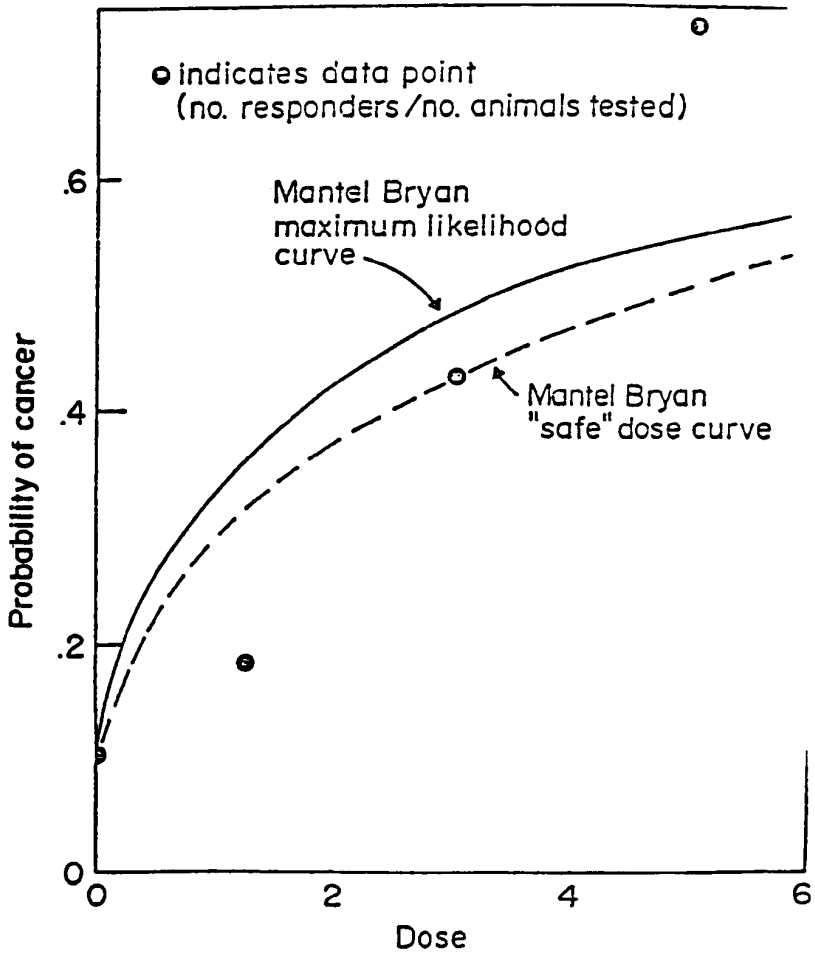


Figure 2. Typical fit of Mantel-Bryan curve to experimental data (from Crump, 1977b).

directly acting carcinogens in the presence of background carcinogenesis. This has led Peto (1974) to recommend extrapolation procedures using only dose response functions from a class containing only dose response functions which are linear at low dose. At the very least, however, it would seem prudent not to go to the opposite extreme and use a dose response function which rules out linearity at low dose by assumption. However, the Mantel-Bryan procedure, through its use of the probit curve [A1] rules out linearity at low dose in favor of a "flatness property" (see Hartley and Sielken, 1977, Mantel, 1977, and Crump, 1977b) at low dose which is anticonservative to the extreme. This property implies that mathematical derivatives of all orders of the probit curve approach zero (through positive values) as the dose approaches zero. This unusual property is most often discussed within the context of mathematical oddities rather than in connection with a scientific investigation. It implies that if the true dose response curve comes from an extremely broad class of functions known as analytic functions and which pervade scientific applications of mathematics, then the probit curve will eventually underestimate the true risk at low doses. Furthermore, at low enough doses, the degree to which the risk will be underestimated will be arbitrarily large (i.e., the ratio of the true risk to the probit estimate will grow arbitrarily large).

It was emphasized earlier that it is important when extrapolating to low doses for the assumed dose response function to incorporate known or at least plausible facts about the mechanisms of carcinogenesis. In neither the original paper

(Mantel and Bryan, 1961) nor in the paper outlining the improved version is biological justification given for the selection of a curve having the above described "flatness property." It should be mentioned at this point that the incorporation of background carcinogenesis into the Mantel-Bryan probit model [A1] using the parameter C implies that the mechanism through which the test carcinogen produces cancer is independent of the mechanisms through which all of the background cancers are produced (Crump, et al, 1976). In keeping with the discussion in the last section it would seem more proper to incorporate background into the probit model by positing an effective background dose d_o which adds to the dose d of the test carcinogen. If background is incorporated in this way the probit curve no longer has the "flatness property" and becomes linear at low dose (Guess, et al, 1977). In fact, with background incorporated in this way, the probit curve assumes a shape similar to the one-hit model, sometimes referred to as the most conservative of all procedures (e.g., Mantel, 1977).

Even though the "flatness property" implies the probit curve should at suitably low doses be anticonservative to the extreme, the "flatness" property holds only for doses approaching zero and the feature of arbitrarily fixing the probit slope at 1 mitigates the anticonservativeness implied by the "flatness" property at any given low dose (although the property itself will hold for all choices of the parameters a, b, C). The cancer risks that are typically extrapolated to are in the risk ranges 1/10,000 to 1/100,000,000. We will examine the outcome of

Mantel-Bryan extrapolations to these risk levels in a later section when we compare several different extrapolation procedures.

B. Linear Extrapolation

The technique for linear extrapolation was recommended by Hoel, Gaylor, Kirschstein, Safiotti and Schneiderman (1975) for use on an interim basis until better procedures could be developed. The procedure is straightforward and is based upon an assumed linear relationship between dose and response at low dose. The procedure utilizes only the data for the group of control animals and a single other dose group, usually either the highest dose that elicits no response or else the lowest dose that elicits some response. In the case there are no cancers in the control animals the 'safe' dose, based upon a maximum risk of 1/1,000,000 and 99% statistical assurance, is calculated as follows: An upper 99% confidence bound is calculated for the cancer risk in the dose group of animals. From this risk and dose one extrapolates back toward zero dose and zero risk using a straight line relationship. The dose corresponding to a risk of 1/1,000,000 on this straight line is taken to be the "safe" dose. If there are cancers in the control animals this procedure is modified to allow for the statistical treatment of the response in the control group while retaining the straight line relationship. When data at other experimental doses are available this method of linear extrapolation has the obvious shortcoming of not fully utilizing the available data.

A linear dose response curve is linear at low dose but the converse is not necessarily true. A curve can be linear at

low dose and still have a high degree of nonlinearity at higher doses.

Linear extrapolation is viewed by some as a very conservative procedure. For example, comments were made during the decision on which extrapolation procedure to incorporate into the SOM document to the effect that linear extrapolation is the most conservative of all procedures. Crump, et al (1976) examined the extent of the conservatism of a linear dose response function when compared with a multistage dose response model (Armitage and Doll, 1961). The multistage model assumes that a cell must go through a number of different stages before cancer is initiated in that cell and the model can encompass a high degree of nonlinearity. It was determined that the maximum possible degree of conservatism of a linear model relative to a multistage model depended rather heavily upon the incidence at the experimental dose relative to the background incidence. (This is consistent with the general relationship between background carcinogenesis and linearity at low dose as discussed earlier.) For example, when the incidence at the experimental dose is four times the incidence at zero dose the extra incidence at low doses derived from the linear dose response differs from the incidence derived from the multistage model by, at most, less than a factor of 2.5 regardless of the number of stages in the multistage process. Thus, when background carcinogenesis is present, the linear dose response curve is not overly conservative relative to the multistage dose response curve. In fact the linear dose response curve is anticonservative when compared to

the one-stage or one-hit models.

Linear extrapolation has long been proposed for use in radiation carcinogenesis (see Brown, J. M., 1976, for a review of the relevant reports). The BIER (1972) report on radiation risks from the National Academy of Science recommended linear extrapolation as a "best estimate" approach as opposed to a conservative approach. Brown reviewed arguments both for and against linearity and concluded that "linear extrapolation of human data from high doses of low LET radiation cannot be said to overestimate the risk at low doses. In fact, there is some doubt as to whether the risk is not underestimated."

Certainly much remains to be learned about both radiation and chemical carcinogenesis. However, if both radiation and chemicals cause cancer through similar mechanisms then it should be expected that there would also be similarities between the respective carcinogenesis dose response functions. Direct damage to DNA by the carcinogenic agent has been implicated as one cancer initiating mechanism for both radiation and chemicals (Brown, J. M., 1976 and McCann and Ames, 1976). Thus, the findings related to the potential linearity of the dose response function for radiation has implications for chemical carcinogens as well, particularly for "directly-acting" carcinogens.

The results of linear extrapolation will be compared with other methods in a later section.

C. Extrapolation Methods Based Upon the Multistage Model

Two methods of low dose extrapolation which are alternatives to the Mantel-Bryan or linear procedures have recently been proposed independently by Guess, Crump, and Deal (Guess and Crump, 1976, 1978 and Crump, Guess and Deal, 1977) and Hartley and Sielkin, 1977. Both of these methods utilize a multistage dose response function of the form

$$P(d) = 1-\exp\{-[q_o + q_1 d + q_2 d^2 + \cdots + q_k d^k]\} \qquad [A2]$$

where q_o, q_1, $\cdots$, q_k are all nonnegative parameters to be estimated from the data. This dose response function is general enough to yield a considerably wide range of responses at low dose. On the one hand, if $q_1>0$ and $q_i=0$ for $i\geq 2$ the dose response function [A2] becomes the one-stage model which yields risks at low doses comparable to what would be obtained with linear extrapolation. On the other hand, the model can produce risks even as low as the probit curve [A1] down to any fixed positive low dose. Thus this model is capable of fitting both highly linear and highly nonlinear dose response relations. Since the model has the property of "linear at low dose" if $q_1>0$ and does not have this property if $q_1=0$, use of this model does away with having to make the arbitrary but crucial decision of having to either assume linear at low dose as in linear extrapolation or else assume a highly nonlinear dose response relationship at low dose as in Mantel-Bryan extrapolation. Thus "safe" doses computed using this model should provide a more realistic measure of the true uncertainty of low dose extrapolation than would "safe" doses based

on either an assumed linear curve shape or an assumed highly nonlinear curve shape.

The dose response relation [A2] contains all of the Armitage and Doll (1961) multistage dose response models as special cases but also contains curves which are much flatter at low dose than any of the multistage curves.

The two extrapolation procedures based upon [A2] have some features which are different. When computing "most likely" estimates the procedure of Guess, Crump and Deal uses an infinite dimensional maximization procedure so that it is not necessary to specify a value of k, the degree of the polynomial in [A2]. However, the two methods differ chiefly in the way the statistical confidence intervals are computed. There have not yet been sufficient comparative calculations made to determine how safe doses may differ using the two approaches. Mantel (1977) has made a critical review of the statistical procedure used by Hartley and Sielkin for calculating the 'safe' dose.

Both the Hartley and Sielkin and the Guess, Crump and Deal (as extended by Crump, 1977) procedures can utilize times at which cancer is detected in the experimental animals rather than just the dichotomous information of whether or not an animal contracted cancer before it died of some other cause or before the termination of the experiment. The utilization of time data in low dose extrapolation is important for at least two reasons: 1) The age at which cancers occur should be important in assessing the magnitude of the harmful effect of a carcinogen upon man (e.g., cancers that occur early in life should be viewed as more

serious than those which occur in extreme old age). 2) In many animal carcinogenicity experiments the response data at the highest doses lies below the trend of the lower dose data. This sometimes appears to be due to the fact that at the highest doses some of the animals are being poisoned by the chemical before they have a chance to develop cancer. When this occurs the high dose data is often just deleted from the analysis. However if the times at which the animals die is properly used the high dose data might not appear anomolous. More research needs to be done on the proper utilization of animal time of death data to assess the harmful effects of chemicals to man.

D. The Gamma-Multihit Carcinogenesis Dose Response Model

Rai and Van Ryzin (1978) have proposed basing risk estimation on the gamma multihit model

$$P(d) = C + (1-C)\int_0^{\lambda d} \frac{u^{k-1}e^{-u}}{(k-1)!}\,du \qquad k \geq 0$$

$$= C + (1-C)\left\{1-e^{-\lambda d}\left[1 + \lambda d + \frac{(\lambda d)^2}{2!} + \ldots + \frac{(\lambda d)^{k-1}}{(k-1)!}\right]\right\}$$

$$k = 1,2,\ldots \qquad [A3]$$

where P(d) is the lifetime probability of cancer in a tissue when subjected to a constant dose-rate d of the carcinogen. This model is obtained by assuming that cancer due to the carcinogen occurs when the tissue has been hit k times, these hits occurring randomly according to a Poisson distribution. The manner in which background carcinogenesis is incorporated into the model is

equivalent to assuming that the event "cancer occurs due to the action of the carcinogen" is independent of the event "cancer occurs spontaneously." This assumption would not apply, for example, to processes in which the effect of the carcinogen is to speed up the rate at which the "spontaneous" events occur which lead to the background cancers. At low dose rates, the response is approximately given by

$$P(d) = \lambda^k d^k / k!.$$

Consequently, this dose response model is linear at low dose rates when and only when $k = 1$. Rai and Van Ryzin calculate confidence intervals for added risk at a given dose and for the dose producing a fixed added risk using asymptotic maximum likelihood theory. Although in the theoretical development k must be an integer, in the applications k is allowed to assume any positive value.

Upper statistical confidence intervals on extra risk at a given low dose computed using this procedure can be compared with those computed from the multistage model [A2] by considering two general classes of data.

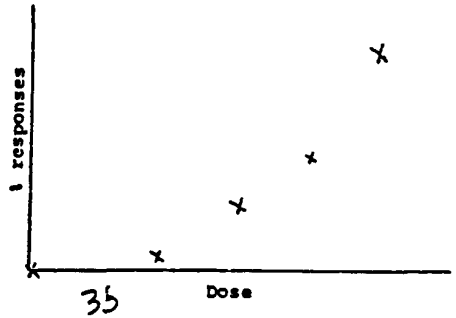
If the data exhibit a general downward curvature as illustrated in Figure 3a, upper confidence bounds on extra risk computed from the gamma multihit model [A3] should generally be greater than or equal to corresponding upper confidence bounds computed from the multistage model [A2]. In certain instances the gamma multihit upper bounds could be much greater than the corresponding multistage upper bounds. This could occur when the data is consistent

with k < 1 in the gamma multihit model (presumably correspond: to a fraction of a hit).

On the other hand, if the data exhibit a general upward curvature as illustrated in Figure 3b the reverse situation wi: hold; gamma multihit upper confidence bounds on extra risk will generally be less than or equal to corresponding multistage bounds. Gamma multihit bounds will not in general share the low-dose-linearity of multistage bounds and because of this may be smaller than the multistage bounds by orders of magnitude at low doses. The reason these large differences can occur is as follows. The multistage family of models contains members whic: are simultaneously linear at low dose and exhibit upward curvat: at moderate doses. For example, the particular multistage model

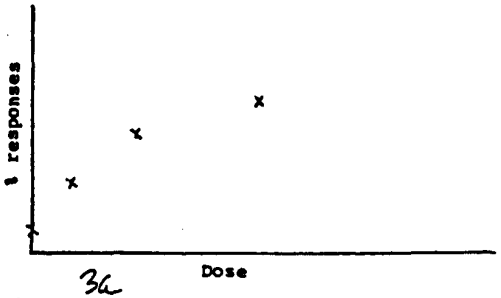
$$1-e^{-(q_1 d + q_2 d^2)} \qquad q_1, q_2 > 0$$

is linear at low dose since $q_1 > 0$ and still can exhibit upward curvature at moderate doses since $q_2 > 0$. This means there are dose response curves in the multistage class which are both linear at low dose and can adequately describe data of the type exemplified by Figure 3b. On the other hand, this will generally not be true of gamma multihit models. All dose-respons: curves in the gamma multihit class which are linear at low dose must exhibit downward curvature and consecuently would generally not be consistent with the data in Figure 3b. When this is true gamma multihit confidence upper bounds will be sublinear (e.g., quadratic) at low dose and consequently much smaller than the multistage confidence bounds.



35

Figure ~~3a~~. Example of Data Exhibiting Upward Curvature



36

Figure ~~3b~~. Example of Data Exhibiting Downward Curvature

Confidence bounds based upon the gamma multihit model will be approximately correct whenever this model is the correct mode A similar statement could be made for the probit model, multistage model, or any other model to which reasonable statistical methods are applied. However, there may be considerable uncertainty as to what the true model may be in a particular situatic The multistage model not only reflects some reasonable assumptic regarding the carcinogenic process which dovetail nicely with epidemiological data for many cancers (Peto, 1977b), but it also reflects some of the uncertainty with regard to the true model by virtue of encompassing a relatively large class of dose-response functions. For example, as noted earlier, the multista class contains dose response functions which are linear at low dose and also exhibit upward curvature at moderate doses. On the other hand, the gamma multihit class is more restrictive at this point in that it does not permit such behaviour. Is this extra restrictiveness of the gamma multihit model justified? To help answer this question, consider the following modification to this model. Suppose that the hits (phenomenological events which are required to occur in a tissue in order that a cancer appear) can possibly occur spontaneously in the absense of the carcinogen. Part of the effect of the carcinogen would then be to speed up the rates at which the spontaneous hits are occurring. For example, if one of the "hits" is an incorrect base substitution in DNA during mitosis, the carcinogen could speed up the rate at which these "hits" are occurring in individual cells by providing more aberrant bases for use in our

an incorrect substitution. With this modification to the model, the gamma multihit upper confidence bounds will no longer be sublinear at low dose and will likely be very close to corresponding bounds calculated from the multistage model [A2]. On the other hand, versions of the gamma model which incorporate such an assumption as this could still be consistent with data with strong upward curvature as exemplified by Figure 3b. Thus, in order to obtain sublinear upper confidence intervals with the gamma multihit model a modification such as the one described above must be ruled out, not on the basis of data, but by assumption.

By was of summary, confidence intervals based upon the multistage model will always be linear at low dosa. Confidence intervals based upon the gamma multihit model may be either "super linear" (corresponding to $k < 1$) or "sublinear" (corresponding to $k > 1$). Superlinearity is achieved by making the model too broad in that a fraction of a hit is allowed which has no biological basis. On the other hand, sublinearity is achieved by making the model possibly too restrictive in that models which are reasonable from a biological viewpoint are ruled out by assumption.

Comparisons and Discussion

To compare low dose extrapolations using the Mantel-Bryan probit model [A1] with those using the multistage model [A2] we present Figure 4 based upon the same data as Figure 2. In this

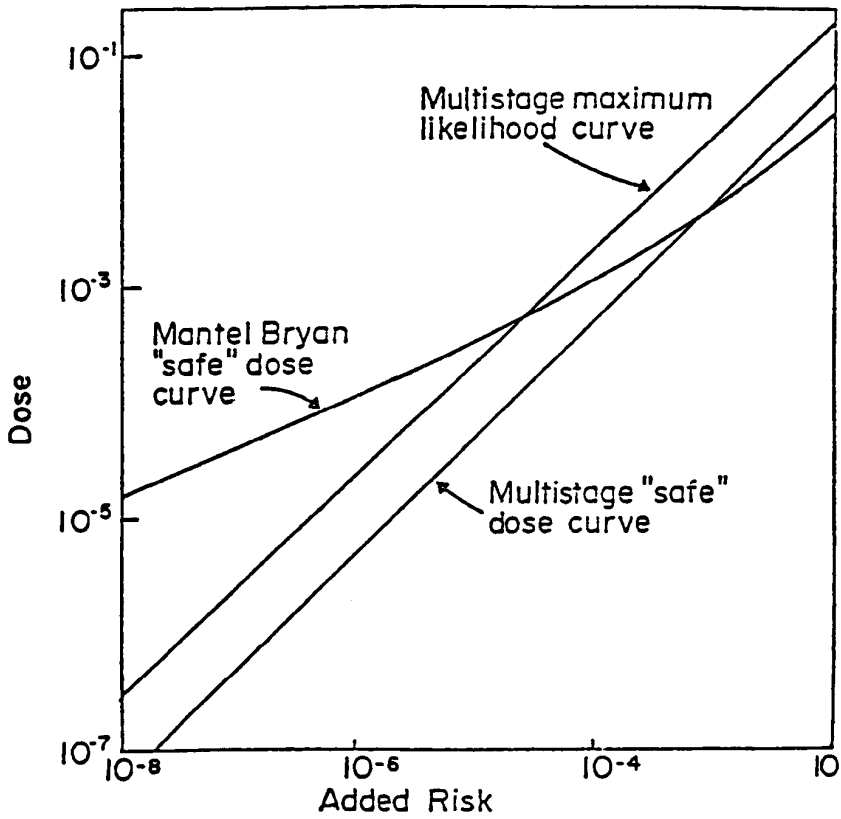


Figure 4. Comparisons of 'safe' doses computed from the Mantel-Bryan procedure and from a procedure based upon the multistage model (from Crump, 1977b).

Figure are plotted on a log-log scale the Mantel-Bryan 'safe' dose as well as both the multistage 'most likely' curve based upon [A2] and the 'safe' dose based upon [A2] and computed as outlined in Crump, et al. (1977). A 99% statistical assurance was used for both 'safe' dose curves. We note that the Mantel-Bryan 'safe' dose lies above the multistage safe dose curve at values of added risk below 5×10^{-4}. The Mantel-Bryan "safe" dose curve lies above the multistage 'safe' dose curve by a factor greater than 20 for an added risk of 10^{-6} and by a factor greater than 300 for an added risk of 10^{-8} Because of the 'flatness' property of the Mantel-Bryan probit function [A1] described earlier, the Mantel-Bryan 'safe' dose curve will lie above the multistage safe dose curve by arbitrarily large factors at extreme low doses. Guess, et al. (1977) have compared the Mantel-Bryan 'safe' dose curves to the multistage 'safe' dose curves and found this to be a typical situation. Thus it is clear that if the true dose response curve could be similar to the multistage dose response function [A1] then the Mantel-Bryan procedure could not be justifiably called conservative. (See also Crump 1977 for further discussion of this point.) On the other hand, we have seen that there are quite plausible arguments for the true dose response curve to have the same shape at low dose (linear) as the estimated multistage curve.

We note that both the multistage 'safe' dose curve and 'most likely' curve have a slope 1 in Figure 4 as plotted on the log-log scales which is equivalent to the curves being linear at low dose. The fact that the 'most likely' curve has slope 1 is

due to the fact that with this particular data set the linear coefficient q_1 in [A2] was estimated to be positive. However the 'safe' dose curve using the multistage model [A2] will always be linear at low dose regardless of whether or not the linear coefficient q_1 is estimated to be positive. This property should be shared by any valid statistical procedure based upon a dose response function that does not rule out linearity at low dose by assumption as Mantel-Bryan does. Just as it is not possible to prove statistically the existence of a threshold, it is likewise not possible to rule out the possibility that the true dose response curve is linear at low dose on the basis of statistical analysis. (See Guess, et al. (1977) for a thorough discussion this important point.) The Mantel-Bryan obtains 'safe' dose estimates which are considerably higher than those obtained using the multistage model because it assumes away linearity at low dose, an assumption that we have seen is probably unwarrented for that majority of carcinogens which are classified as 'directly-acting' carcinogens.

Since extrapolation based upon a model such as the multistage model [A2] must always be linear at low dose, the question arises as to how different the result will be from simple linear extrapolation. For some data the difference will be minimal. For example, for the data upon which Figure 2 is based, 'safe doses' computed using the multistage model is almost identical with 'safe' doses based upon linear extrapolation. For some data sets, however, the difference could be considerable. For example, with the Gass, et al. (1964) DES using the CBA female

mice, the 'safe' dose based upon linear extrapolation is lower than the 'safe' dose based upon the multistage model by a factor of about five and there are doubtless cases where this difference could be greater than an order of magnitude.

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THE TOXICOLOGY OF PCBs

An Overview with Emphasis on Human Health Effects and Occupational Exposures

Prepared by

Gideon Letz, M.D., M.P.H.
Hazard Evaluation System and Information Service

State of California
Department of Health Services/Department of Industrial Relations
2151 Berkeley Way
Berkeley, California 94704
(415) 540-2113

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THE TOXICOLOGY OF PCBs

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I. INTRODUCTION

As a consequence of the Environmental Protection Agency (EPA) ban on further manufacture of polychlorinated biphenyls (PCBs) in 1977, occupational exposures to these compounds have been drastically reduced. However, significant exposures may remain for particular occupational groups. Utility workers, for example, may experience sporadic but potentially massive exposures when cleaning up spills, or when servicing and dismantling transformers and capacitors that still contain PCB fluid. Electricians, appliance service workers and firefighters also may have continued occupational exposure. The National Institute of Occupational Safety and Health (NIOSH) estimates that 12,000 workers have potential exposure as a result of current uses of PCBs (NIOSH, 1977). Despite the vast scientific literature on the toxicology of PCBs, the human health effects likely to result from such exposure remain illdefined.

The Hazard Evaluation System and Information Service (HESIS) has reviewed the literature on PCB toxicology in response to inquiries about worker health. Requests for information have come from unions and workers who handle PCB fluids in cleanup of spills, in maintenance work, and in transportation, storage and disposal of used equipment. Toxicology information has also been requested by medical professionals evaluating the clinical significance of PCB exposures, and public health officials who are attempting to set standards for occupational and environmental exposures. Our primary goal has been to review the data relevant to the human health effects of PCBs especially those resulting from occupational exposures. Since the published epidemiologic evidence is limited we have utilized animal toxicology studies where appropriate in anticipating potential biologic effects in humans. We have not attempted to summarize the extensive literature on PCB toxicology, but the reader is referred

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to a number of recent reviews (DHEW, 1978; IARC, 1978; Fishbein, 1974; Kimbrough, 1974; EPA, 1977; Nelson, 1972; NIOSH, 1977).

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II. GENERAL BACKGROUND INFORMATION

In all animal species that have been studied PCBs have a very low acute toxicity. They are readily absorbed across biological membranes, poorly metabolized and only very slowly eliminated. Because PCBs persist in the environment and accumulate in living tissue, they are concentrated ("biomagnified") in the food chain in a similar manner to other organochlorine compounds like DDT. Concern about exposure to PCBs has, therefore, focused on their resistance to biodegradation with the consequent potential for long-term or delayed health effects.

A number of published reports have established "background" levels of PCBs in the blood and tissues of human populations with no previous history of exposure. Surveys in various geographical areas have found detectable residues in blood, fat and mothers' milk. Measurable levels of PCBs are typically found in greater than 50% of subjects tested with maximum blood levels generally less than 20 ppb (Finklea, 1972). The levels reported from adipose tissue are typically somewhat higher, in the range of 1-2 ppm (Kutz, 1975). Residues of PCBs in human milk have ranged from 40-100 ppb in whole milk (New York State Health Council, 1977).

Two facts complicate the documentation of the human and animal toxicology of PCBs:

1. Commercial products are rarely single agents, but rather are complex mixtures of chlorinated biphenyls with different numbers and arrangements of attached chlorine atoms (see Figure I). The metabolism and toxicology of PCBs seem to vary with the percent of chlorination and with the isomeric structure of the PCB molecule.

2. All commercial products are potentially contaminated with chlorinated naphthalenes and polychlorinated dibenzofurans (PCDFs). The degree of this contamination varies with different commercial mixtures (see Figure III).

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Contamination by dibenzofurans (PCDFs) is of particular concern because of the structural similarity of these compounds to the highly toxic dibenzodioxins (see Figure II). The pattern of observed effects in animals exposed to PCDFs closely resembles that seen following exposure to 2,3,7,8 tetrachlorodibenzodioxin (TCDD). In comparative animal studies the toxicity of PCDFs is much greater than the PCBs, particularly in the thymus, skin (acne), liver and hematopoetic system (Oishi et al., 1978; Moore et al., 1979). In addition, PCDFs are 1000 times more potent than PCBs as enzyme inducers (see Section VI).

Uncertainties in the analytic methods used for detection of PCBs must be considered when reviewing the published data on PCB toxicology. Monitoring PCBs in environmental or biological samples by gas-liquid chromatography/mass spectrometry (GC/MS) is made difficult by the presence of other chlorinated hydrocarbons (e.g., pesticides) which are commonly present at similar concentrations (Stalling et al., 1979). Because of the difficulties in the interpretation of GC/MS spectra and other methodologic problems including extraction and cleanup, the PCB levels reported from different laboratories may show considerable variation.

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III. PHARMACOKINETICS

Absorption

There is relatively little information on the rate or degree of absorption of PCBs by any route for any species of animal. Since similar systemic toxicity has been observed in rodents after dermal, oral and inhalational adminstration of comparable doses, it is likely that PCBs are easily absorbed by all routes. The few quantitative measurements of relative absorption rates indicate that most, if not all, PCBs which contain six or fewer chlorine atoms are efficiently absorbed from the gastrointestinal (GI) tract (Albro and Fishbein, 1972; Van Miller et al., 1975; Matthews and Anderson, 1975).

Distribution, Accumulation (Mammals)

As with other heavily chlorinated chemicals the major storage tissue for PCBs is body fat. The concentration in adipose tissue is 10-1000 times that found in other tissues, both following single oral doses (Grant et al., 1971) and after chronic administration. (Curley et al., 1971) The lowest concentrations are found in whole blood and plasma where levels are usually several fold lower than in other tissues examined. This preferential distribution of PCBs into fat has been well documented after intravenous (i.v.) dosing in the rat (Lutz et al., 1977). Results are consistent with the high distribution coefficient of PCBs in fat and low perfusion of adipose tissue compared to skin, liver, muscle and blood (Anderson et al., 1977).

Two important pharmacokinetic questions cannot now be resolved on the basis of available data:

1. Does the concentration of PCBs reach steady state with constant exposure?

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2. Will mobilization of adipose tissue after starvation or illness lead to a transient increase in PCB concentrations in blood and other tissues ?

Like most heavily chlorinated hydrocarbons the half-life of PCBs in animal tissue is quite long. In a chronic feeding study with Aroclor 1254 at 100 ppm in the diet of rats, a steady build-up of PCBs occurred in all tissues analyzed without a plateau level even after 240 days of treatment. By comparison, in a similar rat dietary study using DDT, plateaus in fat were attained after 90-140 days (Curley et al., 1971). In dairy cows a steady state was reached in 40-60 days (Fries, 1972), probably due to mobilization into fat micelles and secretion into milk. Thus, PCBs are unlikely to reach steady state levels in nonlactating animals; and fat mobilization or lactation may be expected to result in release of stored PCBs.

Transplacental Exposure, Secretion in Milk

Transplacental exposure of PCBs has been documented in mammals. Term fetuses taken from rats exposed to 10 mg/kg/day during days 7-15 gestation contained 0.63 ppm PCB, or about 1/60 the maternal dose. When the dose to the mother was increased five fold, the concentration in the fetuses increased two fold (Curley et al., 1973). The hyperpigmented babies observed in the Yusho incident (see Section VII) represent additional circumstantial evidence of transplacental passage of PCBs, although it is unclear whether these effects were related to PCB or to the PCDF contamination.

Secretion of PCBs into milk has also been observed. In mice, little passage of PCBs occurred across the placenta once PCBs had been sequestered into maternal adipose tissue, but they were readily transferred to suckling offspring through the milk (Vodicnik and Lech, 1980). These observations suggest that secretion of PCBs into milk may be quantitatively much more important as a source of exposure in newborns than is

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transplacental passage. This has recently been documented in a prospective study of Japanese mothers and their infants (Hirokadzu and Ota, 1980).

Metabolism

PCBs are metabolized primarily by hydroxylation and conjugation with glucuronic acid. The primary site of biotransformation is assumed to be the liver, although no data is available currently on the possible role of peripheral metabolism, e.g., skin.

Many experimental feeding studies in both mammals and birds have shown an inverse relationship between percent chlorination and rates of metabolism. Less chlorinated PCBs are more readily metabolized than are more chlorinated ones, the rate of metabolism and excretion decreasing sharply as the number of chlorine atoms increases above five (EPA, 1977). The metabolism of the higher chlorinated biphenyls is also dependent on the position of chlorine atom substitution. The presence of two adjacent, unsubstituted carbon atoms is needed for the rapid enzymatic hydroxylation reaction (Jensen and Sundstrom, 1974). Since the more highly chlorinated biphenyls have a very much slower metabolic rate and longer half-life, they are more generally found as residues in human and animal tissues. This relationship alters with PCBs above 54% chlorination, presumably as a result of lower absorption from the gastrointestinal tract.

Arene oxide intermediates have been described in a major pathway of the metabolic transformation of PCBs by hepatic mixed function oxidases (Safe et al., 1975; Gardner et al., 1973). These intermediates are of particular concern since they are capable of direct interaction with DNA and may be the active form of carcinogenic polyacyclic hydrocarbons (Jerina and Daly, 1974). The PCB molecules which are more readily metabolized and excreted also are more likely to form these arene oxides. It does

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not necessarily follow, however, that those compounds which persist in tissue and are more likely to be measured in population sampling, are less important in terms of their carcinogenic potential.

From the limited data available, it appears that significant differences exist between nonhuman primates and rodents in the metabolism and pharmacokinetics of PCBs. The marked variation observed in PCB toxicity between rodents and primates may be explained by such differences. Primates appear to be more susceptible to the toxic effects of PCBs than are rats or mice (see Section IV and Figure IV). When single doses of radiolabeled PCB were administered by gastric intubation to infant monkeys, the metabolites measured in urine, tissue (liver) and serum included hydroxylation products derived from arene oxide intermediates while in the rat, direct hydroxylation is the rule (Hsu et al., 1975).

There is virtually no pharmacokinetic data in humans. A few generalizations can be made, however, based on studies reporting PCB blood levels: the higher the exposure levels, the higher blood concentration of PCBs (Hara et al., 1975; Inoue et al., 1975; Karppanen and Lolho, 1973; Baker et al., 1980); and the higher the environmental concentration and/or the longer the period of exposure, the longer the blood levels of PCBs remain elevated (Hara et al., 1975; Baker et al., 1980). However, there are a few reports which are inconsistent with this latter trend (Bumgarrer et al., 1975; Hasegawa et al., 1972; Kitamura et al., 1973). PCB levels have also been correlated with race and geographic residence (NIOSH, 1977) and with age and dietary intake of fish (Kimbrough, 1980).

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Comments

Certain generalizations can be made from the limited pharmacokinetic data that is available:

1. Absorption occurs by all routes (skin, GI, inhalation).
2. Distribution is primarily into fat.
3. Metabolism and excretion are dependent on specific molecular structure, varying inversely with percent chlorination.
4. Excretion is in general quite slow so that bioaccumulation occurs even at low exposure levels.
5. Transplacental transfer occurs but may be quantitatively less significant than secretion into milk.
6. Arene oxide metabolites are found in the metabolic transformation of PCBs. These compounds are highly reactive and may represent the active carcinogens (see Section V).
7. The relationship between percent chlorination and potency as carcinogen has not been established.
8. There are essentially no pharmacokinetic data in humans; it is not known, for example, if intermittent high doses are more or less hazardous than low level chronic exposures to the same total dose.

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IV. ANIMAL TOXICOLOGY

Acute Toxicity

When given as a single dose, the acute oral LD_{50} of PCBs in rats, rabbits and mice ranges from 1-10 g/kg of body weight. According to the American Industrial Hygiene Association classification system for acute toxicity, PCBs are classified as "slightly toxic" (0.5-5 g/kg), or "practically nontoxic" (5-15 g/kg). There is some evidence that young animals are more sensitive than adults, and that females are more susceptible than males to the acute effects of PCBs (Kimbrough et al., 1978). In rodents, the acute oral toxicity appears to decrease with increasing chlorine content of the administered PCBs. This may be secondary to decreased absorption of the higher chlorinated compounds or to the differences in metabolic transformation previously discussed.

Although few clinical signs of toxicity have been reported in experimental animals, pathologic findings are extensively documented. Central Nervous System (CNS) depression (decreased pain response and diminished exploratory behavior), anorexia and oliguria followed by ataxia, coma and death have been observed in rats following acute administration of large doses of PCBs (Brackner et al., 1973). Consistent pathologic findings associated with death in rats, rabbits and guinea pigs include liver damage with fatty infiltration, centrolobular atrophy, and in some cases necrosis. Pathologic changes in other organs in these species are not often described, except for chloracne-like lesions which occur at the site of skin or intradermal application.

Comments

The low order of acute toxicity in experimental animals is consistent with the lack of acute effects observed in workers exposed to PCBs. Reported symptoms after occupational exposures include mild irritation of the skin and eyes at levels above 0.1 mg/m^3 with unbearable irritation occurring above 10 mg/m^3 (ACGIH, 1976). Systemic symptoms of nausea and headache have been reported but may be secondary to the solvents (such as trichlorobenzene) in the PCB mixtures.

Subacute and Chronic Toxicity

In contrast to the low order of acute toxicity, effects from chronic exposures to relatively low doses of PCBs have been consistently observed and are of far greater concern. These subacute effects show appreciable variation among species, but liver damage is again the prominent finding.

The major changes in rats fed Aroclor 1248, 1254, and 1262 at 100 ppm in their diet for six weeks included liver hypertrophy, marked fatty infiltration and degeneration of parenchymal cells. As in acute toxicity studies, PCB mixtures with lower chlorine content were more toxic (Allen and Abrahamson, 1973). In 8-12 month feeding studies increased serum lipids and focal areas of liver damage were observed (Allen et al., 1976; Kimbrough et al., 1972).

Nonhuman primates are more sensitive than rodents to the toxic effects of PCBs (see Table I and Figure IV). Adult female monkeys exposed to dietary levels of 2.5 ppm for 12 months (≈0.08 mg/kg/day) developed facial edema, alopecia, acne, gastritis with ulceration, anemia, hypoproteinemia and bone marrow hypoplasia. At 100 ppm (≈10 mg/kg/day) there was considerably more evidence of tissue damage than in rats,

including marked hepatic hypertrophy with ultrastructural abnormalities (Allen, 1975). Based on extrapolation from the Yusho data, PCBs may cause symptoms to humans at levels (0.2 mg/kg/day) which are comparable to the lowest doses which produce effects in nonhuman primates (see Table 1).

Most of the animal data are derived from feeding or oral intubation studies. There are relatively few reports of dermal or inhalation experiments. Inhalation studies again revealed liver damage to be the prominent finding in rodents. For summary of inhalation data see the NIOSH criteria document, page 125 (NIOSH, 1977). Dermal toxicity studies in rabbits have produced skin lesions at the site of application as well as systemic effects including liver and kidney damage, thymic atrophy, lymphopenia and increased fecal porphyrins (Vos and Beems, 1971).

Comments

Liver damage, documented histologically, is the most consistent finding among the many laboratory animals species tested. Effects of low level chronic exposure does show appreciable variation among species, but liver damage has been observed in all species and is usually the most sensitive indication of PCB exposure. The fact that liver dysfunction has been inconsistently observed in humans may be an artifact of the relative insensitivity of the standard liver function tests (SGOT, SGPT) as compared to biopsy and histologic analysis (see Sec. VII, p. 25).

Reproductive Effects

Adverse reproductive effects of PCBs have been noted in many mammalian and avian species. The pattern of reproductive effects include alterations in estrus cycles, failure of implantation, increased frequency of spontaneous abortions, low birth weight offspring

and decreased post-natal survival. No specific teratogenic effects of PCBs have been observed in a variety of avian species. Transplacental effects, however, have been documented in both animals and humans (see Section VII).

PCBs given to mice for 10 weeks at dosage of 1.0 mg/kg/day lengthened the estrus cycle by more than two days and decreased the number of successfully implanted ova (Orberg and Kihlstrom, 1973). Similarly, mice that received PCBs as sucklings in a long-term transgenerational study showed subsequent alterations in estrus cycles, decrease in implantations, and when mated to each other (F1 studies), reduced number of offspring per litter (Kihlstrom et al., 1975).

In rats, studies suggest that reproductive effects of PCBs decrease as chlorination increases. No reproductive effects have been found with Aroclor 1260 (60 percent chlorination) at 1, 10, 100 ppm, but significant effects have been noted with Aroclor 1242 and 1254 (42 and 54 percent chlorination, respectively) at doses of 20 and 100 ppm. Aroclor 1260 began to exert toxic effects at doses of 500 ppm. Rats chronically fed from 20 to 100 ppm Aroclor 1242 and 1254 had reduced numbers of offspring. Surviving newborns showed increased mortality, with only 30 percent surviving to weaning. Five ppm of either Aroclor 1242 or 1254 produced no effects over two generations. Thus, the minimum effective doses ranged from 20 ppm for the lower chlorination mixtures to 100-500 ppm of the more highly chlorinated compounds (Keplinger et al., 1971; Linder, et al., 1974).

Evidence of adverse reproductive effects is also available for nonhuman primates. Rhesus monkeys fed 2.5 and 5.0 ppm Aroclor 1248 for 18 months in the diet showed changes in menstrual cycles in addition to other systemic signs of toxicity. Evidence was also obtained for frequent resorptions and spontaneous abortions following breeding

to normal males. In all, six infants were carried successfully to term out of 14 pregnancies. The offspring were of low birth weight and by two months began to show evidence of PCB toxicity, presumably from PCBs in the maternal milk; only three infants survived to six months. Behavioral tests in the three surviving animals showed marked deficits in several learning tasks, with increasing errors correlated with increasing body burdens of PCBs (Allen and Barsotti, 1976; Bowman et al., 1978; Barsotti et al., 1976).

The effect of PCBs on the male reproductive system is not known. There is one report of four male Rhesus monkeys exposed to 5.0 ppm Aroclor 1248 in the diet for 18 months. After 12 months, one of four animals developed clinical signs of PCB intoxication, showed marked sperm count depression and was functionally sterile. A testicular biopsy revealed a marked decrease in spermatogonia. A second biopsy one year after exposure showed complete recovery (Allen et al., 1979). PCBs are negative in the mouse sperm morphology assay (Heddle and Bruce, 1977).

Comments

PCBs show significant effects on reproductive competence in a variety of species. These effects increase in intensity with increasing dosage and decrease with increasing chlorination of the PCB isomers. PCBs do not appear to be mammalian teratogens. A reasonable explanation for most of the reproductive effects of PCBs could be based on their estrogenic activity (see below).

PCBs have been detected in human semen (Dougherty et al., 1980), but there have been no studies of semen quality in relation to PCB exposure in humans. The effects of PCBs on the male reproductive system in animals or humans has not been adequately

studied. The only other evidence to date on reproductive toxicity in humans come from the Yusho incident and is summarized in Section VII.

Other

1. Immunosuppressive Effects

A number of reports implicate PCBs as immunosuppressants (Fishbein, 1974). Lymphoid atrophy has been observed in rabbits, chickens and guinea pigs. Suppression of humoral immune responses to several antigens was observed in rabbits and guinea pigs, and decreased cell-mediated immune response followed PCB exposure in guinea pigs. A decreased tolerance to hepatitis virus was seen in ducklings without apparent intoxication. In monkeys exposed transplacentally and through contaminated milk, the lymph nodules of the spleen were extremely small and without germinal centers (Allen and Barsotti, 1976); morphologic changes were indicative of reduced immunologic competence.

2. Endocrine Effects

Subcutaneous administration of Aroclor compounds with lower chlorination produced an estrogenic effect on the rat uterus which was not shown with Aroclors of higher chlorination (Bitman and Ceal, 1970). Female monkeys fed Aroclor 1248 for six months showed an increase in concentration of urinary ketosteroids and a prolongation of their menstrual cycles with increased bleeding (Barsotti et al., 1976). Antiandrogenic effects have been described in birds although the mechanism is not clear. It may be secondary to an increased rate of androgen metabolism in the liver by induction of microsomal enzymes (see Section VI), or by virtue of PCBs exerting estrogenic effects.

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Comments

The effect of PCB exposure on immune and endocrine system function has not been carefully studied in humans, so the relevance of these animal observations to human health remains unknown. There is one cross-sectional study of occupational exposure to PCBs which will include analysis of serum hormone levels and urinary metabolites, but results have not yet been published (Selikoff et al., in progress).

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V. CARCINOGENICITY/MUTAGENICITY

Carcinogenicity

Several PCB mixtures are clearly carcinogenic in rodent bioassays, producing liver tumors (hepatocellular carcinomas). Kanechlor 500 and Aroclor 1254 are carcinogenic in male mice (Ito et al., 1973; Kimbrough and Linder, 1974); and Aroclor 1260 is carcinogenic in separate studies in two strains of female rats (Kimbrough et al., 1975; Norback et al., 1980). In addition, a purified component of a PCB mixture, 2,4,5,2',4',5'-hexachlorobiphenyl, has recently been found to be carcinogenic in female rats, causing hepatocellular carcinomas (Norback et al., 1980).

Because high doses of PCBs are known to cause extensive injury to liver tissue it is important to consider the dose levels at which liver carcinomas were produced in the rodent bioassays. In two studies in rats, significant increases in hepatocellular carcinomas were present at doses which did not produce gross histologic changes. Hepatocytes were somewhat enlarged (probably due to microsomal enzyme induction), but no extensive fatty infiltration or necrosis occurred, as was characteristic of bioassays at higher dose levels (Kimbrough et al., 1975).

Test Results

1. Mice (Male)

   A. Kanechlor 300, 400, and 500 fed to groups of 12 eight-week-old male mice at 100, 250, and 500 ppm in the diet for 32 weeks produced hepatocellular carcinomas in 5 of 12 survivors in the high dose group fed Kanechlor 500. The remaining 7 mice in this group had nodular hyperplasia (neoplastic nodules). No metastases or other tumors were

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present in this or other dosed groups. The control group (6 mice) was likewise tumor-free (Ito et al., 1973).

B. Aroclor 1254 administered to groups of 50 five to six-week-old male BALB/cJ mice at dietary levels of 0 or 300 ppm (about 50 mg/kg body weight during the exposure) for 11 months produced neoplastic nodules (hepatomas or hyperplastic nodules) in 9 of 22 survivors in the dosed group. Other liver lesions (adenofibrosis) were present in all 22 survivors. Additional morphological changes in the livers of these animals included pleomorphism and areas of necrosis. Such changes and tumors were absent among survivors (24) in the control group (Kimbrough and Linder, 1974).

2. Rats

A. Kanechlor 400 administered to ten-week-old Donryu rats (10 males and 10 females) at dietary levels which varied from 40-600 ppm during the 400-day study produced liver tumors (multiple adenomatous nodules) in 6/10 treated female rats. Such lesions were absent from the controls (5 males and 5 females) and the treated males (Kimura and Baba, 1973).

B. Kanechlor 300, 400, or 500 administered to groups of 30 eight-week-old male Wistar rats at dietary levels of 0, 100, 500, or 1000 ppm produced increases in the incidence of cholangiofibrosis at the highest dose level of all Kanechlors (2/15, 2/10, and 4/13, respectively). All three compounds also produced hepatic nodular hyperplasia, the incidence of which increased with dose and extent of chlorination (Kanechlor 300 at

100 ppm: 1/22; Kanechlor 400 at 100 ppm: 2/16, and 1000 ppm: 3/10; Kanechlor 500 at 100 ppm: 3/25, at 500 ppm: 5/16, and at 1000 ppm: 5/13); (Ito et al., 1974).

C. Aroclor 1260 administered to groups of 200 three to four-week-old female Sherman rats at 0 and 100 ppm in the diet (varying between 5-10 mg/kg body weight during the 21-month exposure) produced at 23 months among the dosed survivors clearly significant increases of hepatocellular carcinomas (controls 1/173; dosed group 26/184) as well as neoplastic nodules (hyperplastic nodules: controls 0/173; dosed group 146/184). The incidences of nonhepatic tumors did not differ between the dosed and control groups (Kimbrough et al., 1975).

D. Aroclor 1254 administered to groups of 24 eight-week-old Fisher 344 rats of either sex at dietary levels of 0, 25, 50, or 100 ppm for 105 weeks was not carcinogenic to any of the treated groups under the test conditions. It is important to note that two of the dose levels used were lower than those which produced a positive response in Sherman rats. Rare adenocarcinomas and carcinomas of the gastrointestinal tract appeared in both sexes and may be related to the administration of the PCBs (males: historical controls 6/600, dosed group 2/24). In addition a high incidence of hyperplasia was present among the dosed groups (males: controls 0/24, low-dose 5/24, mid-dose 8/24, high-dose 12/24; females: controls 0/23, low-dose 6/24, mid-dose 9/22, and high-dose 17/24); (NCI, 1978).

E. Aroclor 1260 administered to groups of 50 male and female Sprague-Dawley rats at dietary levels of 0 and 100 ppm for 105 weeks was carcinogenic in female rats, causing significant increases in liver hepatocellular carcinomas (Norback and Weltman, 1980).

F. A purified component of a PCB mixture, 2,4,5,2',4',5'-hexachlorobiphenyl administered to groups of 50 male and female Sprague-Dawley rats at dietary levels of 0 and 100 ppm for 105 weeks was carcinogenic in female rats, producing an increased incidence of liver hepatocellular carcinomas among the dosed animals (Norback and Weltman, 1980).

Mutagenicity

PCB mixtures have not been observed to have mutagenic activity nor to measurably affect chromosomes in repeated studies using a variety of in vitro or in vivo test systems. Evidence of genetic damage from PCBs in laboratory test systems including chromosomal aberrations, nondisjunction, loss of sex chromosomes or increased frequency of sister chromatid exchange has not been observed. Report of a weak effect of Aroclor 1221 and of a stronger effect of 4-chlorobiphenyl in Salmonella using PCB-induced rabbit liver homogenate as a liver activation system appears unfounded (Wyndham et al., 1976). Further attempts to repeat these results have been unsuccessful using a variety of Salmonella tester strains and liver activation systems (Katzenellenbogen and Ames, 1980; Safe, 1978).

However, PCBs belong to the class of heavily chlorinated animal carcinogens, most of which are not positive in short-term tests for mutagenicity. Examples in this class include dieldrin, chlordane, kepone, mirex, TCDD*, chloroform, and carbon tetrachloride.

Whether this is because the in vitro metabolic activation systems do not produce the same spectrum of metabolites that occur in vivo or because heavily chlorinated compounds such as PCBs are carcinogenic by nonmutagenic mechanisms is not known at this time.

Validation of the carcinogenic effects in rodents is provided by a positive cell transformation assay using C3H10T1/2 clone eight mouse fibroblast cells in culture by two separate PCB mixtures (Aroclor 1254 and 1260) and a purified component 2,4,5,2',4',5'-hexachlorobiphenyl (Norback and Weltman, 1980).

Comments

A wide variety of PCB mixtures have been subjected to rodent cancer bioassays and to numerous in vitro and in vivo short-term tests for mutagenicity. Several of these PCB mixtures are carcinogenic. None of the PCB mixtures are active in short-term tests for mutagenicity, a finding that holds true for most heavily chlorinated carcinogens. However, substantial confirming evidence for carcinogenicity is provided by positive cell transformation assays using these same PCB mixtures. Thus, under OSHA published criteria, PCB mixtures should be considered Category I* carcinogens. Both IARC (IARC, 1978) and EPA (EPA, 1978) have concluded that based on available animal data PCBs should be considered as potential human carcinogens.

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* Category I: Human evidence or two positive mammalian bioassays or 1 positive mammalian bioassay with supporting results in short-term tests.

Category II: One positive mammalian bioassay. (Source: Occupational Health and Safety Letter Vol. 9, No. 24 November 8, 1979)

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VI. BIOCHEMICAL EFFECTS OF PCBs

Enzyme Induction

The principal biochemical effect of PCBs is the stimulation and induction of certain enzyme systems. Enzyme induction occurs in both the microsomal monooxygenase or cytochrome P-450 system and the aryl hydrocarbon hydroxylase or cytochrome P-448 system, and it has been observed in both man and experimental animals. Induction is not restricted to the liver. It occurs in numerous other organs including kidney, adrenal, lung, gut, skin, and testes. Fetal enzyme induction may occur via transplacental exposure, and induction may also occur by exposure to contaminated milk (Alvares and Kappas, 1975).

Identification of structure-activity relationships for enzyme induction is difficult because of the large number of isomers in commercially prepared PCBs and because all commercial products contain trace amounts of polychlorinated dibenzofurans (PCDFs) which are orders of magnitude more potent as enzyme inducers than PCBs (Matthews et al., 1978).

In early studies using commercial Aroclors, potency for enzyme induction was found to be dependent on chlorination of the PCB mixture. Later, when purified isomers were tested, potency was found to vary with the position of chlorine atom substitution (Ecobichon and Comeau, 1975; and see Section III). Since rate of metabolism is also known to vary with isomeric configuration of the PCB molecule, it may be that potency for enzyme induction is simply a function of the relative rate of metabolism and excretion.

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The enzyme induction properties of PCBs are utilized in the metabolic activation system of in vitro bioassays for mutagenicity. It is unlikely, however, that enzyme induction would consistently enhance the effects of carcinogens or pro-carcinogens: it might function synergistically to activate a chemical, but they also might function to deactivate reactive carcinogens. Both phenomena have been observed in rodent cancer bioassays.

Porphyria

Porphyria cutanea tarda (PCT) in humans is an acquired defect in hepatic porphyrin metabolism characterized by uroporphorinuria, photosensitivity and mechanical fragility of the skin. PCT can be produced experimentally by a number of drugs, including tetrachlorodibenzodioxins and PCBs. All of these agents have the ability to stimulate the activity of 2-aminolevulinic acid (ALA) synthetase which is the initial enzyme in the heme synthetic pathway.

Experimental hepatic porphyria was observed in Sherman rats exposed to Aroclor 1254 in the diet. At doses of 100 ppm the animals became porphyric after a delay of approximately 2-4 months. The porphyria resembled hexachlorobenzene poisoning and human PCT (Goldstein et al., 1973).

In chronic feeding studies ALA-synthetase induction occurs after rats have become porphyric, although with large single doses the enzyme induction is seen almost immediately after dosing the animals (Goldstein et al., 1973).

It has not been established whether only certain isomers in the PCB mixtures or

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contamination with PCDFs is responsible for the production of hepatic PCT. Porphyria has not been reported in humans exposed to PCBs.

Comments

Enzyme induction has two important implications for human health:

1. the occurrence of disease secondary to the increased metabolism of endogenous or exogenous substances, and
2. the interference with medical therapy due to increased metabolism of administered drugs.

PCBs are more potent enzyme inducers than phenobarbital, a drug that occasionally causes clinical problems due to its enzyme inducing effects. While the effects of phenobarbital decline after administration ceases, enzyme induction from PCBs persists long after cessation of exposure.

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VII. HUMAN TOXICOLOGY AND EPIDEMIOLOGY

Few good epidemiologic studies of the health effects of PCBs are available. Most studies reported in the literature have been characterized by one or more of the following shortcomings:

1. small study populations,
2. lack of accurate exposure data,
3. simultaneous exposure of workers to other potentially harmful chemicals,
4. lack of control for confounding variables, such as alcohol consumption, and
5. inability to separate PCBs from contaminants and/or difficulty in comparing PCBs manufactured by different firms.

In spite of these problems, some health effects have been consistently reported in studies of workers occupationally exposed to PCBs. In addition, a large-scale poisoning which resulted from ingestion of PCB/PCDF-contaminated rice oil has been well documented and resulted in multiple signs and symptoms attributable to PCBs and/or PCDFs.

The health effects identified in a review of the epidemiologic literature are summarized below, and Table II briefly describes the major epidemiological studies from 1954 through 1980.

Dermatologic Changes

Chloracne, contact or allergic dermatitis, and brown chromodermatosis have been consistently reported in studies of workers exposed to PCBs (Hara et al., 1975; Hasegawa et al., 1972; Inoue et al., 1975; Kitamura et al., 1973; Baker et al., 1980; Meigs et al., 1958; Ouw et al., 1976; Schwartz, 1936).

Systemic Symptoms

Nausea, digestive disturbances, headaches, upper respiratory problems, and persistent body odor have been reported as a result of occupational exposures (Ouw et al., 1976; Schwartz, 1936; Warshaw et al., 1979).

Liver Damage

Abnormal liver function tests have been reported in a number of occupational studies and clinical hepatitis was observed in the Yusho epidemic. However, some of the earlier investigations reporting abnormal liver function did not control for exposure to additional chemicals, previous medical history or drinking pattern and some of the marginal differences observed could have been related to these confounding variables.

More recently, Fischbein et al., (1979) found no significant differences in LFTs between capacitor manufacturing workers with low level chronic exposure and nonexposed controls. However, in a cross-sectional survey by Maroni et al., (1981 a & b) abnormal LFTs were observed and seemed to correlate with serum PCB levels. With the exception of a few cases of chloracne, these workers had no other symptoms, signs or laboratory abnormalities.

Yusho (Japanese word translated as "oil disease")

Both dermal and systemic health effects are well documented in the epidemiologic study of a poisoning epidemic in Japan caused by ingestion of contaminated rice oil in 1968 (Higuchi, 1976; Kuratsune et al., 1972).

It is not clear how much the health effects observed in Yusho victims can be extrapolated to occupational exposures for the following reasons:

1. The average amount of PCB (Kanechlor 400) ingested was estimated to be 2 grams and the minimum, 0.5 gram (Kuratsune et al., 1972). This is a higher dose than has been reported in most occupational exposures. In addition, the PCBs were ingested as opposed to inhaled or skin-absorbed as is the case with occupational exposures.

2. The contaminated oil contained "used" Kanechlor 400, the exact chemical compositon of which is unknown.

3. Frying of foods with the rice oil could have produced new compounds which may have altered the toxicity of the PCBs or the toxicity of possible contaminants.

4. Yusho oil was shown to contain high concentrations of dibenzofurans.

5. Reported concentration of PCBs in the oil may not have been accurate enough to permit a rigorous quantitative analysis since the methods for estimating PCBs in foods were not fully developed at the time.

Clinical features of the Yusho patients are listed in Table III. The Yusho incident is also important because it clearly documents the potential for reproductive and transplacental effects in humans.

A study was made of the 13 infants of 11 mothers affected by Yusho and of 2 unaffected wives of patients: 2 of the Yusho mothers had stillbirths; 10 of the babies had transient greyish or dark-brown pigmentation of the skin, and 5 had similar pigmentation of the gingiva and/or nails; increased ocular discharge was present in 9; and 12 of the 13 infants were small when compared with the national average (Funatsu et al., 1972; Kikuchi et al., 1969; Kuratsune, 1976; Taki et al., 1969). Babies born to patients even 3 years after severe PCB exposure tended to show pigmentation of the skin on the back and the gingiva, although the degree of pigmentation was less than that of babies born to the same mothers up to one year after the poisoning (Kuratsune, 1976).

Congenital abnormalities have also been observed in PCB-intoxicated infants. In the population of 13 offspring of Yusho mothers, premature eruption of teeth was observed in 2 cases, and larger than normal frontal and occipital fontanelles, exophthalmos and the persistence of an abnormally wide sagittal suture were observed in 3 others. No other gross malformations were reported nor was any relationship between dose and outcome considered (Funtasu et al., 1972).

Mothers' milk contaminated with PCBs also appears to be a source of exposure for infants: one baby showed signs of poisoning even though the mother had ingested the contaminated rice oil only after the baby was delivered. The infant began to show signs of PCB intoxication after 3-4 months of breast feeding (Kuratsune, 1972; Yoshimura, 1974).

Neurotoxicity

Paresthesias were reported in over 30% of Yusho patients (see Table III). In the Yusho epidemic more detailed neurologic examinations were performed in 21 cases admitted to a university hospital in northern Japan. Ten of the patients complained of numbness or pain in the distal extremities, and in five cases decreased pain, touch and temperature sensations were observed. Sensory conduction velocity in sural and radial nerves was below normal in 6 of 10 individuals with neuropathic symptoms (Murai and Kuroiwa, 1971).

A decrease in amplitude of muscle action potential evoked by nerve stimulation, and a decrease in sciatic nerve conduction velocity has been reported in rats intoxicated with tetrachlorobiphenyl. Thus, PCBs can affect peripheral nerve function in both

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humans and experimental animals, but these have been reported only at doses which cause other systemic signs of poisoning.

Cancer

There is too little epidemiological evidence available yet to evaluate the potential of PCBs as human carcinogens (Bahn et al., 1980; Brown and Jones, 1980). A follow-up of the Yusho patients through 1977 has reported 51 deaths (31 with cause of death confirmed) of the 1,665 identified victims. There were 11 deaths from neoplasms, or 35.4% of the total. While this rate is higher than the 21.1% in the population of the same prefecture in 1977, these data were not age-adjusted. No particular site was elevated, and there were no deaths from malignant melanoma, a tumor previously suspected to be linked to PCB exposure (Bahn et al., 1976). Two liver cancers and two lung cancers were reported but smoking and drinking patterns were not available (Urabe et al., 1979).

A retrospective cohort mortality study of 2,567 workers in two capacitor manufacturing plants was recently completed by NIOSH. The report did not find any statistically significant SMR for any cause of death among exposed workers. Deaths from liver cancer, cirrhosis of the liver and rectal cancer were slightly higher than expected, though these excesses were not statistically significant and no information was available on medical histories, drinking patterns, etc. There was no relationship between increased mortality from all causes of cancer, rectal cancer or liver cancer, and length of exposure to PCBs. Limitations in the study design, however, might have obscured a true association. In particular, there was a relatively small sample followed over time thereby limiting the statistical power of this study. Second, there were on the average

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only 15.19 years of follow-up for each exposed worker in the study. Usually the latent period between exposures and deaths from cancer is longer.

Third, exposure to PCBs was quantified for March 1977 only; there was no data on actual PCB exposures during the time when most of the population at risk was working with PCBs.

Finally, over 50% of the sample has exposure to PCB for only two years or less.

Ongoing Occupational Studies

Two additional cohort mortality studies are currently underway. The first is a mortality survey of the entire workforce employed between 1952-1957 at the largest United States' facility that manufactured capacitors and transformers. There is detailed information available on exposure levels in the plant. While the duration from onset of exposure is shorter than optimal (only 25 years in some cases), the information will at least give data on the short-term mortality experience of a heavily exposed occupational group (Selikoff et al., in progress).

The second is a similar occupational mortality study, also of workers exposed in capacitor and transformer manufacturing. Over 2,000 workers have been identified for this study but no further details are yet available (Bertazzi et al., in progress). One case control study is currently being conducted to assess whether there is excess risk of malignant melanoma among PCB-exposed workers. This data will not be available until March, 1982 (Bahn et al., 1976).

There is also one cross-sectional clinical field survey of 326 capacitor manufacturing workers at two sites, encompassing a total workforce of 800 (Fischbein et al., 1979). Exposures were classified as none, low, medium, and high based on job description at the time of the survey (1975). Researchers were able to identify the PCBs used and had some data on environmental air levels in the plants. A number of parameters were measured, including complete history and physical examinations, SMA panels and pulmonary function tests. Results have been published on respiratory function (Warshaw et al., 1979) and general signs/symptoms, and results of serum lipids, endocrine function and dermatologic findings are forthcoming. To date, the only positive association involves dermatologic signs and symptoms.*

Further investigations of the effects of PCB exposure on serum lipids have been done in both occupational and general environmental exposure settings. Smith et al., (1978), reported some statistically significant differences between exposed and nonexposed workers at two sites. They reported higher serum triglycerides and lower levels of high density lipo-proteins in the exposed group. Whether the magnitude of the difference is biologically significant is not clear from this study. For example, the nonexposed group at site #1 compared to the nonexposed group at site #2 showed a greater difference than the exposed and nonexposed comparison at either site. In another study (Baker et al., 1980) workers and community residents with exposure to fertilizer

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* Warshaw et al. (1979) concluded that there was also an association between PCB exposure and impaired pulmonary function (restrictive pattern). However, there were major methodologic problems with the data: the particular spirometer used (heated wire flow sensor) is notoriously inaccurate; it was not possible to link exposure data with particular PFT results; there was no information on race, and finally the magnitude of the observed effects was low and no statistical comparisons were done with nonexposed controls.

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made from sewage sludge contaminated with PCBs were studied. Plasma triglyceride levels were found to increase significantly with serum PCB concentration (both in drinkers and nondrinkers), and the authors concluded that PCBs may alter lipid metabolism at levels of exposure and bioaccumulation insufficient to produce other identifiable signs of toxicity.

Comments

Although many problems have been identified in the studies evaluating the health effects of PCBs, it is clear that occupational exposure, at a minimum, can produce dermatologic effects. The long half-life of PCBs and their bioaccumulation in various human tissues leaves open the possibility of substantial chronic and delayed effects analogous to those seen in animal bioassays. These effects have only recently begun to be studied in a rigorous manner, and although the epidemiological evidence is neither complete nor entirely consistent there can be no question of the necessity to protect the worker from exposure.

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VIII. MEDICAL SURVEILLANCE AND BIOLOGIC MONITORING

Medical surveillance and biologic monitoring are of limited usefulness in predicting health hazards if dose-response relationships are not known. This certainly is the case with PCBs. Based on animal toxicology, there are many suspected adverse effects of PCBs which might result from exposure in occupational settings, but very few have been documented well enough to give even rough estimates of "no-effect" or "safe" levels. A large percentage of nonoccupationally exposed people have detectable PCB levels in body fat, blood and milk. However, any attempt to estimate an adverse health effect associated with increases above this background level necessarily involves extrapolation from animal data and, therefore, is subject to considerable error, especially when the marked variation in sensitivity of various animal species is appreciated. Furthermore, not enough is known regarding the relative dose-response characteristics of the various documented effects (e.g., liver damage, skin changes) to state that in the absence of a particular sign, symptom or laboratory abnormality, the risk of long-term effect (cancer, reproductive toxicity) will be negligible (see Table I).

For the clinician confronted with a worker who has a history of exposure to PCBs the approach to management cannot be easily outlined. Given the current analytic methodology, residues can be measured in blood or tissue in the ppb range and compared to background; but assigning a health risk to a given level is virtually impossible, especially given the lack of pharmacokinetic data. Often patients are being evaluated after a considerable lag period (years) since last exposure occurred and extrapolation to peak blood levels is not possible. In fact, it may be that residue levels bear little relationship to the health risk. For example, the lower chlorinated compounds may be more toxic but they are more rapidly metabolized and excreted and, therefore, less likely to persist in blood or fat. Further, with the possible exception of chloracne,

the presence of specific signs, symptoms or laboratory abnormalities is very difficult to definitely relate to PCB exposure in any given patient.

Given these uncertainties and the potential for serious health effects, the approach to monitoring should emphasize environmental sampling and every attempt should be made to minimize exposure by engineering controls or personal protective measures in those settings where occupational exposure still occurs (e.g., utility repair workers). Biologic monitoring may be used to assess the effectiveness of environmental control, but it is really best utilized within a specific research protocol and probably has little value in the routine work-up of individual patients.

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SUMMARY AND CONCLUSIONS

PCBs have low acute toxicity but are of public health concern because of their persistence in the environment and in human tissues and their demonstrated potential for chronic or delayed toxicity. They are potent inhibitors of reproductive function in both rodents and nonhuman primates and are positive in animal cancer bioassays. As potent inducers of hepatic enzyme systems, PCBs may have additional unpredictable long-term health effects.

Some of the conflicting reports in the toxicology literature are undoubtedly related to the variable composition and trace chemical contamination of the tested mixtures. Occupational and environmental exposure is usually to those mixtures; but if we are to accurately assess the associated health hazards, further animal studies are needed which carefully define the toxicology of the individual agents.

Epidemiologic studies of occupational exposures to PCBs to date have failed to detect serious adverse effects but are considered insufficient, and further studies are clearly needed. Of particular interest is the continued exposure among utility workers. Because of the potential ability to cause cancer and other long-term adverse effects such as infertility and hepatic injury, human exposure to PCBs should be kept to the lowest level technically possible. The persistence of PCBs in the body and the irreversibility of some of its effects make it necessary to act now, rather than to wait until more definitive data are available.

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TABLE I

DOSE-RESPONSE FOR ANIMAL TOXICOLOGY

Species	Age	Agent	Route	Dose mg/kg/day	Duration	Total Dose mg/kg	Effect	References
Rat	Adult	Aroclor 1254, 1260	Oral	4,000 - 10,000	Single Exposure	-----	LD_{50}	Kimbrough et al., 1978
Rat	Weanling	Aroclor 1254, 1260	Oral	1,200 - 1,300	Single Exposure	-----	LD_{50}	Kimbrough et al., 1978
Rat	Adult	Aroclor 1248, 1254, 1262	Oral	50	6 weeks	2100	Liver hypertrophy, fatty infiltration	Allen & Abrahamson, 1975
Rat	Weanling	Aroclor 1262, 1016	Oral	3.9-6.6	6 months	700-1200	Fatty liver	Durao et al., 1976
Rat	Adult	Aroclor	Oral	100	7-15 day gestation	700	↓survival - offspring no terata.	Linden et al., 1976
Rat	Adult	Aroclor 1260	Oral	25.0	2 months prior to mating	1500	↓litter size ↓survival offspring	Linden et al., 1976
Rat	Adult	Aroclor 1254	Oral	5.0	2 months prior to mating	300	↑mortality - offspring ↓mating behavior - offspring	Linden et al., 1976
Rat	Adult	Kanaclor 500	Oral	1.0	Day 8-14 or 15-21 gestation	6.0	↓various learning assays offspring	Shiota, 1976
Mice	Adult	"PCB's"	Oral	7.0	6 weeks starting at birth	200	↓implantations, litter size-offspring; changes in estrous cycle-offspring	Kihlstrom et al., 1975
Mice	Adult	Clophen A60	Oral	1.0	"chronic"	Unknown	lengthened estrous cycles ↓implantations	Uberg & Kihlstrom, 1973
Monkey	Adult	Aroclor 1248	Oral	10	6 weeks	840	weight loss, alopecia, facial edema, eye discharge	Allen, 1975
Monkey	Adult	Aroclor 1248	Oral	3.3	1 month	100	liver abnormalities (histological)	Allen, 1975
Monkey	"young"	Aroclor 1242	Oral	0.1-10	9 months	27-2700	death, gastric ulceration, facial edema, thymic atrophy	Allen, 1975
Monkey	Adult	Aroclor 1248	Oral	0.08-0.17	1 year	29-62	facial edema, alopecia acne, ↓fertility, irregular menses, ↑early abortions- offspring; ↓weight, head circumference, (detectable PCB's in tissue)	Allen, 1975
Rats	Adult	Aroclors	Dermal	≈100	25 days	2500	slight Δ's- liver histology	Miller, 1966
Guinea pig	Adult	Aroclors	Dermal	≈70	Single Exposure	----	death -- delayed up to 21 days with liver atrophy	Miller, 1966
Rabbit	Adult	Aroclor 1260	Dermal	≈20	38 days	760	skin, liver and kidney damage	Vos & Beems, 1971
Rat, Mouse, Guinea pig, and cat	Adult	Aroclor 1254	Inhal.	2.5 *	17 weeks	650	microscopic liver Δ's	Treon, 1956
	"	"	"	0.7 *	31 weeks	217	reversible liver Δ's	Treon, 1956
Mice	8 weeks	Kanaclor 500	Oral	50	32 weeks	11.2 **	↑hepatocellular carcinomas (control 0/6; dosed 5/12) ↑neoplastic nodules (control 0/6; dosed 7/12)	Ito et al., 1973
Mice	5 weeks	Aroclor 1254	Oral	50	46 weeks	16.1 **	↑neoplastic nodules (control 0/26; dosed 9/22)	Kimbrough & Linden, 1976
Rats	4 weeks	Aroclor 1260	Oral	10	21 months	6.3 **	↑hepatocellular carcinomas (control 1/173; dosed 146/184) ↑neoplastic nodules (control 0/173; dosed 26/184)	Kimbrough et al 1975
Rats	8 weeks	Aroclor 1260	Oral	10	104 weeks	7.2 **	↑hepatocellular carcinomas (unpublished, 1980)	Norbach et al., 1980
Rats	8 weeks	2,4,5,2',4',5' hexachlorobiphenyl	Oral	10	104 weeks	7.2 **	↑hepatocellular carcinomas (unpublished, 1980)	Norbach et al., 1980

* Animals were exposed to 1.4 or 1.5 mg/m³ of Aroclor 1254 for 7 hours/day, 5 days/week for 17 weeks. To approximate dose in mg/kg/day, the following corrections were applied: 0.2 (volume of air breathed in m³ by animal per day); 0.5 (weight of animal in kg); 24/7 (correction for 24 hour/day exposure); 7/5 (correction for 7 day/week exposure). Resulting value assumes 100% absorption.

** Total dose in gm/kg

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TABLE II - OCCUPATIONAL EXPOSURE TO PCBs

Study	Exposure Level & Time	Study Population Exposed	Study Population Controls	Dermal Effects	Liver Function	Findings: Blood Concentrations	Findings: Cancer/ Mortality	Comments
Meigs 1994: Outbreak of dermatitis in a chemical plant	0.1 mg/m^3 Aroclor™ - 3 to 19 mos. intermittent exposure through vapor leakage	14 potentially exposed	0	7 mild to moderate chloracne, contact dermatitis	6 normal, 1 borderline abnormal			There was not a good correlation between apparent degree of exposure and development of signs of disease
Nasagawa et al., 1972: Study of 6 industrial plants including PCB manufacturing, capacitor, manufacture, and biphenyl recovery	Vapors: 13-965 ug/m^3 Particulates: 4-650 (6,270 in a spill) <1 to 28 years	99	32	Various	Slightly abnormal	Exposed: 370 ppm Nonexposed: 20 ppm		Dermal ailments were unrelated to blood centrations; based on 3 plants, there was no relationship of exposure to blood concentrations, fat metabolism was apparently affected.
Hara et al., 1973-1974: Study concentrated on 17 insulation process worker	Level of exposure not reported in NIOSH Criteria Document	110		45% blackheads, 37% acne, 13% irritation	not reported	Exposed: 7-300 ppb		Effects correlated with duration of exposure; one year later blood concentrations were decreased by varying amounts. The longer the duration of exposure, the longer the PCB half-life in blood.

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TABLE II- OCCUPATIONAL EXPOSURE TO PCBs (cont'd)

Nitanuen 1973: Study of workers in a capacitor manufacturing plant	Exposure level not reported in NIOSH Criteria Document; duration 2.5 yrs.	13		Various: acne, seborrhea, adipose, etc.	Normal	Average: 820 ppb (range: 320 -2100 ppb)	No relationship was found between concentration in blood and duration of exposure.
Inoue et al., 1973: Study of a family exposed during silk thread glossing operation.	Not reported in NIOSH Criteria Document	Family members and 1 helper. (Later 54 more persons were studied)		Skin lesions and comedones on face and back	Unknown	130-250 ppb	PCBs were found in mothers' milk
Bato and Hasegawa 1974: Pressure sensitive carbonless paper manufacturer	0.13 - 4.4 ug/m3 and 0.15 - 1.2 m (measured 2 yrs. post PCB use)	Not reported in NIOSH Criteria Document				Exposed: 73 ppb Nonexposed: 20 ppb	
Harpponen and Nolke 1972: Study of 3 groups: 1) no exposure 2) analytical lab workers 3) capacitor impregnation workers (Aroclor 1242)	Low, medium and high exposure < 1 ug/m3 (with skin protection)	High exposure: 8 males 4 females Medium exposure: 6 females	4 males 5 females			Unexposed: 5.6 - 12 ppb Medium 36-63 ppb High exposure 74-1,900 ppb	No biologic effect observed.
Rungarner et al., 1973: Study of refuse workers exposed to PCB in incineration of waste	Incinerated waste	37	36 lumber yard workers			Measurable concentrations in 32 of the 37 refuse workers (4-14 ppb)	Concentrations not well correlated with duration of exposure.

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TABLE II- OCCUPATIONAL EXPOSURE TO PCBs (cont'd)

Guo et al., 1976: Study of capacitor manufacturer workers.	Aroclor 1242: 1.1 - 1.4 mg/m^3 (19 workers); 0.32 mg/m^3 (15 workers) Workers were no protective clothing. Time 1 mo. to 23 yrs.	34	30	Mild burning, irritation of face, eyes and skin; 5 had rashes 1 chloracne, several dermatitis	BSP elevated in 4 of 7 with blood levels > 500 ppb	Exposed: 100 - 402 ppb (mean 400 ppb). Not detected in nonexposed.		Systemic effects reported such as nausea and persistent body odor. There was no adverse response at blood concentrations below 200 ppb.
Rohn, et al., 1976: Study of workers in a refinery	Aroclor 1254 over a 9 yr. period	31 males and 41 females					2 malignant melanomas observed, .04 expected (based on THCB data)	These were preliminary results reported in a letter to the editor. Workers were also exposed to other chemicals. Study is in progress.
Brown and Jones 1980: Cohort mortality study of capacitor manufacturers	Aroclor 1016 Plant 1: 24 - 303 ug/m^3 Plant 2: 170 - 1260 ug/m^3	Plant 1: 968 Plant 2: 1,509				All cause mortality was lower than expected (163 obs. vs. 174 exp.) All cancer mortality was lower than expected (39 obs. vs 40.6 exp.) Rectal and liver cancer were slightly elevated but not significantly.		Lower observed mortality attributable to the "health worker" effect. NIOSH will continue to follow-up mortality experience.

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TABLE 11- OCCUPATIONAL EXPOSURE TO PCBs (cont'd)

Baker, Landrigan et al., 1980: Study of exposure to PCBs in sewage sludge.	Liquid sewage entering plant 30-470 ppb. Upstream sewage 1250-5500 ppb (Aroclor 1016) Concentrations in sludges (Aroclor 1242) were as high as 1700 ppm (mean 479.1 ppb) and 107.3 ppm in treated soil (mean 17.1 ppm)	89 sludge users, 18 workers exposed to PCBs, 19 members workers families	22 community members	Acne, increased pigmentation in 4 workers		Sludge users 17.4 ppb; workers 75.1 ppb; families 33.6 ppb; community 24.2 ppb	Plasma triglyceride levels increased significantly with serum PCB concentrations. Data indicate that PCBs may alter lipid metabolism.
Fishbein, et al., 1979: Cross-sectional field survey of capacitor manufacturing workers.	None, low, medium, high based on job classification and air monitoring (high= 0.6-11 mg/m^3 TWA) duration 40% ≥ 20 yrs. 10% < 5 yrs.	326 currently employed, 27 retirees (not broken down into exposure categories for most endpoints monitored).	None	Apparent increase in prevalence of various dermatologic complaints including 35 with history of acne since onset of employment and 16 with acneform rash on examination.	Statistical significance associated with SGOT with serum levels of PCB but low incidence of "abnormal" values; no association with other liver enzymes.		Results severely limited by fact that there was no attempt to correlate exposure or blood levels with endpoints being measured - so that no possibility of observing "dose-response" effect or even exposed vs control difference.

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TABLE III

PERCENT DISTRIBUTION OF SYMPTOMS OF YUSHO REPORTED BY 189 PATIENTS EXAMINED BEFORE OCTOBER 31, 1968.

Symptoms	Males (N-89)	Females (N- 100)
Dark brown pigmentation of nails	83.1	75.0
Distinctive hair follicles	64.0	56.0
Increased sweating at palms	50.6	55.0
Acnelike skin eruptions	87.6	82.0
Red plaques on limbs	20.2	16.0
Itching	42.7	52.0
Pigmentation of skin	75.3	72.0
Swelling of limbs	20.2	41.0
Stiffened soles in feet and palms of hands	29.7	29.0
Pigmented mucous membrane	56.2	47.0
Increased eye discharge	88.8	83.0
Hyperemia of conjunctiva	70.8	71.0
Transient visual disturbance	56.2	55.0
Jaundice	11.2	11.0
Swelling of upper eyelids	71.9	74.0
Feeling of weakness	58.4	52.0
Numbness in limbs	32.6	39.0
Fever	16.9	19.0
Hearing difficulties	18.0	19.0
Spasm of limbs	7.9	8.0
Headache	30.3	39.0
Vomiting	23.6	28.0
Diarrhea	19.1	17.0

Source: Kuratsune et al, 1972

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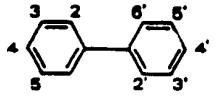
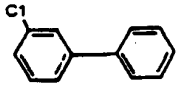
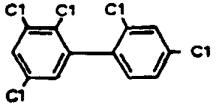
FIGURE I



BIPHENYL MOLECULE AND RING NUMBERING SYSTEM



3-chlorobiphenyl



2,2',3,4',5-pentachlorobiphenyl

EXAMPLES OF NOMENCLATURE SYSTEM OF CHLOROBIPHENYL COMPOUNDS

NUMBER OF ISOMERS AND PERCENT CHLORINE FOR THE 10 CHLOROBIPHENYL (PCB) CLASSES

Chlorobiphenyl	Empirical Formula	No. of Isomers	Weight % Cl
mono	$C_{12}H_9Cl$	3	18.79
di	$C_{12}H_8Cl_2$	12	31.77
tri	$C_{12}H_7Cl_3$	24	41.30
tetra	$C_{12}H_6Cl_4$	42	48.56
penta	$C_{12}H_5Cl_5$	46	54.30
hexa	$C_{12}H_4Cl_6$	42	58.93
hepta	$C_{12}H_3Cl_7$	24	62.77
octa	$C_{12}H_2Cl_8$	12	65.98
nona	$C_{12}HCl_9$	3	68.73
deca	$C_{12}Cl_{10}$	1	71.18

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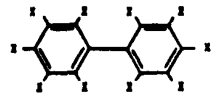
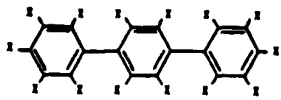
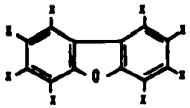
FIGURE II



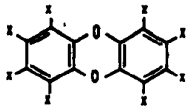
Polychlorinated Biphenyls (PCB's)



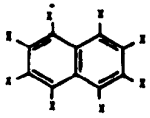
Polychlorinated Terphenyls



Chlorinated Dibenzofurans



Chlorinated Dibenzodioxin



Polychlorinated Naphthalenes

Source: Kimbrough, 1974

FIGURE III

CHLORODIBENZOFURAN TYPES AND CONCENTRATIONS (μg g) IN COMMERCIAL PCB PREPARATIONS

Mixture*	Chlorodibenzofurans di	tri	tetra	penta	hexa	hepta	Total
(1) 1016	0.5						0.5
(1) 1016			<0.0001	<0.0001	<0.0001		
(1) 1248			0.5	1.2	0.3		2.0
(1) 1254			0.1	0.2	1.4		1.7
(1) 1254			0.2	0.4	0.9		1.5
(1) 1260			0.1	0.4	0.5		1.0
(1) 1260			0.2	0.3	0.3		0.8
(2) A-60			1.4	5.0	2.2		8.4
(3) DP-6			0.7	10.0	2.9		13.6
(4) K300			(a)	(a)			1-1.5
(4) K400	(c)**	(e)	(e)	(c)			17-18
(4) K500				(a)	(c)	(a)	2,3-4
(4) K600			(a)	(a)	(b)	(b)	3-5

*(1) Aroclor, (2) Clophen, (3) Phenoclor, (4) Kanechlor
**(a), (b), (c), (d), (e) represent relative amounts in increasing order

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FIGURE IV

Responses of primates and rats to PCB's*

Response	Man	Monkey	Rat
Susceptibility to toxicity	High	High	Moderate
Acne	Yes	Yes	No
Hyperpigmentation of skin	Yes	Only infants	No
Alopecia	NA	Yes	No
Hyperactive Meibomian glands	Yes	Yes	No
Conjunctivitis	Yes	Yes	No
Oedema of eyelids	Yes	Yes	No
Subcutaneous oedema	Yes	Yes	No
Keratin cysts in hair follicles	Yes	Yes	No
Hyperplasia of hair follicle epithelium	Yes	Yes	No
Gastric hyperplasia	NA	Yes	No
Thymic atrophy	NA	NA	Yes
Hepatic hypertrophy	Yes	Yes	Yes
Liver enzyme change	NA	Yes	Yes
Decreased no. of red-blood cells	Yes	Yes	No
Decreased haemoglobin	Yes	Yes	No
Serum hyperlipidaemia	Yes	Hypolipidaemia	Yes
Leucocytosis	Yes	Yes	No

Source: IARC, 1978

* This table summarizes acute and subacute clinical effects but does not include chronic or delayed effects such as reproductive effects or cancer.

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ASSESSMENT OF THE HUMAN RISKS TO PCBs ASSOCIATED WITH THE EXPECTED ENVIRONMENTAL EXPOSURES

Robert C. James, Ph.D.
Department of Interdisciplinary
Toxicology
University of Arkansas for
Medical Sciences
4301 W. Markham
Little Rock, Arkansas 72205

Raymond D. Harbison, Ph.D.
Department of Interdisciplinary
Toxicology
University of Arkansas for
Medical Sciences
4301 W. Markham
Little Rock, Arkansas 72205

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During the past decades, a combination of "open" systems and sloppy or illegal disposal practices have resulted in the release of large quantities of chemicals into the environment. In the late 1960s, when it became apparent that persistent chlorinated hydrocarbon polychlorinated biphenyls (PCBs) were ubiquitous environmental contaminants which took years to biodegrade, attention was focused on their potential to bioaccumulate to what was believed to be toxic levels in animals and humans. As a result, questions arose regarding the chronic side effects caused by long-term exposure to these chemicals. Reflecting public concern, Congress enacted the Toxic Substances Control Act in 1976, which mandated a phaseout of PCB manufacturing and use. At that time, PCBs were considered a highly toxic and dangerous chemical because of their environmental persistence and their potential for causing permanent adverse health effects, such as cancer. In recent years, however, a substantial increase in scientific data has resulted in a better understanding of both the actual effects of human exposure to PCBs and the chemically-induced processes leading to cancer.

While it was appropriate a few years ago to act on the premise that all potentially carcinogenic chemicals represented similar hazards, recent experience has shown that there are important theoretical and practical differences in the actual hazard each "carcinogen" represents to public health. Similarly, there has been a substantial increase in the amount of data reflecting the toxicity of PCBs in animals and humans. Considering the national concern expressed for environmental contaminants, and in particular for PCBs, it seems both appropriate and necessary to reevaluate the hazard and risks posed by PCBs now that we have more information.

It is the purpose of this paper to provide a framework for identifying the important toxicological considerations used in interpreting the risks inferred by toxicity data, as well as to provide a discussion on the PCB data within this framework so as to arrive at an assessment of the risk to human health.

DEFINITIONS AND BASIC PRINCIPLES OF ASSESSING RISKS

A toxicant is a chemical agent that can produce an adverse effect in a biological system. Such an adverse effect may be an alteration of normal function or destruction of life. This definition is broad since all chemicals are toxic at some dose, i.e., all chemicals are capable of altering some function or producing death in some biological organism. While this statement may seem obvious, it serves to emphasize the basis of risk assessment, i.e., those circumstances and conditions under which an adverse effect can be produced. As Emil Mrak stated years ago, "there are no harmless substances; there are only harmless ways of using substances." A chemical is toxic and produces harm only within prescribed conditions of usage.

Risk is defined as the probability that a substance will produce harm under specified conditions (1); i.e., it is a practical consideration to determine whether or not some harm will be elicited from a specific chemical exposure. Safety is the reciprocal of risk, or the probability that a substance will not produce harm under the specified conditions. Thus, when determining the risk or safety of a chemical, the critical factor is not necessarily the intrinsic toxicity of the chemical per se, but the likelihood that the level of exposure to the chemical is sufficient to express its intrinsic toxicity.

In general terms, then, the risk is approximated by the equation:

$$R = T \times E$$

where R is risk, T is toxicity, and E is exposure. More accurately, the equation for risk is equal to the toxicity as a function (f) of the exposure, or:

$$R = Tf(E)$$

This better defines the extrapolation, since under certain conditions the risk is not always linear over the entire dose-response curve; and since, depending on how one defines function (f), threshold or nonthreshold dose-response curves may be fitted to this equation. However, regardless of how one chooses to express the risks to chemical exposure, it is clear that: (a) the actual risk is dependent upon both the toxicity (i.e., hazard) and the exposure (i.e., amount of chemical) and (b) to change either alters the risk. Therefore, to make a risk assessment, one must compare the exposure probability with the various dose-response curves for each toxicity to determine whether or not a harmful response is likely to be induced.

In evaluating the risk associated with exposure to PCBs, we will attempt to answer two questions. First, is the level of exposure of a sufficient magnitude such that a hazard exists? Second, if so, what is the hazard or undesirable response expected for that level of exposure. To answer both questions it is necessary to first evaluate the hazards associated with PCBs; i.e., what are the toxic responses and at what levels of exposure will they occur?

Many aspects must be considered and weighed before the hazards to humans associated with PCB exposure can be evaluated. An evaluation of the human hazard and subsequent risk estimation for any chemical must address the data base utilizing thorough comparative toxicologic assessments. This means that the animal and human data available must be carefully considered in terms of: (a) the breadth and variety of the toxic responses manifested; (b) the degree of species variation or species consistency in the effects monitored; (c) the possible and/or proposed mechanisms of toxicity; (d) the validity of the tests performed and their relevance for extrapolations to man; (e) the dosage used in animal tests versus the expected level of human exposures; and, finally, to the extent that the data are available, (f) the outcomes of serious poisonings and long-term occupational exposures as a guide to the expected human consequences and as a test of the extrapolations made from animal data. Only when a consistent pattern of toxicity in animals coincides with human experiences can accurate and safe guidelines be promulgated.

The following sections of this chapter will discuss the hazard associated with PCB exposure as interpreted from the animal and human data; the choice and use of risk assessment models to define the risk to PCBs from various environmental exposures; the accuracy with which the health risks for a PCB exposure can be estimated at the present time; and the conclusions reached by this study.

EVALUATING THE ACUTE HAZARD ASSOCIATED WITH PCB EXPOSURE FROM ANIMAL DATA

Several reviews of the mammalian toxicity of PCBs have been published within the last decade (2-7). Since much of this

information has already been given in the previous chapters, a cursory summary rather than an exhaustive review is provided here. This summary presents the types of hazards to be expected and documents the extrapolations one might make to the high exposure human situation based on the animal data. It must first be stated that PCBs have a low order of acute toxicity as measured by the median lethal doses (to 50% of the population) (LD_{50}) for rodent species. As shown in Table 1, the median lethal doses for various commercial PCB mixtures lie between 1.3 and 19.2 g/kg of body weight. Median lethal doses as high as these classify PCB mixtures, especialy the higher chlorinated mixtures, as only slightly toxic chemicals (1).

PCBs produce a variety of physiologic changes in animals. For example, in the liver, PCBs increase the amount of endoplasmic reticulum, resulting in enlarged hepatocytes and thereby increasing liver size and weight. Higher doses can cause liver damage and necrosis. PCBs applied directly to the skin of rabbits have produced hyperkeratosis, erythyma, blisters, and desquamation. In primates, oral doses of PCBs have led to facial edema, hair loss, and acne-like pustules, as well as prolonged menstrual cycles and increased bleeding in female animals. Additional symptoms reported in various species include gastric hyperplasia, decreases in red and white blood cells, atrophy of the thymus and spleen, and increases in serum levels of phospholipids, triglycerides, and cholesterol.

However, as with lethality, the doses required to cause these acute effects are generally high. The doses required to cause subchronic effects can also be considered high when the slow rate of metabolism, and therefore a tendency to bioaccumulate, is taken into consideration. While a number of effects have been reported for PCBs,

Table 1

MEDIAN LETHAL DOSES FOR VARIOUS COMMERCIAL PCB MIXTURES

Species	Commercial Brand of PCBs	LD_{50} (mg/kg body weight)
Mouse (oral)	Aroclor 1254	2,000
	Kanechlor	>1,873
Rat (oral)	Aroclor 1221	4,000
	Aroclor 1232	4,500
	Aroclor 1242	8,700
	Aroclor 1248	11,000
	Aroclor 1254	4,000-10,000
	Aroclor 1260	10,000
	Aroclor 1262	11,300
	Aroclor 1268	10,000
	Aroclor 4465	16,000
	Aroclor 5460	19,200
Rabbits (skin)	Aroclor 1221	3,200
	Aroclor 1232	2,000
	Aroclor 1242	1,300
	Aroclor 1248	1,300
	Aroclor 1260	1,300-2,000
	Aroclor 1262	1,300-2,000
	Aroclor 1268	2,500

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those of the liver (i.e., enlargement and necrosis) are the most consistently reported, as are those of the skin (i.e., chloracne or dermatitis). These physiologic responses observed in the liver and skin are fairly predictable effects of many chlorinated compounds.

In assessing the acute and subchronic tests of animals, PCBs do not appear to be remarkably toxic chemicals. The dermal irritation caused by PCBs is not an unusual physiologic response for an organic, solvent-like chemical. The chloracne observed in animals and humans is also a frequently observed effect of other chlorinated chemicals and is reversible in cases where PCBs are the only suspect agent. The observed liver effects (i.e., increased liver weight, proliferation of endoplasmic reticulum, deposition of fat, cell death, and tissue necrosis) are common responses to persistent, chlorinated hydrocarbons, which in general are enzyme inducing agents at lower doses and hepatotoxins at higher doses. Many other chemicals share one or both of these characteristics. While enzyme induction may increase the toxicity of some chemicals and lower the dose producing toxicity, this is not a general phenomenon. In many instances, an increase in metabolism decreases the toxicity of other chemicals. Similarly, inducing agents often increase other routes of biotransformation that detoxify toxic chemicals. In fact, enzyme induction is sometimes used therapeutically. Therefore, induction by itself cannot be considered a toxic response, nor can its consequences be accurately predicted in humans.

In monkeys, PCBs cause a conversion of the gastric epithelium that can be described as a dysplastic growth pattern. This does not constitute a neoplastic transformation (39). While PCBs have been reported as inhibiting the immune system in mammals, this occurs at high doses at which general toxicity leads to a reduced food intake

and thus a reduced nutritional status. In some test species, PCBs produce changes in reproductive performance, but again usually at high doses. In monkeys, this problem occurs only with the female animals and at doses clearly producing general toxicity and signs and symptoms of intoxication. Reproductive dysfunction during chemical intoxication is not a particularly unusual finding. Therefore, it is concluded that the acute toxicity of PCBs in animals is not particularly remarkable, nor does the chemical represent an unusual acute hazard.

CHRONIC EFFECTS OF PCBs

Mutagenicity

A genotoxic chemical is any compound capable of inducing a permanent, inheritable change in the genetic composition of a cell. Genotoxic effects are divided into three types, depending on the cellular level of the genetic lesion. Mutagenesis refers to mutations or structural changes at the DNA level, called microlesions (1). The other two types of genotoxic effects are: clastogenesis, which refers to structural changes at the chromosomal level, and aneuploidization, which refers to a change in chromosomal number. Both clastogenesis and aneuploidization can alter the amount or expression of genetic material; both types of changes are referred to as macrolesions (1). For the sake of discussion, all genotoxicity tests are referred to in this paper as mutagenicity tests.

The "Ames test," which uses mutant strains of the bacteria Salmonella typhimurium that have lost the ability to synthesize their own histidine, is probably the most popular and best known test for

mutagenic activity. Since this amino acid is important to protein synthesis, and therefore growth, these cells can grow only if histidine is added to the culture medium. A chemical mutagen can be identified by a mutation in the locus of the histidine defect which reverts the bacteria to the normal state, thus allowing easily identifiable bacterial colonies to grow in a histidine-deficient medium.

Wyndham and co-workers (8), using the Ames assay, tested the several chlorinated biphenyl mixtures and reported that they were weakly mutagenic. A review of their data indicated that 4- chlorobiphenyl had significant activity. , Aroclor 1221, which has a chlorine content of 1.15 chlorine a per molecule and is therefore largely a monochlorobiphenyl mixture, showed a greatly reduced activity. This would seem to indicate that either the "heavier" PCB molecules were inhibiting mutagenicity or that the activity is greatest for the 4-chloro-isomer of the monochlorobiphenyl compounds. The test results for the polychlorinated biphenyl compounds 2,2',5,5'-tetrachlorobiphenyl and Aroclor 1268 seem to indicate no substantial mutagenic activity. Subsequent attempts to reproduce the Wyndham et al. results have failed (9-13) (see Table 2). The majority of assays discount any suggestion that PCBs or monochlorobiphenyl are mutagenic in the Ames assay.

Several studies have demonstrated that PCBs lack the ability to damage or alter chromosomes. Green et al. (14) looked for significant chromosomal damage in the bone marrow and sperm cells of rats administered the following dosage regimens: a single dose of Aroclor 1242 at 1250, 2500, and 5000 mg/kg; or 500 mg/kg per day for five days. Even though some of the animals demonstrated definite signs of intoxication, there was no evidence of chromosomal abnormalities. These findings are consistent with the results reported by Dikshith et al.

Table 2

PCNA: TABULATION OF MICRONUCLEAR MUTAGENICITY TESTS

Product \ Tester Strain	S. typhimurium										E. coli	
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	--	--	--	--	--	--	--	--	--	Neg.	--	--
[illegible]	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	--	Neg.	Pos./ Neg.	Neg.	Neg.
[illegible]	--	--	--	Neg.	Neg.	--	--	--	--	--	Neg.	--
[illegible]	--	--	--	Neg.	Neg.	--	Neg.	--	Neg.	Neg.	--	--
[illegible]	--	--	--	Neg.	Neg.	--	Neg.	Neg.	Neg.	Neg.	Neg.	--
[illegible]	--	--	--	--	--	--	--	--	--	Pos.	--	--
[illegible]	--	--	--	--	--	--	--	--	--	Pos./ Neg.	--	--

Source: reference 13.

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(15) or Garthoff et al. (13) in rats and the study reported by Koeplingarmar et al. (14) using cultured human lymphocytes. Heddle and Bruce (11) reported that Aroclor 1254 was negative in the micronucleus test, which measures clastogenic activity (chromosomal breakage) by measuring chromatin bodies in red blood cells. Green et al. (17), using the dominant lethal test, which measures mutagenic events in germ cells by the embryotoxicity it induces, reported that Aroclor 1242 and Aroclor 1254 gave negative results in rats. Keplinger et al. (18) and Calandra (19) also reported a similar lack of mutagenic activity in mice using the dominant lethal test.

Levinskas (13) has recently reviewed the mutagenicity data for PCBs. Besides the above-mentioned tests, Levinskas discusses many additional, though in several cases less often used, procedures. In his review he refers to a study by Odashima in which Kanechlor 300 and 500 were negative in the standard strains of Salmonella typhimurium used in the Ames assay, as well as several additional bacterial strains. However, Kanechlor 300 was reported positive in one or more of four additional strains, while Kanechlor 500 was listed as negative.

On the basis of sedimentation rates, Stadnicki et al. (13) have reported that the epoxide of tetrachlorobiphenyl caused single-stranded chromosomal breaks in the DNA of L-929 cells at concentrations ranging from 1 μg/ml to 100 μg/ml. A mixture of two hydroxy metabolites, and to a lesser extent tetrachlorobiphenyl, caused some damage at 20 μg/ml and significant damage at 100 μg/ml. The significance of this test at these high in vitro concentrations is questionable.

Using Drosophila melanogaster and Bombyx mori as the eukaryote test species, neither the French PCB mixtures, Clophen 30 and Clophen

50, or the Japanese mixtures, Kanechlor 300 and 500, were mutagenic. Odashima (7, 13) studied chromosomal aberrations in Yoshida sarcoma cells at PCB concentrations causing 50% growth inhibition: Kanechlor 300 gave a positive response and Kanechlor 500 a negative one. Odashima reported cytogenetic analysis of bone marrow cells in mice exposed to PCBs at a near lethal dose. This test gave paradoxical results. Odashima listed exposure to Kanechlor 500 as positive and exposure to Kanechlor 300 as negative (7, 13).

Norback et al. (13) reported that Aroclor 1254 transformed C3H10T1/2 cells to Type III foci after six weeks of continuous exposure to 10 ug/mL of Aroclor 1254, while a concentration of 1 ug/mL was negative. Norback and co-workers suggested that the effects of PCBs in culture include promotion. In contrast to this study, Pienta (13) reported Aroclor 1254 as negative in the Syrian hamster cell transformation test.

Peakall (13) reported chromosomal aberrations in doves fed a 10-ppm diet of PCBs. The frequency changed from 0.8% in controls to 1.8% in treated birds. The average rate of chromosomal aberrations among treated eggs was higher than the highest control value in only 4 of 17 pretreated embryos. In contrast, PCBs injected into white Leghorn eggs up to concentrations of 20 ppm, while toxic, were not clastogenic.

A thorough review of the mutagenicity tests reveals that PCBs gave primarily negative responses. While some positive results were reported, these were largely in vitro tests and for the Kanechlor brands, which gave inconsistent and mixed results for the 300 and 500 brand mixtures. The relevance of some of the in vitro tests that found positive scores only at concentrations of 10 ug/mL or greater

(very high and unlikely in vivo concentrations) is questionable. This interpretation is supported by the fact that in many cases a similar experiment gave correspondingly opposite, i.e., negative, results. According to Lavinskas, "considering the large number of tests conducted, it is not surprising that an occasional suspicious positive finding resulted, simply on a statistical basis" (13). A comparison of the number of Ames tests unable to reproduce the results of Wyndham et al. (8) supports his contention.

It is the consensus of this review that PCBs do not represent a significant mutagenic risk to humans; a fact borne out and reinforced by the numerous negative carcinogenic studies of PCBs in animals.

Teratogenicity

A teratogen is an agent that produces congenital defects. Although teratogenic responses are generally identified by definite anatomical defects in the offspring, authorities also regard functional or biochemical changes as evidence of teratogenicity.

An important consideration in evaluating teratogenicity data, sometimes referred to as "Karnofsky's rule," is that "any compound administered at the proper dosage, at the proper stage of development, to embryos of the proper species, will be effective in causing disturbances in embryonic development." What Karnofsky's rule calls attention to is the fact that maternally toxic doses capable of killing the fetus or producing teratogenic effects in the offspring are of much less concern than those chemicals causing the same effects at doses far below a maternally toxic level. If the pregnant female is made sick, then the delicate balance between mother and fetus is likewise affected or disrupted and an adverse fetal effect can be expected.

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Depending on the stage of the fetus, this disruptive pressure can be manifested in many ways. For example, disease, malnutrition, and stress have all been shown to produce changes in the number and quality of offspring produced. Even reversible acute effects on the mother's central nervous system, though of short duration, may disrupt feeding enough to cause undesirable responses in the unborn. Therefore, fetotoxicity is of most concern only when it occurs at doses far below those eliciting toxicity in the mother. In any study, neither death of the fetus (i.e., fetotoxicity) nor a smaller birth size are equated with birth defects (i.e., teratogenicity).

The studies concerned with the teratogenicity of PCBs in mice are contradictory. Tocruek (20) reported that PCBs are not teratogens in mice at dosages up to 500 mg/kg. However, more recent studies have revealed chemically-induced effects in the fetus or in newborns at lower doses. Watanabe and Sugahara (21) injected mice with Kanechlor 500 at dosages approximating 36 to 182 mg/kg/day on days 6 through 13 of gestation. At the higher doses, the pregnancy rate declined to one third of the control values, the number of resorbed fetuses doubled, and the rate of fetal cleft palates reached 5.8%. The authors stated that since there was no change in maternal or fetal weight gain, the PCBs used had a specific teratogenic effect not due to general maternal toxicity. However, their own results do not support this contention. At the higher dosages, the maternal mortality was higher than the rate of cleft palates among the newborn (12% vs. 6%). Also, the authors noted skin lesions, alopecia, and enlarged livers in the dams, indicating significant chemical intoxication.

Marks et al. (22) reported teratogenic effects for the specific chlorinated biphenyl compound 3,3',4,4',5,5'-hexachlorobiphenyl.

At dosages of 2 to 16 mg/kg/day given on days 6 through 15 of gestation there were significant increases in the percentage of resorptions and fetal malformations. Liver damage occurred in the dams and consisted of single-cell centrolobular necrosis and microabscesses. The fetal livers had even a more pronounced injury, including massive necrosis and the formation of tubule-like pattern of hepatocytes.

Tilson et al. (23) reported that 32 mg/kg/day of the 3,3',4,4'-tetrachlorobiphenyl, when given on days 10 through 16 of gestation, induced signs of neurotoxicity in the offspring. Some of the newborn were labeled "spinners" because of their increased motor activity and episodes of head bobbing and rotational movements. The spinners had decreased forelimb grip strength and all treated animals had difficulty in crossing wire rods. Subsequent studies (24) revealed that this exposure level of tetrachlorobiphenyl significantly altered the dopamine binding sites and the dopamine levels in the corpus striatum of newborn mice.

Contrary to Marks et al. (22), Mattsson et al. (25) reported that doses of approximately 30 mg/kg/day of 2,2',4,4',5,5'-hexachlorobiphenyl did not increase the resorption frequency, and no fetal effects were noted other than enlarged livers. Likewise, Gellert and Wilson (26) reported that no reproductive effects were seen in the offspring of mice exposed to Aroclors 1221, 1242, and 1260 at dosages of 30 mg/kg/day on days 14 through 20 of gestation.

Rats have also been extensively studied using dosages up to 100 mg/kg per day. Although these studies indicate that fetotoxicity increases with dose, no teratogenicity has been reported (18, 19, 27-29).

Malformations (teratz) have been reported in dogs and pigs in an abstract by Earl et al. (30). However, the dosages of PCBs used resulted in a severely reduced food consumption in both the dogs and pigs and the authors reported that there may have been an underlying genetic defect that contributed to the teratogenic response in dogs (39).

Several studies have been published using monkeys as test species (31-34). For six females fed 25 ppm of PCBs for two months, conception was inhibited (31). Of the six, only one was able to give birth; all female animals were clearly intoxicated and one died. A second study (32) tested 18 female animals fed diets of 2.5 or 5.0 ppm of Aroclor 1248. After seven months' exposure, the eight survivors from each dosage level were bred. All animals on the low-dose diet conceived. There were three resorptions and five births. Of those animals given the higher dose diet, one resorption, three abortions, one difficult delivery and subsequent death, and one normal birth occurred. All newborns were small in size and showed hyperpigmentation, but were otherwise normal (32).

In a number of species (e.g., mice, rabbits, rats, and monkeys), PCBs showed no or contradictory teratogenic activity. The study conducted by Earl et al. (30), still unpublished, provides unconvincing data since it is possible that the malformations observed in the offspring were the result of severe maternal malnutrition. This conclusion was substantiated by Hansen et al. (35), who failed to find teratogenic effects in pigs when the mothers were fed a diet of 20 ppm of Aroclor 1242 during gestation and nursing.

PCBs have produced contradictory results in mice. Tests conducted by Marks et al. (22) and Tilson and coworkers (23, 24) indicate that the recorded effects are seen only with symmetrically chlorinated

biphenyl compounds and that chlorination in the three and four positions is critical. This may explain why Tosruek (20) and others (25, 26) saw no or lesser effects with mixtures containing small amounts of the specific isomers or with other hexachlorobiphenyl isomers at higher doses. However, studies by Biocca et al. (36), like the negative data, greatly lessen the impact of the teratogenic findings in mice. These authors demonstrated that the 28-day LD_{50} for 3,3', 4,4',5,3'-hexachlorobiphenyl is about 19 mg/kg/day (ranging between 11 through 33 mg/kg/day). Moreover, extending the observation interval to 50 days, it was found that the dosage levels 10 times lower caused 100% mortality. Disposition studies revealed that the toxicity of the isomers was related to tissue accumulation and that for the 28-day interval the adipose tissue levels at the LD_{50} dosage were approximately 2,000 ppm. These data reveal that the teratogenic effect seen by Marks et al. (22) occur at doses greater than those that allow for chronic survival. This is consistent with the findings of Watanabe and Sugahara (21) for which the teratogenic effects of PCBs in mice appear at doses of significant maternal toxicity and lethality. In summary, then, the animal data do not indicate that PCBs represent a significant teratogenic risk at doses not causing significant maternal toxicity. Furthermore, the data suggests that preventing subchronic lethality or organ toxicity would prevent teratogenic effects. Thus, the risk to humans is expected to be minimal, considering the much lower doses that humans are generally exposed to in the environmental and the apparent lack of toxicity expected at these doses.

Studies in animals similarly demonstrate that PCBs represent a minimal reproductive and fetotoxic hazard (38, 39). While effects on reproduction or fetotoxicity have been reported, the doses causing such effects are generally high. Rats are fairly resistant, while

minks seem to be particularly sensitive. Aulerich and Ringer (30) reported that minks fed 2 ppm Aroclor 1254 in their diets had decreased reproductive success. The effect at this level was specific for Aroclor 1254 and was not seen for Aroclors 1016, 1221 or 1242. The reproductive impairment was not permanent and consistently occurred at maternally lethal doses. Orberg (37) has demonstrated an increased metabolism of progesterone, estradiol, and testosterone in animals pretreated with PCBs. It may be proposed, then, that doses that greatly increase the metabolism of important hormones could alter the normal hormone homeostasis and result in reproductive problems.

The series of studies by Allen and co-workers (31-34) have demonstrated that PCBs may disrupt menstrual cycles and significantly alter reproductive success in monkeys. However, the doses used were clearly maternally toxic, fetotoxic, and toxic to the offspring. Studies similar to these in mice indicate that the body burdens in monkeys at the time of death are quite high (41). Since (a) high, maternally toxic or lethal doses were generally required, (b) there are a number of negative studies, (c) the general human environmental exposure is very low, and (d) no reproductive problems in humans have been associated with exposures to PCBs only, PCBs do not appear to represent a significant reproductive risk to humans at the low exposure levels generally occurring via the environment (39).

Carcinogenicity

The carcinogenicity of PCBs has recently been reviewed by several authors (6, 7, 13, 38, 39). The following paragraphs provide a summary of the data. Studies reporting the tumorigenicity of PCBs are

listed in Table 3. While many investigations have been conducted, recent studies have inconsistently reported a significant increase in hepatocellular carcinoma. Ito et al. (42) reported hepatocellular carcinoma in mice after 12 months' exposure to a diet of 500 ppm of Kanechlor 500. Kimbrough and co-workers (43) also reported hepatocellular carcinoma in female rats fed 100 ppm of Aroclor 1260 for 21 months.

However, contrary to these findings, many similar studies have shown no ability of PCBs to produce cancer. Kimbrough and Linder (44) found that 300 ppm of Aroclor 1254 failed to produce hepatocellular carcinomas in mice after 11 months. Studies using less chlorinated Kanechlors were similarly unable to produce cancer (13). Likewise, Calandra (19), Lavinskas (13), and the National Cancer Institute (NCI) (45) have reported tests on both Aroclor 1254, Aroclor 1260, and HCB in rats at doses up 100 to 200 ppm; none were found to be carcinogenic. Calandra (19) has also reported a two-year study of dogs given doses of 1, 10, and 100 ppm that was negative. Studies of rhesus monkeys were also negative (39, 46).

PCB mixtures present a distinct problem when attempting to estimate the cancer hazard, and therefore the cancer risk, to humans based on data developed in rodent studies. The crux of the problem is the relevance placed on an increase in rodent liver tumors when interpreting the human risk. This dilemma is actually twofold.

First, there has been controversy over the relevance and nomenclature of rodent hepatic lesions. Some of this controversy relates to the criteria used to diagnose cancer. The NCI has recommended a scheme for the classification of hepatocellular tumors and related lesions in rats (47). This recommendation has not been universally accepted, and is used in only some of the reports of PCB carcinogenesis.

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Table 3

HYDROGENIC EFFECTS OF PCBs

Authors	Year	Species	Compound, Dosage	Effects
Kimbrough et al.	1972	Rats	Aroclors 1248, 1260, and 1254: 300 ppm/52 weeks	Hypertrophy
Nagasaki et al.	1972	Mice	Kanechlors 300, 400, and 500: 500 ppm	Hepatomas induced by Kanechlor 500 only
Allen & Abrahamson	1973	Rats	Aroclors 1248, 1254, and 1262: 0.1%/6 weeks	Hypertrophy; regressive changes
Ito et al.	1973	Mice	Kanechlor 500: 500 ppm/32 weeks	Nodular hyperplasia and well differentiated hepatocellular carcinoma in the liver; PCBs increased hepatic neoplasms in mice and increased the tumors induced by NDC
Allen & Norbert	1971	Rhesus monkeys	Aroclor 1248: 300 ppm/3 months	Hyperplasia and dysplasia of epithelial mucosa with invasion of adjacent tissues
Kimura & Hoke	1973	Rats	Kanechlor 400	Neoplastic nodules
Kurun et al.	1974	Rats	Aroclors 1242 and 1016: 100 ppm/10 months	Liver cell necrosis
Ito et al.	1974	Rats	Kanechlors 500, 400, and 300: 1000 ppm	Nodular hyperplasia
Kimbrough et al.	1974	Mice	Aroclor 1254: 300 ppm/11 months	Hepatomas; adenofibrosis
Nakiura et al.	1974	Rats	Kanechlor 500: 0.5% PCBs	Inhibited the induction of liver tumors by several liver carcinogens
Nagasaki et al.	1974	Mice	Kanechlors 500, 400, and 300: 500 ppm/32 weeks	Hepatocellular carcinoma only for Kanechlor 500
Kimbrough et al.	1975	Rats	Aroclor 1260: 100 ppm/21 months	Hepatocellular carcinoma 26/100; hyperplastic nodules 146/100; adenofibrosis

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Table 3 (Cont.)

Authors	Year	Species	Compound, Dosage	Effects
[illegible] et al.	1976	Rats	PCBs	Anti-promoters in experimental carcinogenesis
[illegible] et al.	1978	Rats	Aroclor 1254: 200 ppm/ 20 months	Hepatocellular adenomas
Levinskas	1981	Rats	Aroclors 1248, 1254, and 1260: 100 ppm/24 months	Nuclear hyperplasia; hepatomas

[illegible] reference 38.

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The NCI classification scheme is extensive and specific in defining neoplastic lesions. It was concluded by NCI that benign hepatic cell tumors (i.e., tumors without the potential for malignant behavior) could not be diagnosed consistently. Therefore, a term such as "adenoma," which refers to a benign tumor, was not recommended. It was also determined that the term "hepatoma," used to denote a benign liver tumor, was imprecise and thus was not recommended to describe any of the lesions under discussion. Contrary to tradition, then, detection of vascular invasion or metastases was not considered by NCI to be essential for the diagnosis of hepatocellular carcinoma. Instead, the use of inclusive cytological criteria describing changes that may or may not have the potential to become the disease process we call cancer, including many responses that will never progress to cancer, was accepted at the expense of the more definitive criteria of malignant or invasive neoplasms. Thus, it seems that the criteria for establishing liver cancer may vary among pathologists.

Only PCBs with a chlorine content of 60% produced cellular morphological changes in rat liver that were classified as hepatocellular carcinoma using NCI guidelines. However, this same PCB mixture was tested in another strain of rat and did not significantly increase the incidence of tumor formation. Several other studies also failed to show any PCB-induced tumors, including a study performed by NCI. Since there is only one report of PCB-induced hepatocellular carcinoma in rats, we must weigh this single report against the majority of tests, which were negative.

As previously stated, the use of inclusive cytological criteria will define as cancer some hepatocellular changes that will never progress to cancer. Furthermore, the liver changes associated with

PCB exposure were reported to regress after the animal has been removed from the chemical exposure (48). While some investigators have used the inclusive cytological criteria for classifying hepatocellular lesions, other investigators feel this classification scheme lacks sufficient diagnostic discrimination. Thus, the single report of PCB-induced cancer in rats may use a pathological description that differs from the terminology used for describing the benign tumors seen in the other studies.

The second problem stems from the need to determine the mechanism by which a chemical induces cancer. Chemically-induced carcinogenesis is a special aspect of toxicology, since chemical carcinogens may or may not obey traditional toxicologic principles. For example, although carcinogens show dose-response relationships, may undergo biotransformation to active or inactive metabolites, and demonstrate specific structure activity relationships as other toxicants do, they may also be unlike other toxicants: they may not demonstrate thresholds and there may exist a long and indefinite latency period between the critical biochemical effect and any cellular or physiologic expression.

In recent years, the scientific community has concluded that even among chemical carcinogens there are vast differences in the mechanisms by which cancer is induced. Chemical carcinogens can be separated into two groups: one which obeys traditional toxicologic principles and one which does not. Weisburger and Williams, in Casarett and Doulls' Toxicology: The Basic Science of Poisons (1), separate carcinogens as either genotoxic (initiator) or epigenetic (promoter), the distinction being that genotoxic carcinogens induce cancer by initiating a permanent change in DNA. Epigenetic chemicals comprise

those chemicals which alter the manifestation of cancer by other than genetic means and include hormones, immunosuppressants, cocarcinogens, and promoters.

This distinction between types of carcinogens is extremely important (1, 49, 50), since initiating (genotoxic) carcinogens may cause irreversible damage and may not have thresholds. The concept was generally proposed for all carcinogens early in the last decade and was the basis for developing certain nonthreshold risk assessment models for which some risk is present at any level of exposure. On the other hand, chemical carcinogens that promote cells already predisposed to cancer do have demonstrable threshold levels. Therefore, the risk associated with promoters differs from initiators at low doses in that the risk exists only for the duration that the level of the promoter exceeds the threshold.

Rodents used in cancer tests have a high spontaneous incidence for liver tumors. Therefore, if a statistically significant increase is seen after chemical exposure, it is important to determine whether or not this phenomenon represents true initiation or merely promotion of the background incidence. Such is the problem for PCBs. To make the distinction between initiators and promoters, the mutagenicity data and other characteristics of the chemical or the carcinogenic response become critically determinant factors.

Initiators are defined as those agents producing damage to DNA which permit cell survival but predispose the cell for uncontrolled growth. Therefore, initiators must possess significant mutagenic activity. There are several other characteristics seperating initiating carcinogens and promoting agents; these are listed in Table 4. The characteristics of PCBs are also listed in Table 4. It can be

Table 4

CHARACTERISTIC EFFECTS OF CHEMICAL CARCINOGENS UPON TISSUE

Effect	Initiators	Promoters	PCSs
Chemical produces increases of spontaneous tumors at multiple sites.	+	-	-
Chemical increases malignancy.	+	-	-
Chemical produces a tumor capable of transplantation.	+	±	-
Chemical produces a tumor which does not regress once chemical is removed.	+	±	-
Chemical must be mutagenic.	+	-	-
Chemical is effective at nontoxic doses.	+	-	-
Chemical may cause the effect after a single dose.	±	-	-
Chemical should increase the effect of other carcinogens acting on the target organ.	+	±	±
Progression of neoplastic differentiation does not require the continued presence of the chemical.	+	-	-

+ = generally
± = sometimes
- = seldom or never

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seen that the characteristics of PCBs resemble those of a promoting agent and not those of an initiator. In his review of the mutagenic and carcinogenic potencial of PCBs, Lavinskas (13) likewise cites several authors and experiments supporting the contention that PCBs have promoting activity, including the NCI bioassay (45).

In summary, when assessing the carcinogenic hazard of PCBs, one must decide what weight to give each portion of the data. While one cannot ignore the fact that positive carcinogenic activity has been reported in rodents, one must take into consideration the weakness of this response since it was not reproduced in several subsequent studies. Furthermore, there is a great deal of evidence to suggest that if PCBs induce changes, it is by way of a promotion mechanism. Thus, on the basis of the animal data and considering the inconsistency of the response, PCBs, as weak promoting agents, at low doses would represent a relatively small cancer hazard in man.

Recognizing the problems associated with accurately interpreting the relevance of and risk inferred by animal carcinogenesis bioassays, Robert Squire, former acting director of the Carcinogenesis Testing Program and head of NCI's Tumor Pathology Section, has proposed a ranking scheme for the animal evidence (49). Squire proposes that the basis for determining the strength of a positive test residue is whether the "suspect carcinogen": is positive in a number of species, gives rise to histogenetically different types of neoplasms in one or more species, induces malignant rather than benign tumors, and is consistently positive in an appropriate battery of tests measuring genotoxicity. The dose required to induce tumors as well as the spontaneous incidence of neoplasms in the control animals are also criteria.

By ranking the test data for each criteria according to a point system developed by Squire, one gets an overall score to assess the strength of the evidence. Squire's approach is appealing because it recognizes several features of an animal bioassay that should be considered when attempting to estimate the likelihood that the human response is similar. Since there are several cancer tests in animals for PCBs, the aggregate score that PCBs would receive depends on the weight assigned to the positive and negative data. However, the total score for PCBs, regardless of the scoring, would probably be about 31 or less. Squire classifies a chemical receiving a score of less than 41 as a class V carcinogen, a class for which he suggests that the regulatory options are many and far less restrictive than for chemicals scoring higher in the ranking scheme. Thus, according to this scheme, even the "positive" evidence for PCBs does not rank them as a human cancer hazard that is as significant as many other chemicals, some of which are still commonly used.

EPIDEMIOLOGY

Acute and Chronic Human Data

In recent studies of occupational exposure, PCBs have not been proven to be a remarkably toxic chemical to persons in the work place, who have probably received the most significant exposure to PCBs. Ouw and co-workers (31) studied 34 workers from a single capacitor plant using Aroclor 1242. Of this group, 31 were exposed for more than one year and 14 for five years or more. Although industrial hygiene at the plant had been generally poor prior to their study (e.g., air

concentrations were 150% to 222% of the allowable workroom air standard of 1.0 mg/m^3), the clinical tests did not identify any significant health problems. One case of chloracne was reported as well as five cases of an eczematous rash. Even though the average PCB blood levels of the group were over 400 ppb compared to none detected in the control study group, the clinical tests measuring liver function revealed that bilirubin, alkaline phosphatase, serum protein, albumin, SGPT, and immunoglobulins for the group of factory workers were within the normal limits for each test. In addition, bromosulphalein clearance did not correlate well with either PCB blood levels or length of employment.

A more recent study of a far larger group of employees from a capacitor plant reported a similar lack of untoward findings (52). Based on this study of 326 employees, it was possible to separate the employment records into the following categories for years of exposure: 10% had been exposed for 5 years or less; 20.9% 5 to 10 years; 17.3% 10 to 15 years; 11.4% 15 to 20 years; 29.1% 20 to 25 years; and 11% had been exposed for more than 25 years. A summary of the skin complaints revealed that 10.7% of the employees reported rashes and 24.8% reported a burning sensation of the skin. Physical examination further revealed some redness, swelling, dryness, or thickening of the skin in approximately 30% of the individuals, while 2% experienced abnormal secretions from the eyes.

The clinical chemistry of the study was generally unremarkable, and the researchers commented on the "paucity of abnormal results." Of 321 persons examined, the percentage of samples outside of the normal range were: BUN 5.3%; creatinine 1.7%; SGOT 2.2%; SGPT 7.2%; LDH 3.5%; alkaline phosphatase 1.2%; SGGT 1.9%; bilirubin 0.0%;

cholesterol 17.8%; triglycerides 10.3%; and total lipids 1.4%. These data can be considered indicative of the type of random test results to be expected when 321 persons are tested without simultaneously running a control group to compare against the standardized "normal" values used to indicate an abnormal finding. Likewise, the neurologic examinations failed to produce any prevalence of abnormal findings. There was a decrease in the forced vital capacity of the lungs in 14% of these workers compared to only 5.6% in the normal population (53). While this is an unusual finding, this change was not seen in one group, i.e., the non-smoking women tested. The significance of this finding is unknown at this time and requires verification from other studies.

Maroni et al. (54, 55) have reported an Italian study of employees in a capacitor plant exposed to a foreign PCB mixture similar to Aroclor 1242. The mean age and employment of the 80 employees examined was 37±8 and 12±6 years, respectively. PCB air concentrations ranged from .048 to .275 mg/m^3, and all tested surfaces were heavily contaminated, indicating that employee exposures were both dermal and inhalation. The results showed that PCB blood concentrations ranged from 88 to 1319 ppb. Fourteen workers were found to have skin disorders consisting of dermatitis, folliculitis, or chloracne. Sixteen employees were reported to have abnormal liver effects, consisting of hepatomegaly and sometimes an increase in serum level of liver enzymes. The liver findings did not correlate well with either the duration of employment or the PCB blood levels, and the pattern for hepatic enzyme changes was a random finding inconsistent with hepatotoxic chemicals. It is evident from these data that the clinical changes were unremarkable. Furthermore, control subjects were not

least three months in areas of PCB exposure. The vital status of 98% of the population was determined and 39,018 person years were accumulated. The types of PCBs used were Aroclor 1016, 1242, and 1254.

The major causes of death for the 163 persons who had died by the time of the report are separately listed in Table 5. The only statistically significant difference observed was for cancer of the rectum, but only if the female population of plant #2 was considered alone. However, the plants studied are located in an area where mortality from rectal cancer is greater than the United States average (56). As mentioned, this unusual increase stemmed from a high number of deaths in the female population of plant 2; similar findings were not reflected in the female population of plant 1 nor in the male population of either plant. While the liver cancer incidence was higher than expected, it was not significant. There was no relationship between duration of employment involving PCB exposure and the risk of mortality due to cancer or cirhosis of the liver. There was no statistically significant relationship for any cause of death when the total exposed population was considered.

Bertazzi et al. (70) studied 27 deaths in 1310 workers exposed to PCBs for 20,365 person years. Mortality was studied for the 25-year period between 1954 and 1978 for employment between 1946 and 1970. The study group had been employed for at least six months and the exposure was largely to Aroclor 1254. For all cancers, the observed mortality was 14 versus 5.65 expected. This increase, however, was significant only for the male population. Higher than expected incidences in cancer of the digestive organs and in cancer of the lymphatic or hematopoietic systems were also observed, although these were not significant. There were no reports of liver cancer.

Table 5

MAJOR CAUSES OF DEATH FOR PLANT WORKERS EXPOSED TO PCBs: AROCLOR 1016, 1242, AND 1254

Cause of Death	Observed/Expected	Standard Mortality Rate
	All Causes	
All malignant neoplasms	39/43.79	(89)
Diseases of nervous system	11/12.55	(88)
Diseases of circulatory system	60/62.93	(95)
Accidents	13/18.29	(71)
All other causes	40/44.79	(88)
All causes	163/182.35	(89)
	Malignant Neoplasms	
Cancer of stomach	1/1.66	(60)
Intestine	4/4.03	(99)
Rectum	4/1.19	(336)
Liver	3/1.07	(280)
Pancreas	1/1.90	(53)
Respiratory	7/7.98	(88)
Breast	7/6.84	(102)
Lymphatic	2/4.34	(46)
Other	10/14.78	(68)

Source: Reference 67.

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included to determine the normal test variations among unexposed persons of similar ages. Serum bilirubin and alkaline phosphatase levels were within the normal range of variation for all subjects.

Some of the conclusions reached in two recent reviews of the various studies of PCB exposures to date (56, 57) are noteworthy. First, while higher exposures to PCBs tend to cause a higher body burden, there was a general lack of correlation between exposure duration and body burden. Second, although not all studies agree, there was also a suggestion that the higher chlorinated PCBs were more likely to accumulate in adipose tissue, suggesting a slower metabolism rate. Third, the general health of the occupationally exposed group was considered good.

While two of the studies reviewed failed to report clinical findings (other than stating that the workers were in good health), one measured PCB blood levels of up to 1900 ppb in Finnish workers. Of 15 studies reporting clinical measurements, 11 reported dermatologic effects, 9 reported liver function tests, 6 reported lipid measurements, and 5 reported on blood chemistry. Gaffey concluded that while there is no clear correlation between PCB blood levels and chloracne, the studies suggest that when PCB blood levels exceed 150 to 200 ppb, chloracne can occur (56). He also concluded that dermatitis, like chloracne, was a frequently observed effect, and that it may be associated with the higher chlorinated PCB compounds (56).

Of the nine reported studies of liver function, only five found some mild change in liver function tests. No consistent pattern was identified, nor was an association between these changes and PCB blood levels identified. No adverse health effect was associated with PCB exposure in any of the studies. Of the six studies that considered

lipid metabolism, no consistent pattern associates with PCB exposure; one study, by reporting a decrease in all parameters, contradicted all of the studies reporting an increase. Most studies did associate increased triglycerides with the PCB exposure, but the results for cholesterol were inconsistent. No clinical significance has been attached to these findings. Of the five studies of blood chemistry, none reported any relationship between the tests and PCB blood levels. Of the two studies that measured blood pressure, one found no association, while one reported an association between PCB levels and diastolic blood pressure (56).

In summary, a review of the human data from studies of persons occupationally exposed or whose PCB levels were increased via fish consumption reveals that the combined results of all studies, while demonstrating PCBs caused dermal problems, failed to identify any significant clinical disease associated with electrical grade PCBs. While some physiologic changes were noted, no clinical significance could be attached to any of these, particularly the changes in liver function, which were minimal and generally not compared to an appropriate control group. It has also been noted that PCBs can induce oxidative metabolism in persons occupationally exposed to them (58). Animal studies suggest that inducing agents can increase serum transaminase levels, e.g., SGOT (59, 60) and triglycerides (60). Thus, the random, minimal increases in serum transaminase levels and increased triglycerides found in persons occupationally exposed to PCBs may represent the predictable phenomena of modest enzyme induction. The National Institute of Occupational Safety and Health (NIOSH) study (37) likewise indicates that chronic liver, nervous, or circulatory diseases are not associated with long-term exposure to levels of PCBs

which were much higher than those encountered in the environment. Therefore, if the environmental exposure to PCBs is insufficient to induce chloracne (the most frequently observed effect), acute, subchronic, or chronic toxicity is probably not to be expected in humans.

Yusho

In 1968 a mass outbreak of chloracne and other symptoms, later termed "Yusho," was caused by the ingestion of cooking oil contaminated by PCBs and other chlorinated compounds. Higuchi (61) and Kuratsune (62) reported that approximately half of the patients complained of a variety of neurologic distresses such as headaches, numbness, hypothesia, and neuralgia. Most of the headaches were transient, but some recurred over a period of months to years. Higuchi (61) concluded that the majority of these headaches probably arose from emotional stress or migraine conditions, and were not related to PCB exposure. Measurements of nerve conduction velocities in Yusho patients revealed, however, that up to 50% of the 20 patients studied had lower than normal sensory nerve conduction velocities, though their motor nerve conduction velocities were normal (61). Female patients, 60%, suffered abnormal menstrual cycles, though the effects varied. Some women suffered prolonged intervals of menstruation, while others had shortened or irregular intervals. Determinations of urinary estrogens revealed a decrease. A possible explanation for this could be an increased degradation of estrogens due to increased liver metabolism (61).

Hematologic examinations of Yusho patients revealed a slight leukocytosis and monocytosis, and serum levels of IgA and IgM were

generally decreased. Surprisingly, serum indicators of liver damage such as GOT, GPT, and bilirubin were normal. Thus, although PCBs can cause liver injury in experimental animals, as many halogenated hydrocarbons do, the clinical evidence of Yusho indicates that this is not a prominent toxicity in humans (61, 62). Microscopic changes were observed in liver biopsy samples. The major finding, an increase in the smooth endoplasmic reticulum, is interpreted as representive of the induction of the hepatic enzymes for oxidative metabolism, a finding predicted from animal studies and not an indication of toxicity. Analysis of other serum parameters also suggested a disruption of normal lipid metabolism. Serum triglycerides were elevated, while cholesterol was not.

Of 43 affected children examined, 23 boys showed transitory decreases in height and weight gain when compared to unaffected children, while 19 girls did not differ from the control group. Also, some of the infants born to women affected by Yusho were small-for-date. Other symptoms in newborns included dark-brown pigmentation, parchment-like skin, eruption of teeth, and larger than usual fontanelles, indicating transplacental passage of PCBs to the fetus during gestation.

Probably the most common symptoms and the ones largely responsible for the identification of Yusho's disease were eye and skin problems. These consisted of acne-like eruptions, follicular accentuation, swelling of the eyelids with discharge from the eyes, and increased pigmentation of the skin. Unfortunately, even though the chloracne was not a permanent condition, it was a discomforting disfigurement that lasted for a period of months to years.

Urabe et al. (63) have reported on the cause of the deaths of 31 of the 51 persons who died during the first decade after the Yusho incident. Eleven deaths resulted from various neoplasms; a 35.4% cancer rate, which is higher than the 21.1% rate generally reported for that area of Japan. No conclusion can be drawn from this at present, since the Yusho rate was not age-adjusted and further analysis of the Yusho disease must be done at a later date. Of the reported cancers, the types of neoplasms varied. The numbers of cancer for each tissue were: two stomach, one stomach and liver, two liver, three lung, one breast, and two malignant lymphoma.

While the above effects described in Yusho patients give some idea of the possible consequences of overexposure to PCBs, the exact cause of these symptoms is debatable. The type of PCB mixture contaminating the rice oil, Kanechlor 400, has been discovered to contain polychlorinated dibenzofurans (PCDFs) at concentrations as high as 18 ppm (61, 64). Measurements of the rice oil used by Yusho patients revealed that it contained PCBs ranging from 1 to 3000 ppm, 5 ppm of PCDFs, and approximately 1000 ppm of polychlorinated quaterphenyls (PCQs) (62, 65, 66). Therefore, it is not known which of the Yusho side effects can be attributed solely to PCBs (66, 67) and, if cancer is found in the future to have been significantly increased in this group, the source of cancer induction will remain unknown. (Note: The PCDFs found in the Yusho PCBs are about 1000 times higher than those usually measured in American sources of PCBs). Recently, Kuratsune (66) reviewed the Yusho episode and suggested that the levels of PCBs and contaminants were actually about half of the amount previously reported. He also suggested that since a considerable number of victims did not recover from their symptoms after their levels of

PCBs had dropped to near normal levels, the high levels of contaminants still present in the victims may be the more likely causal factors of the Yusho problem (56).

Mortality Studies

Reports of high cancer rates among Mobil Oil employees exposed to PCBs (Aroclor 1254) at Mobil's Paulsboro, New Jersey, refinery have been interpreted as indicative of a possible link between PCB exposure and skin (melanoma) or pancreatic cancer (68). The preliminary Mobil study reported eight cancers which developed between 1937 and 1975 among 92 research and development and refinery workers exposed to varying levels of Aroclor 1254 for five or six years in the late 1940s and early 1950s. Of the eight cancers, three were malignant melanomas and two were cancers of the pancreas. According to NIOSH, "This is significantly more skin cancer (melanoma) and pancreatic cancer than would be expected in a population of this size, based on the Third National Cancer Survey." However, it is difficult to draw any conclusions from this study because of the small numbers of individuals exposed and the variety of other chemicals to which they were exposed. In any case, the study was withdrawn for revision and has not yet been re-released (56).

Of the studies reporting the effects of PCBs on the chronic illnesses or the mortality incidence in humans, only two provide large populations of apparently single chemical exposure. Brown and Jones (69) conducted a retrospective cohort mortality study of 2567 employees from two plants where PCBs were used to manufacture electrical capacitors. All workers included in the study were employed for at

In assessing the epidemiologic evidence for carcinogenicity, it must be remembered that in any epidemiologic study it may be impossible to eliminate all of the unrelated but confounding variables in the observed populations. Moreover, it is not uncommon to see measurable increases in one type of cancer over what is mathematically expected, since we cannot choose a subpopulation that reflects exactly the baseline cancer rates of the total population. In fact, it is well known that different areas of the United States have different backgrounds for many of the specific types of cancer. All this must be considered carefully, and no conclusions should be made concerning any finding of excess cancer which is not statistically significant, but only above expected values, unless this same excess for that specific type of cancer is repeatedly demonstrated in subsequent studies.

A positive correlation between exposure to a chemical and a resultant adverse health effect relies on the following conditions (69):

- A positive association must be seen in individuals with known exposures;
- The positive association cannot be explained by bias in recording, detection, or experimental design;
- The positive association must be statistically significant;
- The positive association should show both dose and exposure period dependency; and

The positive association must be observed repeatedly in subsequent studies and cannot be a single, confounding, variable observation.

To date, the mortality studies concerned with PCB exposures present several problems of interpretation, the most obvious and important of which is the different increases in cancer type reported. Taken as a whole, these studies provide no support for assertions that PCBs are a cancer-causing chemical. The variety of tumor sites found to be of most concern within each study largely differs from the animal data and is inconsistent with the selectivity of currently known promoting agents or initiating carcinogens.

In summary, epidemiologic studies have demonstrated that commercial PCBs are not remarkably toxic chemicals after acute exposure and that, when excess exposure does occur, the usual consequences are dermatologic and not of a serious or permanent nature. Data from investigations involving chronic exposures yield similar conclusions. The majority of studies has not identified a clinical disease associated with PCB exposure, nor has it provided persuasive evidence of health impairment. There is no persuasive evidence of an excess in total mortality or in mortality due to cancer, cardiovascular disease, or nervous system disease associated with occupational exposure to PCBs. PCBs have not been linked to any human cancer. Future investigations of occupationally exposed populations will no doubt further clarify this issue as the total mortality within the test group increases with time and yields a larger mortality data base.

PROCEDURES FOR ASSESSING RISK

In attempting to extrapolate the human risk from chemical exposure using animal toxicity as the basis for the risk extrapolation, there are several models to choose from. The model chosen is primarily determined by the type of health hazard of most concern. However, speaking in general terms, there are only two types used. The first type consists of those methods used for extrapolating the human risk directly from the dose for which there was no observable animal toxicity. This method can be applied to most toxicities (except cancer), since thresholds are assumed for these responses. The second type of model is generally used to assess the risk associated with carcinogens. Since many scientists assume no identifiable threshold for this toxicity, there is some risk attached to any exposure. This concept dictates that mathematical models be used to extrapolate to exposures far below those dosages inducing observable responses in the test animal population.

For noncancer toxicities (i.e., threshold toxicities), the models for extrapolating risk are relatively simple and similar to the Suggested No Adverse Response Level (SNARL) proposed by the National Research Council of the National Academy of Science (72), or the Lowest Observable Effect Limit (LOEL) used by the United States Environmental Protection Agency (EPA) (7). Basically, this type of calculation is computed by assuming that humans are as sensitive as the test species used. Therefore, the amount ingested by the test animal that gives no toxic response is the safe upper limit of exposure for humans, i.e., the human threshold dose.

The calculation essentially makes the conversion on the basis of the size differential between humans and the test species, usually a body weight comparison rather than surface area. It should also take into consideration those factors that affect a truly comparative dose, e.g., absorption factors if the human exposure differs from the test conditions or if the animal dosage regimen differs from the human exposure interval. The calculation is similar to the following:

$$\text{Safe Human Dose} = \frac{\text{TDo.e(mg/ kg)} \times 70\text{(kg)} \times F \times \text{E.R.} \times t1/2}{\text{S.F.}} = \text{mg/day}$$

TDo.e = threshold, or no observable effect dose in the test species;

F = absorption factor, or ratio of animal absorption divided by the human absorption (absorption animal/ absorption human);

E.R. = exposure ratio (dosage regimen animal/exposure regimen human);

t1/2 = ratio of elimination (half-life in animal/ half-life in humans); and

S.F. = safety factor, which depends on the reliability of the data used for extrapolation.

Typically, the safety factor used varies from 10 to 1000, depending on the extent of animal data available and whether or not there is any human data to substantiate the reliability of the number. Of course, the number calculated should use chronic data where chronic exposures are expected. This type of model calculates one value. Exposure at or below this value is considered safe.

The second type of calculation also has several methods or models from which to choose. However, all differ in their basic assumptions or in the mathematical expression used. Hence, at the low exposures in question, their estimation of risk can vary dramatically (38). Regulatory agencies currently use the multistage model proposed by Crump (7, 73). Using this model, the risk is linearly proportional to the exposure at low doses. While each exposure is considered to carry some risk, the acceptable risk or safe dose is usually suggested as the exposure range for a 10^{-5} to 10^{-7} risk. This means that daily exposure to that dose would increase cancer by 1 person in 100,000 exposed (i.e., 10^{-5}) or 1 in 10,000,000 persons (10^{-7}) with a lifetime exposure.

Risk to PCBs

As stated earlier in this chapter, the determinant factor for assessing the risks associated with chemical exposure is usually the toxicity (acute or chronic) of most concern that can be expected to occur in humans. With PCBs, as for any chemical, determining the toxicity of most concern is extremely important to setting safe exposure limits. Likewise, determining the toxicity of most concern also

determines the public's perception of the harm of overexposure to PCBs, which in turn affects risk assessment. As demonstrated by the types of analysis used, the difference of whether or not a chemical is carcinogenic can translate into magnitudes of differences in the calculated dose considered to be safe.

PCBs are a good example of this dilemma. As seen in the EPA's ambient water quality criteria for PCBs (7), the safe dose calculated if PCBs are not considered to be carcinogenic is 210 ug/day; if PCBs are considered to be carcinogenic, the 10^{-5} risk dosage is approximated at 140 ng/day. This is greater than a 1000-fold difference in the "safe" exposure based on the chemical's carcinogenic potential. Thus, determining the carcinogenic potential of PCBs accurately has a large impact on its perceived risk.

Even though many arguments may be made regarding the carcinogenic potential of PCBs, the answer to the question regarding which level may be safe can be found by a simpler, more direct method. While the preceding extrapolations might provide useful guidelines for safe exposures when only animal data are available, they can be and should be tempered by the human experience whenever possible. While human data may not prove that the extrapolations from animal data are correct, they can be utilized in some instances to determine if those extrapolations are incorrect. Such is the case for PCBs.

The model predicting the cancer risk from PCBs based on the data from the Kimbrough et al. study (7) is linear in the dosage range calculated for acceptable risks. Therefore, linear extrapolation to that dose approximating a 100% cancer incidence in humans using the slope for the curve in that portion of the dose response for low risks provides an overestimation of the actual dose required for a high

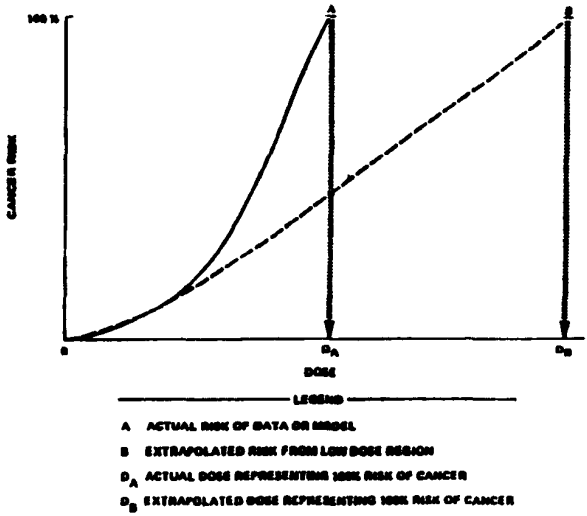

Figure 1 EXTRAPOLATION FROM LOW CANCER RISK EXPOSURE TO HIGH CANCER RISK EXPOSURE

incidence of cancer (see Figure 1). Performing this extrapolation for PCBs (i.e., 10^{-5} risk is 160 ng/day, so a risk of 1 is 10^5 x 160 ng/day equals 16 mg/day), we should expect a cancer incidence of 10:2 in the exposed population at about a 16 mg/day-exposure of PCBs if the low exposure perception of the risk is correct.

However, the Occupational Safety and Health Administration (OSHA) limit for occupational exposure to PCBs was 0.5 mg/m^3 for Aroclor 1254 and 1.0 mg/m^3 for Aroclor 1242 and other, lower chlorinated biphenyls until PCBs were banned. Assuming that the average volume of air inhaled per workday is approximately 10 m^3, then the allowable workday intake of PCBs could approximate 5 to 10 mg. Granted that perhaps not every worker was exposed daily to these levels, reports such as Ouw et al. (51) or Brown and Jones (69) illustrate that in several instances exposures were higher; therefore, we can assume that the daily exposure approximates of our assumption are a practical consideration. Also, the slope of the extrapolated line would be such that the cancer risk above 1 mg/day of PCB exposure would be easily observable. Since the largest study, by Brown and Jones (69), did not find any statistically increased liver cancer, and could not demonstrate any cancer risk, one must conclude that the cancer risk extrapolated from the animal data for low dose exposure is wrong and by at least two to three orders of magnitude or greater.

By comparing the risk calculated using animal data to that found in 2367 capacitor workers (69), we might conclude that one of three possibilities or a combination of all three exists to explain this error in our calculations: (a) the model is wrong, (b) the animal species used does not represent man, or (c) PCBs are not carcinogenic

in humans. The first possible explanation may contribute to the problem, but is least likely to be the causal factor for, if reasons 2 and 3 were false, then the occupational cancer would have been measurable. Therefore, one can conclude that either 2 or 3 is the more likely reason for the discrepancy. Regardless of the cause for the discrepancy, it can be demonstrated that, at the very least, the results of the animal tests of Kimbrough et al. (43) do not appear to represent an animal model relevant for assessing the cancer risk in humans using the extrapolation posed by Crump (38). Interestingly, if the data suggesting that PCBs are promoting agents are ignored and if the above model is adopted for the human data (the comparison in Figure 1 demonstrates how the model is excessive by several orders of magnitude at least), we reach an approximate 10^{-5} risk of cancer that is equivalent to the LOEL calculated by the EPA of 210 ug/day.

It might also be noted that this same test of the 10^{-5} risk based upon animal data for DDT and chlordane shows a large overestimation of the risk for these chemicals as well. Thus, this type of extrapolation seems to be inappropriate for other chlorinated, persistent chemicals which enhance or produce liver tumorigenesis in rodents.

ESTIMATION OF THE HEALTH RISKS ASSOCIATED WITH ENVIRONMENTAL EXPOSURES

Early in this paper it was stated that a thorough evaluation of the hazards associated with PCB exposures must consider and weigh six different characteristics of the data.

The first two factors deal with the breadth and variety of toxic responses produced and the degree of species variation associated with the effects monitored. Many of the PCB-induced adverse effects are

characteristic of a chlorinated organic compound of the PCB type, or at least these effects are consistently produced by many chlorinated organics. These effects include liver injury, liver enlargement, liver enzyme induction, irritation when applied to the skin, chloracne, and (possibly) a disruption of the estrogenic balance in females due to increased liver metabolism. Although these may indeed be considered adverse effects, all chemicals are capable of altering some physiologic function at a high enough dose. In the more relevant reproductive mutagenic, teratogenic, and carcinogenic tests, tests of chlorinated biphenyls were consistently negative, with only a few exceptions. Some of the exceptions can be discounted because of inadequate study design, disputable interpretations, or use of unusual test methodology. It is unnecessary to display a disproportionately high concern for those few positive studies when their findings cannot be reproduced in a number of subsequent studies conducted under similar or identical conditions.

Third, regarding mechanisms, sufficient evidence exists to indicate that PCBs have the potential to promote cancer rather than initiate tumors. Similarly, the metabolism and elimination of PCBs in primates is far lower than that of rodents, suggesting that man is far less likely to generate toxic metabolites than rodents, i.e., man is probably less susceptible to liver injury and any impact this may have on tumorigenesis.

The fourth factor regards the relevance of the performed test. For the most part, this was not a factor when considering the results of most tests. There are, however, some problems in attaching the

same significance to all of the mutagenicity tests. The human relevance of single-stranded breaks in DNA at high in vitro PCB concentrations or the applicability of the chromosomal tests in birds is questionable when compared to the more often used and better established tests for mutagenic or clastogenic activity in mammalian and bacterial test systems. Thus, we have concluded that the mutagenic, and therefore initiating, activity of PCBs in humans is minimal, i.e., it is not a significant hazard to humans considering the overwhelmingly negative test responses and the lower human rate of PCB metabolism. The relevance of extrapolating one positive carcinogenesis bioassay without balancing it against numerous negative ones also seems inappropriate considering the likelihood that PCBs are promoters; that the organ response (i.e., liver cancer) has a high background incidence in rodents (74) and is susceptible to promotion by such effects as induction (75, 76) and recurrent liver injury (77-79) (two known effects of PCBs); the strain preference of the positive effect; and the irreproducibility of this effect. Considering the promoting pressures that high, chronic doses of PCBs could exert, it is probably more unusual to find the majority of responses in the rat negative.

The fifth factor deals with the dosages required to produce animal toxicities as compared to the expected human exposure. In animals, PCBs are acutely toxic only at high doses. Similarly, their chronic effects generally occur at relatively high doses or high body burdens. Thus, taking into consideration the expected low environmental exposures to humans, PCBs do not appear to pose a significant risk. If skin disorders are not induced (highly unlikely), other effects seem unrealistic.

The last factor deals with risks determined by human exposures. The epidemiologic studies have demonstrated that PCBs are not remarkably toxic chemicals after acute exposure and that, when excess exposure does occur, the usual consequences are dermatologic and not of a permanent nature. In spite of over 50 years of use, PCB chronic exposures have added little or no additional adverse effects of note to this picture. The majority of studies has not identified a clinical disease associated with PCB exposure other than chloracne, nor has it provided persuasive evidence of an unusual health impairment. There is no evidence of an excess in total mortality or in mortality due to cancer, cardiovascular disease, or nervous system disease that can be associated with occupational exposure to PCBs. PCBs have not been linked to any human cancer. Therefore, it appears that PCBs are not a remarkable toxicant, but chemicals that require high doses to produce harmful effects.

In evaluating the risk associated with the environmental exposure to PCBs, we should answer two questions. First, is the level of exposure of a sufficient magnitude to constitute a hazard? Second, if so, what is the expected hazard? Jelinek and Cornelissen (80) estimated that the daily PCB intake for a young male adult dropped from approximately 13 ug/day in 1971 to 8.7 ug/day in 1975. This estimate was based on the assumption that most of the intake would come from existing PCB-contaminated fish (an unlikely consideration for most U.S. citizens). The estimate would not be accurate for people who were not eating such fish, or were eating larger amounts of fish, or for those who were exposed to waste sites, contaminated water, or other unusual sources.

MacLeod (31) more recently reported that indoor air pollution with PCBs is greater than outdoor air pollution, and often ranges from 0.1 ug/m^3 to 0.2 ug/m^3 of air for many of the locations tested. This approximates to a 1.0 to 2.0 ug/day exposure to PCBs from many indoor air sources. This exposure also approximates the currently suggested NIOSH exposure level for industry (32). Thus, it appears that persons within the United States are, in general, environmentally exposed to microgram amounts of PCBs per day in what are probably the higher exposure instances (excluding unusual conditions). This exposure is approximately 1000 times lower than former occupational exposures, which, according to recent evidence, produced no identifiable problems other than chloracne. It would seem that a 1000-fold reduction in exposure would be a sufficient margin of safety for any weak threshold effects that were identified, e.g., skin disorders and induction of liver enzymes. While the NIOSH level is lower than the OSHA standard, it would seem that the old limit reasonably protected the occupationally exposed persons. This bodes well for the rest of us considering our far lower expected exposure from the environment. Furthermore, calculations reveal that PCB exposures of micrograms per day are not likely to significantly alter a person's steady-state tissue concentrations. For example, the average 70-kg man is made up of 15% or greater body fat. In other words, he has at least 10.5 kg of fat in which to store PCBs. Since non-occupationally exposed persons contain 2 ppm or less of PCBs in their body fat, at 2 ppm the average man would contain 21,000 ug or less of PCBs. If one assumed a worst-case estimate without considering metabolism, excretion, other tissues etc., it would take 28.8 years at a daily exposure of 2 ug/day to double his fat levels of PCBs. At 10 ug/day, it would take 5.8 years; at 50 ug/day, it would take 1.2 years; and at 100 ug/day, it would

take 0.5 years. Since the half-life of PCBs is probably no longer than a month or two, the actual time to double the body burden is much longer than the above calculations and would never be reached for the lower exposures. Thus, the exposure to PCBs faced by the general population, estimated at about 3 ug/day or less for those exposed, is not likely to have much of an impact upon the low body levels of contamination that have been measured in nonoccupationally exposed persons. Since these levels are far lower than the tissue concentrations experienced by capacitor workers, it is unlikely that any untoward consequences can be expected in the general population. The calculations also demonstrate that occasional exposures to much higher levels are not likely to increase a person's adipose levels above the 1 to 2 ppm commonly measured.

From the above discussion, it can be seen that the current daily environmental exposure most likely encountered from the environment is not of a sufficient magnitude to constitute an additional hazard because it is not likely to significantly alter our current body burdens. The animal data has identified certain hazards, but the negative data suggest that these hazards are not consistent or potent responses in every species. While we might speculate that very large doses of PCBs may cause various detrimental effects, the highest exposure group, capacitor workers, appears to have been exposured at levels below those that would cause serious adverse effects in humans. Thus, the current environmental exposures to PCBs, which are much lower than previous occupational exposures, do not appear to be associated with an identifiable hazard, and so the human risk seems to be minimal or insignificant. In order that this paper is not misinterpreted, it is emphasized that this conclusion does not apply to concentrated wastes or chemical waste sites where the exposure may be

higher or of a different composite nature. It is also emphasized that higher than microgram-per-day exposures to "pure" PCBs do not necessarily carry an added risk. The Federal Drug Administration (FDA) guidelines of 1 ug/kg/day, or a single exposure of 100 ug of PCBs, is still far below the previous OSHA regulation or even the EPA's conservative estimate of the LOEL. Until definitive evidence clearly demonstrates a chronic toxicity in capacitor workers or other exposed persons, environmental exposures to commercial grade PCBs (with low levels of PCDFs), which are far less than the former occupational exposure levels, appear to carry a minimal risk to humans.

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Comments and Studies on the Use of Polychlorinated Biphenyls in Response to an Order of the United States Court of Appeals for the District of Columbia Circuit

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and

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to

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Volume II
Potential Health Effects in the Human from Exposure to Polychlorinated Biphenyls and Related Impurities

DRILL, FRIESS, HAYS, LOOMIS & SHAFFER, INC.
Consultants in Toxicology
1901 N. Fort Myer Drive — Suite 204 — Arlington, VA 22209

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EXECUTIVE SUMMARY

The present study on the potential health effects in human populations from exposure to commercial polychlorinated biphenyl (PCB) mixtures under occupational or other environmental conditions was conducted by a team of specialists in the medical, toxicological, and epidemiological sciences designated as the Category I team. Draft material for the study report was reviewed by a second group of specialists designated as the Category II team, and other scientists, leading to comments and suggestions for improvement which were incorporated into the draft report. The available body of scientific literature on health effects of PCBs in humans and in test animal systems was reviewed and analyzed with emphasis on the relationships linking exposure, dosage to the biological target, and occurrence of specific health effects in the animal or human. Both the toxicological and epidemiological data from acute and chronic animal and human exposures were considered in generating assessments of the probability of occurrence of any specific health effect in humans. The results of these assessments are summarized below, separately itemized under each major health effect. It should be noted that each assessment applies to the potential for development of that effect under the type and level of human exposures actually encountered in the U.S. during the past decades, with the most intensive integrated exposures having occurred in manufacturing operations that were terminated in this country in 1977.

Yusho Disease

Separate consideration was devoted to the Yusho episode recognizing the special character of the human exposures to high concentrations of mixtures of PCBs and their thermal degradation products, polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Several conclusions reached by the Category I team are of importance: (a) it is impossible to stipulate whether any of the health effects observed is causally related to PCB exposure, since the other halogenated compounds are also biologically active; (b) the dosage patterns experienced by Yusho patients and U.S. industrial workers (PCB-exposed) are not at all comparable; the latter group experienced low level, long time period exposures primarily via inhalation and skin contact, with only minimal oral ingestion; (c) the similar health effects seen in Yusho patients from the Japanese and Taiwanese episodes of exposure to contaminated cooking oils point to the same type of toxic mixtures resulting from thermal heat exchanger action in the two events; (d) because of points (a)-(c) above, and the fact that at least the PCDFs in the Yusho oils are potentially more toxic than the PCBs on the basis of animal data, it is not possible to extrapolate the Yusho experience to prediction of acute and sub-chronic effects of commercial PCB mixtures in the human; (e) finally, with respect to predictions of human carcinogenesis from the Yusho type of exposure the data are so incomplete that conclusions regarding any types and amounts of excess cancers attributtable to those exposures have to await further definitive study.

Body Burdens, Metabolism, and Kinetics

Some general observations derive from consideration of the data on the storage, distribution, metabolism, and excretion of commercial PCB mixtures (with associated impurities such as the PCDFs) in mammalian systems. The dynamics of the pathways by which these processes occur in test animal models have been explored intensively and have been fairly well worked out. The variability of PCB effects with species of test animal model has been investigated for a number of important effects, and some general structure versus activity rules have emerged from these studies. There thus exists a conceptual framework, but not experimental data, for describing such phenomena in humans. Further, important data on the biochemical interactions of PCBs, PCDFs, and metabolites with tissues have been obtained that bear directly on interpretation of toxic effects in these tissues.

General Toxicity

From acute, subchronic, and chronic studies of PCB effects in test animal models, a general summary of health effects encountered includes: (a) a low order of acute toxicity; (b) skin lesions; (c) affects on liver tissue that are generally reversible at lower doses but that trend toward irreversibility with increased dosing; (d) effects on the gastric mucosa; (e) effects on the menstrual cycle and on reproduction;

(f) porphyria; (g) effects on the kidney; and (h) miscellaneous changes including hematologic alterations, thymic atrophy, and lymphatic changes.

There is a considerable range of species susceptibility to biological activity of the PCBs, with one representative comparison of order of decreasing activity being mink, monkey, rat. It is concluded that there is no basis for determining which species most accurately serves as a model for prediction of general subchronic/chronic toxicity in man; rather, the judgment of the most suitable surrogate for man must be made independently for each major health effect. Finally, it is noted that although there is some similarity between acute health effect phenomena produced by PCB exposure in the monkey and human Yusho disease, it would be incorrect to equate Yusho disease with PCB intoxication because of the much more complex mixture of compounds encountered in Yusho oil than in a commercial PCB mixture.

Skin and Other Cutaneous Tissues

Commercial PCBs are capable of producing skin lesions in the monkey model and in exposed humans. Chronic administration of PCBs to the monkey produces chloracne. In humans occupationally exposed to PCBs skin disorders including chloracne have occasionally been observed. These skin disorders have been shown to be reversible in some of the animal and human studies.

Liver Effects

PCB mixtures are capable of generating important effects on liver tissue in animal models. These effects include: (a) increase in liver weights; (b) histopathologic changes in liver including enlarged hepatocytes, deposition of fat droplets in tissue, and tissue necrosis and cell death; (c) enlargement of the liver; (d) the occurrence of adenofibrosis, a benign lesion; and (e) an increase in proliferative lesions of the liver, including increases in hyperplastic foci and nodular hyperplasia. These increases in proliferative lesions appear to increase in severity with increasing degree of chlorination of the PCB mixture, as seen in the greater potency of Aroclor 1260 over Aroclor 1254. The effects on liver tissue are generally reversible at lower doses but trend toward irreversibility with increased dosing.

However, in contrast with the positive findings of PCB effects on liver tissue in animal models, no significant effects on liver function tests have been observed from clinical data on human populations exposed to PCBs in the occupational setting. Further, there has been no epidemiological finding of liver disease in U.S. occupationally-exposed personnel. Also, as noted in the Yusho discussion about persons exposed to contaminated cooking oil with a PCB content of 1000 ppm, there was no finding of liver disease in the categories of either jaundice or hepatocellular injury.

Gastric Lesions

When tested in monkeys and rodents, PCBs show species specificity with respect to a toxic effect on the gastric epithelium, or stomach lining. In the monkey, with Aroclor 1242, there is a mucous conversion of the gastric epithelium that can best be described as a dysplastic growth pattern. This growth pattern does not constitute a neoplastic transformation. In rodents, PCBs do not evoke this effect on the gastric mucosa. In humans occupationally exposed to PCBs there are no clinical findings to date of gastric lesions, and no evidence of stomach cancer due to this exposure.

Carcinogenesis: Experimental and Clinical

A sizeable volume of animal experimental work has been directed toward chronic studies in several species: the mouse, the rat, and the dog. There are some areas of interpretation that are still under debate by the investigators concerned, but in the opinion of the Category I team the following represents conclusions that can be drawn from presently available data: (a) the evidence on carcinogenicity is negative for gastrointestinal carcinoma and bladder carcinoma in rats and hepatocellular carcinoma in the dog; (b) some studies have reported an increase in hepatocellular carcinoma in mice and rats exposed to commercial PCBs chronically, whereas other studies have afforded negative results.

With respect to the possibility of cancer linked to exposure of humans to PCBs, epidemiological studies show to date essentially negative results for hepatocellular carcinoma, gastrointestinal carcinoma and all other forms of cancer. There is a single preliminary study that purports to show an increase in melanoma (skin cancer) in occupationally exposed people, but the full data display and analysis have not been made for this study. In contrast, in two larger and more detailed studies, this finding has not been confirmed; no excess incidence of melanoma in exposed personnel has been observed.

Retrospective mortality studies of PCB-exposed human populations have not demonstrated a consistent relationship between extent of exposure and the development of any particular type of cancer. The human studies in hepatocellular carcinoma are not comprehensive, but to the extent that they have been developed the results do not confirm the projection of a risk for liver cancer based on the animal studies. Some findings of increases in lymphatic and hematopoietic malignancies were below the level of statistical significance, and were refuted by observations of changes in the opposite direction in other epidemiological studies. Even findings of statistically significant differences between exposed and control populations with respect to the incidence of rectal cancer in women at one plant have not been confirmed by observations in other studies. The variance in these findings points up the important principle that the Standard Mortality Ratio (SMR) may vary widely in different

studies, and that undue emphasis should not be placed on the SMR found in one study unless it has been confirmed by similar findings in repeat or parallel studies.

Reproductive Effects

Experimental work with commercial PCB mixtures and animal models has been directed to the reproductive process itself, to teratogenesis in the offspring, and to possible fetotoxicity. In most test species PCBs produce deleterious effects on reproduction at high dosages. In the female monkey at relatively high dosages, difficulties are encountered in conception, in implantation of the fertilized ovum, and in carrying the fetus to term. Similarly dosed, the male monkey does not transmit these difficulties to the reproductive process. In the human, exposed occupationally or otherwise to PCBs, there is in general no evidence for adverse effects on the reproductive process, although there are little data from which to draw conclusions. In the very special case of Yusho exposure to high levels of PCBs and other polychlorinated hydrocarbons, the newborn in significant proportion were pigmented, small, and showed a retarded rate of growth. However, this pigmentation disappeared and the infants caught up with control population infants in total growth.

The potential for PCB-induced teratogenesis, or production of defects in the embryo or fetus, has been investigated in several species of test animals. Most animal tests have yielded negative results when PCBs were administered to pregnant females during the critical periods for organogenesis.

several possible exceptions to this statement might be noted. In mice, a single congener, 3,4,3',4'-tetrachlorobiphenyl, induced a behavioral defect ("waltzing syndrome") that may be related to an anatomical defect in the inner ear. PCBs in mice may produce some delay in implantation. In rats, no gross teretological changes were observed, but some alterations in thyroid structure or function produced by PCB administration might fall under the definition of terata. In dogs and in swine, no teratological effects were noted at lower PCB doses; however at the highest doses of PCB in the feed, at which the dam suffers marked reduction in food consumption and is therefore nutritionally deficient, there are dose-related teratological effects in the offspring. In monkeys dosed with PCBs, there are no dose-related abnormalities in the offspring, but they are smaller in size. Based on those observations, it is the Category I team's conclusion that commercial PCBs present no appreciable risk of teratogenicity in offspring of human females exposed under occupational conditions.

In test animals, i.e. rats, dogs, and rabbits, PCBs are fetotoxic when administered at relatively high doses to the pregnant female. In the human, the only reported epidemiological evidence for fetotoxicity in exposed populations stems from the unique Yusho event, in which causation may not be linked to PCBs.

Mutagenesis

Investigations of possible mutagenesis from acute or chronic exposures to commercial PCBs have shown negative results in a series of *in vitro* and *in vivo* test systems. Isolated bacterial test systems (Ames test) and human lymphocytes in culture showed no evidence for PCB-induced mutation or transformation. With *in vivo* systems in intact animals: (a) cytogenetic tests for alterations of cell structures or for induction of chromosome abnormalities yielded negative results; and (b) both the mouse micronucleus test and the dominant lethal test demonstrated negative results. Incubation of human lymphocytes in culture with PCBs caused an alteration in glucose transport through the cell membranes.

There is no significant evidence that PCBs are mutagenic in test systems, and no reports of such activity in human populations. It is quite unlikely that commercial PCB mixtures would exert mutagenic activity in humans. This conclusion is consistent with the lack of excess cancer incidence observed in PCB-exposed human populations.

Other Health Effects

This grouping includes enzyme induction, immunocompetence, and porphyria. PCBs induce mixed function oxidases (MFO) in the liver of test animals. The important issue is whether or not this process includes the specific induction of cytochrome P-448 as a general property of the PCBs, with the added implication that some oxidase system is being induced that

could be involved in chemical carcinogenesis. Several conclusions were reached with respect to this issue: (a) the predominant effect of commercial PCBs is cytochrome P-450 induction, not P-448; (b) commercial PCBs in the U.S. can contain up to about 2 ppm of PCDFs; and (c) the PCDFs can induce cytochrome P-448. From these observations in animal model systems and our judgment, it is concluded that under conditions of U.S. occupational exposure to PCBs, none of the MFO-inducing actions of the commercial mixtures will be of toxicological significance over the lifetime of a PCB-exposed person.

With respect to potential PCB effects on immunocompetence in test animal systems, some observations are pertinent to the assessment of probable hazard in the human. It has been observed in chicks that if the PCB dosages are high enough, atrophy of the splenic pulp and necrosis of the lymphoid system can be demonstrated. Similar indicators of change in immunocompetence can also be produced in ducklings, mice, and monkeys as a consequence of severe change in nutritional status. High doses of PCBs leading to marked reduction of food intake and utilization can lead to such changes in nutritional status. These considerations lead to two general conclusions relative to the PCB-exposed humans: (a) as projected from animal studies, if the PCB dosage is high enough to lead to general toxicity in the human (e.g., decreased food intake, fall in body weight, fall in weight gain),

immunosuppression may be demonstrable secondary to malnutrition; and (b) at lower dose levels, there is no likelihood of significant immunosuppression.

Porphyria, or deposition of porphyrin-derived pigments in liver and urine, has been observed in experimental animals such as the rat and rabbit dosed with PCBs. The effect has a delayed onset, and, especially in the rat, seems to take place by mechanisms different from those employed by known chemical porphyria-producers in the human. It is concluded that, aside from the unique case of Yusho disease, no evidence has accrued for the occurrence of porphyria in populations exposed to PCBs even under high level occupational exposure conditions.

Epidemiology

This section (XII) of the study presents a separate, independent assessment of the recorded epidemiological literature and data bases on human exposures to commercial PCBs, and on the significance of the health effects attributed to these exposures.

Summary points in this assessment include the following: (a) mortality data, based on very small numbers of deaths, do not confirm a carcinogenic effect of PCBs in man; (b) data on human skin lesions in relation to PCB exposures have shown variability in incidence of this effect with geographical locus and with increasing blood level indicators of exposure; (c) data from studies of liver enzymes and liver function suggest changes in one or more enzymes related to PCB exposure that are not associated

with liver disease and that occur at levels below those at which chloracne occurs; (d) there is frequently a positive correlation between PCB levels and triglyceride levels in blood; and (e) epidemiological data on reproductive effects, hematology and immunology in humans exposed to PCBs do not suggest abnormalities in these systems or processes.

Human Occupational Exposure Levels

Of the various effects noted in animal test systems, only dermatological effects, including some chloracne, have been clearly demonstrated in human populations at the dosage levels associated with occupational exposures. Table 1 summarizes the nature and intensity of some exposures that have occurred to personnel involved occupationally with PCBs and the biological indices that have accompanied these exposures, measured as PCB content in blood and adipose tissue.

Since the risk to human health from even high level occupational exposures has been shown by the studies available to be low, it may be concluded that much lower human exposure levels do not present significant risks.

TABLE 1

INDUSTRIAL OCCUPATIONAL EXPOSURE OF WORKERS TO PCBs
(Capacitor plant workers unless otherwise noted)
Data reported in human epidemiology references

References				PCB Concentration in Air Range	PCB Concentration in Air mg/m^3	Dermal Contact Noted?	PCB Level in Blood Plasma Parts per billion** No. Subjects*	PCB Level in Blood Plasma Parts per billion** Mean	PCB Level in Blood Plasma Parts per billion** Range	PCB Level in Adipose Tissue Parts per million** No. Sub.*	PCB Level in Adipose Tissue Parts per million** Mean	PCB Level in Adipose Tissue Parts per million** Range
Fuscinelli	(1984)				5200-6000							
Hansgrove	(1972)	Plant	A (PCB Mfg.)		50- 200							
		"	B		100- 500							
		"	D		500- 700		99	370	60- 920			
		"	E		200-1700							
		"	F									
Harpenson	(1972)				< 1000		12	440	110-1900	3	360	160-635
Hitchcock	(1973)						13	820	320-2100			
Gow	(1976)				320-2220	Yes	34	~ 400	Tr.-1200			
Fischbein	(1979)		Lo expos.		70- 410		158	L- 73 H- 41				
			Med. "		410- 600		62	L-171 H- 25				
			Hi "		600-1100		43	L-266 H- 82				
Wolff	(1981)				As Above		26	L- 83 H- 19	2-1412 1-60	26	L-24 H- 6	2-271 .2-19
Brown	(1981)				24- 393 170-1260							
Smith	(1981a)				N.D.- 264	Yes	14	L-502 H- 44	210-3330 20- 150			
							12	L-237 H- 51	34-2400 10- 250			
							55	L-140 H- 27	8-1500 7- 130			

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TABLE 1 (continued)

Reference		PCB Concentration In Air Range ug/m³	Dermal Contact Noted?	PCB Level in Blood Plasma Parts per billion** No. Subjects*	Mean	Range	PCB Level in Adipose Tissue Parts per million** No. Sub.*	Mean	Range
Smith	(1981b)	37- 215		14	L- 23 H- 26	5- 52 7- 74			
(2 utility worker transformer repair groups)				8	L- 16 H- 7	1- 52 4- 19			
				6	L- 36 H- 10	23- 59 7- 17			
				13	L- 24 H- 6	12- 35 1- 10			
				7	L- 11 H- 6	1- 30 4- 10			
		3- 82	Yes	15	L- 22 H- 31	9- 47 11-140			
				10	L- 22 H- 26	12- 48 7-250			
				13	L- 23 H- 8	13- 52 5- 25			
				8	L- 19 H- 6	12- 42 3- 11			
Maroni	(1981)	48-275	Yes	48 12	377 288	88-1319 61-670			
Chase (locomotive repair)	(1981)		Yes	86 35	33.4 14.2	16-312 10- 30	36 5	5.6 1.4	1.6-21.6 1.0- 1.8

* Excluding controls

** Note: PCB plasma analyses are expressed in parts per billion (including some ng/ml), while adipose tissue analyses are expressed in parts per million.
"L" PCBs (lower homologs) and "H" PCBs (higher homologs) are defined as species having, respectively, shorter and longer gas chromatographic retention timeses than the DDE metabolite p,p' (prism) -DDE.
"L" PCBs include 3-PCBs through 4-PCBs, plus some 5-PCBs; "H" PCBs include 5-PCBs and hueher, plus some 4-PCBs.

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I. INTRODUCTION

A. Origins and Methodology of the Study

In August 1981, the firm of consultants in toxicology, Drill, Friess, Hays, Loomis and Shaffer, Inc., Arlington, Virginia, (DFHLS) entered into a contract with the Edison Electric Institute (EEI) and the National Electrical Manufacturers' Association (NEMA) whereby DFHLS agreed to examine the toxicological and epidemiological literature on polychlorinated biphenyls (PCBs) and provide EEI and NEMA with DFHLS' independent, professional opinion on the human health effects of PCBs at varying dosages or exposure levels. To this end, the principal scientific studies and data compilations available on toxicological and epidemiological effects of PCBs, as commercial mixtures and as purified single congeners, have been reviewed by a team of scientists designated as the Category I team. Members of the Category I team are Drs. V.A. Drill, S.L. Friess, H.W. Hays, T.A. Loomis, and C.B. Shaffer from DFHLS. Additionally, Dr. G. Matanoski of the Johns Hopkins University has acted as an independent member of the Category I team charged with study of the pertinent epidemiological literature on PCBs and their human health effects, leading to an independent assessment and evaluation of the probability, causality, and reality of these effects.

Category I team review of the animal and human data resulted in draft material on the relationships between PCB exposure and specific health effects in test animals and in

exposed human populations. Further, where human data were lacking or incomplete, the Category I team members developed specific projections or opinions as to the probability of occurrence of certain health effects in exposed humans, based on the existing animal/human data bases. Health effect areas scrutinized included: general toxicity; effects on skin and other cutaneous tissues; effects on liver; effects on gastric tissues; carcinogenesis (experimental and clinical observations); reproductive effects including fetotoxicity and teratogenicity; mutagenesis; Yusho disease and occurrence of cancer; and other health effects including enzyme induction, changes in immunocompetence, and porphyria. Dr. Matanoski's treatment of epidemiological observations constituted an independent section of the draft report.

Draft sections from the Category I team were then reviewed for content, conclusions, and opinions by the members of a scientific team of pharmacologists and toxicologists designated as the Category II team: Dr. F.G. Standaert (Georgetown University), Dr. A. Alvares (Uniformed Services University of the Health Sciences), Dr. J.A. Thomas (West Virginia University), and Dr. P.E. Enterline (University of Pittsburgh). Dr. Enterline was the prime reviewer of the epidemiological contribution made by Dr. Matanoski.

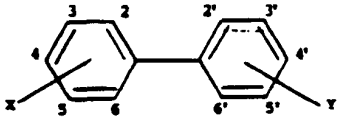
Comments and critique from Category II team members, singly and as a group, were then transmitted to the Category I team for consideration, leading to revisions and amplifications

that are in place in the final draft of this study. Comments and suggestions from scientists representing the sponsors of this study, EEI and NEMA, were also considered.

In the final version of the study, to the extent possible, a section on summary and opinion is appended to each discussion of a potential human health effect attributable to PCB exposure. The primary responsibility for each of these sections is assumed by the Category I team, even though the content may have benefitted from useful contributions by Category II personnel.

B. Commercial PCB Mixtures

Polychlorinated biphenyls (PCBs) are members of a class of non-polar chlorinated hydrocarbons based on the biphenyl nucleus, in which multiple chlorine atoms are substituted on



either or both the primed and unprimed aromatic rings. Certain individual members of the PCB family have been prepared in a relatively pure state, with substitution of ring positions by chlorine ranging from dichloro isomers (symbolized as 2-CB) up to the nonochloro (9-CB) and decachloro (10-CB) derivatives. Commercially, PCBs were marketed in the United States under the trade name of Aroclors. They were also manufactured abroad under the tradenames "Phenoclor" and "Pyralene" (France), "Clophen" (Germany), and Kanechlor (Japan). They are comprised of mixtures of chlorinated biphenyls. The last two digits of the U.S. commercial name denote the percentage of chlorine in each mixture, e.g., Aroclor 1242 contains 42% by weight of Cl corresponding to an average of approximately three chlorines per biphenyl molecule. Likewise, Aroclor 1254, Clophen A50, and Kanechlor 500 all contain 54% chlorine corresponding to five chlorine atoms per molecule on the average.

Commercially useful mixtures of PCBs have been widely distributed over the world in the past few decades, usually in applications that have precluded excessive exposures of user populations. However, because of the great chemical stability of these polychlorinated molecules, their persistence in the environment after accidental release can be lengthy leading to possible exposures of people and biota in the biosphere. The results of these exposures, as well as those of personnel occupationally exposed to PCBs in the course of chemical synthesis

and manufacturing operations, are of great importance from the standpoint of potentially harmful health effects that might occur on an acute or chronic basis.

C. PCB Impurities

Commercial PCB mixtures are truly complex, containing variable numbers and amounts of congeners within a given family of compounds, and traces of impurities, all of which are potentially toxic to humans and animals. Impurities that have been identified in PCBs as manufactured are polychlorinated derivatives of napthalene (PCNs), terphenyls (PCTs), methylbiphenyls, and dibenzofurans (PCDFs).

The occurrence of PCDFs is particularly noteworthy in view of the higher toxicity for certain congeners, relative to PCBs. It is important to note that there are theoretically 135 possible PCDF congeners, a few of which are believed to be highly toxic.

While reviewing PCB toxicological or epidemiological data, a number of factors related to the actual material involved must be considered. The PCDF content of commercial PCBs varies: for Aroclors the reported range is 0-2 ppm of total PCDF congeners. For European and Japanese PCBs, the reported range for PCDF content is 5-20 ppm. The impurity levels can also be affected by exposure to high temperatures and oxygen. For example, Aroclor 1254 is converted to 2-3% PCDFs at 550-600 degrees C. These same conditions result in the formation of polychlorinated quaterphenyls (PCQs).

II. Yusho Episode

In 1968 a mass outbreak of food poisoning occurred in Japan, following ingestion of a cooking oil contaminated with PCBs and other compounds, that aroused worldwide concern over the potential human health effects from exposure to PCBs. However, this poisoning, which became known as Yusho disease, differs significantly in several ways from occupational exposure to PCBs in the United States so that data from the Yusho incident cannot be extrapolated to indicate the effects of PCBs in industrial situations.

Recent studies of the rice oil involved in the Yusho poisoning show that the oil contained relatively large amounts of other chlorinated hydrocarbons such as PCDFs and PCQs (see Kuratsune et al., 1976; and Hayabuchi et al., 1979). The rice oil that caused the disease was found to contain about 1000 ppm of PCBs, 5 ppm of PCDFs, and 1000 ppm of PCQs; the amounts of the latter two classes of chlorinated hydrocarbons in the rice oil are higher than in the Aroclors used in the United States. Hayabuchi reanalyzed the intake data for the Yusho patient, and calculated that the average intake for the mean latent period was PCB 466 mg, PCDF 2.5 mg, and PCQ 439 mg; the smallest intake by a patient was estimated to be 111, 0.6, and 105 mg respectively.

PCB concentrations in the tissues of Yusho patients were much lower than those of asymptomatic individuals with body

burdens of PCBs resulting from occupational exposure. Further, PCB fractions of blood, tissues, and breast milk of Yusho patients yielded gas chromatographic patterns showing a larger amount of late-eluting peaks than do PCB fractions of tissues of individuals subject to other types of PCB exposure (Koda and Masuda, 1975). These patterns have never been observed in individuals (human or animal) exposed to PCBs in other situations. They are unique to Yusho disease. Also, PCDFs have been found in tissues of Yusho patients.

Further evidence for the uniqueness of the syndrome in humans exposed to the Yusho oil is furnished in two recent studies. Hayabuchi et al. (1981) in follow-up studies on these patients five or more years after the poisoning found significant positive correlations for the years 1973-1976 between blood concentrations of PCBs and the total amount of rice oil consumed, but not with the dosage of rice oil consumed per unit of body weight per day. Kashimoto et al. (1981) found that Yusho is quite different from ordinary PCB toxicity in the sense that, even 12 years after the first outbreak, PCQs have been found in the patients' blood and both PCQs and PCDFs have been found in their tissues and organs.

It is obvious from this brief review that Yusho cannot be considered a model to reflect the possible effects of the PCB exposure in man. Although much can be learned from the Yusho

incident, it would be misleading to attempt to interpret the observations on Yusho patients as valid signs and symptoms of overexposure to PCBs or to attempt to quantify the possible effects of PCB exposure based on Yusho disease.

A. Yusho Disease

Yusho disease is characterized by the ingestion of a mixture of chlorinated hydrocarbons containing PCBs in large amounts over a relatively short period of time (latent period from start of ingestion to onset of the disease averaged 71 days). In contrast, the studies of PCB exposure in workers in the United States have been concerned with the possible effects of chronic exposure to small amounts of PCBs through inhalation or skin contact.

The principal signs of Yusho disease are skin conditions such as acneform eruptions, pigmentation of the skin and nails, and hypersecretion of the Meibomian glands. Chloracne and hypersecretion of the Meibomian glands are believed now to be caused predominantly by PCDFs. Hyperpigmentation of the skin is observed rarely, if ever, in human populations with heavy occupational exposure to primarily PCBs.

The actions of PCDFs appear to differ in several ways from those of the PCBs. Kuratsune et al. (1976) showed, for example, that the liver appears to concentrate PCDFs selectively relative to PCBs. It was also found that relative to PCBs, the concentration of PCDFs was about 250 times higher in the rice oil than in unused Kanechlor-400. Additionally, the PCDFs appear to

be highly toxic, at least in the rabbit; a single oral dose of 0.5-1 mg/kg of the tri- and tetrachlorodibenzofurans caused severe and often lethal necrosis in the rabbit (Hofmann, 1958; Bauer et al., 1961).

B. Yusho Disease and Liver Function

In view of the effect of PCBs on the liver of the rat and the highly toxic action of PCDFs on the liver of the rabbit, it was anticipated that the Yusho patient would have severe liver damage, but such has not been found.

In their review of Yusho disease, Kuratsune et al. (1972) list "the subjective symptoms of Yusho as stated by 189 patients"; 11% report jaundice. Data to confirm the patients' "subjective symptoms" are not provided, nor is the presence of this "symptom" confirmed by other statements of clinical findings. Prof. Urabe (Chief of the Study Group) did not list jaundice as a sign or symptom of Yusho disease and the diagnostic criteria adopted in 1972 do not make reference to jaundice or the need for a liver function test in these patients (see Kuratsune et al., 1976).

The following two papers on Yusho disease and liver function are in Japanese and the brief summary given below is taken from the report of Kuratsune et al. (1976).

Okumara and Katsuki (1969): They examined 24 patients soon after the onset of the disease:

(i) There were no objective signs of liver disorders; (ii) No patients were jaundiced and only three had palpable livers (in one patient examinations of a liver biopsy showed marked hypertrophy of the smooth endoplasmic reticulum).

Okumara (1972): Liver function tests were performed in 38 Yusho patients with various subjective symptoms. An increase in lactic dehydrogenase (LDH-5) and in thymol turbidity titer was observed in some of the severe cases, "but no definite evidence for liver disorders was obtained."

In a follow-up study of 121 Yusho patients the mean serum bilirubin was 0.48 mg/100 ml compared with 0.87 mg/100 ml in control patients (Hirayama et al., 1974). The difference was statistically significant and the authors suggest that there may be accelerated bilirubin disposal from the blood.

It may be concluded that the Japanese findings do not provide evidence for the development of hepatocellular injury or jaundice in patients with Yusho disease.

C. Yusho Disease and Carcinogenicity

Urabe and co-workers (1979) report that 51 of 737 Yusho patients in the Fukuoka district had died and they list the cause of death for 31 of the patients. There were 11 deaths (35.4%) from neoplasms which they state is substantially higher than the 21.1% rate that is "the mortality rate from neoplasms in the

same prefecture this year." A further analysis is not provided. The following malignant neoplasms were listed as the cause of death for the 11 patients with cancer.

Anatomical Site	No. of Cases
Stomach Cancer	2
Stomach Cancer & Liver Cancer	1
Liver Cancer & Liver Cirrhosis	2*
Lung Cancer	2*
Lung Tumor	1
Breast Cancer	1
Malignant Lymphoma	2
TOTAL:	11

*Autopsied

Information on age and other relevant epidemiological data are not given, and even a tentative conclusion regarding Yusho disease and any malignancy must await further analysis.

III. Body Burdens, Metabolism, and Kinetics

A. Introduction

The degree of chlorination (two to 10 atoms of Cl per PCB molecule) and the positions of the chlorine substituents on the biphenyl rings both exert a profound influence on how mammalian systems handle any given PCB molecule. The degree and position of chlorination play a major role in determining the pathways for metabolism and elimination of the parent molecules and their metabolites by animal models and the human. These structural factors also bear on lipid solubility of the molecules, and therefore influence to some extent the kinetics of PCB tissue distribution and storage. The following sections deal with the present state of knowlege on these PCB handling mechanisms employed by animal models and the human, recognizing that there is a strong linkage in the dynamic processes beginning with exposure and ending in excretion. These topics will be treated in three groupings: (1) distribution and storage of PCB metabolites in tissues; (2) metabolism and excretion; and (3) kinetics or the dynamics of PCB turnover in animal models and the human. Presently, some generalizations emerge with regard to PCB structure versus reactivity relationships and mechanisms for handling PCBs in test animal systems that make reasonable extrapolation to potential events in the human organism possible, even when direct evidence for actions of a given compound or PCB mixture in human populations is not available.

Additional attention has been directed to available information on the actions of PCDFs in animal models and the human, and to a variety of biochemical effects recorded for PCBs and their metabolites in mammalian systems. PCDFs may be contaminants of some commercially used PCBs. Although 10-20 ppm of these contaminants have been found in PCBs manufactured in Europe and Japan, only trace amounts on the order of one or two micrograms of total PCDF congeners per gram of PCB have been reported in the American manufactured mixture Aroclor 1254 (Bowes et al., 1975).

B. PCB Distribution and Storage in Tissues

A considerable body of literature exists on studies of the time dependance of the distribution, movement, and storage of PCBs and their metabolites in the tissues of experimental animal models and of humans, following exposures to chlorinated biphenyls as pure compounds or mixtures. In test animal models using unlabeled or radiolabeled (^{14}C or ^{3}H) PCBs, controlled exposures were generally by the oral route (stomach tube, or in the feed) or by intravenous injection, followed by study of the changing distribution of the agent and its metabolites in the circulating blood, in tissues, in bile fluid, and in excreta as a function of elapsed time after dosing. In the human, exposures with resulting body burdens of PCBs were generally of the subchronic type stemming either from massive poisoning events, as in the Yusho events, from chronic occupational exposures in air and via skin contact, and via PCB contaminants in air, water, food, and surface contacts in the ambient. Humans

may also have been exposed to PCBs occupationally in the chemical manufacturing process, in the manufacture of capacitors, and in the manufacture and repair of transformers. Until recently, several microscope immersion oils contained 30-40% PCBs as Aroclor 1254, causing potential exposures of students, pathologists, microscopists, etc.; the degree of exposure is low and the penetration through skin from these products may not be as extensive as in large scale manufacturing processes.

In human studies, PCB distribution and storage in readily obtained tissues was generally followed epidemiologically in exposed populations by monitoring levels in blood, sometimes in mother's milk as a function of time and sometimes by measuring PCBs in adipose and other tissue samples obtained clinically and post mortem.

Animal Model Results

The picture of distribution and storage of PCBs and their metabolites in tissues over time has been developed most completely from controlled dose experiments in animal models. Generally, rats and mice were the animals of choice for this work (Burse et al., 1974; Geyer et al., 1980; Guiney et al., 1978; Matthews and Anderson, 1975; Morales and Matthews, 1979; Albro and Fishbein, 1972; Burse et al., 1976), but the dog, as well as the monkey, has also been used (Hsu et al., 1975a; Milling et al., 1979; Sipes et al., 1980). The dynamics of tissue distribution vary with different isomers and congeners, and depend in large measure on whether or not the specific PCB

molecular structure allows rapid metabolism and excretion of polar metabolites via bile, feces, and urine (Milling et al., 1979; Safe et al., 1975; Sipes et al., 1980; Matthews et al., 1978; Guiney et al., 1978; Guzelian, 1979) or slower metabolism with retention of parent compounds and metabolites in tissues. As will be discussed in the following section, metabolic transformation in the liver is particularly facile for those PCBs with lower chlorine content (2-CB through 4-CB, i.e. 2-4 chlorines per PCB molecule) and with adjacent ring carbon atoms unsubstituted by chlorine atoms (Matthews and Tuey, 1980; Sundstrom et al., 1976; Kato et al., 1980; Jensen and Sundstrom et al., 1974b; Ghiasuddin et al., 1976; Matthews et al., 1978). For many PCB molecules in which metabolic transformation and excretion is not excessively rapid, the dynamic distribution of parent compounds and metabolites in tissues following dosing has been studied carefully (Mizutani et al., 1980; Safe et al., 1975; Sipes et al., 1980). The following generalizations appear valid in animal models for structures ranging from 1-CB to 6-CB and higher.

First, the PCBs are readily absorbed from the gut following oral administration and appear rapidly in the bloodstream (Albro and Fishbein, 1972; Berlin et al., 1975; Chen and Matthews, 1974). Within minutes to hours, the materials largely clear from the blood and accumulate in the liver and in muscle tissue (Berlin et al., 1975; Burse et al., 1974; Chen and Matthews, 1974). However, traces of PCBs have been found in the

blood of humans, probably by redistribution from other tissues, years after exposure. The liver is the primary locus for metabolism of the PCBs, especially for reactive species, leading to mixtures of parent molecules and metabolites that then either translocate to other tissues or are excreted by both bile/gut, lumen/feces, and urinary pathways. As translocation from liver and muscle occurs in the rodent model and other species over time periods ranging from hours to many days, the ultimate depots for major amounts of the non-polar PCBs and their polar metabolites appear to be adipose tissue and skin (Berlin et al., 1975; Hansen, 1979; Guiney et al., 1978; Burse et al., 1974). The general distribution pathway in rodents may therefore be characterized as sequential migration from gut and bloodstream entry points to liver and muscle tissues, in a rapid process, and thence to depot storage in body fat and skin.

When the PCB structure is such as to permit ready metabolism to polar hydroxy, dihydroxy or diol derivatives, the metabolic process may be closely linked in time with excretion of the metabolites (Jensen and Sundstrom, 1974; Lay et al., 1979; Matthews and Tuey, 1980; Matthews et al., 1978; Matthews and Anderson, 1975). Animal studies on urinary and fecal excretion of PCBs (Guselian, 1979; Matthews and Anderson, 1975; Berlin et al., 1975; Lay et al., 1979; Chen at al., 1976; Van Miller et al., 1975), and rates of elimination of PCBs from liver into bile and then into gut/feces, show that the larger

proportion of excretion in rodents is by fecal elimination (Kato et al., 1980; Lay et al., 1979; Chen et al., 1976; Van Miller et al., 1975; Chen and Matthews, 1974) of polar metabolites, mostly glucuronides, eliminated via the bile.

The dynamics of distribution and elimination of PCBs in two monkey species have been studied (Hsu, et al., 1975a; Sipes et al., 1980; Hsu et al., 1975b), and are found to follow a similarly complex pathway, but with wider tissue distribution ultimately than that seen in the rat. In our opinion, this difference may relate in part to the ability to analyze more tissues in larger animals. With fat tissues present in only small proportions in the infant Rhesus monkey, the ultimate depots included bone marrow and the adrenal glands, in addition to skin (Hsu et al., 1975a).

Long-term studies involving chronic administration of PCBs at low dosage levels to animal models for significant fractions of their lifetimes, with determinations of total burdens and tissue distributions achieved over time periods of one to two years of ingestion, are lacking.

Human Body Burden Results from Epidemiological Studies

Experimental data on body burdens and tissue distributions of PCBs in humans as a result of precisely-measured intakes are not available. However, there are several population sectors for which exposures to PCBs can be at least roughly estimated, and from which tissue samples (blood, subcutaneous and other fatty tissue, etc.) have been taken to obtain indices of

body burden. These sectors include: (1) humans occupationally exposed to PCBs during years in which they were employed in manufacturing processes (Karppanen et al., 1972; Hasegawa et al., 1972; Kitamura et al., 1973; Ouw et al., 1976; Fischbein et al., 1979; Wolff et al., 1981; Maroni et al., 1981a, b; Smith et al., 1981a, b; Chase et al., 1981); (2) humans accidentally poisoned by PCBs ingested in contaminated foods, as in the Yusho experience in 1968 and in corresponding ingestions of contaminated rice oil in Taiwan (Chen, 1980; EPA summary, 1980); and (3) humans living in areas in which PCBs have somehow entered the food chain or water supply in measurable amounts, leading to long-term, low-level body burdens in adults that may also be present in the human milk supply for transmission to infants (Humphrey, 1975, 1980; Kuwabara et al., 1979a; Kuwabara et al., 1979b; Mes and Davies, 1979; Watanabe et al., 1980). An additional source of exposure that is more difficult to characterize quantitatively stems from the exposure of families to contaminated clothing of PCB workers. Survey work has been done in all of these population sectors worldwide. The results are sketchy, but tentative qualitative generalizations can be drawn.

Blood or plasma levels of PCBs are most readily followed in potentially exposed population data using highly sensitive analytical techniques such as gas chromatography and mass spectrometry. For occupationally exposed people (NIOSH, 1977; Smith et al., 1980a) values ranging from 10 ppb up to a maximum of 3330 ppb have been observed, with the additional

qualitative finding from Japanese references that the half-life for disappearance of PCBs from blood following cessation of exposure ranges from three to 30 months. PCB blood levels were higher with increased duration of exposure. For Yusho victims in Japan, with blood samples taken five to seven years following exposure to PCBs, in the 1973-1975 time frame (NIOSH, 1977) values in the range 3-33 ppb were observed. Enhancement factors over control group levels (mean, 3 ppb) as great as 10 were calculated, but the observed blood levels were still much lower than levels found in Japanese capacitor workers. It is of interest to note the observation of Humphrey (1975) on the very slow clearance of PCBs from the tissues of humans exposed by eating fish. In general populations, blood plasma or serum levels of PCBs in the range 5-29 ppb have been found (NIOSH, summary p. 36).

A current and well-documented study of body burdens of PCBs in persons employed for many years in capacitor manufacturing (Wolff et al., 1981) is of special value from the standpoint of its correlations of tissue concentrations with extent of exposures. With highly chlorinated PCBs (H-PCBs), plasma concentrations of 1-546 ppb in exposed personnel correlated with total accumulated exposure time. For the less highly chlorinated PCBs (L-PCBs), plasma levels in the range 6-2530 ppb correlated better with specific tasks of individuals working with these 2-CB to 4-CB molecules. Also observed in this study was a correlation of levels in plasma with levels in adipose

tissue for each class of PCBs, with H-PCBs and L-PCBs taken as separate classes, and an overall adipose/plasma partition coefficient of 190.

The levels of PCBs and metabolites in subcutaneous fat in humans have also been surveyed in general populations (NIOSH, 1977), in groups such as Yusho patients with high exposures, and in some occupationally exposed individuals. For the general population, levels in fat range from less than 1 ppm to greater than 2 ppm. For Yusho individuals, elevated fat PCB levels in the range 13-75 ppm have been observed, corresponding to peak enhancement factors as high as 30 over the population at large. It should also be noted that the spectrum of compounds in human tissues is not necessarily identical with the spectrum in the mixture to which a given population was exposed (Kuwabara et al., 1971a). Ranges of adipose tissue PCB levels in occupationally exposed individuals have been reported as 160-635 ppm (Karppanen et al., 1972), 1-12.6 ppm (Chase et al., 1981), and 2-271 ppm (Wolff et al., 1981).

Special surveys have been made of PCB levels in the milk of lactating human mothers (Mes and Davies, 1979; Watanabe et al., 1980; NIOSH summary) and of levels in human embryonic and fetal tissues resulting from in utero transfer from Yusho females (NIOSH, 1977). Human milk samples with values of PCBs in the range 0.008-0.1 ppm have been observed. Clearly, concentrations in milk are higher than those in blood primarily because milk is rich in fat. Organs from the embryonic and

fetal tissue displayed PCB levels in the range 0.002-0.750 ppm for whole tissues, with fat derived from these organs yielding levels in the range 0.06-1.14 ppm.

C. PCB Metabolism and Excretion

Animal experiments involving exposure by feeding, intubation, or injection of purified PCB isomers in test animal models have yielded some important generalizations on the mechanisms employed by mammalian species to metabolize PCBs to more polar derivatives, and to excrete both parent compounds and metabolites. Beginning with ready absorption from the gut and transfer to circulating blood, or with direct injection into the bloodstream, a given PCB molecule ultimately reaches the liver where major metabolic actions are initiated. The processes of metabolism and excretion as a result of these actions are complex, and dependent on the molecular structure of the PCB. General features of these processes include the following points:

(1) Variable amounts of PCB metabolites are excreted via the feces after delivery to the gut lumen via the bile flow pathway. Unchanged PCBs can occur and be discharged in milk. Relatively lesser amounts are excreted as polar metabolites in urine than in feces in most animal models (Kato et al., 1980; Lay et al., 1979; Chen et al., 1976; Van Miller et al., 1975; Chen and Matthews, 1974).

(2) Metabolites are formed in patterns that differ quantitatively or qualitatively among mammalian species. They are generally formed by oxidative processes that are thought

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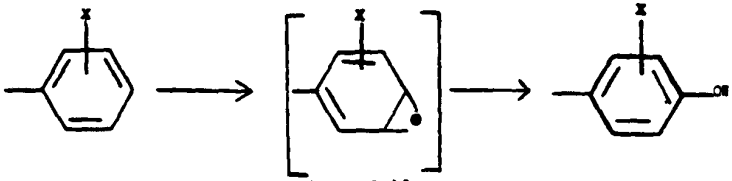
to involve an arene oxide formation that results in monohydroxylation, dihydroxylation, hydroxylation and methylation, or diol formation accompanied by partial reduction of an aromatic ring (Berlin et al., 1975; Lay et al., 1979; Lucier et al., 1978; Milling et al., 1979; Sundstrom et al., 1976; Gardner et al., 1973; Chen et al., 1976; Matthews et al., 1978; Van Miller et al., 1975; Hsu et al., 1975a; Hsu et al., 1975b; Burse et al., 1976). Evidence also exists for dechlorination of a PCB in the process of metabolism (Kato et al., 1980; Hutzinger et al., 1974b). For some PCB structures, the process of oxidative metabolism may be closely followed by excretion via the liver-bile-feces pathway (Chen and Matthews, 1974).

(3) Compounds with lower levels of chlorination (2-CB to 3 or 4-CB) generally undergo metabolism more readily, and faster than the more highly chlorinated PCBs. The more highly chlorinated PCBs may persist in tissues for years because they are not metabolized. Indeed, 10-CB is virtually inert.

(4) In the case of metabolism by oxidative pathways, the most facile process involving formation of hydroxylated products occurs when one or both aromatic rings contains adjacent pairs of ring carbon atoms (called vicinal ring atoms) that are unsubstituted by chlorine atoms. In the absence of unsubstituted vicinal positions, direct hydroxylation can occur in the ring, but with greater difficulty (Geyer et al., 1980; Matthews and Tuey, 1980).

The importance of vicinal unsubstituted positions on PCB rings in facilitating oxidative metabolism in the liver is explained by a mechanism that involves an arene oxide intermediate (Daly et al., 1972). When either or both of the vicinal positions contain chlorine, reaction rates will be lower, but the mechanism is not entirely ruled out. Additional molecular rearrangements, including the so-called NIH (National Institutes of Health) shift of a ring substituent (Daly et al., 1972), may be involved. Less is known about mechanisms of direct enzymatic hydroxylation that do not proceed through an arene oxide intermediate.



Arene Oxide

(5) Hydroxylated metabolites of the PCBs and their conjugates will generally display different orders of toxicity than those shown by the parent molecules.

(6) A general point of interest with respect to PCB metabolites lies in the observation that they are usually more polar than their parent compounds. Conjugation of the hydroxy and dihydroxy metabolites as glucuronides or sulfates can occur, leading to polar conjugates that can readily be excreted. The polar character of metabolites, in contrast with the non-polar

characteristics of the starting PCBs, can lead to differing distribution, storage, and excretion patterns for the two classes of chemical compounds. Polar metabolites are not readily partitioned into fat or reabsorbed from the urinary or gastrointestinal tracts. Therefore they are excreted relatively rapidly.

D. PCB Kinetics

Profiles of the dynamic growth and decay of PCB/metabolite concentrations in each key tissue can be drawn from controlled toxicological experiments. The distribution of a given PCB and its metabolites in the blood, tissues, and excreta of test animals is followed as a function of time after administration. Tissues are viewed as body compartments into which materials are delivered from the arterial blood supply, in which some metabolic processes may occur, and from which materials are delivered into the venous drainage systems. A collection of such compartments communicating with the blood supply and controlled by rates of flow through the compartments, with postulated equilibration of any given chemical in a compartment with its venous blood flow, constitutes an appropriate modeling system for correlating PCB distribution, storage, metabolism, and excretion kinetics in an animal over time. This multi-compartment model has been employed by Matthews and co-workers and others (Anderson et al., 1977; Bungay et al., 1979; Tuey and Matthews, 1977; Luts et al., 1977), to sort out the kinetics of specific PCB isomers in rodent models. The PCB administration can be either direct

injection of a PCB into the blood circulation, or its absorption into blood from the gut after feeding or intubation of the compound. Excretory pathways are via the liver/bile/gut route or the blood/kidney/urinary elimination system.

The success of a model equation system in fitting analytical data for a given PCB and predicting the shape of its concentration versus time curve for each organ or compartment depends in large measure on several factors, including: (1) the assignment of suitable values for distribution coefficients of PCB compounds in each compartment; (2) the differential blood flow to various organs; and (3) the clearance from organs and the body. This fitting process has now been carried out for a number of PCBs for which kinetic data are available (Anderson et al., 1977; Chakreborty, 1978). The goodness of fit of the model to each set of PCB kinetic data available attests to the validity of the assumption that materials partition at equilibrium between blood and tissue according to purely physical properties involving solubility parameters of the chemicals.

E. Miscellaneous Biochemical Effects of PCBs

Studies of the actions of PCBs in animal models and humans exposed to these chemical agents accidentally or in the occupational setting have revealed a variety of biochemical effects on mammalian organisms. Some, such as alteration of drug metabolism by virtue of PCB induction of microsomal mixed function oxidases (MFO), are treated elsewhere in this documen

Other effects appear to be unrelated to MFO actions, and have been detected in the course of acute or chronic toxicological experiments with laboratory animal models or epidemiological surveys of exposed human populations.

In an animal study (Bastomsky et al., 1975) aimed at probing the previous evidence on reduced serum bilirubin levels in Yusho patients, it was found that Aroclor 1254-treated rats showed increased liver microsomal protein, as expected, but with no significant elevation in liver bilirubin UDP-glucuronyl transferase activity that could have accounted for reduced serum levels. Other studies (Grote et al., 1975; Lake et al., 1979) have shown enhanced levels of this transferase activity. At present therefore, the mechanism underlying the hypobilirubinemia in Yusho patients remains speculative.

From epidemiological studies of Yusho patients (Strik, 1979), a rather general biochemical finding has been the observation of porphyrins in urine and porphyrin accumulation in liver, as a result of exposure to chlorinated hydrocarbons including PCBs. Chronic hepatic porphyria is the designated condition, which increases with exposure and can therefore be taken as an indicator of the extent of PCB exposure. Porphyria is discussed elsewhere in this text (section XI).

A biochemical factor that may bear on the toxicity of PCBs in certain sensitive human populations, e.g., fetuses, neonates, enzyme deficient adults, etc., is related to the ability to excrete the toxic phenolic metabolites rapidly and efficiently.

Since a common route of excretion involves preliminary conjugation of the phenolic hydroxyl groups with glucuronic acid in the body, or sulfate conjugation, it has been pointed out (Calabrese, 1977b) that human groups that are biochemically deficient in the ability to conjugate could be predisposed to accumulate PCBs and metabolites because of this deficiency. A more serious consequence of altered liver capability would be a reduced capacity to deal with arene oxide intermediates effectively.

An interesting biochemical defect in human lymphocytes has been studied (Lee and Park, 1980) that can be attributed to direct action of PCBs on these white blood cells. For both human lymphocytes and monocytes, it has been found that incubation of the cells with Aroclor 1254 in culture medium causes a decrease in their ability to take up glucose from the medium. A non-metabolizable analog of glucose, 2-deoxyglucose, was used to detect the biochemical defect, which was attributed to PCB exposure but which may well be more general for any organic chemical that concentrates in the fat of the cell wall. It may entail direct action of PCBs on an active transport process in cell membranes. In this regard, liver glucose-6-phosphatase has been found to be inhibited in rats fed various Aroclor mixtures (Litterest et al., 1972).

The processes by which PCB pretreatment influences rates of protein and nucleic acid (RNA) synthesis and turnover in rat liver tissues have been investigated systematically

(Marbonne, 1979a, b, c, e), using radiolabeled substrates. It is clear that liver tissue, in vivo and in vitro, responds to PCB treatment (Phenochlor DP6) by increasing the protein synthesis in liver microsomal fractions in a process that is both age and sex dependent. Concomitant increases in liver fat are also seen in vivo, as well as changes in levels of RNA synthesis in various liver fractions and increases in liver weights. From the turnover experiments in rats, it is also observed that microsomal membrane protein metabolism is enhanced by ingestion of Phenochlor DP6.

Some further biochemical effects of PCB exposures on the human are seen in workers occupationally exposed to these chemicals for extended periods of time (Smith et al., 1978). The findings, as yet unexplained in terms of requisite dosages or underlying mechanisms, are that: (1) the circulating triglyceride levels in blood plasma are elevated for exposed workers over controls, but are still within normal levels; and (2) the circulating levels of high density lipoprotein are lowered in exposed groups of workers.

Another biochemical effect seen in PCB-treated rats is worthy of note, since it relates to an impairment of excretion of an important drug and its metabolites (Schmoldt et al., 1979). In the Wistar rat pretreated with Aroclor 1248, the drug digitoxin and its metabolites were blocked to a significant degree from excretion via the bile. The results suggest that the

blockage is due at least in part to a PCB-induced impairment of the cleavage of one of the sugars from digitoxin.

Finally, the action of PCBs leading to induction of mixed function oxidases (MFOs) in the liver, with elevation of associated cytochromes P-450 or P-448, has potential consequences. These are discussed elsewhere (section XI).

F. Some Observations on Polychlorinated Dibenzofurans

The PCDFs are of special interest since they are known to be highly toxic in their own right, and the degree to which, as contaminants, they add to the potencies of PCB mixtures in production of adverse health effects in animal models and humans has not been fully evaluated. However, toxicological studies in animals with PCDFs containing one to four or more Cl atoms per molecule (Morita and Oishi, 1977; Goldstein et al., 1976; Veerkamp et al., 1981) have shown that the PCDFs are qualitatively quite similar to their structural PCB analogs with respect to properties of tissue distribution, metabolism, and excretion. In the mouse, the heavily chlorinated isomers localize in liver, spleen, and fat (Morita and Oishi, 1977), with a half-life for clearance from the body of about two weeks. In the rat, metabolism occurs by oxidative pathways leading to mono- and dihydroxylated derivatives (Veerkamp et al., 1981), with a wide variation in ring position by the hydroxy function among the lower chlorinated PCDFs. The octachloro derivative yields no metabolic products in tissues or excreta (Veerkamp et al., 1981). In

the chick (Goldstein et al., 1976), the 2,3,7,8-tetrachlorodibenzofuran (TCDF) has been shown to be relatively poor in enzyme induction. However, Goldstein et al. (1978, 1979a) have shown that 2,3,7,8-TCDF is a potent inducer of cytochrome P-450 and aryl hydrocarbon hydroxylase.

Some important data on PCDF metabolism and excretion in the human were obtained (Rappe et al., 1979) by analysis of liver tissue from two deceased patients in the Yusho disease group in Japan. From the differences in PCDF structural relationships in the contaminated rice oil and in the PCDF fractions isolated from the livers, inferences could be drawn with respect to PCDF structure (all containing four to six chlorine atoms per molecule) retained by the liver versus those that had disappeared from liver by processes of metabolism/elimination. In striking parallelism with PCB disposition in mammalian tissues, it was found that none of the PCDFs retained in liver had two vicinal unsubstituted (by Cl) positions in either aromatic ring. Apparently, all such molecules had been sufficiently susceptible to oxidative metabolism to be hydroxylated and excreted from liver in the bile.

The above observations are not to be taken as all-inclusive with respect to the body of information that must be developed in the toxicology of the PCDFs. This class of compounds, even at low contaminant levels, is an important contributor to the total spectrum of toxic effects from commercial PCB mixtures.

G. Summary and Opinion

Some general reflections and opinions can reasonably be drawn from the previous discussion regarding the use of animal-derived biochemical and kinetic information to predict certain events and hazards in human PCB intoxications.

(1) Pathways of absorption, distribution, metabolism, and excretion have been explored fairly extensively in animal models. From the species variability seen, coupled with limited observations in the human, educated guesses and predictions can be made on the occurrence of certain toxic effects and processes in the human.

(2) Mathematical analyses of kinetic data from animal modeling experiments lead to some generalizations (Luts et al., 1977) that could apply to PCB turnover kinetics in the human: (1) kinetic rate constants for metabolism of PCBs by the liver decrease as the degree of chlorination increases; (2) rate constants for biliary clearance of PCB metabolites from the liver are nearly the same for all PCBs; (3) urinary clearance rates for PCBs decrease as the degree of chlorination of the parent molecules increases; and, (4) for each PCB, the value of the distribution coefficient between fat and blood is greater than that in any other major tissue, indicating that the fat compartment of all tissues may constitute the major PCB depot.

(3) Kinetic models derived from animal data may be useful for prediction of time courses of action in the human once

additional data on metabolism and clearance rates for individual PCBs in human tissues are obtained.

(4) Some general PCB structure versus activity relationships have emerged from animal studies, particularly rodents, that can have useful predictive power for the human.

(5) There is some relevance of the features of the absorption/distribution/metabolism/clearance processes discussed in this section to the toxicology of PCBs in animals and humans. For example:

(a) The possibility that an arene oxide intermediate can occur in PCB metabolism has special significance in terms of potential reactions with protein, RNA, or DNA to cause tissue damage or damage to a cell's nuclear functions.

(b) The retention of PCBs in adipose or other tissue can have major significance by creating reservoirs from which material can be leached over time for reaction at other tissue sites.

(c) There is little evidence in humans for acute cytotoxicity of the kind usually associated with reactive metabolites. Rather, some of the adverse effects of PCBs, e.g., chloracne, could stem from the physical presence of unreacted material in the cells along with oils and/or sebaceous materials of the skin.

IV. General Toxicity

A. General Considerations

Any attempt to undertake a systematic evaluation of the toxicity of PCBs is confounded by a number and variety of factors that complicate the interpretation of the findings and limit their generalization. Therefore, these factors should be recognized at the outset of consideration of the available body of toxicological literature. The more important of these factors are listed as follows:

(a) The multiplicity of commercial products of both U.S. and foreign manufacture;

(b) The multiplicity of isomeric forms of PCBs in commercial products;

(c) Qualitative and quantitative differences in metabolism of different isomers within the same species;

(d) Qualitative and quantitative differences in metabolism of the same isomer between species;

(e) Differences in rates of metabolism of different isomers within the same species;

(f) Differences in rates of metabolism of the same isomer between species;

(g) Differences in the biological half-lives of different isomers within the same species;

(h) Differences in the biological half-life of the same isomer between species;

(i) The presence in commercial products of impurities of much greater toxicity than that of PCBs;

(j) The variability between commercial products of the same type (i.e., same degree of chlorination) in the concentration of impurities of much greater toxicity than that of PCBs;

(k) The variability between commercial products of the different types (i.e., different degrees of chlorination) in the concentrations of impurities of much greater toxicity than that of PCBs; and

(l) Differences between species in susceptibility to the toxic action of (i) individual isomers and their metabolites, and (ii) the impurities that may be present in commercial products.

The preceding factors may underlie the conclusion reached by the Panel of Hazardous Trace Substances (1972) that "[t]here is no consistent relationship between toxicity and degree of chlorination which is valid for different species and different routes of exposure." To this might be added the observation that there is often no consistent relationship between the results of investigations on products of the same degree of chlorination from different manufacturers. These observations constitute caveats that should be borne in mind as individual toxicological experiments and results are evaluated.

B. Impurities in Commercial Products

The work of Vos and his associates (Vos and Koeman, 1970; Vos et al., 1970; Vos and Beems, 1971) led to a recognition

the significant role played by traces of impurities in commercial PCBs in influencing the apparent toxicity of the latter. In studies involving three commercial PCBs of the same degree of chlorination, these investigators found marked differences in toxicity that were traced to the presence, in two of the products, of small amounts of chlorinated dibenzofurans (PCDFs) and chlorinated naphthalenes. The PCDFs are related closely, both structurally and toxicologically, to the chlorinated dibenzodioxins. The 2,3,7,8-tetrachlorodibenzo-p-dioxin isomer is an extremely potent toxicant in mammals, especially for the fetus. The chlorinated naphthalenes are less toxic than the chlorinated dioxins, but nevertheless cause chloracne and other symptoms in man similar to those produced by PCDFs.

The extent of the contribution made by contaminants to the toxicity of commercial PCBs is uncertain, but the consensus is that it is substantial. There seems little doubt that the skin lesions, including chloracne, are caused by PCDFs. The Panel on Hazardous Trace Substances (1972) states that the PCDFs "are probably the chief if not exclusive cause of chloracne in man." Fishbein (1974), in his review of the toxicity of chlorinated biphenyls, observes that "[l]iver damage and skin lesions are believed to be caused primarily by chlorinated dibenzofuran contaminants and to a minor extent by PCB itself." Furthermore, since the chlorinated dibenzodioxins exhibit pronounced embryotoxicity, it is not unreasonable to expect that the PCDFs share this property and, hence, are largely responsible for the fetal

deaths and resorptions that have been observed experimentally with commercial PCBs.

An appreciation of the role played by contaminants in the toxicity of commercial PCBs is important for two reasons. First, it may explain discrepancies between the results of studies of apparently similar commercial products. Second, it points up the difficulty of attempting to use PCB tissue levels to correlate the results of laboratory studies with observations of occupationally or environmentally exposed populations. For example, some animal populations in the environment appear to be unaffected by PCB tissue levels that are equal to or greater than those associated with adverse effects on comparable species in the laboratory.

C. General Toxicology

1. Acute Toxicity

The Aroclors of the PCB class have a low order of acute toxicity. The acute oral LD50s for rats range from 1-10 g/kg. The LD50s by single application to the skin of rabbits are approximately 1-3 g/kg. Oral and dermal LD50 data have been summarized by Fishbein (1974), Kimbrough et al. (1978), and the Panel on Hazardous Trace Substances (1972).

2. Subchronic and Chronic Toxicity

(a) General

Subchronic and chronic toxicity are grouped together for purposes of this discussion since the effects of chronic

exposure to PCBs are essentially extensions of those observed from repeated exposures of shorter duration.

There are numerous published studies in which commercial PCBs (Aroclors) have been administered by various routes for varying periods of time to most common mammalian species of laboratory animals. Out of this mass of observations, one may identify two principal classes of biological effects of these substances. These classes are (a) alterations in the liver, and (b) skin lesions.

(b) Alterations in the Liver

Enlargement of the liver, both in absolute terms and as a percentage of body weight, has been observed consistently in most species consequent to repeated exposure to PCBs, although it is more pronounced in rodents than in others. This phenomenon has been reported for mice (Kimbrough and Linder, 1974), rats (Bruckner et al., 1973, 1974a, b), guinea pigs (Voo and Van Driel-Grootenhuis, 1972), rabbits (Koller and Zinkl, 1973), dogs (Calandra, 1976), and monkeys (Allen et al., 1973). Early enlargement of the liver is primarily the result of an increase in the size of the hepatocyte associated with an increase in the amount of the smooth endoplasmic reticulum (SER). These developments are associated also with increased enzymatic activity of the liver (Bruckner et al., 1973).

A detailed discussion of the effects of PCBs on liver in test animal systems is given in section VI.

(c) Skin Lesions

Cutaneous effects from repeated exposure to commercial PCBs can be elicited by feeding to monkeys or skin application to rabbits, although the results are somewhat more dramatic in the former. The results of these animal studies are discussed in section V.

(d) Miscellaneous Effects

Hyperplasia and dysplasia of the gastric mucosa have been observed in monkeys fed a diet containing 300 ppm of Aroclor 1248 for three months (Allen and Norback, 1973). Gastrointestinal lesions do not appear to occur in rodents, except at very large single doses by mouth (Kimbrough, 1979). A dietary concentration of 2.5 ppm of Aroclor 1248 produced alterations in the menstrual cycles of adult, female rhesus monkeys (Allen et al., 1979). Menses were prolonged, and there was an increase in menstrual bleeding. Hepatic porphyria has been demonstrated in mice after feeding Aroclor 1254 (Kimbrough and Linder, 1974), in rats after feeding Aroclors 1254 or 1260 (Kimbrough, et al., 1972), and in rabbits after repeated skin application of Aroclor 1260 (Vos and Beems, 1971). Urinary excretion of coproporphyrin was increased in rats fed Aroclor 1242 (Bruckner et al., 1974), and both urinary and fecal excretion of porphyrins was increased in rabbits receiving repeated skin applications of Aroclor 1260 (Vos and Beems, 1971). Other effects reported for one species or another include structural changes in the kidney (Vos and Beems, 1971; Bruckner et al., 1974a, b), hematologic alterations

Bruckner et al., 1974a, b), and thymic atrophy together with a reduction in the number of germinal centers in the spleen and lymph nodes (Vos and Beems, 1971).

D. Summary and Opinion

Voluminous literature establishes that commercial PCBs are capable of producing a variety of biological effects when administered in large quantities to experimental animals. The majority of these effects can be grouped into two categories, namely, those involving the skin and those involving the liver. A number of miscellaneous effects that have been observed in one species or another can be considered secondary to the action of the substances on the liver. In general, these effects are only elicited by relatively high dosages of the PCBs, reflecting the low order of acute toxicity of the U.S. commercial mixtures.

There is a considerable range of species susceptibility to the biological activity of PCBs as measured by the size of the dosage, the duration of the exposure, and the severity of the effect. Mink appear to be the most susceptible, monkeys somewhat less so, and rodents the most resistant. There is no basis for a judgment as to which species most accurately serves as a model for man. A comparison of the observations on humans in the Yusho incident with those on monkeys fed relatively small amounts of PCBs has led some investigators to conclude that the latter species is an appropriate surrogate for man. Although there are some similarities between Yusho disease and the findings in monkeys, they are not sufficient to justify such a conclusion.

There is evidence throughout the literature that some of the biological effects observed experimentally with commercial PCB mixtures are caused not by PCBs themselves but by other chlorinated aromatic compounds present as impurities, such as the PCDFs. The significance of this finding is that PCB levels resulting from occupational or environmental exposures cannot be interpreted in the same way as those observed in experimental animals. A broader implication of this circumstance is that the results of laboratory studies are not necessarily predictive of what may be expected from incidental exposures since the nature of the exposure may have differed in the two instances.

As is always the case in experimental toxicology, the validity of test results as predictors of hazard to man must await confirmation or denial by observations of exposed human populations. Fortunately, the reports of actual injury to man from PCB exposure are few, although extensive epidemiological surveys have been conducted and others are in progress. An evaluation of the epidemiology of exposure to PCBs is the subject of section XII of this report. Still other sections of the report deal with specific potential health effects in greater detail.

V. Skin and Other Cutaneous Tissues

Epithelial and follicular hyperplasia and hyperkeratosis have been reported to occur following the application of PCBs on the skin of rabbits (Voe and Beems, 1971). Skin lesions have also been observed in rats and guinea pigs from the application of PCBs. Repeated application of Aroclor 1260 to the skin of rabbits caused thickening of the skin as a result of hyperplasia and hyperkeratosis of the epithelium (Voe and Beems, 1971).

Cutaneous effects have been elicited in male rhesus monkeys fed a diet containing 300 ppm Aroclor 1248. Within one month the animals lost considerable hair from the head, neck, and back (Allen et al., 1973, 1975). Similar effects have been observed in female rhesus monkeys fed a diet containing 25 ppm Aroclor 1248 for two months (Allen et al., 1974). Within six weeks the animals began to lose hair and developed obvious signs of edema of the lips and eyelids. Small pustules involving hair follicles appeared about the mouth, cheeks, and neck. Abraham and Allen (1973) showed that the infant monkey was able to tolerate doses of PCBs that produce extreme morbidity in adult monkeys. They suggested that there may be variations in absorption, distribution, metabolism, storage, and excretion in adult and infant monkeys that may account for these differences.

Follicular hyperkeratosis is an important feature of the occupational disease known as acne, which is characterized by the appearance of papules, comedones, and cysts. Industrial

dermatosis of the acneform type has been observed among workers exposed to chlorinated hydrocarbons (Jones and Alden, 1936; Mayers and Silverberg, 1938; Maroni et al., 1981). Seven cases of chloracne of the face and head have been reported among 14 chemical operators exposed from 5-19 months intermittently to low concentrations of chlorinated biphenyls (Meigs and Albom, 1954). Puccinelli (1954) and Hofman et al. (1962) report chloracne in several capacitor workers, whereas Smith et al. (1981) noted that none of the capacitor workers examined in this recent survey were found to have acneform lesions suggestive of chloracne.

The acneform eruptions that occur in the skin of both monkeys and rabbits may be caused by a squamous metaplastic change in the epithelium lining the sebaceous glands, which result in a change in the character of the secretion from normal oily to keratinaceous. This condition frequently results in plugging and rupture of the glands with consequent inflammatory reactions (acne). The question of whether a similar condition can occur in man from exposure to PCBs will be dealt with in another section of this report.

It has been suggested that the cutaneous eruptions that occur in both animals and man from exposure to commercial preparations of PCBs may be due to certain impurities. Chemical analysis of the PCBs that contaminated the rice oil that caused the Yusho disease in Japan showed high levels of polychlorinated dibenzofurans (Kuratsune, 1976).

VI. Effect of PCBs on Liver

A. Experimental Data

1. Liver Weight

The administration of PCBs may induce an increase in liver weight (Table 2). The effect is more prominent at the higher dose levels; the lower doses of PCBs do not increase liver weight. The detailed data of Kimbrough et al. (1972) are not included in the table. They found that Aroclor 1260, administered with the diet in doses of 500 and 1000 ppm for eight months, significantly increased liver weight in male and female rats; doses of 20 and 100 ppm were effective only in male rats. Aroclor 1254 increases liver weight in both male and female rats at doses of 20, 100, and 500 ppm.

Although the data in Table 2 illustrate the effect obtained in subchronic and chronic studies, it should be noted that liver weight may also be increased in acute toxicity studies. PCB congeners (penta-, hexa-, and heptachlorobiphenyls) given in a high single dose of 50 mg/kg, can increase liver weight in the rat; in most but not all tests, liver triglycerides, cholesterol, and phospholipids were increased (Yoshihara et al., 1979). In the monkey a single oral dose of 1.5 g or 3.0 g/kg of Aroclor 1254 produced slight enlargement of the liver in 4 days (Allen, Norback, and Hsu, 1974).

The increase in liver weight is correlated with hepatic cell hypertrophy and an increase in smooth endoplasmic reticulum

Table 2

Effect of PCBs on Liver Weight and Morphology

			Weight Changes +=increase 0=no change	Major Histological findings
Studies in Mice				
Kimbrough & Linder, 1974, Aroclor 1254			+	Plasmorphism, necrosis
Studies in Rats				
Bonnett, et al., PCB, 63% Cl	300 mg	6 days	+	Cells swollen, hyaline granules
	250 mg	up to 100 days	+	" "
Koplinger et al. 0247	100 ppm	18 months	+	
Aroclor 1254, 1260	10 ppm	18 months	0	
	1 ppm	18 months	0	
Aroclor 1242	100, 10, 1 ppm	18 months	0	
Litterest et al., 1972	500 mg	4 weeks	+	
Aroclor 1242, 1248	50 mg	4 weeks	+	
1254, 1260	5 mg	4 weeks	0	
	0.5 mg	4 weeks	0	
Allen & Abrahamson, 1973, Aroclor 1248, 1254, 1262	0.1% in. diet	6 weeks	+	Fat droplets, areas of necrosis
Brummer et al., (1973) Aroclor 1242	100 mg/k every 2nd day	3 weeks	+	Submucosal vacuolation
Brummer et al., 1974	25 ppm 5 ppm	2,4,6 months	0	No change with H&E stain, increase lipid with Sudan IV stain

CONTINUED

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Table 2 (CONTINUED)

Effect of PCBs on Liver Weight and Morphology

			Weight Changes +=increase 0=no change	Major Histological findings
Studies in Rats (Continued)				
Durse et al., Aroclor 1242, 1016	100 ppm	up to 18 months	0	Enlarged hepatocytes, vacuolated cytoplasm, characterized as mild changes
Studies in Rabbits				
Yee et al., Aroclor 1260 hexachlorobiphenyl	120 dermal 5 x week	4 weeks	+	Hydropic degeneration, necrosis
Keller & Siani, 1973				
Aroclor 1254	300 mg each/wk	14 weeks	+	Enlarged hepatocytes, necrosis
Aroclor 1242	" "	" "	+	Enlarged hepatocytes, some necrosis
Aroclor 1221	" "	" "	0	No histological change
Studies in the Monkey				
Allen et al., 1973				
Aroclor 1248	300 ppm	90 days	+	Enlarged hepatocytes, no necrosis
Aroclor 5460	5000 ppm	" "	+	" "

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Table 2A

Liver Lesions in Albino Rats Treated with Aroclors for 2 Years*

(Data from Levinskas, 1981)

	Control	Aroclor 1242			Aroclor 1254			Aroclor 1260		
Diet level, ppm	0	1	10	100	1	10	100	1	10	100
No. animals examined	23	32	29	16	30	26	26	26	25	25
Vacuolar change	1	7	8	9	7	9	13	5	7	9
Focal necrosis	1	1	1	0	1	1	1	4	3	6
Focal lymphoid infiltration	1	0	0	0	2	0	1	0	1	0
Focal hypertrophy hepatocytes	0	2	3	0	3	4	14	3	13	9
Nodular hyperplasia	1	1	1	0	0	3	14	0	7	6
Diffuse hyperplasia	5	3	3	3	6	3	14	6	7	12
Hepatoma	0	0	0	3	0	0	4	0	1	7
Cholangiohepatoma	0	0	0	1	0	0	2	0	0	4
Hepatocellular carcinoma	0	0	0	0	0	0	0	0	0	0

*The results of this study were presented in a summarized form by Calandra (1975) and were later reanalyzed and tabulated by Levinskas (1981)

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the rat, rabbit, and monkey (Vos et al., 1972; Allen and Hanahamson, 1973; Bruckner et al., 1974a; Allen, Norbeck, and Hsu, 1974; Allen, Carstens, and Barsotti, 1974). Ecobichon and Comeau (1974a, b) found that the effect of PCBs administered intraperitoneally on liver weight and on hepatic enzymes associated with hepatic endoplasmic reticulum was related to the position of the chlorine substitution on the biphenyl nucleus. However, all of the congeners and isomers administered at a dose of 50 mg/kg intraperitoneally for three days produced an increase in smooth endoplasmic, lipid droplets and microbodies, although the quantitative response varied (Hansell and Ecobichon, 1974).

2. General Histology

The administration of PCBs to experimental animals will produce histopathological changes in the liver. The main effects obtained are the production of enlarged hepatocytes, fat droplets, and slight degree of necrosis; the occurrence of these changes depend particularly on the dose of the PCB and to some extent on the particular Aroclor (Tables 2 and 2A). Necrosis seems to be more severe in the rabbit then in the rat. In general, the morphological changes observed in the liver of PCB-treated animals are similar to those found after treatment with other chlorinated hydrocarbons.

In a detailed study, Kimbrough et al. (1972) found that Aroclor 1260 (20, 100, 500, and 1000 ppm) and Aroclor 1254 (20, 100, and 500 ppm), given in the diet of rats for eight months, produced

enlarged liver cells and cytoplasmic inclusions. At the higher doses, there was evidence of lipid accumulation, which was associated with a foamy cytoplasm, and pigment accumulation in the Kupffer cells. The pigment gave a positive Prussian-blue reaction, indicating the presence of hemosiderin. Studies of rats four to six months after exposure to different doses of Aroclors 1016 and 1242 indicated that the morphological changes are reversible and disappear gradually after dosing is stopped; the hepatocytes were still larger than controls, but the frequency of vacuolated cytoplasm or inclusions within the cytoplasm had decreased (Bursa et al., 1974).

Aroclor 1254 was evaluated by the National Cancer Institute (1978). Fischer rats receiving 25 ppm in the diet for eight weeks had enlarged livers, but without evidence of histological abnormality. The administrations of doses of 25, 50, and 100 ppm for 104-105 weeks did not increase the frequency of liver lesions such as congestion, inflammation, necrosis, or angiectasis.

3. Adenofibrosis

Adenofibrosis (synonyms: bile duct proliferation, bile duct adenomatosis, cholangiofibrosis, fibroadenoma) has been observed in some rats receiving PCBs. Adenofibrosis is generally regarded as a benign lesion. In their review of experimental tumors, Stewart and Snell (1957) stated that there is no convincing evidence that adenofibrosis is a precancerous lesion.

It should be noted, however, that Reuber (1968), studying 2-acetamidofluorene and 2-diacetamidofluorene, suggested that adenofibrosis is a precancerous lesion for the development of cholangiocarcinoma.

(i) Studies in mice. Kimbrough and Linder (1974) observed foci of adenofibrosis in the liver of some mice with 300 ppm of Aroclor 1254 in the diet for 11 months. Ito et al. (1974) comment that they did not observe cholangiofibrosis in mice receiving Kanechlor.

(ii) Studies in rats. Kimbrough et al. (1972) observed adenofibrosis in rats treated with Aroclor 1260 and 1254; the effect was observed at the higher dose levels and particularly in animals receiving Aroclor 1254. When the feeding of 500 ppm of Aroclor 1254 was discontinued and the animals studied up to 10 additional months, the fat and liver content of PCB remained high and the adenofibrosis persisted (Kimbrough et al., 1973). In a later paper involving treatment with Aroclor 1260 at 100 ppm for 21 months, mention is only made that a few rats showed areas of adenofibrosis, indicating a low degree of response, but data are not tabulated (Kimbrough et al., 1975). In further studies by the same group adenofibrosis was not observed in rats fed Aroclor 1016 or 1242 (100 ppm) for up to 10 months (Burse et al., 1974).

In a study with three Aroclors, administration of 100 ppm in the diet for 24 months produced a low incidence of

cholangiohepatoma (Table 2A), but concentrations of 1 ppm or 10 ppm were without effect (Calandra, 1976; Levinskas, 1981). Treatment did not significantly affect ductal hyperplasia.

The study of the National Cancer Institute (1978) did not observe adenofibrosis in rats receiving Aroclor 1254 at doses of 25, 50, and 100 ppm for 104-105 weeks.

In studies with various Kanechlors, Ito et al. (1974) administered Kanechlor 500, 400, and 300 in the diet at concentrations of 1000, 500, and 100 ppm. At the concentration of 1000 ppm of the Kanechlors, the incidence of cholangiofibrosis ranged from 13 to 30% in the rats; cholangiofibrosis did not occur at levels of 500 or 100 ppm. Kimura et al. (1976) also reported cholangiofibrosis in rats treated with Kanechlor 400.

4. Hyperplastic Foci and Nodular Hyperplasia in the Liver

Hyperplastic foci or hyperplastic areas represent minimal changes in the hepatocytes. Such foci or areas of hyperplastic changes are uncommon in untreated young rats, but increase with age. The hyperplastic areas or foci may coexist with nodular hyperplasia and/or hepatocellular carcinoma. The significance of hyperplastic foci is that they may be part of a spectrum capable of progressing to a nodule (Squire and Levitt, 1975).

The hyperplastic nodule (nodular hyperplasia, neoplastic nodule, hepatoma) is generally as large or larger than the area of several lobules, and the lesion is sometimes elevated

[redacted]ove the surface of the liver. The lesion is frequently re-[redacted]rred to as a neoplastic nodule and some consider it to be a [redacted]anifestation of a carcinogenic process, the earlier stages [redacted]which may be represented by the hyperplastic foci discussed [redacted]bove. The use of these terms in the literature is confusing, [redacted]s some who use the word "hyperplastic nodule" regard the [redacted]esion to be part of the neoplastic process whereas others consider it to be unrelated to neoplasia. Some investigators [redacted]se the terms adenoma or hepatoma to designate the lesion, implying that it is a benign neoplasm.

Despite the differing terminology, it may be considered that the hyperplastic foci and nodular hyperplasia (neoplastic nodules) occurring in the liver are benign lesions rather than carcinomas. However, such nodules may be part of a sequence of neoplastic changes that eventually progress on to hepatocellular carcinomas. Although the data on hyperplastic foci and nodular hyperplasia are discussed in this section and hepatocarcinogenes[illegible] are discussed in section VIII, the experimental data on the incidence of benign and malignant lesions are given in the same table so that the overall biological effect of the treatment can be observed as a unit.

(i) Studies in mice. Ito et al. (1973) observed nodular hyperplasia in mice only at the highest dose level of Kanechlor 500. (Nagasaki et al., 1972, reported the same data.) Whereas Kanechlor 500 produced nodular hyperplasia at 500 ppm, lesser doses were not active and Kanechlor 400 or Kanechlor 300

was inactive at all doses studied (Table 3). There was some evidence that the administration of Kanechlor 500 increased the nodular hyperplastic response induced by α or β isomers of benzene hexachloride.

Kimbrough and Linder (1974) observed adenofibrosis and hepatomas in nine of 24 mice fed Aroclor 1254 (300 ppm in the diet) for 11 months; in animals fed Aroclor for only six months followed by a five month recovery there was no adenofibrosis and the incidence of hepatoma was only 1/24 mice.

(ii) Studies in rats. Keplinger et al. (1971) did not observe hepatic lesions in rats receiving different Aroclors for 18 months; however, re-evaluation of the slides indicated a significant increase of nodular hyperplasia in the treated animals (see National Cancer Institute, 1978).

Ito et al. (1974) observed nodular hyperplasia in rats receiving 100, 500, or 1000 ppm of Kanechlor 500; a lesser effect was observed with Kanechlor 400 and there was no significant effect of Kanechlor 300.

Kimbrough et al. (1975) reported a significant increase in the incidence of hyperplastic foci or areas and neoplastic nodules in female rats given 100 ppm of Aroclor 1260, mixed with the diet for 21 months (Table 4). In another study, the dietary administration of 100 ppm of Aroclor 1242, 1254, and 1260 for 24 months increased the incidence of nodular hyperplasia (Table 2A); a lesser effect was obtained with 10 ppm,

TABLE 3

Incidence of Liver Lesions in Male Mice

Treated with PCBs for 24 Weeks

(Data of Ito et al, 1973)

	ppm in diet	Incidence	
		Nodular Hyperplasia	Hepatocellular Carcinoma
Kanechlor 500	500	7/12	5/12
	250	0	0
	100	0	0
Kanechlor 400	500	0/12	0/12
	250	0	0
	100	0	0
Kanechlor 300	500	0/12	0/12
	250	0	0
	100	0	0
Controls	-	0/6	0/6

TABLE 4

Incidence of Liver Lesions in Female Rats

Treated with Aroclor 1260

(Data from Kimbrough et al., 1975)

Lesion	Incidence	
	Controls	Experimental
Hyperplastic foci or areas	28/173	182/184
Neoplastic Nodules	0/173	144/184
Hepatocellular Carcinoma	1/173	26/184

TABLE 5

Incidence of Liver Lesions in Male and Female Rats
Treated with Aroclor 1242, 1254 and 1260
100 ppm in Diet for 24 months
(Data from Calandra, 1975)

	Aroclor		
	1242*	1254**	1260
Nodular hyperplasia	8/20	13/27	7/27
Hepatomas	2/20	4/27	5/27
Hepatocellular carcinoma	0/20	0/27	0/27

*10 males and 10 females

**13 males and 14 females

TABLE 6

Incidence of Liver Lesions in Male and Female Rats

Treated with Aroclor 1254

(Data from National Cancer Institute, 1978)

	Males			Females		
	Low Dose	Mid Dose	High Dose	Low Dose	Mid Dose	High Dose
Number of animals necropsied	24	24	24	24	22	24
Hyperplastic foci** or areas	5	8	12	6	9	17
Adenoma, NOS+	0	0	1	0	1	2
Hepatocellular carcinoma	0	1	2	0	0	3

* Hyperplastic foci, hepatocellular adenomas or carcinomas were not diagnosed in the controls.

+ Not otherwise specified

** As defined in report

and 1 ppm did not produce a positive response (Calandra, 1976; Kinskas, 1981). All three Aroclors produced an increased number of hepatomas at the high dose (Table 5). There was no evidence of metastasis or invasiveness, and the lesions were regarded by the pathologists as benign tumors.

The results of a bioassay of Aroclor 1254 for carcinogenicity, using doses of 25, 50, and 100 ppm in the diet, are summarized in Table 6 (National Cancer Institute, 1978). Their use of terms is confusing, for although they use the words "nodular hyperplasia" in their table, they state in the text that "the areas of nodular hyperplasia appeared to be microscopically similar to what is currently termed 'focal areas of cellular alteration.'" Thus, we have used the term "hyperplastic foci or areas" in Table 6 to describe their results. It is evident from the data in Table 6 that the hyperplastic foci were present in a dose-related frequency. Although the incidence of the hyperplastic foci did not differ significantly from the controls, this incidence appeared to be related to treatment. The biological significance of the increase in "focal areas of cellular alteration" is not clear as relatively few adenomas were found.

Both the above studies (Kimbrough et al., 1975; National Cancer Institute, 1978) demonstrate an increase in proliferative lesions of the liver; the effect is greater with Aroclor 1260 than with Aroclor 1254.

(iii) Studies in dogs. Hepatic nodular hyperplasia did not occur in the dogs receiving dietary levels of 1, 10, or 100

ppm of Aroclor 1242, 1254, or 1260, respectively, for two years (Calandra, 1976). Each treatment group consisted of eight dogs (four female and four male).

5. Summary and Comment

The administration of high doses of PCBs to animals can produce hepatic enlargement and an increase in liver weights, which is associated with an increase in smooth endoplasmic reticulum. Other effects include a slight degree of necrosis and the presence of fat droplets and a vacuolated cytoplasm. These changes, which are similar to those found after treatment with other chlorinated hydrocarbons, are readily induced by high doses of PCBs, but are absent when lower doses of PCBs are given. The response appears to be greater with increased chlorination of the biphenyl nucleus but, depending on dose, even the high chlorinated derivatives may not produce a positive response.

Treatment with PCBs usually increases the occurrence of hyperplastic foci. The nodular hyperplasia, neoplastic nodules or hepatomas have been reported to be increased in some studies, but other evaluations have not confirmed these effects. The effects of PCBs on the occurrence of nodular hyperplasia, neoplastic nodules, hepatomas, or adenofibrosis is highly variable; some studies have reported a positive effect whereas others failed to show an effect of treatment. Again the change in histological response or in frequency of benign hepatic tumors is related to both the dose of PCB administered and the degree of chlorination of the PCB.

Data on hepatocellular carcinoma in PCB-treated animals are discussed in section VIII.

B. Clinical Data

1. Liver Function in PCB-exposed Workers

Based on results in animals, it was expected that if PCBs produced a significant degree of injury in man, it would be to the liver. Such has not been the case, as the clinical studies summarized below have provided little evidence for the occurrence of hepatic dysfunctions in PCB-exposed workers even though the blood level of PCB may be relatively high.

(i) Ouw et al. (1976) studied liver functions in 34 workers exposed to Aroclor 1242 for one month up to 23 years; 31 were exposed for more than one year and 16 for five or more years. Scattered individual abnormal test results were obtained: serum bilirubin was normal and in all 34 subjects, alkaline phosphatase was elevated in one of 34 subjects and serum transaminase (SGPT) was increased in five tests.*/ There was no relationship of the results to the blood level of PCB and the mean of each hepatic function test for the whole group was within normal limits. BSP

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*/ The abbreviations used in this section are as follows:

SGOT = serum glutamic oxaloacetic transaminase
SGPT = serum glutamic pyruvic transaminase
SGGT = serum gamma glutamyltranspeptidase
LDG = serum lactic dehydrogenase
AST = aspertate aminotransferase
ALT = serum alanine aminotransferase
SOCT = serum ornithin-carbamoyltransferase
BSP = bromsulfonphthalein

tests were also performed on seven workers with relatively high blood PCB; four of the seven tests were slightly above the normal limit of 5% but, as the authors state, since other conditions such as fever may increase BSP retention, these results by themselves could not be taken as proof of hepatic damage. The BSP test results did not show a significant correlation with blood PCB levels or the length of exposure (five to 23 years) to PCB.

(ii) Fischbein et al. (1979) studied liver function tests in 321 workers exposed to PCBs in an electrical manufacturing plant for less than five years to more than 25 years. The percent of tests that gave an abnormal test result was SGOT 2.2%, SGPT 7.2%, LDH 2.5%, alkaline phosphatase 1.2%, and serum bilirubin 5.3%, and indicated a "very low prevalence of abnormal liver findings." There was no comment or analysis to state that a certain number of the subjects showed a pattern of abnormal liver function tests indicative of hepatic dysfunction. These data can be taken to represent a series of random test results that might be expected in a population of 321 individuals ranging in age from less than 30 years to over 70 years. Control subjects or non-exposed workers were not included for comparison. There was perhaps some indication of a relationship of SGOT levels to plasma levels of PCBs, but the two exposure categories of PCB levels are too broad and require a finer analysis.

(iii) Baker et al. (1980) studied liver function in 148 individuals with various degrees of exposure to PCBs; the

an PCB serum levels for the four test groups varied from 17.4 to 75.1 ppb. There was no change in liver function tests (SGOT, SGPT, LDH, alkaline phosphatase, or serum bilirubin) in relation to PCB blood levels in either drinkers or nondrinkers of alcohol. Serum GGTP (gamma glutamyl transpeptidase) correlated with serum PCB, but a correlation did not exist when alcohol drinkers were removed from the analysis.

(iv) Maroni et al. (1981a, b) studied liver function in 80 workers exposed to PCBs for an average of 12 years and reported that 16 individuals had an abnormal liver finding as judged by clinical examination or by laboratory tests.

Inspection of the data shows relatively few instances of abnormal liver function tests. The most frequently altered laboratory tests were as follows:

8 of 80 subjects with increase of SGGT activity

7 of 80 subjects with increased serum amino-transferase activity (AST or ALT)

6 of 80 subjects with increase of SOCT activity.

It is evident from their data that many of the changes are slight, and as test results from control subjects were not included, we do not know what the normal test variations may be for 80 control subjects of a similar age. Further, examination of the data for the 14 subjects with clinical hepatomegaly shows only one subject with an abnormal test in three types of tests (SGGT, AST/ ALT, and SOCT); only two of the subjects gave a positive response in two of

the test types; eight subjects had an abnormality in only one test; three subjects had normal test results. Serum bilirubin and alkaline phosphatase activity were within the normal range in all subjects.

Based on the above review, it is evident that only one of the 80 subjects showed a pattern of test results indicative of abnormal liver function; the other test results reflect only random variations from normal.

Maroni et al. also reported that the mean level of blood PCBs in the 16 workers with abnormal liver findings was significantly higher than that of 64 workers without abnormal liver findings, but the ranges for the two groups show considerable overlapping and the two subjects with the highest blood PCB levels had normal liver function tests. The only control we can use to evaluate the suggested relationship between PCB blood level and liver function are the 10 subjects with chloracne; these 10 individuals had normal liver test results despite the fact that their mean blood PCB concentration was high and not significantly different from the mean blood PCB level found in the 16 workers discussed above. Thus, it cannot be said that this study demonstrates a relationship between a high blood PCB level and abnormal liver function tests, attesting further to the randomness of the liver function test results in the study.

(v) Smith et al. (1981a, b, c) evaluated liver function tests in PCB-exposed employees from an electrical manufacturing plant, a municipal electric utility company, and

privately-owned electric utility company. The data on SGOT and GGPT are difficult to evaluate as the results of the measurements are not given, and therefore may be assumed to be within normal population levels; rather, the authors sought correlations between the log of SGOT and GGTP with the log of the lower serum PCBs and the log of high serum PCBs. Calculations include simple correlations, separate regressions with the confounders as predictors, and squared partial correlation, plus other computations to see if associations existed. Their Tables 6, 7, and 8 summarize many of their calculations, and data for transaminases from table 7 are summarized below.

	Correlation With Serum log L-PCB	Serum log H-PCB
Electric equipment company		
log SGOT	NS	Sig
log GGTP	Sig	Sig
Municipal electric utility company		
log SGOT	NS	NS
log GGPT	NS	NS
Privately-owned utility company		
log SGOT	Sig	NS
log GGTP	NS	NS

Sig = statistically significant
NS = not significant
L-PCB = lower chlorinated biphenyls
H-PCB = higher chlorinated biphenyls

Correlations (associations) were found at the equipment company but the data cannot be examined to determine if the calculated value has any medical significance. Correlations at the publicly-owned utility company were not significant. At the privately-owned utility company, the only positive finding was a positive association of SGOT with serum L-PCB. It is not clear what the change in this one test result means as the serum L-PCBs were not significantly different between the exposed and nonexposed groups.

The test results for total bilirubin, alkaline phosphastase, and lactic dehydrogenase are not discussed, and it is presumed that these measurements of liver function were not abnormal.

2. Liver Disease in PCB-Exposed Workers

Medical examination of PCB-exposed workers has not shown the presence of liver disease. In the study of Fischbein et al. (1979), physical examination of 326 individuals (age less than 30 to over 70 years) revealed four individuals with abnormal liver size, two of whom had a history of heavy alcohol intake; one of the four had a slight elevation of one liver function test (SGOT of 55).

In another study of 148 individuals with varying degrees of PCB exposure, there was no evidence of liver disease as determined by medical history and physical examinations (Baker et al., 1980). Smith et al. (1981) did not find evidence for liver

disease in their subjects, there being no significant findings on physical examination of workers at an electrical equipment manufacturing plant who were heavily exposed to PCBs, or workers at a municipal utility company or a private utility company who were less heavily exposed.

Deaths from cirrhosis of the liver were not increased by exposure to PCB (Brown and Jones, 1981); six deaths were observed (three of the six consumed alcohol regularly) versus 5.6 expected.

3. Summary and Opinion

The review of clinical data demonstrates that exposure to PCBs does not significantly affect liver function tests. Liver function remains normal in individuals with measurable, and frequently high levels of serum PCB. Also, exposure to PCBs does not result in the production of clinically detectable liver disease. The induction of enzyme systems in the liver and the biological significance of this process, as mediated by PCBs, are discussed in section XI.

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VII. Gastric Lesions

The oral administration of PCBs to nonhuman primates has been shown by Allen and co-workers to induce hypertrophy and hyperplasia of the gastric mucosa. Mucosal cysts may be present within the epithelium of the stomach, but in the mucosal lining and the submucosa, there may be edema of the submucosa of the stomach. In addition, there is frequently invasion of the underlying mucosa by isolated glandular elements of the mucosal epithelium. General effects of this nature have been produced in the monkey by:

(i) A single oral dose of 1.5 g or 3 g of Aroclor 1248 (Allen, Norback, and Hsu, 1974).

(ii) Aroclor 1248, 300 ppm and Aroclor 5460 (a polychlorinated triphenyl), 5000 ppm in the diet for 90 days (Allen, Abrahamson, and Norback, 1973; Allen and Norback, 1973).

(iii) Aroclor 1248, 25 ppm in the diet for 2 months (Allen, Carstens, and Barsotti, 1974).

(iv) Aroclor 1248, 100 ppm in the diet for 2-3 months (Allen, 1975).

(v) Aroclor 1248, 2.5 ppm and 5.0 ppm in the diet for up to one year (Barsotti and Allen, 1975). (Gastric changes were not listed for these doses in Allen's review.)

(vi) The hyperplastic gastritis may persist for over one year following discontinuance of PCB exposure (Allen, 1975).

A mixture of low chlorinated biphenyl (Clophen A-30) was not observed to produce gastric lesions in the monkey (Iatropoulos et al., 1977).

The findings of Allen et al. were recently confirmed and extended by Becker et al. (1979). Their study involved six monkeys, one untreated and one each receiving a diet containing 3, 30, or 300 mg/kg of PCB (Aroclor 1242); two monkeys received a diet containing 10 mg/kg. Monthly biopsies taken from the greater curvature of the stomach showed a dramatic decrease in the number of parietal cells with a concomitant increase in the number of mucous neck cells. The zymogenic (chief) cells were also reduced in number. This was followed in all treated animals by a mucous conversion of the gastric epithelium, with down-growth of the gastric glands into the submucosa and the eventual formation of cysts. It is noteworthy that the lesions were confined to the stomach; no changes were found in other regions of the gastrointestinal tract.

The gastric changes can be described as a dysplastic growth pattern, but there is no neoplastic transformation (Allen and Norback, 1973). However, the authors speculate that they are "suggestive" of an eventual neoplastic transformation.

Analysis of the results obtained in the monkey indicates that the PCB-induced morphologic changes in the gastric mucosa

may be specific to this species and not predictive of possible effects in man.

(i) Even within the monkey a specificity of action is present, as the lesion induced by PCBs is found only along the greater curvature of the stomach; neither the cardiac nor pyloric portions were affected (Becker et al., 1979).

(ii) Hypertrophy and hyperplasia of the gastric mucosa have not been reported in the rodent (Allen and Abrahamson, 1973), rabbit (Vos, 1972), or in other species (Vos and Koerman, 1970).

Clinical findings to date have not suggested or indicated that exposure to PCBs increases the occurrence of cancer of the stomach in the human (see also section VIII, relating to carcinogenicity).

VIII. Carcinogenesis: Experimental and Clinical

A. Experimental Studies

All authors do not use the words tumorigenesis and neoplasia to indicate the same type of response. Tumorigenesis is a general term that refers to both benign growths and malignant growths; compounds may affect the occurrence of benign tumors without inducing cancer. Neoplasia means simply a new growth. The term "neoplasia" can refer to a benign or malignant growth. Oftentimes authors may combine data relative to benign and malignant growths so that when the terms tumorigenesis or neoplasia are used, they must be carefully defined.

1. Hepatocellular Carcinoma

(i) Studies in mice. Ito et al. (1973) observed hepatocellular carcinomas in mice only in the high dose group given Kanechlor 500; lower doses of Kanechlor 500 or the other Kanechlors did not produce a carcinogenic response (Table 3). The administration of 300 ppm of Aroclor 1254 in the diet for 11 months did not induce hepatocellular carcinomas in mice (Kimbrough & Linder, 1974).

(ii) Studies in rats. The administration of Kanechlor 400 for 400 days did not induce hepatocellular carcinomas (Kimura & Baba, 1973), but the period of treatment may have been too brief to detect a carcinogenic effect. In a further study Kimura et al. (1976) administered Kanechlor to rats for six months but due to body weight changes a variable dosage schedule was employed. Following the cessation of treatment, the rats were

fed on a normal diet for 270-410 days; autopsy, after a total experimental period of 450-590 days, did not reveal hepatocellular carcinoma in any of 12 rats.

Ito et al. (1974) treated rats with different doses of Kanechlor 500, 400, and 300 for periods up to 52 weeks; hepatocellular carcinomas were not observed, but the duration of treatment was probably too short to rule out the possibility of a positive response.

The three major studies pertaining to PCBs and hepatic carcinoma in the rat are those of Kimbrough et al. (1975), Calandra (1975), and the National Cancer Institute (1978). Kimbrough and co-workers, using the Sherman strain of rat, found that 100 ppm of Aroclor 1260 in the diet for 21 months produced a significant increase in the incidence of hepatocellular carcinoma in female rats (section VI, Table 4). Male rats were not studied.

The administration of three different Aroclors at a dose of 100 ppm to rats for 24 months (Table 5) did not induce hepatocellular carcinoma (Calandra, 1975). The author states that this negative finding was based on evaluation of the liver sections by three pathologists, who read the slides independently and separately. He states further that Professor P. Pour re-evaluated the Kimbrough slides and did not agree with the reported findings (see also section VI, Table 2A).

The results of the National Cancer Institute (1978) bioassay of Aroclor 1254 for possible carcinogenicity are shown in section VI, Table 6. Fischer 344 rats were used and the PCB

mixture was administered at three dose levels (25, 50, and 100 ppm) in the diet for 104-105 weeks. The effect of the treatment on body weight and mortality at the higher dose levels demonstrated that maximum tolerated doses were used, thus providing a satisfactory test of carcinogenic potential. A sufficient number of rats of both sexes was available for meaningful statistical analyses of the incidence of late-developing tumors. Treatment was associated with only three hepatocellular carcinomas in male rats, which was not significantly different from the controls, and it was concluded that Aroclor 1254 was not carcinogenic in the bioassay.

(iii) Studies in dogs. Hepatocellular carcinoma did not occur in dogs (four male and four female per group) receiving 1, 10, or 100 ppm of Aroclor 1242, 1254, and 1260, respectively, in their diets for two years (Calandra, 1975).

(iv) Discussion. Data from the mouse provide only limited and restricted evidence for a carcinogenic effect of the Japanese compound Kanechlor 500 (Table 3). Studies on the rat give conflicting results on hepatic carcinoma. (Section VI deals with the benign hepatic proliferative lesions found in the treated rats, which may or may not indicate carcinogenic potential.) Kimbrough et al. (1975) reported an increase of hepatocellular carcinomas in female rats receiving Aroclor 1260, whereas the studies of Calandra (1975) and the National Cancer Institute (1978) did not observe a significant increase in hepatocellular carcinomas in rats receiving different Aroclors. Whether the

divergent results are related to the different strains of rats that were used, represent differences in the effect of the two Aroclors, or are due to other factors is not known. It is obvious, however, that in view of the differing results obtained it is not possible to extrapolate or project possible effects in man. Hepatocellular carcinomas did not develop in dogs treated with Aroclor for two years.

2. Bladder Cancer

Kimbrough (1972) observed bladder cancers in two rats fed 100 ppm of Aroclor 1260 for eight months. In a later study with 200 rats receiving 100 ppm of Aroclor 1260 for 21 months the only bladder tumor observed (a transitional cell papilloma) was in a control animal, and it was concluded that "the occurrence of the bladder tumor in the previous experiment was apparently unrelated to the ingestion of Aroclor 1260" (Kimbrough et al., 1975). This type of variation demonstrates the unreliability of attaching significance to small changes in tumor incidence in a given experiment, particularly when the incidence does not show a statistically significant difference from a control group.

Benign or malignant bladder tumors did not occur in rats treated with Aroclors 1254 (25, 50, and 100 ppm) for 104-105 weeks (National Cancer Institute, 1978).

The above studies do not demonstrate that administration of Aroclor 1254 or Aroclor 1260 induces bladder cancer in the rat.

3. Stomach, Intestinal Tract Cancer

Treatment of female rats with Aroclor 1260 (100 ppm in diet) for 21 months did not induce tumors in the gastrointestinal tract (Kimbrough et al., 1975).

Treatment of rats with Aroclor 1254 (25, 50, and 100 ppm in the diet) for 104-105 weeks did not induce gastrointestinal carcinomas (National Cancer Institute, 1978). Tumors occurred in random manner as illustrated in Table 7.

4. Carcinogenesis - Other Organs

Studies with PCBs in relation to cancer of the liver, gastrointestinal tract, and urinary bladder have been discussed separately above. In the studies with PCBs other organs have been evaluated in detail without finding any effect of chronic administration of Aroclors on the incidence of benign or malignant neoplasms. The following appraisals refer to tumors of these other organs.

Kimbrough et al. (1975) found that the chronic administration of Aroclor 1260 to rats did not affect the incidence of benign tumors or carcinomas of the thyroid gland, adrenal gland, uterus, lung, and other organs. Frequently investigators look only for increases in tumor incidence, when in fact decreases are often obtained. It is worth noting that mammary adenocarcinoma occurred in 5/173 control animals versus an incidence of 1/184 in treated animals. If the incidence had been reversed, some authors may have commented or suggested that PCBs may increase the occurrence of mammary cancer, but such would not have been

Table 7

Incidence of Gastrointestinal Carcinomas
in Rats Treated with Aroclor 1254
(Data from National Cancer Institute, 1978)

	Number of Carcinomas			
	Control	Low Dose	Med. Dose	High Dose
Males				
Stomach, adenocarcinoma	0	0	1	0
Jejunum, carcinoma	0	0	0	1
Cecum, adenocarcinoma	0	0	1	0
Females				
Stomach, adenocarcinoma	0	1	1	0

the case as the number of mammary adenocarcinomas in control groups can vary significantly from study to study. If the incidence of spontaneous tumors can vary, then the number of malignancies in the treated group will vary with each experiment independent of the treatment given. An additional illustration of tumor variability is the incidence of ovarian granulosa theca cell tumors which was 5/149 in controls versus 0/163 in the treated animals.

In the National Cancer Institute (1978) study, the chronic administrations of Aroclor 1254 was without effect on the development of benign or malignant neoplasms in the various body organs of the rat (the liver, gastrointestinal tract, and urinary bladder were discussed separately above). In the study, interstitial cell tumors of the testes were present in nearly all control and treated animals, there being no effect of treatment. Leukemias, which were the second most common neoplasms, were found in 13% of control males and 17% of control females. A statistically significant dose-related trend for leukemia was present in the treated males but not in the female rats. However, direct dose comparisons between each treatment group (male or female) and the control group were not statistically significant, so that an affect in males could not be clearly related to the administration of Aroclor 1254. Adding the few lymphomas to the leukemias for the analysis did not change the

conclusion. Kimbrough et al. (1975) also did not find a significant effect of Aroclor 1260 on leukemia incidence (1/173 in controls versus 0/184 in treated animals).

It may be concluded from these studies that the chronic oral administration of high doses of Aroclors 1260 or 1254 does not induce benign or malignant tumors of the thyroid gland, adrenal gland, uterus, lung, hematopoietic system, pituitary gland, thymus, kidney, and other organs in rats.

5. Summary and Opinion

Animal studies do not provide convincing evidence that PCBs induce liver cancer. Of the major studies in the rat, one has been judged positive and two have been negative. Hepatic carcinoma was not produced in the dog. Chronic administration of Aroclors in the rat did not induce bladder cancer, gastrointestinal carcinomas, or cancer of the thyroid gland, pituitary gland, adrenal gland, uterus, lung, hematopoietic system, or other organs.

B. Clinical Studies

The studies of Brown and Jones (1981) and Bertazzi and co-workers (1981) have evaluated the relationship between exposure to PCBs and the subsequent development of cancer. Both analyses are retrospective mortality studies of workers to determine the cause of the death and, for malignancies, the specific type of cancer causing the death; the deaths are designated as "observed cases." The person-years of exposure

of the workers to PCB were determined and combined into calendar time periods and five-year age groups to calculate from mortality statistics the number of "expected" deaths. The number of observed versus expected deaths was then compared. Background data relative to these studies are summarized briefly, as follows:

(i) Brown and Jones (1981). The authors analyzed 163 known deaths occurring among 2,567 workers exposed to PCBs for 39,018 person-years. Exposure to PCBs ranged from three months to over 20 years. The type of PCBs used at the plants were Aroclor 1254, 1242, and 1016.

(ii) Bertazzi et al. (1981). The authors analyzed 27 deaths occurring in 1,310 workers exposed to PCBs for 20,565 person-years, determining "observed" versus "expected" rates for malignancies. Mortality was studied for a 25-year period (1954-1978). Exposure up to 1964 was mainly to Aroclor 1254 and Pyraline 1476; starting in 1965 mixtures with 42% chlorine were used (mainly Pyraline 3010 and 3011).

(iii) Bahn et al. (1976, 1977). These authors report two cases of malignant melanoma in 31 men exposed to Aroclor 1254. It is not clear from their studies if they are discussing morbidity or mortality; Brown and Jones (1981) interpret the report as mortality.

Pertinent data on the mortality from malignancies are summarized in Table 8 and are discussed below.

All Malignancies. Brown and Jones reported 39 observed cases of cancer versus 43.8 expected cases, whereas Bertazzi et al. found a statistically significant increase in males, but not in female workers (Table 8). There was no increase in the risk of mortality from all malignancies with length of exposure or with the number of years of employment (Brown and Jones, 1981).

Rectum. The only statistically significant difference observed in the study of Brown and Jones was for rectal cancer in females from Plant 2 (Table 8). There was no significant finding for females in Plant 1, males in Plant 1 or 2, or for the combined data for males and females. The incidence of rectal cancer showed a slight, but statistically insignificant, increase with increase in latency; no direct relationship with increased length of exposure is apparent.

Bertazzi et al. (1981) did not report a case of rectal cancer in PCB-exposed individuals.

Stomach, Pancreas. The studies did not demonstrate an increased risk for stomach or pancreatic cancer (Table 8).

Hepatocellular Carcinoma. Three cases of liver cancer were observed in the study of Brown and Jones (1981), but the difference from the control rate was not reported to be statistically significant (Table 8). Bertazzi and coworkers did not mention observing any case of hepatic cancer. Examination of the data for latency effect or for length of exposure to PCBs did not show any relationship to development of liver cancer (Brown and Jones, 1981).

Table 8

Deaths from Specific Types of Cancer

Comparison of Observed Deaths in PCB Workers
With Expected Deaths

Reference	Malignancy	Sex	Number of Cases: Observed	Expect	SMR	Statistical Significance
1	All	M,F	39	43.79	89	NS
2	"	M	8	3.32	241	P=0.04
2	"	F	6	2.33	258	NS
1	Rectum	M	1	0.51		NS
1	"	F(plant 1)	0	0.18		NS
	"	F(plant 2)	3	0.58		P<0.05
1	"	M,F	4	1.19	336	NS
1	Stomach	M,F	1	1.66	60	NS
1	Pancreas	M,F	1	1.98	51	NS
2	Digestive Organs (stomach, pancreas, biliary tract)	M	3	0.88	340	NS
		F	0	-	-	NS
1	Hepatic Carcinoma	M,F	3	1.07	280	NS
1	Lymphatic & Hematopoietic	M,F	2	4.34	46	NS
2	"	M	2	0.46	435	NS
2	"	F	2	0.45	444	NS
3	Melanoma	M	2	0.84		P=0.061
1	"	M,F	0	-	-	NS
2	"	M,F	0	-	-	NS

Ref 1. Brown and Jones, 1981
Ref 2. Bertazzi et al., 1981
Ref 3. Bahn et al., 1976, 1977
SMR. Standardized mortality ratio (observed deaths/expected deaths x 100)
NS. Not significant

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Lymphatic and Hematopoietic Cancer. The two studies show diametrically opposite risk values, although neither is statistically significant (Table 8).

Melanoma. Bahn et al. (1976, 1977) reported two cases of malignant melanoma occurring among 31 men who had been exposed to Aroclor 1254. Based on the Third National Cancer Survey incidence rates, Bahn et al. calculate for a person-year analysis that only 0.04 malignant melanomas would be expected, the difference being statistically significant (P=0.001). The extensive studies of Brown and Jones and of Bertazzi et al. fail to confirm the increased risk of mortality for malignant melanoma reported by Bahn and co-workers (Table 8), raising doubts about the significance of the Bahn studies. Even an association with the low P value of 0.001 has not been confirmed.

Summary. The clinical evaluation of PCBs relative to cancer is currently based on a limited amount of data, and any conclusion regarding their effects must be regarded as tentative. Nevertheless, some detailed analyses are available and conclusions based on them, as listed below, are of some significance.

1. Retrospective mortality studies have not demonstrated a consistent relationship between exposure to PCBs and the development of a particular type of cancer.

2. The clinical findings on hepatocellular carcinoma are of great interest as some experimental studies report an

increase in liver cancer in rodents receiving PCBs. Although Brown and Jones (1981) observed three cases versus 1.07 expected cases, the difference is not statistically significant. Their analysis of PCB exposure and risk of mortality from liver cancer is also noteworthy since it did not demonstrate an effect of latency (number of years from date first employed) or a relationship to increased duration of employment in jobs involving PCB exposure. These latter observations are, however, based on small numbers. Bertazzi et al. (1981) did not report any significant relationship between PCB exposure and liver cancer. Taken together these studies do not confirm the projection of a risk for liver cancer in humans based on the animal studies.

3. The SMR (Standard Mortality Ratio) may vary widely in different studies, and emphasis should not be placed on an increase in the SMR found in one study unless a significant change in SMR can be confirmed in several repeat studies. For example, Brown and Jones found the SMR for lymphatic and hematopoietic malignancy to be decreased while Bertazzi et al. reported an increase, although neither result was statistically significant (Table 8).

4. Brown and Jones observed a statistically significant increase in SMR for rectal cancer in women at one plant, but not in a different plant, and no significant effect in male workers at either plant was observed. Bertazzi et al.

did not report any rectal cancer (Table 8). Overall, therefore, a convincing demonstration of rectal cancer as a result of extended exposure to PCBs has not been made.

IX. Reproductive Effects

A. Reproduction

Numerous reports have appeared in the literature on the effects of polychlorinated biphenyls on reproduction in animals. Gellert and Wilson (1979) showed that female Sprague-Dawley rats given 30 mg/kg Aroclor 1221, 1242, and 1260 by gavage during days 14 through 20 of pregnancy had no effect on the reproductive function of the offspring as judged by (a) normal estrus cycles, (b) normal appearance of ovaries and uteri, and (c) fertility of males. Feeding 550 ppm of Aroclor 1254 for 67 days to Sherman rats resulted in fewer litters, smaller litter size, and 100% mortality by day three of the $F1_a$ pups. At 100 ppm survival of both $F1_a$ and $F1_b$ offspring was reduced. The pups were smaller than controls but appeared normal at weaning. Aroclor 1260 fed at a dietary level of 500 ppm (35.4 mg/kg) for 67 days prior to mating markedly reduced litter size and survival-to-weaning in the $F1_a$ and $F1_b$ generation. Dietary levels of 5 ppm Aroclor 1254 and 100 ppm Aroclor 1260 had no effect on reproduction in rats exposed through two generations (Linder et al., 1974). A dietary concentration of 2.5 ppm of Aroclor 1248 produced alteration in the menstrual cycle of adult female rhesus monkeys. Menses were prolonged and menstrual bleeding was increased (Allen et al., 1979).

Keplinger et al. (1971) fed rats and dogs Aroclor 1242, 1254, and 1260 at doses of 1.0, 10.0, and 100 ppm. No adverse

effect on reproduction was observed in rats given 1.0 and 10 ppm Aroclor 1242, but there was a decrease in survival of pups at 100 ppm of Aroclor 1242, 1254, and 1260 as well as a decrease in mating indices. The effect of PCBs on reproduction in beagle dogs and swine has been studied by Earl et al. (1974). Aroclor 1254 interfered significantly with reproduction in dogs at doses above 2.5 mg/kg/day while in swine 10.0 mg/kg/day lowered fertility and survivability of neonates. The reproductive effects in dogs are questionable because of unexplained changes in the reproduction pattern among controls.

B. Teratogenicity

1. Introduction

Teratogenicity is that property of an agent whereby it is capable of inducing congenital defects in the developing embryo. Such agents that are chemical substances are known as "teratogens" and the defects they induce are known as "terata." Although teratogenicity is considered generally to involve only anatomical defects, some authorities regard functional or biochemical changes as manifestations of teratogenicity.

A distinction must be made between teratogenicity and fetotoxicity, i.e., toxicity to the fetus. The finding of dead or resorbing fetuses in the uterus of an experimental animal is not evidence of a teratogenic action of the test substance. Similarly, a smaller size of the newborn is indicative of fetotoxicity rather than teratogenicity.

A substance may appear to be teratogenic if it produces severe toxic effects on the pregnant female. Maternal disease and malnutrition affect the number and quality of the offspring. Defects in the offspring that are secondary to toxic effects of the substance on the mother are not considered teratogenic.

Teratogens produce their harmful effects during the period of formation of cells, tissues, and organs. Hence, once development of the fetus has been completed, a teratogenic event can no longer occur. Chemical substances administered to the mother can be transmitted, together with their metabolites, via the milk to the suckling young, and may produce toxic effects in the latter. However, such effects are not indications of teratogenicity.

Conventional tests for the detection of teratogenicity involve administration of the test substance to pregnant females at repeated intervals throughout the period of organogenesis, e.g., days six through 15 of the gestation in the rat. The treated females are sacrificed on the day prior to parturition, and the fetuses removed from the uterus surgically for examination. Alternatively, the test substance may be administered over relatively long periods of time, and the animals allowed to breed normally as in the usual one- to three-generation reproduction studies. The appearance of malformed offspring among the succeeding generations would be evidence of teratogenicity.

In order for a chemical substance to which the mother is exposed to exert a direct action on the conceptus, it or one

or more of its metabolites must be able to cross the placental barrier. Transplacental passage of PCBs has been demonstrated in several animal species (Allen et al., 1980; Curley et al., 1973; Couvillion et al., 1974; Grant et al., 1971), and is known to occur in the human (Funatsu et al., 1972).

2. Mice

PCBs were not teratogenic in mice at dosages up to 500 mg/kg given on days one through six or days seven through 11 of gestation (Toeruek, 1973). However, a recent study (Marks et al. 1981) with the hexachlorocongenar 3,3',4,4',5,5'-hexachlorobiphenyl in mice at dosages in the range of 0.1-16 mg/kg/day during days six through 15 of gestation produced a significant increase in fetal malformation, a significant decrease in average fetal weight, and an increase in the percentage resorptions.

Torok (1976) reported that oral administration of 375 mg/kg or 750 mg/kg of 2,2'-dichlorobiphenyl to mice on days one through three of gestation resulted in prolongation of the interval between breeding and parturition. He attributed this observation to delayed implantation. Although the treated animals had fewer litters and lesser mean litter sizes, there was no indication of teratogenicity.

Some mice exposed to 3,4,3'4'-tetrachlorobiphenyl were reported to exhibit a "waltsing syndrome" (Davis et al., 1979; Tilson et al., 1979). The dosage was 32 mg/kg administered by gavage to the mothers on days 10 through 16 of gestation. The

syndrome consisted of increased motor activity, hyperreflexia, and episodes of head bobbing and rotational movements that were present up to at least eight months of age. Not all exposed mice were affected similarly, but even those that did not exhibit the syndrome showed diminished performance in various neurobehavioral tests. Tilson et al. (1979) refer to these observations as the "behavioral teratology" of 4-CB.

3. Rats

There are a plethora of studies in which the reproductive effects of feeding various Aroclors to rats have been investigated (Calandra, 1976; Gellert and Wilson, 1979; Keplinger et al., 1971; Keplinger et al., 1972; Linder et al., 1974; Villeneuve et al., 1971a). Collectively, these studies reported fetotoxicity as the dosage was increased, but no teratogenicity was demonstrated. It may be useful to note the order of magnitude of the dosages involved. Villeneuve et al. (1971a) found no effect from the administration of dosages of up to 100 mg/kg per day orally to pregnant females from the sixth through the fifteenth day of gestation.

Ultrastructural lesions in thyroid follicular cells and a reduction in serum thyroid hormones have been reported in neonatal and weanling rats whose mothers had been fed a diet containing 50 ppm or 500 ppm of Aroclor 1254 throughout the period of gestation (Collins and Capen, 1980). The authors suggest that alterations in thyroid structure and function in the fetus or neonate may be related to subsequent disturbances in growth or development.

4. Dogs

In the study conducted by Earl et al. (1974), pregnant bitches were given dosages of 0.25, 1.0, or 5.0 mg/kg of Aroclor 1254 from the day of breeding to the day on which they were necropsied. At 5.0 mg/kg, there was an increase in the percentage of resorptions, a decrease in the number of live pups per litter at birth, and a reduction in the percentage of those surviving to two weeks. The terata observed consisted of enlarged fontanelles, cleft palates, and supernumerous phalanges. This dosage was said to limit diet consumption severely. The authors state that one litter of the controls "may have had a genetic defect that caused an unusually high incidence of terata."

5. Swine

Earl et al. (1974) included miniature swine (Hormel strain) in the investigation described immediately above. Pregnant sows were given daily oral dosages of 1 mg/kg, 10 mg/kg, or 30 mg/kg of Aroclor 1254. Dosing began 21 days before breeding and was continued until the day of necropsy. The authors concluded that dose-related effects were seen at all treatment levels as evidenced by decreases in the number of pregnancies, number of live pigs farrowed per litter, and percentage of live offspring after two weeks of age. Syndactyly and cleft palates were observed in the young of sows receiving 10 mg/kg, and patent fontanelles and cleft palates in the offspring of those receiving 30 mg/kg. As in the case of the dogs, the higher dosages caused a marked reduction in food consumption.

6. Monkeys

In a study reported by Allen et al. (1974), six adult, female rhesus monkeys were fed a diet containing 25 ppm of Aroclor 1248 for two months. During this period, all animals developed characteristic signs of toxicity, although they maintained a regular menstrual cycle. One animal died. At the beginning of the fifth month, or three months after discontinuance of exposure to the test substance, an attempt was made to breed the survivors. Three animals appeared to conceive, but only one succeeded in carrying her fetus to term. Although this infant was well developed, its body weight was considerably lower than that of the average rhesus infant. Examination of the tissues showed no gross or microscopic lesions.

In a second study by the Wisconsin group (Barsotti et al., 1976) involving 18 adult, female rhesus monkeys, nine were fed a diet containing 2.5 ppm, and nine were fed a diet containing 5 ppm of Aroclor 1248. After seven months on these diets, the eight surviving animals from the 2.5 ppm group and eight from the 5 ppm group were mated with control males. All animals in the 2.5 ppm group became pregnant, but three of these resorbed their embryos; the remaining five gave birth to live infants. In the 5 ppm group six animals became pregnant. These impregnations resulted in three abortions, one resorption, one stillbirth (suffocation during difficult delivery), and one uncomplicated birth. At birth, the six infants were small; however, other than their small stature and focal areas of dermal

hyperpigmentation, their general appearance, hemograms, and osseous development as evaluated radiographically were normal.

The adult, female rhesus monkeys that were the original subjects in the study discussed above were fed the diets containing 2.5 ppm or 5 ppm of Aroclor 1248 for six months prior to breeding, throughout gestation, and for three months after delivery for a total of about 18 months (Allen et al., 1980). Only 16 females were bred, inasmuch as one had died and another was dropped from the study for some reason not explained. About one year after discontinuance of the Aroclor-containing diets, the animals were bred again to control males. All of the seven survivors in the 5 ppm group conceived, but only four gave birth to live infants. In the 2.5 ppm group, one animal had an abortion and the remaining seven had uncomplicated deliveries. Apart from their somewhat smaller size compared to the young of the control animals, the infants appeared normal. Analyses of adipose tissue from two stillborn infants of mothers in the 5 ppm group showed the presence of PCBs, but histological evaluation of adipose and other tissues showned no abnormalities.

7. Clinical Data

Funatsu et al. (1972) studied in detail four babies born to mothers who had ingested rice oil contaminated with a heat-exchange fluid containing PCBs, PCDFs, and PCQs. The mothers were among the population exposed in the "Yusho" episode. Three of the four babies exhibited some evidence of intrauterine malnutrition or retardation of growth, and all four had dark brown

pigmentation of the skin that was most pronounced at the genitalia, axillae, and near the fingernails. The same pigmentation was noted on the lips, gums, and palate. While one or more of the infants displayed other clinical signs, no neurological or cardiovascular abnormalities, nor any malformations were observed. The pigmentation of the skin and mucous membranes disappeared within two to five months of age in all cases.

8. Summary and Opinion

(a) In a variety of tests, commercial PCB mixtures (Aroclors) showed no teratogenic activity in mice, rats, rabbits, and monkeys.

(b) Earl et al. (1974) have not demonstrated convincingly a teratogenic action of Aroclor 1254 in dogs or swine. An evaluation of their work suffers from a paucity of information and the possible presence of a genetic defect in the dog colony. The published abstract tends to be misleading. Examination of the unpublished manuscript shows that the authors did not regard the two lower dosages as teratogenic for either species. The highest dose is said to limit food consumption severely in both species. Therefore, it is likely that the defects observed in the offspring were the result of severe maternal malnutrition. Hansen et al. (1975) failed to find teratogenic effects in swine when the mothers were fed a diet containing some 20 ppm of Aroclor 1242 throughout gestation and nursing.

(c) The observations of Collins and Capen (1980) on ultrastructural alterations in the thyroid glands of perinatal

rats whose mothers were exposed to Aroclor 1254 are indicative of functional changes rather than of teratogenicity.

(d) The occurrence of a "waltzing syndrome" in mice exposed prenatally to 3,4,3',4'-tetrachlorobiphenyl might represent a true teratogenic effect (Davis et al., 1979). This phenomenon usually results from a structural or functional defect of the middle ear. The dosage used to produce the syndrome is relatively high. While the exposed animals were not uniformly affected insofar as the overt signs are concerned, Tilson et al. (1979) presented evidence to show a wider prevalence of more subtle neuro-behavioral effects. It is not known whether this condition could be induced by a commercial PCB mixture.

(e) The scientific literature presently supports the conclusion that PCBs present no appreciable risk of teratogenicity for humans, in our opinion, in view of the essentially negative test results in four test species and the questionable positive findings in the dog and in swine.

C. Fetotoxicity

Rabbits given 1.0 mg/kg of Aroclor 1254 daily for 28 days of gestation had no effect on the developing fetus but doses of 12.5 to 50 mg/kg were fetotoxic. Rats appear to be more resistant than rabbits, as doses up to 100 mg/kg do not cause fatal deaths or malformations (Villeneuve et al., 1971a). Embryotoxic effects of Kanechlor 300 and 500 were produced in

Sprague-Dawley JCL rats when fed at levels of 500 ppm in the diet throughout gestation (Shiota, 1976b). Diets containing 0 ppm of Aroclor 1248 were fetotoxic to rhesus monkeys.

Fetuses and neonates of mothers with Yusho disease have developed some of the characteristic signs of disease as a result of transfer of PCBs to the fetus and infant through the placenta and breast feeding (Yamashita, 1977; Matsuda, et al., 1978; Yakushijji et al., 1978). Studies in mice on the transfer of PCBs to fetuses and offspring indicate that the amount transferred depends upon the chemical structure of the individual compounds and the position of the chlorine atoms within the chemical structure (Matsuda et al., 1978, 1979).

Aroclors 1242 and 1254 are potent inducers of hepatic microsomal enzymes. A single intraperitoneal injection of 100 mg/kg of Aroclor 1242 to rats increased liver weight, total microsomal activity, as measured by hydroxylation of acetanilide and N-demethylation of aminopyrene, and hepatic cytochrome P-450 (Bruckner et al., 1973). The breakdown of endogenous substances such as progesterone, estradiol, and testosterone has been shown to be increased in animals pretreated with chlorinated biphenyls (Orberg, 1978). It is possible that alterations in the metabolism of the endogenous substances by PCBs may upset the normal balance that is essential for implantation of the fertilized ova in the uterus (Smith, 1968). Feeding a PCB mixture containing 60% chlorine significantly increased the uterine weight of guinea pigs (Voo, 1972).

Yamashita (1977) studied the clinical features of PCB, PCDF, and PCQ induced fetopathy in four babies born from mothers poisoned by contaminated rice oil. There was intrauterine retardation of growth, dark brown pigmentation on the skin and mucous membranes, edematous face, and exopthalmus. In some cases the retardation persisted for many months but the infants eventually gained their weight for the age group.

Although over 100 nursing mothers residing in Michigan during 1977-1978 had residues of PCBs in breast milk ranging from 1.0 ppm to over 3 ppm, there have been no reports of serious adverse effects on reproduction or infant mortality (Wickizer, 1981).

Summary and Opinion

1. It is apparent from studies on humans and animals that certain classes of polychlorinated biphenyls are more toxic than others and that the degree of chlorination is one of the determinant factors in their toxicity. But, as stated previously under cutaneous toxicity, the presence of contaminants may be responsible for the adverse effects on reproduction. Oishi et al. (1978, 1980) compared the activities of PCBs and dibenzofurans in rats and found that dibenzofurans markedly depressed body weight, decreased weights of the thymus, ventral prostrate, and seminal vesicles and reduced hemoglobin and hematocrit values, while PCBs had little or no effect.

2. On the question of fetotoxicity in PCB-exposed females, positive results are seen in certain test animals (rats, dogs, rabbits) when the PCBs are administered at relatively high doses (greater than 10 mg/kg) to pregnant animals. In the human, the only reported evidence for fetotoxicity in exposed populations stems from the unique Yusho event, in which causation may not be linked to PCBs. No such reports have been made on other exposed human populations, suggesting the absence of this effect in the human under occupational exposure conditions.

X. Mutagenesis

A. General

The term "mutagenesis" refers to any process that induces a permanent change (mutation) in the genetic composition of a cell, thereby causing that cell to differ in a consistent way from its parent. If a mutation occurs in a germ cell, the offspring resulting from the union of that cell with another will have an altered genetic composition that will persist in the germ line unless the alteration is lethal. Mutations occur spontaneously through unknown mechanisms, but they also may be caused by radiation or chemical substances (mutagens). While in a strict sense the term "mutation" applies only to changes in the DNA at the molecular level, it is considered broadly to include alterations in the number and structure of chromosomes.

Mutagenicity is the property of an agent, chemical or physical, to induce mutations. Chemical subetances may be tested for mutagenicity by a variety of methods, among which are those that employ (a) bacterial test systems, (b) cytogenetic analysis in vivo, (c) cytogenetic analysis in vitro, and (d) dominant lethality in a rodent.

B. Bacterial Test Systems

The "Ames test" is the most popular test of mutagenesis employing a bacterial test system. It is a so-called "backward" mutation system that uses a series of mutant strains of salmonella typhimurium that have lost the ability to synthesise the amino

acid histidine. Hence, they can grow only if exogenous histidine is supplied. A mutation has occurred if, after exposure to the chemical substance, the organisms regain the ability to grow in the absence of histidine.

Aroclors 1221, 1254, and 1260 showed little mutagenic activity in the Ames test (Wyndham et al., 1976) with indications that Aroclors with lower chlorine contents are weakly positive in the Salmonella test systems. However, these results must be discounted since they could not be replicated (McMahon et al., 1979; Safe, 1980). As a general finding, Heddle and Bruce (1977), McMahon et al. (1979), Schoeny et al. (1979), and Safe (1980) were unable to find evidence of mutagenicity of PCBs in bacterial test systems.

C. Cytogenetic Analysis in Vivo

In this procedure, the experimental animal is treated with the test substance and, after a suitable period of time, sacrificed for examination of rapidly dividing tissues. Bone marrow and the seminiferous tubules are generally the most frequently used tissues for this purpose. It is customary to inject the animals with colchicine several hours before sacrifice in order to promote the accumulation of cells in the metaphase stage of division. In this stage, the chromosome can be examined more readily for abnormalities.

In two investigations, PCBs were judged not to have produced chromosomal abnormalities. Dikshith et al. (1975)

examined seminiferous tubules of rats at different intervals after daily dosages of 50 mg/kg of Aroclor 1254. Green et al. (1975a) examined both bone marrow and spermatogonial cells of rats after either a single dose of 5000 mg/kg of Aroclor 1242, or four daily doses of 500 mg/kg. In all cases, it was concluded that no significant chromosomal damage had occurred.

The micronucleus test is a test for agents that tend to break chromosomes (clastogens). A micronucleus is a fragment of chromatin that has broken away from a chromosome during cell division and has failed to be included in either of the daughter nuclei. The phenomenon can be observed best in newly formed erythrocytes since these stain differently from the mature erythrocytes in that they exhibit polychromasia for a period of 24 hours or so. Furthermore, the nucleus has been extruded at the last maturation division so that the micronuclei, which remain behind, are readily visible in an otherwise chromatin-free cell. Micronuclei occur in a small fraction of normal red cells, but their incidence is increased by the action of clastogens. The test is carried out by administering the agent to the test animal, and examining the polychromatic erythrocytes in bone marrow smears after some interval of time has been allowed for micronuclei to form.

Heddle and Bruce (1977) reported Aroclor 1254 as negative in a micronucleus test.

D. Cytogenetic Analysis in Vitro

Hoopingarner et al. (1972) activated cultured human lymphocytes with phytohemagglutinin and treated them with 100 ppm of Aroclor 1254 at various stages of a division cycle. The cells then were examined for chromosomal aberrations for the different stage treatments. Aroclor 1254 had no apparent effect on chromosomal integrity as measured by cytological evidence.

E. Dominant Lethality in Rodents

A dominant lethal mutation is one that occurs in a germ cell. While it does not impair the function of that cell, it kills the fertilized ovum or the developing embryo. Mice and rats are the preferred experimental species. In its simplest form, the test consists of treating males with the suspected mutagen, mating them with normal females, and counting the number of viable offspring. The test could be used to detect dominant lethal mutations in females, but it would be difficult to rule out adverse effects on the embryo that might be secondary to non-genetic effects on the mother.

Green et al. (1975b) concluded that Aroclors 1242 and 1254 were not mutagenic since they failed to induce dominant lethal mutations in rats. In similar studies reported both by Keplinger et al. (1972) and Calandra (1976), Aroclors 1242, 1254, and 1260 were administered to male, albino mice in a single intraperitoneal dosage of either 500 mg/kg or 1000 mg/kg. Subsequent matings of these animals to control females

showed no effect of treatment on the number of implantation or resorption sites, number of viable embryos, or preimplantation loss.

F. Summary and Opinion

There is no evidence from in vivo test systems that any commercial PCB mixture is mutagenic. The same observation holds true for the bulk of the investigations employing in vitro techniques. In our opinion, therefore, it is quite unlikely that the PCBs as a class evoke mutagenic activity in the human, either acutely or chronically. Since chemical mutagenesis and carcinogenesis often correlate for a given active chemical, this opinion is reinforced by the essentially negative findings on carcinogenesis in populations occupationally exposed to PCBs (sections VIII and XII).

XI. Other Health Effects

A. Enzyme Induction

1. Introduction

Most chemicals that are allowed to enter the body are converted by the body to a variety of different chemical entities. In this manner, food becomes transformed into energy. Chemicals, other than food or those that are naturally present in the body, that are introduced into the body are generally called "xenobiotics," and they also are frequently converted by the body to derivatives of the original compounds. The conversion processes are regulated by the enzymatic systems generally termed biotransformation systems. Although there are a multitude of xenobiotic substances to which humans are exposed, there are only a few different enzyme systems involved. The body basically biotransforms chemicals by oxidizing, reducing, hydrolysing, or combining (conjugating) the agent with other chemicals. Although each of these systems is important, of particular interest here are those systems that result in conversion of the original compound to the oxidized derivatives.

It is not uncommon for the body to react to some xenobiotic compounds that it normally biotransforms by increasing its ability to perform the biotransformation function by producing an increase in the amount of enzymes available. This process, which is called "induction" of the enzyme system, effectively makes the body more capable of biotransforming not only the compound that initiated the induction but also all other compounds

that are oxidized by the same enzymatic system. In this manner it is feasible for a given xenobiotic agent to induce a biotransformation system that affects the ability of the body to biotransform not only the original compound but also a large number of other xenobiotics as well as some naturally existing chemicals within the body. Shortly, it will be shown that the PCBs in general have been described as being effective, that is, potent inducers of major oxidative biotransformation systems in experimental animals and in the human. Via induction of enzymes, the concentration of various normally occurring chemicals may be altered. The scientific evidence associated with these subjects will be evaluated in terms of the available current literature.

The major oxidative biotransformation system in the body, as far as xenobiotics are concerned, is present in greatest activity in the liver and is present in lesser activity in most other tissues. In experimental studies, the liver generally serves as a monitor of drug or chemical effect on the oxidizing enzymes. The enzymes are located in the "microsomal" fraction of the liver cells. This is a fraction of the cell that can be obtained by proper ultracentrifugation techniques. The biotransformation system of interest is known as the "microsomal mixed function oxidase system" (MFO). Functionally this system operates to incorporate oxygen into the xenobiotic agent via a series of enzymatic actions. The system does this by making an "active" oxygen atom available via a hemeprotein enzyme. This hemeprotein is in fact a family of proteins

[redacted]llectively identified as "cytochrome P-450." The ability [redacted]the enzyme to operate as an oxidative system is dependent [redacted]the existence of several naturally occurring substances [redacted], in particular, on the existence and quantity of available [redacted]tochrome P-450 in the microsomal fraction of the liver.

Microsomal P-450 can be measured directly or indirectly [redacted]ing various substrates. Direct measurement of P-450 is based [redacted] measurement of the protein system from which these enzymes [redacted]btained their name, that is, when the enzymes are reduced and [redacted]ombined with carbon monoxide they exhibit, in a spectrophotometer, maximal absorption of light energy at the wavelengths of 450 nanometers, hence the name cytochrome P-450 system. The P-450 system can also be measured in terms of its activity on specific substrates such as ethylmorphine and antipyrine. Induction of this system is measured in terms of an increase in P-450 and/or its activity (based on units of protein per sample of microsomes). Investigations of enzyme induction have separated the P-450 enzymes into two groups, identified as P-450 and P-448 groups, on the basis that various components of the P-450 group of enzymes are "induced" to different degrees by different xenobiotic agents. The P-450 enzymes are those that are mainly induced by the barbiturates, whereas the P-448 enzymes are mainly induced by 3-methylcholanthrene and show maximal absorption at 448 nanometers. The literature includes studies that suggest that the P-448 enzymes as well as the P-450 enzymes are induced

by certain PCBs although there appears to be some species and tissue specificity in their inductive properties.

Investigations of the effects of PCBs on cytochrome P-450s have centered on two areas of interest. One involved the induction mechanism via the use of either a commercially available sample of a single PCB congener (such as 2,4,5,2',4',5'-hexachlorobiphenyl) that was synthetically prepared and could be tagged with a radioactive atom to facilitate analytical work. Generally, a group of experimental animals (rats) was administered the PCB. Samples were then obtained at various levels. Livers were then examined directly for the quantity of cytochrome P-450 or indirectly for P-450 and P-448 activity via its enzymatic action on various substrates. The liver may also be examined histologically and for evidence of the state of protein synthesis. Induction of the P-450 enzymes in the human is estimated by measuring the plasma elimination rate (plasma half-life) of antipyrine in controls as compared to exposed subjects. Antipyrine is a drug that is completely absorbed when given orally and completely metabolized by the liver P-450 microsomal system.

The second area of interest concerned the ability of the liver microsomal system to biotransform PCB. Of particular interest was the nature of the intermediate and final products of the biotransformation process. This subject is important in understanding the toxicology of the PCBs because of the following hypotheses:

(a) Certain PCBs induce the microsomal mixed funtion [redacted]dation systems thereby influencing not only their own [redacted]tabolism but also the metabolism and time course of action [redacted]ravailable endogenous hormones as well as other xenobiotics [redacted]cluding drugs) administered to humans.

(b) Certain PCBs or contaminants of commercial [redacted]operations of PCBs may lead to the formation of intermediate [redacted]oxide type derivatives, and these derivatives can covalently [redacted]d to macromolecules in the liver thereby leading to hepatic [redacted]icity.

2. Induction of Liver Enzymes

Various studies have reported on the effect of short [redacted]m exposure of rats to mixtures of chlorinated biphenyls. [redacted] such study by Ecobichon et al. (1974) used the Aroclors identified as Aroclor 1016, 1221, 1242, and 1254, and another study by a French investigator, Narbonne (1980), used a French preparation known as Phenoclor DP6. In both studies the sample material consisted of a mixture of congeners of the chlorinated biphenyls. These studies showed that when rats were administered 10 ppm of the PCBs in their diet for only one day, the livers from the animals showed induction of P-450, aniline hydroxylase, and aminopyrine-N-demethylase. The induction of these enzymes was maximum in about five days. If the rats were given 10 ppm of the PCBs in the diet for eight consecutive days, induction occurred in three to five days and to a lesser extent over the remain-

ing eight-day interval. In the Ecobichon study, intraperitoneal injection of the Aroclors in doses of 50 mg/kg was made for three consecutive days. Animals were sacrificed 96 hours later. Mixed function oxidative enzymes were found to be induced in the liver. The greatest induction was seen with the more highly chlorinated Aroclors. The conjugation enzyme induction occurred rapidly on exposure to the Aroclors, and particularly to those Aroclors that are more highly chlorinated. The PCBs used in these studies were commercial grade.

In order to better understand which of the P-450 cytochromes are induced by the PCBs, Ryan et al. (1979) treated groups of rats with Aroclor 1254, phenobarbital, or 3-methylcholanthrene. The livers were used to prepare three different P-450 fractions on the basis of differing molecular weights and they identified the three fractions as P-450$_a$, P-450$_b$, and P-450$_c$. All three of the P-450s were obtained from the PCB-treated animals. P-450$_a$ and P-450$_b$ were obtained from the phenobarbital-treated rats and P-450$_a$ and P-450$_c$ were isolated from the 3-methylcholanthrene-treated rats. (P-450$_c$ is probably equivalent to P-448). Therefore, this study showed that the Aroclor induced at least three identified cytochromes including the type induced by phenobarbital and the type induced by 3-methylcholanthrene.

In 1980 Parkinson et al. investigated the validity of the concepts that were current at that time regarding the structure-activity relationship between specific PCB congeners

hepatic enzyme induction. The study was designed to yield structure versus activity data. Basically, they conducted experiments in rats using eight synthetic PCB congeners plus phenobarbital and methylcholanthrene as enzyme inducers. They concluded that in order for a PCB to induce a methylcholanthrene-type or a mixed-type liver enzyme system, the PCB would have to contain chlorine substituted at specific positions on the phenyl rings, whereas the PCB inducers of the phenobarbital type had multiple diverse structures that could not readily be defined.

Whether PCBs are administered for as short a time as one to three days or whether they are administered daily for up to a year, various liver enzymes appear to be induced, but the phenomenon of induction does not seem to be specifically very harmful to the animals. Allen and Abrahamson (1979) fed rats diets containing 100 ppb of Aroclor 1248, 1254, and 1260 for 13, 26, and 52 weeks. The growth rate of these rats was comparable to the controls but the test animals did show liver hypertrophy, some focal cellular degeneration, and an increase in serum lipids. In general, the effects were no greater in those animals that received the diet for a year than in those that received the diet for 13 weeks.

Alvares *et al.* (1973) published results from experiments that involved treatment of rats with Aroclor 1254. Intraperitoneal administration of 25 mg/kg/day for six days

produced a tripling of cytochrome P-448 content of the livers and a 10-fold increase in the enzyme activity involving benzo(a)-pyrene hydroxylation (which is a typical 3-methylcholanthrene type of induction), as well as an increase in ethylmorphine-N-demethylation (a typical phenobarbital type of induction). They therefore concluded that Aroclor 1254 induced a mixture of both P-448 and P-450. In 1977, Alvares and Kappas described some additional work that showed the ability of Aroclor 1254 to cross the placental barrier of the rat, to be transmitted to the neonatal rat through the mother's milk, and to cause increases in biotransformation enzymes in the fetus and newborn.

Goldstein et al. (1978, 1979) attempted to resolve the question of whether pure PCB congeners had enzyme-inducing properties that were different from those produced by commercial preparations of the single congeners or the PCB commercial mixtures (such as Aroclor 1254). These authors synthesized a "pure" sample of 2,4,5,2',4',5'-hexachlorobiphenyl and showed that it had different enzyme induction properties than did the same commercially obtainable, specially prepared, congener that was reported to be "99% pure." The difference in the induction capability of the two preparations was primarily in regard to the induction of P-448 cytochromes in which the synthetically pure isomer, at doses of 250 mg/kg administered to female rats, induced aryl hydrocarbon hydroxylase (AHH: a P-448 enzyme system) only five-fold; whereas the commercial isomer at a dose of 50mg/kg produced a 30-fold increase of AHH. Also, a GC-MS analysis

of the two preparations of hexachlorobiphenyl showed that the commercial preparation contained four contaminants that were not present in the pure congener. Two of these contaminants were identified as a tri- and a tetrachlorodibenzofuran (TCDf). TCDF was then shown to be a potent inducer of AHH and cytochrome P-448. The ED (effective dose, 50% of test animals) for TCDf re: enzyme induction was found to be 0.5 ug/kg for three days. Therefore, the conclusion was that even a 99% pure congener that was commercially obtainable can contain sufficient dibenzofuran to alter the enzyme induction action.

In one report, Alvares et al. (1977) had studied alterations in drug metabolism in both rats and humans. In the rat study Aroclor 1016 elicited a barbiturate type of induction of hepatic enzymes. That Aroclor did not induce cytochrome P-448; however Aroclor 1254 did induce cytochrome P-448. The human study involved five workers in a capacitor manufacturing plant who handled primarily Aroclor 1016. These exposed workers showed a low half-life (10.8 hours) of antipyrine as compared to control non-exposed subjects (who showed a half-life of 15.6 hours). The volume of distribution of the drug in the two groups was not different, so the comparison of the half-lives of the drug in the two groups is valid. Thus, enzyme induction occurs in the human in response to occupational exposure to Aroclor 1016 and the induction

as measured by antipyrine metabolism is a P-450 type of induction.

In 1975 Bickers et al. reported on the effects on liver enzymes associated with topical administration of immersion oils (as used in microscopy). These immersion oils were known to contain approximately 30% PCBs. One to 10 microliters of the oils were applied daily for six days to the shaved backs of rats and the animals were sacrificed on the seventh day. The authors found that both skin and liver enzymes were induced. In a second experiment 10 microliters of the oil were topically administered on one occasion only, and the animals were sacrificed at various intervals following application of the oil. P-450 and liver monooxygenases were induced (including benzo a-pyrene hydroxylase, a P-448 enzyme system) showing maximal effect in two days with a slow return to normal by 28 days. In this study there must have been very large differences between individuals in the control group because their data show very large differences between groups with only a 95% significance. The immersion oils currently marketed in the U.S. do not contain PCBs.

3. Metabolites of PCBs

Shimada and Sato (1980) studied the reactive metabolites of PCB metabolism. Their work involved the use of isotope-labeled PCB congeners. This work suggests that PCB epoxides may be the activated forms that covalently bind the macromolecules in the liver cells. A hexachlorobiphenyl congener

(2,4,5,2',4',5'-hexachlorobiphenyl) that has no adjacent unchlorinated atoms in the biphenyl ring and that cannot be converted to the epoxide was found not to be covalently bound although accumulation of this PCB in the liver was found to occur. Other PCBs show covalent binding that is principally with microsomal proteins rather than the ribosomal RNA; a conclusion based on the finding that various proteases would solubilize the radioactivity of the labeled atom. Treatment of the animals with phenobarbital produced livers that showed good covalent binding to the PCB, but treatment of the animals with methylcholanthrene produced livers with poor PCB binding capability. The authors concluded that PCB epoxides were formed by the monooxygenase system and these epoxides were responsible for the binding of the compound to microsomal proteins. Their conclusions are based on indirect findings.

4. Interactions Based on the Induction of Enzymes by PCBs

One report (Murphy et al., 1979) described studies that the authors claimed indicated the existence of a drug interaction in the form of potentiated lethality of fluroxene in Aroclor pretreated animals. The authors did show that the Aroclors induced hepatic enzymes. Their method of measuring enzyme induction was to measure the metabolism of warfarin by livers of the Aroclor-treated animals according to a procedure that they had developed and that they claimed could differentiate between induction of P-450 as compared to P-448. They found that Aroclor 1254 in rats mainly induced cytochrome P-448 whereas Aroclor 1260 induced mainly

cytochrome P-450. The authors then indicated that both Aroclors caused animals to show increased lethality on subsequent administration of fluroxene. We have difficulty interpreting this article. We do not believe that the conclusions are supported by the data that are given. In one case involving Aroclor 1260 the data are not given in the table and in the other case the data obtained following administration of fluroxene do not appear to be different from the control data.

5. Enzymes Other Than Cytochromes Affected by PCBs

Two additional reports deal with an action of the Aroclors on ATPase activity. One of these reports (Lee and Park, 1979) used cultured human lymphocytes and showed a dose-response relation for Aroclor 1254 and inhibition of mitochondrial respiration. From this effect they indicated that there may be a decrease in adenosine triphosphate (ATP) concentration. We can see no way to evaluate what this report means since the concentrations of the Aroclor used are not correlated with concentrations that might be involved in intact biological systems. The other report (LaRocca and Carlson, 1979) indicated that the Aroclors produced in vitro inhibition of rat magnesium ATPase activity at a concentration of 30 ppm. A weak correlation was found between increasing inhibition and increasing chlorination. A strong correlation was found between PCB-induced inhibition of the ATPases and decreasing aqueous solubility. We do not know what these results signify

ether than that they seem seem to be incidental findings many other chlorinated hydrocarbons do the same thing.

6. Summary and Opinion

The available data from experimental studies on animals and man indicate that the commercially available preparations of the PCBs (Aroclors) as well as some highly purified PCB congeners set to induce some of the hepatic enzymes. Considerable effort has been devoted to determine which of the microsomal enzymes are induced by the Aroclors. There are some data that indicate that the predominant induction occurs for the P-450 type of cytochromes (identified as a phenobarbital-type of induction). When experiments are conducted with the "more pure" congeners there is very little evidence for induction of any enzyme systems other than the P-450 cytochromes. In general, induction is greatest with the most highly chlorinated derivatives, but the least chlorinated derivatives also induce the P-450 cytochromes.

The subject of whether the "pure" congeners of the PCBs have less action on the cytochrome systems than the commercial materials may be only of academic interest, since the preparations that are available to industry and the public are the commercial preparations such as the Aroclors. It should be recognized that authors tend to describe effects due to PCBs whereas they are usually referring to effects of Aroclors (such as Aroclor 1254), which are mixtures of PCBs plus various trace contaminants.

The commercially-available preparations of the PCBs are capable of inducing certain hepatic enzymes in the rat and there is one report suggesting that occupational exposure to

commercial PCBs may induce a hepatic enzyme. There are no data suggesting that the overall health of the animals or man is influenced as a consequence of PCB-induced microsomal enzymes. Although it is suggested by some people that changing the metabolic transformation capability is inherently detrimental to the animal, there is no real evidence to support such a hypothesis. When enzymes are induced and they are then involved in the bioactivation of xenobiotic agents, such enzyme induction could be harmful depending on the dosage sequence and the inherent toxicologic properties of any specific agent. On the other hand, if the enzymes that are induced are involved in bioinactivation of xenobiotic compounds, then induction may be beneficial to the animal again depending on the dosage sequence and inherent toxicologic properties of any specific agent. There is no good experimental or clinical evidence that PCBs may act through their enzyme induction capability to effect "hormone" levels and result in harmful effects on the body.

B. PCB Effects on Immunocompetence

A few reports appeared prior to 1970 that suggested indirectly that PCBs may influence immunocompetence. In 1970, Vos and Koeman showed that when chicks were fed 400 ppm PCB for 60 days they showed atrophy of the splenic pulp and lymphoid necrosis. (Chicks at higher doses all died during the test.) The chicks also showed porphyria and liver necrosis. In 1971, Vos and Beems reported that commercial PCB samples applied to

the skin of rabbits daily five times weekly for 38 days (27 applications each containing 118 mg PCB) produced histologic atrophy of the cortex of the thymus and a reduction in the number of germinal centers in the spleen. At this time the animals showed marked chloracne of the skin, increased fecal coproporphyrin and protoporphyrin, as well as liver and kidney damage. The authors stated that these effects were strong indicators of an immunosuppressive action of the PCBs.

In 1977, Loose and co-workers fed Aroclor 1242 to mice for six weeks. The animals were then immunogenically stimulated with sheep red blood cells as an antigen and the antibody response was measured. The method of measuring antibody activity involved plaque-cell estimation in the spleen and the measurement of the plasma immunoproteins. Positive findings were obtained as compared to controls and the authors particularly remarked about the reduced IgA levels found in the PCB-treated animals. It was also noted that clinically subtoxic levels of Aroclor 1242 were profoundly immunosuppressive. These authors also cite the work of Koller and Thigpen (immunosuppression by a PCB to pseudorabies virus in rabbits), Vos and van Driel-Grootenhuis (immunosupression by PCB in guinea pigs), and Friend and Trainer (increased mortality in ducklings that had been previously exposed to Aroclor 1254 and then inoculated with duck hepatitis virus).

In 1978, Loose and co-workers studied the effects of PCBs on host resistance systems. Mice that were fed diets containing 167 ppm Aroclor 1242 for three weeks and for six weeks exhibited increased sensitivity to salmonella endotoxin and a decreased survival time to inoculation with malaria. Thus they concluded that host resistance was impaired by prior treatment with PCBs.

Also in 1978, Thomas and Hindsdill reported on studies in which they fed monkeys 2.5 to 5.0 ppm PCB (Aroclor 1248). After six months the monkeys developed chloracne, alopecia, and facial edema. After 11 months control and treated monkeys were tested with antigens (sheep red blood cells and tetanus toxoid). The only positive finding was in the 5.0 ppm monkeys who showed significantly lower antisheep red cell antibodies as compared to controls. No effect was obtained regarding the antibody response to tetanus toxoid. These authors also fed mice up to 1000 ppm of the PCB for three to five weeks without evidence of overt toxicity, but these animals did show a higher mortality when challenged with the pathogen salmonella typhimurium as compared with the controls.

In 1980, Oishi and Hiraga reported on their studies in which they had given mice PCBs (commercial product) by oral intubation once weekly for four weeks. Other groups of mice were fed CDF (chlorinated dibenzofuran) or CDD (chlorinated dibenzo-p-dioxin). Only the groups of animals that had received 10 or 100

pg/kg CDF showed decreased thymus weights. All groups were challenged with endotoxin and again only the CDF-pretreated animals showed increased lethality compared with the controls. It is noteworthy that the authors found no deaths in their control animals given endotoxin, a finding that raises doubt about their experimental design. In this study the PCB pretreated animals did not show increased susceptibility to endotoxin. In the same year (1980) Imanishi et al. showed that mice fed PCBs for 21 days at 100, 200, or 400 ug/gm were significantly more susceptible to herpes simplex virus and electromelia virus than were animals fed a PCB-free diet.

In 1981, Cheng et al. reported on the immunologic evaluation of patients from Taiwan who developed an acne-like skin disease, termed Yu-Cheng disease, that was related to the consumption of rice-bran oil contaminated with PCBs, PCDFs, and PCQs (in an accident very similar to Yusho). The authors had 30 such patients who showed average whole blood PCB levels of 45 ppb, with a range of 15 to 98 ppb, plus an additional control group of 23 healthy persons matched according to age and sex who showed no detectable levels of PCB in their blood. The patients had decreased concentrations of IgA and IgM immune globulin but not IgG. Their study of subpopulations of lymphocytes showed that the percentage of B cells was not affected by the disease but the percentage of some species of T cells was decreased as compared to the controls.

Environmental chemical effects on immunocompetence have been extensively reviewed by Faith, Luster, and Vos (1980). A number of studies cited by them found PCBs to be immunosuppressive in various species (from ducklings and chicks to mice and monkeys), in some cases at dose levels that produce little effect other than hepatocyte hypertrophy. Only one study (Street and Sharma, 1975), which involved feeding low levels (0.18 to 6.5 mg/kg/day) of Aroclor 1254 to rabbits, showed no significant effect on humoral or cell mediated response. Our review of the Street and Sharma report indicated that there was a dose-related trend toward immunosuppression in their animals and at the higher doses (2.1 and 6.5 mg/kg/day) for four to eight weeks the animals showed significant increase in liver weight. The Faith, Luster, and Vos review lists several general factors (nutritional status, hormonal levels, and amounts of immunoregulatory proteins such as alpha-fetoprotein) that influence immune function. Therefore those studies in which immune function was studied following exposure to levels of the PCBs that resulted in overt toxicity are meaningless from an immunotoxicologic viewpoint. In contrast, immunosuppression at dosage levels that do not produce general toxicity would be significant.

Summary and Opinion

The overall conclusion that can be reached in regard to the studies on the effects of PCBs on immunocompetence is:

[illegible] with exposure conditions that lead to general toxicity, [illegible]unosuppression may be demonstrable, but it may be indirectly [illegible]duced; (2) with experimental conditions wherein only subclinical [illegible]icity is observed, such as hepatocyte hypertrophy, there is the [illegible]ssibility that immunosuppression is also produced; and (3) under [illegible]ill lower PCB exposure conditions it is impossible that immuno[illegible]ppression is involved. Perhaps the best study to estimate a no-[illegible]ffect dose for exposure to PCBs would be the Thomas and Hinds[illegible]dill (1978) study which suggests that six months' exposure to between [illegible]5 and 5 ppm of PCBs in the daily diet of monkeys is a threshold [illegible]r effects on the immune system. Unfortunately, there are few data [illegible]irectly concerned with the dose-response relationship for effects [illegible]f the PCBs on the immune system in animal models or the human.

C. Porphyria

The administration of PCBs to rats will produce a delayed type of porphyria, i.e., deposition of porphyrins and their degradation products in tissues and excreta. Although the mechanism of action of the PCBs is unknown, it apparently differs from that of other porphyrogenic compounds such as hexachlorobenzene or isopropylacetamide. It has been thought that the effect of PCBs in animals may indicate that these compounds can induce conditions such as porphyria cutanea tarda in man, but clinical data have not shown this to occur in PCB-exposed workers.

(1) Experimental Data. The fecal content of coproporphyrin and protoporphyrin of rabbits was increased by Aroclor 1260

and by hexachlorobiphenyl, but the difference was statistically significant only for coproporphyrin (Vos et al., 1972b). Bruckner et al. (1974) observed an increased excretion of urinary coproporphyrin in rats given Aroclor 1242, 5 or 25 ppm for two, four, and six months.

Goldstein et al. (1974) emphasized the delayed onset of the PCB-induced porphyria; rats fed 100 ppm of Aroclor 1254 became porphyric after two or seven months of treatment. Although the excretion of coproporphyrin and other porphyrins was increased, the largest elevation was in the uroporphyrin fraction. There was also a marked accumulation of uroporphyrin in the liver. The studies of Goldstein et al. suggest that PCBs may effect uroporphyrin formation or utilization. The induction of delta-aminolevulinic synthetase (ALA synthetase, a rate-limiting enzyme in heme synthesis) does not appear to be the mechanism by which porphyria is induced by PCB, as it is for many porphyrogenic chemicals. In their studies the increase in ALA synthetase activity was probably secondary to the porphyria. Also, Aroclor acts to increase liver cytochrome P-450 rather than to decrease it.

Hexachlorobenzene is known to induce a delayed type of hepatic porphyria similar to that produced by Aroclor 1254. However, the two responses apparently differ significantly as Goldstein et al. reported that the rats fed PCBs did not exhibit the nervous or cutaneous signs associated with hexachlorobenzene poisoning.

(ii) Clinical Studies. Some of the Yusho patients ingesting rice oil contaminated with PCBs reported pigmentation of the skin and nails, but there were no studies to evaluate a possible relationship of the reported symptoms to any change in porphyrin metabolism (Kuratsune, 1972).

Smith et al. (1981 a,b,c) determined urinary coproporphyrin, uroporphyrin and porphobilinogen in PCB-exposed workers; they did not find a correlation between the urinary porphyrins and the serum level of the lower chlorinated PCBs or the higher chlorinated PCBs. The subjects did not have any recognizable dysfunction and there was no clinically apparent illness with high levels of PCB exposure or with high serum PCB.

Other investigations evaluating the health effects of PCB exposure have not reported cases of porphyrin-related disease or cases of porphyria cutanea tarda (Fischbein et al., 1979; Maroni et al., 1981).

The observation that PCBs increase ALA synthetase in animals raises the possibility that PCBs can cause an attack of porphyria in patients suffering from acute, intermittent porphyria. However, a case of this type has not been reported in the medical literature. As noted above in studies on the rat, the action of PCBs appears to differ from that of other porphyric agents.

XII. Epidemiology

Although case reports of toxic effects, especially skin lesions related to exposure to chlorinated organic chemicals, have been recorded almost from the beginning of their use (Jones and Alden, 1936), few epidemiological studies appeared until the accidental exposure of a large Japanese population to PCBs, PCDFs, and PCQs from the contamination of rice oil. Since that time, numerous studies have been undertaken to determine the health effects related to exposure to PCBs in the workplace and general environment. It must be remembered that there were problems in these studies in assessing the effects because some of the environmental exposures may have involved PCBs that had been altered by processing at high temperatures (Brown, J.F., Jr. et al., 1981). The numbers of individuals exposed occupationally are relatively small, although some may represent the heaviest and most protracted exposures of any reported, and their added burden of PCBs from the workplace must be compared to the background levels that are currently present in all populations. Many of the commonest changes noted in biochemical and other medical measurements obtained in screening surveys have not yet been associated with any subsequent development of disease.

In order to evaluate the epidemiological studies that assessed the effects of PCBs, we will discuss the results of mortality data, morbidity data, and screening surveys separately even though many studies include data on several outcomes.

A. Mortality Studies

In 1968, an unknown number of persons in the western part of Japan ingested rice oil containing Kanechlor 400 that was contaminated with polychlorinated dibenzofurans (PCDFs) in amounts 250 times more than the usual levels in Japanese PCBs (IARC, 1978) and more than 1000 times the usual levels in U.S. Aroclors. By 1977, 1665 cases of "Yusho" had been recognized based on symptoms of ocular disturbances, skin lesions, primarily subjective neurological symptoms and blood PCB levels (Urabe, 1979). Fifty-one deaths have occurred in these patients and the causes have been reported to include liver cancers and lymphomas. However, there have been no reports on the numbers of expected deaths by specific causes based on the usual death rates in similar Japanese populations. The distribution of causes may simply represent the usual distribution of deaths found in the age groups characteristic of Yusho patients, and so it is impossible to assess the mortality patterns of these cases at the present time.

Bertazzi et al. (1981) have reported a study of 1,310 workers, predominantly women, who, beginning in 1946, initially were exposed to Aroclor 1254 and Pyralene 1476 and subsequently were exposed to mixtures with 42% chlorine content. Mortality data were collected on all individuals with six months or more of employment over a 25-year period ending in 1978. The total number of deaths (27) was small but there was an excess of mortality

in female workers compared to the general population, which is unusual for any working group. This study demonstrates a significant excess for all neoplasms for the combined sexes and an excess specifically of lymphomas. It is difficult to interpret these data since the type of cancer incriminated seems to differ from that of other studies. Further, the data of Brown and Jones (1981) (see below, and also the compilation in Table 8, section VIII) on workers in two manufacturing plants do not confirm a finding of excess malignancies in PCB-exposed personnel. The unusual two-fold excess in mortality of female workers in the Bertazzi et al. study deserves further attention.

A retrospective cohort mortality study of 2,567 workers in two electrical capacitor manufacturing plants that had used PCBs for over 30 years, identified 163 deaths (Brown and Jones, 1981). The type of PCBs used over the years had varied and include Aroclors 1254, 1242, and 1016. The overall mortality and total cancer mortality were low, but there were three-fold excesses of cancers of both the rectum and the liver (with a total of seven deaths) although the results were not statistically significant. The only significant excess was that of the subset of rectal cancers in females in Plant 2. The standardised mortality ratios (SMRs) for rectal cancer, liver cancer, or cirrhosis did not increase with increasing latency or duration of employment. Unless one can demonstrate that the risk of cancer increases in association with increasing duration of employment, which serves

as a proxy measure of dose, it is difficult to suggest that the agent is possibly causative for the disease.

Although this study has devoted strict attention to details such as the completeness of identification of workers and ascertainment of outcome it has not verified the diagnosis of cases nor investigated the presence of confounding variables. Rectal cancers are often misclassified by location in the intestinal tract. The classification "liver cancers" may include cancers of the gall bladder and biliary system as well as metastatic lesions to the liver from cancers at other sites. Therefore when one has an excess of liver cancers, verification of specific site within the liver system as well as identification of primary liver lesions is extremely important, especially since the number of deaths from this cause is small. The investigators have not verified the diagnosis of either liver or rectal cancers. Since alcohol is considered a frequent etiological agent for cirrhosis of the liver and possibly for liver cancer, some information on consumption would be relevant as a confounding variable. No data on possible confounding variables have been reported in the paper.

The mortality data from the occupational groups and the Yusho patients are based on very small numbers of deaths and at present do not confirm a carcinogenic effect in man. The observation of excess liver cancer deaths in workers occupationally exposed to PCBs is of major interest since the liver

was a target site for changes in animals and since man has demonstrated evidence of subclinical alterations in liver function. If liver cancers are to be evaluated, the diagnosis of primary cancers of the hepatic cells must be confirmed in the mortality studies since the number of cancers in the group will be very small. The available data demonstrate no consistency in the cancer mortality patterns in the studies and no data on a possible relationship of cancers to dose of PCBs.

B. Morbidity or Incidence Data

Skin

Skin lesions have been reported in association with exposure to chlorinated aromatic compounds since the early 1900's (Jones and Alden, 1936). Taylor has emphasized that acneform eruptions are more frequent with the chloronephthalenes and the dibenzofurans and that the variation in the quantity of these substances that may be present as contaminants in PCBs may account for differences in reporting of skin eruptions with exposures. Taylor has also reported that the acnegenic capacity of various compounds changed according to their form (fumes, liquid, or solid) and the degree of chlorination (Taylor, 1979). These factors may also influence the presence of reported skin disorders in studies.

Not only the frequency but the characteristics of skin lesions have differed in the various studies. Jones and Alden's early description of the lesions they associated with chlorinated biphenyls included "blackheads" or "carbon-colored" comedones

sometimes distributed in unusual areas of the body and often associated with cystic areas and yellow pus (Jones and Alden, 1936). Taylor noted that the cystic swelling and hypersecretion of the meibomian glands are important characteristics of the chloracnegenic effect of PCBs compared to other similar chemicals. These were the typical lesions reported by Meigs et al. in seven of 14 workers exposed to a PCB vapor leak from a heat exchanger in a plant in Connecticut (Meigs et al., 1954). The exposure to vapors was intermittent but of extended duration. Liver function tests were normal in most of these workers and no PCB levels in individuals were obtained, although an air sample prior to the onset of skin disease was 100 ug per m^3, which was within the accepted standards.

The patients who were initially described with Yusho disease had lesions similar to that described above in about 33% and a brownish pigmentation of the skin and nails in 10% of patients. These frequencies were increased subsequently to include about 70 to 85% of patients because of new definitions of characteristics of disease or delayed development of the signs. The eyes were also involved, exhibiting swelling of the upper lids, hyperemia of the conjunctiva and eye discharge (Kuratsune, 1972). Pigmentation of the skin and eye discharges also occurred in newborns of affected mothers. No comparison groups have been included in these studies of Yusho patients. Where the lesions are pathognomic of PCB-related disease this may not be necessary

but when the lesions are more general, comparison groups are essential. There were histopathological changes in five patients biopsied that seem to be associated with contaminated rice oil ingestion. These changes included hyperkeratosis of hair follicles and increased melanin pigment in the basal layer of the epidermis (IARC, 1978). Three out of the five cases also had proliferation of ductal epithelium of esophageal glands. It would have been helpful if these pathological assessments had been made blindly so that qualitative judgments such as "increased melanin" could have been compared in exposed and non-exposed groups. Correlating these pathological findings with changing levels of PCBs, PCDFs, and PCQs would also have been helpful but there are no reported data relating to these issues in the papers available. It is known that the amount of used Kanechlor in the rice oil consumed by the patients was between 0.5 and 2.0 g, which would indicate a PCB exposure similar to levels in occupational settings.

Hara et al. in two separate papers (1974, 1975) have described the skin lesions in workers in a capacitor factory where Kanechlor had been used. The serum PCBs of all workers ranged from 7 to 300 ppb but it is not known how these values correlated with the presence of skin lesions (Hara et al., 1974; Hara et al., 1975). Discontinuance of the exposure not only decreased the overall PCB level to 75% of the original value but the skin lesions disappeared to "vestigial markings on a few individuals." The summary of the report does not indicate

the correlation of the blood PCB and skin lesions although there are data in this paper on the half-life of PCBs in relation to duration of exposure.

Hasegawe has reviewed the health of workers in five plants whose industrial process includad exposure to Kanechlor (Hasegawe et al., 1972). The industries included capacitor manufacture, PCB manufacture, and biphenyl recovery. The vapor concentrations ranged from 13 to 965 ug/m^3. Skin lesions were reported to be unrelated to blood PCBs but generally related to direct skin contact. The average blood PCB level was 370 ppb. The principal dermal findings included brown chromodermatosis of the dorsal joints of hands, fingers and nail beds and acne. There were no further descriptions of the latter lesions so that the presence of chloracne could not be confirmed, but the brown skin discoloration certainly is typical of the Japanese worker reports.

Kitamura et al. described 13 workers from an electrical capacitor manufacturing plant (Kitamura et al., 1973). The lesions in 10 of the workers described in this group are even more vague. They did not include the typical coloration of nails; chloracne was not directly diagnosed; and the follicular lesions did not occur at points of contact with PCBs. From the description of the study it is not clear that the author's conclusions that the skin lesions were due to PCBs was justified without further information on the usual frequency of similar types of skin lesions in normal populations or a description of typical chloracne. The blood PCB level in this group was 820 ppb average.

Inoue et al. studied the health of workers who were exposed to Kanechlor 500 in a thread-glossing factory (Inoue et al., 1975). The frequency of skin lesions was low. The blood PCBs were over 50 ppb in seven out of 54 individuals studied. One person had representative chloracne with blood PCBs of 190-210 ppb.

Ouw et al. described one case of chloracne among 34 workers exposed to Aroclor 1242 in capacitor manufacture (Ouw et al., 1976). The average blood PCB was 400 ppb. In addition five workers complained of eczematous rash but there was no description of lesions. Seven out of 15 process workers and six out of 19 impregnation room workers complained of burning and irritation of the eyes, face, and skin. It is difficult to reconcile these complaints with level of exposure since it should have been higher in the latter group of workers than the former. However, Aroclor concentrations in air as high as 2220 ug/m^3 were measured. The investigators indicated that the "dermatological complaints" occur more often among workers with higher "blood Aroclor levels" but they also indicate there is no clear correlation. It is difficult to be sure of the true meaning of dermatitis as elicited by history when the answers can be biased and the authors do not indicate which cases are related to physical findings only.

As part of a health hazard evaluation at a facility that manufactured electrical distribution equipment, NIOSH studied the

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health of eight workers and found no symptoms or physical signs of chloracne (NIOSH, 1977). There were several subjects who reported skin rashes but not those typical of PCB exposure. The mean PCB level in blood was 98 ppb with the highest value being 286 ppb.

Another health hazard evaluation was done after an accidental spill of PCBs (NIOSH, 1980). In this situation there were no signs of chloracne. However, the mean blood PCB level of exposed workers was only 6.4 ppb; this was below the mean for unexposed workers. Humphrey studied the PCB level of individuals on the basis of fish consumption (Humphrey, 1975). He found that the PCB level was correlated with fish consumption with mean blood levels ranging from 46 ppb to 82 ppb and a maximum individual level of 366 ppb. There were no skin lesions or other health problems associated with PCBs.

A medical and biochemical survey was made of 120 male workers exposed to PCBs in the maintenance of railroad cars and locomotives (Chase et al., 1981). Among the exposed group of 86 workers the "medical histories and physical findings" revealed "several cases of chloracne" -- "with none being found in the other groups." No further details are given as to whether the conditions were currently active, nor was there a description of the lesions. It would be of interest to confirm these cases as true chloracne since the current mean plasma PCB level in the exposed group is only 33.4 ppb (range 10-312 ppb), a very low level of PCBs to be associated with chloracne.

Fischbein et al. (1979) completed a medical survey of capacitor manufacturing workers who were self-selected for physical and bio-chemical examinations. A high proportion (45-55%) of both male and female workers complained of skin disorders with 71% giving a history of acne beginning after the onset of exposure. "Dermatologic findings" were present on physical examination in 38 to 41% of female and male workers, respectively. However, these lesions included "erythema, swelling, dryness, and thickening," which would not be lesions characteristic of PCB exposure. Five percent of the study population had acneform eruptions. There is no mention of whether these were typical of chloracne or were the usual acne lesions found in any medical survey. Since skin lesions are common in the general population and since the population was self-selected initially it is difficult to evaluate these findings. The average lower PCB homologues in plasma were 124 ppb and of higher PCBs, 48 ppb. The authors report that the skin findings were correlated with plasma H-PCBs. Unfortunately, if the examinations were done with the observer knowing the job held by the participant, all results can be biased, since reporting might be related to the job held and the PCB levels were related to job. There was no note of skin hyperpigmentation but 15% of workers had eye abnormalities including "injected conjunctiva and palpebral hyperpigmentation and edema." Again, it is not clear how frequently these lesions would have been reported in normal subjects had examinations been done without knowledge of exposure categories.

Maroni et al. (1981) recently reported on two groups of workers who were exposed to PCBs in the manufacture of capacitors One group (A) had been exposed to both 54% and 42% chlorinated biphenyls. Although the levels of the trichlorinated chemical were similar in current employees in the two plants (128 ppb (A) and 137 ppb (B)), the levels of pentachlorinated agent differed (249 ppb (A) and 68 ppb (B)). It is of interest that 10 cases of acne and folliculitis appeared in the two plants and at least four were entirely typical of the condition. All four typical cases occurred in nine employees who had worked in a high power capacitor impregnation area of Plant A where levels of pentachlorinated biphenyls were high. Their mean blood PCB was 450 ppb, a value not different from that of the five unaffected workers but certainly higher than the overall levels in the two plants. Maroni et al. also noted two cases of bleeding hemangiomas, but one had existed from birth and the only difference in his condition was that bleeding had taken place after the job started and the lesion was excised. The other patient had bleeding from the tongue and a cavernous hemangioma was discovered as well as chronic myelocytic leukemia. Case reports such as this and particularly the unusual circumstances surrounding multiple conditions in one patient in the second case make such findings difficult to interpret. The reports of chloracne appear valid and suggest a problem.

Baker et al. examined sludge users, workers in a capacitor plant, workers' families, and community non-sludge users

Baker et al., 1980). Since the sludge contained PCBs, it was felt that its use as fertilizer might seriously affect the PCB level in the blood. The level of Aroclor 1242 ranged from 7.2 to 48.6 ppb and for Aroclor 1254 from 10.1 to 26.5 ppb, with the lowest levels being found in sludge users and the highest levels in workers. No cases of chloracne or other symptoms of toxicity were noted but only two PCB values were above 200 ppb.

Smith et al. examined workers involved in the maintenance, repair, and overhaul of electrical transformers and measured levels of PCBs by job (Smith et al., 1981). The mean serum levels of L-PCBs in the municipal utility workers were 11 to 36 ppb with a maximum of 59 ppb, and of H-PCBs of 6 to 24 ppb with a maximum of 74 ppb. In the privately-owned facility workers had similar values with L-PCB levels between 19 to 22 ppb with a maximum of 52 ppb, and H-PCB levels between 6 and 31 ppb with a maximum of 250 ppb. There was no significant difference in either place in the frequency of skin lesions between those with less than 10 ppb and those with greater than 10 ppb H-PCBs. There was a significant excess of symptoms of eye irritation in one and a history of bronchitis and loss of smell in the other among those with serum levels of H-PCBs greater than or equal to 10 ppb compared to less than 10 ppb. However, since these are subjective measures of disease and since workers may have been influenced to report subjective symptoms differently depending on job it is impossible to evaluate the importance of these observations.

Smith et al. reported on the physical findings and symptoms in 197 workers who manufactured electrical equipment. The serum levels of L-PCBs in the workers varied by job, with the geometric means ranging from 89 to 502 ppb, the highest levels (2400 to 3330 ppb) being found in the department where capacitors were processed, finished, and tested, and in a department that had assigned work throughout the plant. The geometric mean level of H-PCBs ranged from 22 to 51 ppb, with the highest values (150 to 250 ppb) in these departments. This plant had always used 42% chlorinated biphenyls, both Aroclor 1242 and 1016. Although there were some symptoms of skin and eye lesions (darkening of skin and nails, skin rash, and irritated eyes) that appeared to be different between the groups with L-PCB 200 ppb greater than or equal to 200 ppb compared to those with lower values, these differences disappeared when the comparisons were corrected for age and job. Thus one can conclude that symptoms were primarily related to age and job with the latter association being either real or biased. The symptoms were not related to the body burden of PCBs independent of job. No evidence of skin lesions suggestive of chloracne was found on physical examination, in spite of some extraordinarily high PCB blood levels.

In a preliminary report, Bahn (1976) indicated the incidence of cancer in 64 employees exposed to Aroclor 1254 in a research and development laboratory and 65 refinery workers

with a similar exposure from the same area. The investigator reported a significant excess in the incidence of melanoma of the skin as well as pancreatic cancer based on expected cancer rates from the Third National Cancer Survey. In a subsequent letter to the New England Journal of Medicine, Bahn et al. have reported only on the excess of melanoma (Bahn et al., 1976). When Lawrence criticized the study on the basis of the fact that individuals could have been exposed to multiple chemicals in the laborstory environment (Lawrence, 1977), Bahn and colleagues suggested that the reason for emphasizing the melanoma risk was the biological plausibility of such an association whereas an excess risk of pancreatic cancers could have indicated an association with multiple chemicals (Bahn et al., 1977).

The investigators themselves have discussed several of the flaws of this study. Information on true exposure is limited and perhaps more importantly one-fourth of the exposed workers had to be omitted. The author has also suggested that she underestimated the death ratio by including individuals during their early years of employment when there had not been a sufficiently long latency from the time of first exposure of PCB to the expected time of cancer development.

There are other problems with this study related to the identification of cases in the exposed population and the comparability of case ascertainment in the Third National Cancer Survey data. Apparently the investigators identified cases

without attempting to validate the accuracy of diagnosis. Pancreatic cancer is very difficult to recognize and diagnose. The diagnoses of the two cases need to be validated from hospital records in order to make them comparable to data from the survey. Skin cancers such as melanomas may be diagnosed in doctors' offices. Thus, the lesions could be missed in the cancer survey data where records were obtained primarily from hospitals but identified in populations with routine medical care. It would be necessary to validate the cases in this study through the use of hospital and pathology records and then to compare these cases to a comparable group of employed individuals who have had active medical surveillance by physicians.

In summary, the data on skin lesions in relation to PCB exposures have indicated a remarkable consistency. Individuals who have a body burden indicated by a blood level of 200 or more ppb PCBs have an increased risk of chloracne. There is little evidence of risk below this level and those studies that do suggest a risk at lower levels usually do not have a comparison group or they have not collected the data in a manner such that bias might be avoided. The data also suggest that typical skin lesions may occur more frequently in workers exposed to PCBs that have been heated and to PCBs that have 54% or more chlorination. Since the skin lesions occur more frequently after heating, it is possible that chloracne is actually due

as some alteration or contamination of the PCBs with more mutagenic materials such as dibenzofurans, as found in the Yusho incident. Symptoms of chloracne are reported frequently among those who use Kanechlor; this could be related to level of exposure or its high level of PCDFs relative to PCBs. Such a possibility could not be evaluated with the information in these papers. The relationship to direct skin exposure could also not be evaluated.

C. Biochemical Changes and Liver Function

Extensive studies of liver function have been included among the recent papers on PCBs. Some of these are summarized in Table 9. The early study of Meigs et al. involving a PCB leak from a heat exchanger indicated that there were no abnormalities in seven workers with chloracne except for some transient changes in liver function tests in one worker (Meigs et al., 1954). These changes could not be definitely attributed to PCBs.

The study of Hasegawa et al. of 99 workers in six industrial plants in Japan indicated that increases could occur in enzymes such as SGOT, SGPT and decreases in blood cholinesterase (Hasegawa et al., 1972). The authors regarded the changes in liver function as mild and not clinically significant. Kitamura et al. (1973) indicated that in the 13 capacitor workers the hepatic function tests were normal.

Table 9

Biochemical Studies of Enzymes and Liver function

Study	No. Subjects	Average Dose ppb	Correlation or elevation with dose SGOT	SGPT	GGTP	AK	LDH	Bilirubin	Notes
Hasegawa et al., 1972	90	Tot. 370	+	+	N.T.	N.T.	N.T.	N.T.	cholinesterase
Kitamura et al., 1973	13	Tot. 820	Hepatic function tests normal						
Bau et al., 1976	7	Tot. >500	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	BSP abnormal in 57 percent
GISSH 1977	7	Tot. 98.4	Norm.	Norm.	N.T.	Norm.	N.T.	Norm.	
Fischbein et al. 1979	321	Lo 126 Hi 48	Reported % above normal 2.2%	7.2%	1.9%	1.2%	2.5%	0%	No comparison group. No correction confounding variables
Baker et al., 1980	80 Sludge users	Tot. Hi 17.4 (10.)	Correlations with PCB						Analyzed with non-drinkers
	18 workers	75.1 (26.5)	None	None	None after correction alcohol	None	None	None	No other variable controlled
	19 worker fam.	33.6 (14.8)							Hi-PCB used in analysis
	22 Community	24.4 (12.8)							
Maroni et al., 1981	80	Lo 215							Hepatomegaly 88%
	Liver abnorm. 16	Hi 388 Tot. 524	?	?	50% elev. Norm. ? Positive association abnormal liver findings and PCBs			Norm.	Significantly higher PCBs in liver cases
	Liver norm. 64	Lo 92 Hi 176 Tot. 296			?				

TABLE 9 (continued)
Biochemical Studies of Enzymes and Liver Function (continued)

Study	No. Subjects		Average Dose ppb	Correlation or elevation with dose: SGOT	SGPT	GSTP	AK	LDH	Bilirubin	Notes
Chase et al., 1981	120	Tot. Exposed	33.46 (10-312)	Pos.	None	None				Corrected for age Not other risk factor as alcohol.
		Non-exposed	T 12.0 (10-27)							
Smith et al., 1981a	244	Lo	89-582 ng/ml (approx ppb)	None	None	None	None	None		Correlation include corrections
		Hi	22-61	Pos.	None	Pos.	None	None	None	
Smith et al., 1983b	47	Pub. Lo	11-36 ng/ml	None	None	None	None	None	None	
		Hi	6-24	None	None	None	None	None	None	
	46	Priv. Lo	19-23 ng/ml	Pos.	None	None	None	None	None	
		Hi	6-31	None	None	None	None	None	None	
Reanalysis Smith et al., 1 & 2 above	224	Lo		None	None	Pos.	None	None	None	Analysis each PCB independent of other
		Hi		Pos.	None	Pos.	None	None	None	
Smith et al., 1981c	47	Pub. Lo		None	None	None	None	None	None	
		Hi		None	None	None	None	None	None	
	46	Priv. Lo		Pos.	None	None	None	None	None	
		Hi		None	None	None	None	None	None	
Brates et al.,	488		17.2 microg./L (3.2-157.9)	N.T.	None	Pos.	N.T.	N.T.	None	

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Ouw et al. tested the liver function of capacitor workers through the use of biochemical markers and found the overall test data for the group to be normal (Ouw et al., 1976). The BSP liver function test was conducted only on individuals with blood PCBs above 500 ppb; four out of seven workers were above normal levels, but it is not clear whether these values were above the range of error of the test or whether there were other factors that might have influenced the results. It is indicated that the blood PCB level and the BSP test do not correlate.

NIOSH (1977) evaluated the liver function of seven of eight workers exposed to PCBs in the manufacture of electrical equipment. The levels of SGOT, SGPT, alkaline phosphatase, and total bilirubin were normal in a group of seven workers with a mean PCB level of 98 ppb.

Fischbein et al. (1979) examined a group of 321 workers from two capacitor manufacturing plants. The workers had mean levels of L-PCBs of 124 ppb and H-PCBs of 48 ppb. A small proportion of the workers had abnormalities in the biochemical tests. Two percent had abnormally high levels of SGOT, 7% high levels of SGPT, 2% high levels of GGTP, 1% high levels of alkaline phosphatase, and 3% high levels of LDH. However, there were no abnormally high levels of bilirubin. The results of this study have not been corrected for important confounding variables such

as age, alcohol intake, and other diseases currently or in the past (e.g. hepatitis) that may influence these findings. There is no unexposed group for comparison. The investigators have not presented data correlating increasing enzyme levels to increasing PCB levels, which would be an appropriate method of presenting the relationship between two variables that are continuous. The study does include a comparison of the data dichotomized by two levels of SGOT, less than 50 and greater than 50 i.u. and two levels of both lower and higher homologues of PCBs. These data indicated significant differences between the proportion of individuals with high and normal SGOT levels for H-PCBs greater than 75 ppb compared to lower levels and for L-PCBs greater than 200 ppb compared to lower levels. It is not clear whether these PCB levels were selected after examining the data, in which case the conclusions would be questionable.

The 16 individuals involved in a PCB spill (NIOSH, 1980) had normal liver function tests that included total bilirubin, transaminase, alkaline phosphatase, and lactic dehydrogenase. The triglyceride changes could not be evaluated by the investigators because of inappropriate test procedures. Cholesterol levels were normal. This group had very low blood PCB levels of 6.4 ppb as a mean value, a level lower than that of non-exposed groups.

Baker et al. (1980) studied PCB levels in users of PCB-contaminated sludge as a fertiliser compared to workers in

a PCB-using facility, their families, and non-sludge users in the community. The PCB level varied from 17.4 to 75.1 ppb in the four groups with the lowest level being found in the sludge users. There were no signs of changing levels of SGOT, SGPT, alkaline phosphatase, LDH, or bilirubin in relation to blood PCBs in drinkers and non-drinkers of alcohol. The GGTP level correlated with PCB level in the total population but, when alcohol consumers were removed, the correlation disappeared.

Maroni et al. (1981) studied liver abnormalities in 80 workers from a capacitor manufacturing and testing plant. Sixteen workers (20%) had asymptomatic liver abnormalities. Over 80% of these had enlarged livers. Among this group the most frequent enzyme elevations were the gamma glutamyl transpeptidase (GGTP) in half the cases, the transaminases in 44% and the ornithin-carbamoyl-transferase (SOCT) in 38% of cases with enlarged livers. The mean L-PCB level was significantly higher in workers with abnormal liver findings compared to controls (215 to 92 ppb), mean H-PCB level was significantly higher (308 to 176 ppb), and total mean PCB level was significantly higher (524 to 296 ppb). The levels of PCBs in these workers are high compared to values from many of the exposures recently reported. It is interesting that the authors report that although there is an association between liver disease and PCBs there was no such association for chloracne, but the number of cases was smaller for the latter parameter.

Chase et al. (1981) examined the serum PCB levels and the biochemical markers of liver and lipid activity in 120 maintenance workers who had had varying exposures to PCBs in their work. Plasma PCBs were correlated with SGOT and, after adjusting for age, the correlation between these two variables is still significant. There is no significant corralation between plasma PCBs and GGTP or SGPT. If this correlation is correct it has occurred with levels of PCBs in the blood of exposed workers (33.4 ppb) that are lower than those found in other studies relating subclinical changes in liver function with PCBs (NIOSH, 1977). However, without corrections for other potentially confounding variables such as alcohol intake and the history of other diseases such as hepatitis, it is difficult to assess the finding.

Recently, NIOSH has completed three studies representing cross-sectional medical surveys in two groups, individuals working in capacitor manufacturing (Smith et al., 1981a) and individuals working in maintenance and repair of electrical transformers (Smith et al., 1981b). The third study combined the data from each study in an overall analysis.

In the capacitor manufacturing group there were 224 participants for whom L-PCBs and H-PCBs were determined, as well as biochemical studies. Several simple correlations were calculated and, for all those that were significant, multiple regression equations were developed using all other predictor

variables for which information was available. This included drug intake, smoking history, other biochemical markers, age, sex, and others. Serum H-PCB was significantly correlated with SGOT and GGTP. There were, however, no clinical findings suggestive of liver disease and no indication that the levels of these enzymes were abnormally high. Exposures in this plant were high with plasma PCB levels being eight to 50 times the level found in the community.

Smith et al. (1981b) have reported in the survey information on 93 individuals who were about equally distributed between a municipal electric system and a privately-owned electric utility company. The levels of H-PCBs and L-PCBs are similar in the two facilities. There were very few enzyme tests related to liver function that were significantly correlated with PCB levels. The only significant correlation was a positive relationship between L-PCBs and SGOT for the private company.

Smith et al. (1981) subsequently reanalyzed the data for the three sites presenting partial correlations for L-PCBs and H-PCBs independently without correcting the level for alternate homologues since they were closely interrelated. Under these circumstances, there is not only a positive correlation between H-PCBs and SGOT and GGTP at the manufacturing plant but also a correlation with L-PCB and GGTP. The positive correlation between L-PCB and SGOT still remained after corrections for the private utility company. Combining the data for all sites it is

noted that log SGOT and log GGTP demonstrate both significant and homogeneous trends in relation to log L-PCB level. Only log SGOT is related to log H-PCB and in this case the trend for all sites is homogeneous but not significant. In these analyses, the only confounding variables considered were age and sex for one study site whereas the analyses in the previous papers controlled multiple variables such as smoking and other diseases. Reducing the number of variables and increasing the number of subjects available for study may have accounted for the changes in the relationship with biochemical markers and symptoms to the levels of PCBs. Because of the many changes in relationship, it is difficult to indicate precisely the association between specific liver enzymes and specific homologues of PCBs. It does appear that in these studies one or more enzyme levels within normal ranges may be related to one or more types of PCBs in the blood.

In order to identify the enzyme system that is induced by the various chlorinated forms of biphenyls, Alvares et al. (1977) tested the induction of liver cytochrome P-450 and P-448 by Aroclor 1016 in rats and in workers occupationally exposed to the agent. In rats, the lower chlorinated PCB elicited a barbiturate type of effect on the oxidative enzyme system inducing cytochrome P-450, ethylmorphine-N-demethylase, and microsomal protein. Unlike Aroclor 1254, which induces both P-450 and P-448, the rats with Aroclor 1016 showed little effect on benzo(a)pyrene

hydroxylase activity, which suggests little induction of P-448 by the chemical. The tests in exposed workers were conducted by determining the half-life of the antipyrine whose metabolism is stimulated by the barbiturate class of inducing substances. The workers had a significantly shorter metabolic half-life of the drug than the controls suggesting that the Aroclor 1016 had induced cytochrome P-450.

In a study of 458 community residents in a town that had high levels of PCBs in fish, Kreiss et al. (1981) found a correlation between PCBs as measured against Aroclor 1260 and GGTP. There were no correlations with other liver enzymes. Corrections were made for several other variables such as age, sex, fish and alcohol consumption, and obesity.

In summary, the data from the studies of liver enzymes and function suggest that the populations exposed to PCBs usually do not have clinical liver disease, although in one study there was asymptomatic hepatomegaly (see Table 9). Few of the early studies allow us to separate the various homologues of PCBs in order to correlate enzyme response to level of chlorination of PCBs. Recent studies suggest that SGOT and/or GGTP are the most sensitive markers of change in the liver enzyme systems related to PCB exposure. In the studies that included extensive testing of all enzyme systems as well as characterization of the PCBs, the data have inconsistencies that do not allow us to judge clearly the level or the specific type of

PCB that is related to increased levels of specific liver enzymes. Many of the studies have not corrected for other confounding variables such as alcohol consumption. The data are suggestive that there are changes in one or more liver enzymes related to PCB exposure that are not associated with disease and may occur at levels below those at which chloracne occur.

D. Lipid Metabolism

The long-term studies of patients with Yusho disease have revealed several other abnormalities, among which were elevated blood triglycerides (Urabe et al., 1979). In recent reports of individuals exposed to PCBs, assessment of lipid metabolism has indicated some abnormalities, but in general no clinical manifestations of these abnormalities such as increased risks of cardiovascular disease have been noted. Some of these studies are summarized in Table 10.

Table 10

Lipid Studies

Study	Number Subjects	Average Dose	ppb	Correlation or elevation of lipids: Triglycerides	Cholesterol	H-Chol. HDL-	L-Chol. LDL-	Notes
Kanagawa et al., 1982	99	Tot. 3783		Decr.	Decr.	N.T.	Decr.	
Nara et al., 1983	118	Tot. 7-380		Incr.	N.T.	N.T.	N.T.	
Baumgarner et al., 1983	37	Tot. 4		N.T.	Normal	N.T.	N.T.	
Fischbein et al. 1979	321	Lo 124 Hi 48		Reported as % above normal 10.5%	17.8%			No comparison with control. No correction for confounding variabl
Baker et al., 1980	89 sludge users 18 workers 19 worker fam. 22 community	Tot. Hi 17.4 (10.1) 75.1 (25.5) 33.6 (14.8) 24.4 (12.8)		Pos.	None	sl. neg. (NS)	N.T.	Compared for H-PCB onl Analyzed only on non-alcohol drinkers No other variables controlled.
Smith et al., 1981a	224	Lo 50-502 ng/ml Hi 22-51		Neg. Pos.	None None	None None	None None	Corrected for other variables

TABLE 10 (continued)

Study	Number Subjects		Average Dose ppb	Lipid Studies: Correlation or elevation of lipids — Triglycerides	Cholesterol	H-Chol. HDL-	L-Chol. LDL-	Notes
Smith et al., 1984b	47 Pub.	Lo	11-35 ng/ml	None	None	None	None	Positive correlations corrected for other variables.
		Hi	6-24	Pos.	None	Neg.	None	
	46 Priv.	Lo	19-23	Pos.	Pos.	None	None	
		Hi	6-31	Neg.	None	None	None	
Smith et al., 1984c (Reanalyses of papers above)	Capacitor	Lo		None	None	None	None	Included fewer confounding variables
		Hi		Pos.	Pos.	None	None	
	Pub. ut.	Lo		None	None	None	None	
		Hi		Pos.	Pos.	Neg.	None	
	Priv. ut.	Lo		None	Pos.	None	None	
		Hi		None	None	None	None	
Kreiss et al.,	468		17.2 microg/L. (3.2-157.9)	None	Pos.	None	None	

Hasegawa et al. (1972) had noted changes in lipid metabolism of Yusho patients as manifested by decreases in the blood levels of cholesterol, triglycerides, phospholipids and beta-lipoproteins. Other studies such as that of Hara et al. (1973) on Yusho patients had noted elevated triglycerides in 55% of subjects who had blood PCBs above 50 ppb. The latter data were not corrected for any risk factors such as age or weight. Sumgarner et al. (1973) indicated normal cholesterol levels in 37 refuse workers who had a mean PCB level of 4 ppb.

Fischbein et al. (1979) has examined lipid metabolism in 321 capacitor workers. Cholesterol levels of 300 or more mg/100 ml were found in 17.8% of workers and triglyceride levels of 200 or more mg/100 ml were reported in 10.5% of the population. The total lipids were elevated (above 1 g/100 ml) in 3.4% of the population. These metabolic parameters, however, are influenced by age, personal habits, and the presence of other diseases; it is therefore essential that the data be compared to a population with similar age and sex distribution and that confounding variables be controlled before one can assess the role of PCBs in these observed changes. Since these comparisons were not made, no conclusions can be drawn from these observations.

In the study of Baker et al. (1980) in which PCB-contaminated sludge users were compared to exposed workers, their families, and community controls, there was a highly significant

positive correlation of plasma triglycerides and serum H-PCB. This correlation was strengthened when alcohol consumers were removed. There was a negative correlation of HDL cholesterol with H-PCBs that was not statistically significant. The investigators suggested that the mean level of serum PCB in fasting subjects with hypertriglyceridemia was only 25.0 ppb which is lower than the levels at which this abnormality was noted in previous studies (50-200 ppb, NIOSH document). It is not clear, however, whether the other studies with higher levels have used total PCBs, whereas this study used only H-PCBs in the correlation analyses. The H-PCBs constitute 35 to 59% of the total mean PCBs in the groups. Personal characteristics may influence triglyceride levels, and many factors were apparently considered by these investigators including age, sex, and drinking habits. These lipid abnormalities may be occurring at the lower PCB limits, or even below those limits reported previously.

Chase et al. (1981) in their study of maintenance workers exposed to PCBs found that levels of plasma PCBs were significantly correlated with triglycerides but not with cholesterol. Adjusting for age or length of employment does not change the significance of this correlation. The triglycerides are not significantly correlated with fat PCB levels. As mentioned previously the levels of plasma PCBs in this group of workers is low (33.4 ppb).

Smith et al. (1981a), in the study of 224 workers from a capacitor manufacturing plant, found that serum PCBs were correlated with measures of lipid metabolism. Corrections were made for relevant variables such as smoking, history of diabetes and heart disease, drug use, and others. The partial correlations indicated a significant correlation between serum H-PCB level and total cholesterol and triglycerides and a significant negative correlation of plasma triglycerides with serum L-PCB levels. When the levels of H-PCB and L-PCB were combined the correlation was positive as seen in other studies where total PCBs have been examined. There were no signs of clinical disease in relation to the elevated lipids. It was noted that several of the lipid measurements were correlated with GGTP level. As the authors suggested, this may indicate that PCBs induce hepatic microsomal enzymes, as has been found in laboratory animals and man, and these in turn may increase synthesis of specific lipids.

Smith et al. (1981b) in a health study of 93 workers divided between a public and private utility plant found correlations of lipid metabolites with PCB levels that conflicted with data from the previous study. Triglycerides were positively correlated with H-PCBs in one facility and negatively correlated with H-PCBs in the other. Both correlations were significant even after correction for multiple variables. Both triglycerides and cholesterol were positively associated with L-PCBs in only

[redacted]e facility even though the levels of the biphenyls in the [redacted]ood were similar in the two populations. High density lipo[redacted]oteins were negatively correlated with H-PCBs in only one [redacted]tablishment. In this case, the other facility also demon[redacted]rated a similar negative relationship but the level of the [redacted]orrelation was much lower.

Smith et al. (1981c) have combined the data from these two studies and corrected the results for only age, sex, and study site. Under these circumstances there were less conflicting data in the correlations. Only one significant correlation with L-PCB was noted and that was a positive correlation with cholesterol at the private utility. Both cholesterol and log triglyceride were associated with H-PCBs at the equipment manufacturing site. Triglycerides and H-PCB were positively correlated and HDL-cholesterol and H-PCB negatively correlated at the municipal utility site. Combining the data from all study sites indicated that log triglyceride was significantly associated with both L-PCB and H-PCB but the trend for all sites was homogeneous only with L-PCB. Log HDL-cholesterol was significantly and negatively associated with H-PCBs and this trend was consistent across all sites. There was no significant relationship of PCBs with total cholesterol.

Kreiss et al. (1981) have studied a community where high levels of PCBs and DDT were founds in fish. Among the 458 participants, there was a positive correlation between cholesterol

and PCBs measured as Aroclor 1260. There was no additional contribution by serum triglyceride or HDL-cholesterol to the prediction of serum PCB in multiple regression analysis.

In summary, the studies in man suggest that there is frequently a positive correlation between PCBs in blood and triglyceride levels, although there are many studies that demonstrate no relationship. The correlation is often to the higher homologues of PCBs and occurs in some cases with blood levels of H-PCB at 25 ppb or below. The data associating HDL-cholesterol and H-PCBs are not as often significantly correlated, but when they are, the relationship is negative. Lower levels of HDL-cholesterol may be an important risk factor for coronary heart disease but there is no evidence of a relationship of these lipid findings to clinical disease in these studies. The variation in the presence of lipid abnormalities in relation to PCBs in the studies and the variation in the specific lipid changes observed would suggest that there may be a confounding variable that has been ignored and that is influencing these relationships. A positive correlation of blood lipids with plasma PCB levels could in part be a consequence of the tendency of PCBs to distribute equally among all lipid pools in the body.

E. Reproductive Effects

Very few papers have addressed the problems of human reproductive effects related to PCB ingestion. The early paper

by Kuratsune (1972) on the Yusho patients had indicated that out of 11 women patients and two of the wives of patients who were exposed at any time during pregnancy, there were 10 live born and two stillborn infants and three of the live born were small for their age. The authors do not provide comparison figures on reproductive outcomes for that area of Japan so that it is impossible to assess the meaning of these figures. It is clear, however, that for all babies whose records were reviewed, skin staining and eye discharge were usually present. Kreiss et al. (1981) simply indicated that there was no association of miscarriage, still birth or infant death rate independent of age effects in a study of a community with high PCB levels. In general, the data on reproductive effects from exposure to PCBs are limited.

F. Hematology and Immunology

Most of the studies of hematological effects have found no abnormalities and these observations have been made in simple statements. The studies of Kitamura et al. (1973), Baumgarner et al. (1973), Karppanen and Kolho (1973), Fischbein et al. (1979), Baker et al. (1980), and Maroni et al. (1981) have not revealed any abnormalities of hemoglobin or leukocytes. Ouw et al. (1976) reported several protein and globulin tests on exposed workers that were higher or lower than the reported normal. However, the overall levels of globulins were not different in two groups of workers with high and low exposures. In the initial abstract

relating to the Baker et al. (1980) study, the authors reported increased hematocrit and hemoglobin in relation to PCB levels controlled for age. The second complete report corrects for several other variables that may account for the difference in results. In the three reported studies of Smith et al. (1981), the investigators looked at red cell count, white cell count, hemoglobin, and hematocrit and found no significant correlation with either L-PCB or H-PCB when corrected for confounding variables. In the latter studies they have also examined the correlation of total protein, albumin, and the various globulin fractions and found no significant correlations after correcting for other factors.

In general, there are no recent studies that suggest abnormalities of the heme system in man related to levels of PCBs. In addition, the Smith et al. (1981b) study of workers in electrical utilities showed no significant variation in PCBs related to urinary porphyrins, porphobilinogen, or 17-ketosteroids or 17-hydroxysteroids.

G. Other Factors

Kreiss et al. (1981) in the study of a PCB-exposed community found increased diastolic blood pressure to be correlated with PCB levels even after the correction for other variables. No comparison data for a control group were given. The study of workers in the equipment manufacturing plant also demonstrated

correlation between diastolic blood pressure and H-PCB but this disappeared when corrected for age. Other investigators have not found this relationship, so the difference may be associated with an unrecognized interrelated variable or a chance association related to the multiplicity of factors that have been examined.

Warshaw et al. suggested that workers in a capacitor manufacturing plant (population of Fischbein et al.) had decreased vital capacity and restrictive impairment of lung function in the absence of signs of radiographic change (Warshaw et al., 1979). They have compared the FVC to that of other worker populations in previous hazardous exposure studies as well as to a non-smoking normal population. The reported percent abnormality of PCB workers is 14% compared to 5.6% cited for non-smoking populations. The comparisons do not indicate that they have been controlled for smoking habits and sex.

Most studies have reported no clinical disease in PCB-exposed populations with the exception of Yusho disease and chloracne (Karppanen et al.; Humphrey, Smith et al.; Chase et al.; Kreiss et al.). Some have reported symptoms that are difficult to evaluate since most are subjective and could be related to worker bias. Fischbein et al. suggested that neurological symptoms were increased but there is no similar group with which to compare workers and thus make this assessment. Smith et al.

(1981) in the study of the combined work sites found that coughing at work and irritated eyes were related to both L-PCB and H-PCB. Loss of appetite and peripheral "tingling" were associated only with L-PCB. History of skin rash was associated only with H-PCB. Many of these differences were not observed when individual work site data were analyzed separately. The lack of a difference in each site may result because jobs were included as a confounder variable. Most studies have not even reported any symptoms or history of disease (Baker et al. and Kreiss et al.)

In all studies reviewed there was little evidence of clinical disease with the exception of chloracne and this condition seemed to be most frequent under specific conditions of exposure. The other common but not consistent findings were abnormalities of lipid metabolism, especially blood triglyceride levels, and abnormalities of liver enzymes, especially SGOT and GGTP, which were related to levels of PCBs. The lipid and liver changes appeared to occur at lower levels than the skin manifestations and were not associated with clinical disease or symptoms.

Respectfully submitted,

Victor A. Drill, M.D., Ph.D.

Seymour L. Friess, Ph.D.

Harry W. Hays, Ph.D.

Ted A. Loomis, M.D., Ph.D.

C. Boyd Shaffer, Ph.D.

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XIV. Glossary of Terms or Abbreviations

alkaline phosphatase

bromsulfonphthalein liver function test

gamma glutamyl transpeptidase

PCBs with high degrees of chlorination

PCBs with lower degrees of chlorination

lactic dehydrogenase

polychlorinated biphenyls

polychlorinated dibenzofurans

polychlorinated naphthalenes

polychlorinated quaterphenyls

polychlorinated terphenyls

serum glutamic oxalic transaminase

serum glutamic pyruvic transaminase

serum ornithine carbamoyl transferase

the disease noted in Japan following human ingestion of cooking oil contaminated with PCBs, PCDFs, and PCQs.

parental test animals

litters derived from first generation animals at their first (a) and second (b) matings

CURRICULA VITAE

CATEGORY I TEAM

MONS 025507

CURRICULUM VITAE
OF
DR. VICTOR A. DRILL

EDUCATION

Bachelor of Science (B.S.) degree, Long Island University, 1938.

Doctor of Philosophy (Ph.D.) degree, Princeton University, 1941.

Doctor of Medicine (M.D.) degree, Yale University School of Medicine, 1948.

EMPLOYMENT

Instructor in Pharmacology, College of Physicians and Surgeons, Columbia University, 1943.

Instructor in Pharmacology, Yale University School of Medicine, 1944-47.

Assistant Professor of Pharmacology, Yale University School of Medicine, 1947-48.

Professor of Pharmacology, Wayne University College of Medicine, 1948-53.

Associate Physician, Detroit Receiving Hospital, 1949-53.

Director of Education, Chairman of Intern Committee, Detroit Receiving Hospital, 1949-53.

Director of Biological Research, G. D. Searle & Co., 1953-70.

Lecturer, Department of Pharmacology, Northwestern University Medical School, 1954-67.

Director of Scientific and Professional Affairs, G. D. Searle & Co., 1970-74.

Lecturer in Pharmacology, University of Illinois College of Medicine, 1954-75.

Professor of Pharmacology, University of Illinois College of Medicine, 1976-.

Director; Drill, Prince, Rays, Loomis & Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

Alpha Omega Alpha.

American Association for the Study of Liver Diseases.

American Chemical Society, Division of Medicinal Chemistry.

American Fertility Society.

American Physiological Society.

American Society for Clinical Pharmacology and Therapeutics.

American Society for Pharmacology and Experimental Therapeutics.

International Society of Reproductive Medicine.

New York Academy of Sciences.

Pacific Coast Fertility Society.

Royal Society of Medicine.

Sigma Xi.

Society for Experimental Biology and Medicine.

Society of Toxicology.

HONORS

Distinguished Fellow, Society of Toxicology.

Fellow of the National Research Council, Northwestern University Medical School, 1942-43.

Fellow, New York Academy of Sciences.

Fellow, Royal Society of Medicine.

Honorary Member, International Family Planning Research Association.

Honorary Member, Pharmacology Society of Venezuela.

Jessup Fellow, Princeton University, 1941-42.

President, Society of Toxicology, 1972-73.

PROFESSIONAL ACTIVITIES

Member, Endocrine Panel, Cancer Chemotherapy National Service Center, National Cancer Institute, 1958-62.

Consultant, National Cancer Institute, 1965-67.

Member, Board of Directors, Barren Foundation, 1971-72.

Member, Drug Research Board, National Research Council-National Academy of Sciences, 1971-76.

Member, Organization Committee for the Symposium on the Future of Animal Cells, Models and Systems in Research, Development, Education and Testing, Institute of Laboratory Animal Resources, National Research Council-National Academy of Sciences, 1974-76.

Member, Science Advisory Board, National Center for Toxicological Research, 1975-76.

Member, Board of Directors, International Family Planning Research Association, 1969-79. (Vice-President, 1972-74.)

Co-Chairman, The Third Conference on Cutaneous Toxicity, (sponsored by the American Medical Association and Society of Toxicology), May 16-18, 1976, Washington, DC.

Co-Chairman, The Fourth Conference on Cutaneous Toxicity, (sponsored by the American Medical Association and Society of Toxicology), May 9-11, 1979, Washington, DC.

PUBLICATIONS: BOOKS

Drill, V.A., Editor, Pharmacology in Medicine, McGraw-Hill, New York.

First Edition, 1954

Second Edition, 1958

Drill's Pharmacology in Medicine, McGraw-Hill, New York, edited by J.R. DiPalma.

Third Edition, 1965

Fourth Edition, 1971

Drill, V.A., Oral Contraceptives, McGraw-Hill, New York, 1966.

Drill, V.A., Farmacologia Medica, La Prensa Medica Mexicana, Mexico, edited by J.R. DiPalma, 1969.

Trattato di Farmacologia di Drill, Piccin Editore, Padova, Italy, edited by J.R. DiPalma, Vols. 1 and 2, 1971.

PUBLICATIONS: BOOKS (continued)

A. Campos da Paz, V.A. Drill, M. Hayashi, W. Rodrigues and A.V. Schally, editors, Recent Advances in Human Reproduction, Proceedings of the First International Congress on Human Reproduction, Rio de Janeiro, Brazil, Nov. 11-14, 1974. Excerpta Medica ICS No. 370, Excerpta Medica, Amsterdam, 1976.

Drill, V.A., and P. Lazar, Cutaneous Toxicity, Academic Press, New York, 1977.

Drill, V.A., and P. Lazar, Current Concepts in Cutaneous Toxicity, Academic Press, New York, 1980.

PUBLICATIONS: PAPERS

Author or co-author of approximately 180 papers in the scientific literature. (Bibliography available upon request.)

PERSONAL DATA

Birth date: June 10, 1916

Married: September 14, 1940 (Ruth Craig)

Children: Craig A. (November 20, 1942)
Richard W. (March 15, 1945)
Gary A. (July 16, 1947)

August 1, 1980

CURRICULUM VITAE
OF
DR. SEYMOUR L. FRIESS

EDUCATION

Bachelor of Arts (A.B.) degree, University of California at Los Angeles, 1943.

Master of Arts (M.A.) degree, University of California at Los Angeles, 1944.

Doctor of Philosophy (Ph.D.) degree, University of California at Los Angeles, 1947.

EMPLOYMENT

Research Chemist, Manhattan Engineering District, 1944-46.

Instructor, Department of Chemistry, University of Rochester, 1948-51.

Biosciences Research and Administration, Naval Medical Research Institute, 1951-79.
- Research Scientist; 1951-58.
- Head, Physical Biochemistry Division, 1958-65.
- Chairman, Physiological Sciences Department, 1965-70.
- Chairman, Environmental Biosciences Department, 1970-79.

Managing Director; Drill, Friess, Hays, Loomis and Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Chemical Society.

American Institute of Chemists.

International Society of Toxicology

Society of Toxicology

The Society of the Sigma Xi

Undersea Medical Society

Washington Academy of Sciences

HONORS

Adjunct Professor, Department of Pharmacology, Uniformed Services University of the Health Sciences, The Medical School, 1977-.

Honorary Chair, Institute of Biophysics, University of Brazil at Rio de Janeiro, as Chief of the Laboratory of Molecular Pharmacology, 1961-.

Phi Beta Kappa

Du Pont Fellow in Chemistry, 1946-47.

President, Society of Toxicology, 1975-76.

Member, Editorial Board, Toxicology and Applied Pharmacology, 1964-69; Associate Editor, 1970-79.

Member, Editorial Board, Toxicon, 1965-.

Member, Editorial Board, Toxic Substances Journal, 1978-.

Member, Editorial Board, Perspectives in Toxicology, 1979-.

Member, Scientific Advisory Board, Chemical Industry Institute of Toxicology, 1979-.

President, American Board of Toxicology, Inc., 1979-.

President, International Union of Toxicology, 1980-.

Distinguished Fellow Award, Society of Toxicology, 1981.

PROFESSIONAL ACTIVITIES

Member, Committee on Toxicology, Assembly of Life Sciences, National Academy of Sciences-National Research Council, 1967-70. (Vice-Chairman, 1968-71.)

Member and Chairman, Advisory Panels on Research Programs in Space Biology, National Aeronautics and Space Agency, 1970-75.

Member, Toxicology Information Program Committee, Assembly of Life Sciences, National Research Council-National Academy of Sciences, 1972-77. (Chairman, 1976-77.)

Member, Ad Hoc Advisory Committee on Carbon Monoxide, Department of Health, Education and Welfare, U.S. Public Health Service, Bureau of Community Environmental Management, 1972.

Chairman, Scientific Panel for the NASA Apollo-Soyuz Test Program, 1974-75.

PROFESSIONAL ACTIVITIES (continued)

Member, Environmental Protection Agency-National Academy of Sciences Advisory Committee on Tolerance for the Pesticide Leptophos, 1976.

Adviser, Sub-Committee on Program Development and Administration, Review Committee on the National Center for Toxicological Research, National Academy of Sciences-National Research Council, 1976-.

Member, Bureau of Biomedical Sciences (Consumer Product Safety Commission) Review Committee, National Academy of Sciences-National Research Council, 1977-78.

Liaison Representative, Department of Defense, to the Interagency Testing Committee, Advisory to the Administrator of the Environmental Protection Agency for the Toxic Substances Control Act, 1976-79.

PUBLICATIONS

Author or co-author of approximately 130 papers in the scientific literature. (Bibliography available upon request.)

AREAS OF SPECIAL INTEREST AND COMPETENCE

Toxicology of industrial and military chemicals; neuromuscular pharmacology and toxicology; enzyme kinetics and mechanisms of action; physiology and pathology of chemoreceptors; chemical kinetics; hazard assessment and safety evaluation; regulation of toxic substances; hyperbaric toxicology and physiology.

PERSONAL

Birth date:	July 1, 1922
Married:	July 11, 1953 (Mary Eugenia Tarver)
Children:	Philip L. (December 29, 1954) Martin C. (November 23, 1956)
Home address:	6522 Lone Oak Court Bethesda, MD 20034
Business address:	Drill, Friess, Hays, Loomis & Shaffer, Inc. Suite 204 1901 North Fort Myer Drive Arlington, VA 22209
Business telephone:	(703)527-6450

August 1, 1980

CURRICULUM VITAE

OF

DR. HARRY W. HAYS

EDUCATION

Bachelor of Science (B.S.) degree, Franklin & Marshall College, 1933.

Master of Science (M.S.) degree, Princeton University, 1937.

Doctor of Philosophy (Ph.D.) degree, Princeton University, 1938.

EMPLOYMENT

Research Pharmacologist, CIBA Pharmaceutical Company, 1939-48.

Associate Professor of Pharmacology, Wayne State University College of Medicine, 1948-57.

Director, Advisory Center on Toxicology, National Academy of Sciences-National Research Council, 1957-66.

Director, Pesticides Regulation Division, U.S. Department of Agriculture, 1966-70.

Staff Officer, National Program Staff, U.S. Department of Agriculture, 1970-80.

Director; Drill, Friess, Hays, Loomis & Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Conference of Governmental Industrial Hygienists.

American Society of Pharmacology and Experimental Therapeutics.

Society for Experimental Biology and Medicine.

Society of Toxicology.

HONORS

Editor, Toxicology and Applied Pharmacology, 1959-60.

President, Society of Toxicology, 1964-65.

HONORS (continued)

Historian, Society of Toxicology, 1973-.

Merit Award, Society of Toxicology, 1977.

Distinguished Fellow Award, Society of Toxicology, 1980.

President, Toxicology Laboratory Accreditation Board, 1980-.

PROFESSIONAL ACTIVITIES

Member, Committee on Cutaneous Health and Cosmetics, American Medical Association, 1963-69. (Chairman, Legislative and Liaison Subcommittee, 1968-69.)

Member, Program Committee for Symposia on Cutaneous Toxicity, Society of Toxicology, 1968-79.

Member, Committee on Certification of Toxicologists and Accreditation of Laboratories, Society of Toxicology, 1973-79.

Member, Interagency Collaborative Group on Environmental Carcinogenesis, National Cancer Institute, 1973-79.

Member, Chemical Selection Working Group, National Cancer Institute, 1974-79.

Member, Human Studies Committee, U.S. Department of Agriculture, 1974-79.

Member, Technical Advisory Committee to U.S. Department of the Army on the demilitarization program, 1977-78.

Member, U.S. delegation to the Joint FAO/WHO/UNEP Conference on Mycotoxins, Nairobi, Kenya, 1977.

Chairman, Review Committee, Bureau of Biomedical Sciences, Consumer Products Safety Commission, 1977-78.

Member, Council on Accreditation, American Association for Laboratory Accreditation, 1980-.

PUBLICATIONS

Author or co-author of more than 75 scientific publications. (Bibliography available upon request.)

AREAS OF SPECIAL INTEREST AND COMPETENCE

Natural toxicants in food; food additives; toxicology of pesticides and industrial chemicals; regulation of pesticides; hazard assessment and safety evaluation.

PERSONAL

Birth date:	October 23, 1909
Married:	December 14, 1935 (Elsa C. Lutz)
Children:	Thomas Gregory
Home address:	3900 Watson Place Washington, DC 20016
Business address:	Drill, Friese, Hays, Loomis & Shaffer, Inc. Suite 204 1901 North Fort Myer Drive Arlington, VA 22209
Business telephone:	(703)527-6450

August 1, 1980

CURRICULUM VITAE

OF

DR. TED A. LOOMIS

EDUCATION

Bachelor of Science (B.S.) degree, University of Washington, 1939.

Master of Science (M.S.) degree, University of Buffalo, 1941.

Doctor of Philosophy (Ph.D.) degree, University of Buffalo, 1943.

Doctor of Medicine (M.D.) degree, Yale University School of Medicine, 1946.

EMPLOYMENT

Intern, Marine Hospital, U.S. Public Health Service, Seattle, WA, 1946-47.

Assistant Professor, Department of Pharmacology, University of Washington School of Medicine, 1947-49.

Associate Professor, Department of Pharmacology, University of Washington School of Medicine, 1949-53.

Captain, U.S. Army Medical Corps (Active Duty), 1953-55.

Associate Professor of Pharmacology and State Toxicologist, University of Washington School of Medicine, 1955-57.

Professor of Pharmacology and State Toxicologist, University of Washington School of Medicine, 1957-76.

Professor of Pharmacology and Toxicology, University of Washington School of Medicine, 1976-.

Director; Brill, Friana, Hoyo, Loomis & Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Society for Pharmacology and Experimental Therapeutics.

Society for Experimental Biology and Medicine.

Society of Toxicology.

Western Pharmacology Society.

HONORS

Diplomate, National Board of Medical Examiners.

Distinguished Fellow, Society of Toxicology.

President, Society of Toxicology, 1969-70.

President, Western Pharmacology Society, 1969-70.

Recipient, Toxicology Education Award, Society of Toxicology and Forum for Advancement of Toxicology, 1976.

PROFESSIONAL ACTIVITIES

Member, Committee on Tests for Intoxication, National Safety Council, 1951-.

Member, Editorial Board, Clinical Pharmacology and Therapeutics, 1960-.

Member, Agricultural Advisory Board on Pesticides and Insecticides, State of Washington, 1963-77.

Member, Advisory Committee on Protocols for Safety Evaluation, U.S. Food and Drug Administration, 1966-69.

Member, Advisory Committee, Pesticides Regulation Division, U.S. Department of Agriculture, 1966-70.

Member, Pharmacology-Toxicology Review Committee, National Institute of General Medical Sciences, National Institutes of Health, 1966-70.

Research Affiliate, Regional Primate Center, University of Washington, 1968-.

Member, Pharmacology-Toxicology Training Committee, National Institute of General Medical Sciences, National Institutes of Health, 1970-74.

Member, Committee for Identification of Research Needs in Water Supply, Engineering and Urban Health Sciences Study Section, Environmental Control Administration, Consumer Protection and Environmental Health Service, Public Health Service, U.S. Department of Health, Education, and Welfare, 1970.

Member, Advisory Committee to Review the Use of 2,4,5-T, Agricultural Research Service, U.S. Department of Agriculture, 1970-73.

Consultant, Criteria for a Recommended Standard: Occupational Exposure to Phenol, National Institute for Occupational Safety and Health, 1975.

PROFESSIONAL ACTIVITIES (continued)

Consultant. Criteria for a Recommended Standard: Occupational Exposure to Formaldehyde. National Institute for Occupational Safety and Health, 1976.

Member, Committee on Health Hazards of Pyrolysis Products of Polymers, National Materials Advisory Board, National Research Council-National Academy of Sciences, 1973-78.

Member, Committee on Chronic Toxicity Testing, Advisory Center on Toxicology, National Research Council-National Academy of Sciences, 1976.

Panelist, Committee on Marine Ecosystems Analysis (New York Bight Project), 1976-77.

Member, Advisory Board, Springer-Verlag Handbuch Series, 1973-.

Member, Editorial Board, Combustion Toxicology, 1975-.

Chairman, Committee for Peer Review of NASA Life Sciences Proposals, Pharmacology-Toxicology Section, American Institute of Biological Sciences, 1978.

Member, Committee on Sub-Chronic Toxicity Test Protocols, U.S. Environmental Protection Agency, 1979.

Member, Scientific Review Panel for Health Research, U.S. Environmental Protection Agency, 1980.

PUBLICATIONS: BOOKS

Essentials of Toxicology, Lea & Febiger, Philadelphia.

First Edition, 1968
Second Edition, 1974
Third Edition, 1978

PUBLICATIONS: PAPERS

Author or co-author of approximately 100 papers in the scientific literature. (Bibliography available upon request).

AREAS OF SPECIAL INTEREST AND COMPETENCE

Development of biological and chemical methodology for toxicity testing; clinical and forensic toxicology including evaluation of cause-effect relationships and interpretation of clinical analytical findings; development and presentation of special programs and instructional materials in toxicology for industry, educational institutions, and attorneys; effects of alcohol and drugs on automobile driving, including blood and breath tests for intoxication; animal and clinical drug and pesticide toxicology.

PERSONAL DATA

Birth date:	April 24, 1917
Married:	March 19, 1944 (Marion Adams)
Children:	Bonnie J. (November 15, 1946) Becky A. (December 7, 1953)
Home address	2707 East Becker Road Clinton, WA 98236
Business address:	Drill, Friess, Hays, Loomis & Shaffer, Inc. Suite 204 1901 North Fort Myer Drive Arlington, VA 22209
Business telephone:	(703)527-6430

August 1, 1980

CURRICULUM VITAE
OF
DR. C. BOYD SHAFFER

EDUCATION

Bachelor of Science (B.S.) degree, Lebanon Valley College, 1938.

Doctor of Philosophy (Ph.D.) degree, Princeton University, 1941.

EMPLOYMENT

Senior Fellow, Chemical Hygiene Fellowship, Mellon Institute of Industrial Research, 1941-52.

Chief Industrial Toxicologist, Central Medical Department, American Cyanamid Company, 1952-58.

Director of Environmental Health, Central Medical Department, American Cyanamid Company, 1958-64.

Director of Toxicology, Central Medical Department, American Cyanamid Company, 1964-79.

Director of Corporate Toxicology, Environmental Services Division, American Cyanamid Company, 1979-80.

(Member of corporate Label Committee of American Cyanamid Company, 1957-80; Chairman, 1963-80.)

Director; Drill, Friese, Hays, Loomis & Shaffer, Inc., 1980-.

PROFESSIONAL SOCIETY MEMBERSHIPS

American Industrial Hygiene Association.

American Society of Pharmacology and Experimental Therapeutics.

Society for Experimental Biology and Medicine.

Society of Toxicology.

The Society of the Sigma Xi.

HONORS

Adjunct Associate Professor of Environmental Medicine, Department of Environmental Medicine, New York University Medical Center, 1959-80.

HONORS (continued)

Chairman, Gordon Research Conference on Toxicology and Safety Evaluation, 1962.

Certified by the American Board of Industrial Hygiene, Inc., in the TOXICOLOGICAL ASPECTS of Industrial Hygiene.

President, Society of Toxicology, 1962-63.

Editor, Toxicology and Applied Pharmacology, 1965-67.

Distinguished Fellow Award, Society of Toxicology, 1980.

PROFESSIONAL ACTIVITIES IN TRADE ASSOCIATIONS

Chemical Manufacturers Association
(Formerly Manufacturing Chemists Association)

Labels and Precautionary Information Committee (Member since 1958; Chairman, 1965-67).

Intercommittee Task Group on Transportation Hazards, 1965. (Wrote, with input from the Group, the MCA Chem-Card Manual and the MCA Cargo Information Card Manual.)

Transportation Hazards Information Committee, 1967-69. (Wrote a proposal on Transportation Hazards Information System for submission to the U.S. Department of Transportation.)

Toxic Substances Control Group, 1971-76. (Chairman, 1972-76. Presented the MCA testimony on Toxic Substances Control legislation before Committees of both Houses of Congress during the three sessions of Congress over which this legislation was considered.)

Chemical Regulations Advisory Committee, 1976-77 (Chairman).

National Agricultural Chemicals Association

Environmental Advisory Committee (Chairman, 1972-74).

PROFESSIONAL ACTIVITIES IN GOVERNMENT

Member, Committee on Toxicology, National Academy of Sciences-National Research Council, 1969-73.

PROFESSIONAL ACTIVITIES IN GOVERNMENT (continued)

Member, Standards Advisory Committee for Hazardous Materials Labeling, 1974-75. (Convened by the Occupational Safety and Health Administration of the U.S. Department of Labor.)

Advisor on numerous occasions, 1972-78, to the Delegation from the U.S. Department of Transportation to meetings of the Group of Rapporteurs on the Packaging of Dangerous Goods of the Committee of Experts on the Transport of Dangerous Goods. (Meetings held semi-annually in Geneva, Switzerland, under the auspices of the Economic and Social Council of the United Nations.)

PUBLICATIONS

Author or co-author of approximately 40 papers in the scientific literature. (Bibliography available upon request.)

AREAS OF SPECIAL INTEREST AND COMPETENCE

Research design; toxicology of synthetic organic industrial chemicals; toxicology of synthetic organic pesticides; safety evaluation; precautionary labeling of hazardous industrial chemicals; precautionary labeling of household products under the Federal Hazardous Substances Act; precautionary labeling of pesticides under the Federal Insecticide Fungicide, and Rodenticide Act; regulation of chemicals under the Toxic Substances Control Act; transportation of hazardous materials; preparation, submission, and follow-up of food additive petitions.

PERSONAL

Birth date:	August 18, 1917
Married:	June 14, 1941 (Mary Louise Stoner)
Children:	Edward S. (November 20, 1942) William A. (December 17, 1945)
Home address:	2370 NE Ocean Blvd. A-302 Stuart, FL 33494 2660 Pamaquid Court Annapolis, MD 21401
Business address:	Drill, Prince, Hays, Loomis & Shaffer, Inc. Suite 204 1901 North Fort Myer Drive Arlington, VA 22209
Business telephone:	(703) 527-6450

August 1, 1980

CURRICULUM VITAE

Genevieve Elizabeth Matanoski (Nee Murray)

Social Security No.: 034-22-2128

Place of Birth: Salem, Massachusetts Date of Birth: August 26, 1930

Education: Punchard High School, Andover, Mass., 1947
Radcliffe College, Cambridge, Mass., 1947-1951
Johns Hopkins School of Medicine, Baltimore, Md., 1951-1955
Johns Hopkins School of Hygiene & Public Health, Baltimore, Md., 1960-1964

Degrees: Radcliffe College, A.B. in Chemistry, 1951
Johns Hopkins School of Medicine, M.D., 1955
Johns Hopkins School of Hygiene & Public Health, M.P.H. 1962; Dr.P.H. 1964
Research Presentation for degree of Doctor of Medicine, "Primary Biliary Cirrhosis in Children and Adults"
Certified a Specialist in General Preventive Medicine by the American Board of Preventive Medicine, December 1973
Fellow of the American College of Preventive Medicine, April 28, 1975

Honors: Member of the Alpha Chapter of the Delta Omega Honorary Society, May 1960

Genevieve M. Matanoski, M.D., Dr.P.H.
Professor
The Johns Hopkins University
School of Hygiene & Public Health
Department of Epidemiology
Room 2408
615 North Wolfe Street
Baltimore, Maryland 21205

Telephone Nos.: (301) 955-3483
(301) 955-3692

POSITIONS:

Professor:
Johns Hopkins School of Hygiene & Public Health
July 1, 1976 to present

Associate Professor:
Johns Hopkins School of Health Services
September 1973-June 1978

Associate Professor:
University of Maryland Dental School
October 1970 to present

Coordinator & Evaluator of Special Projects:
Evaluation & Biostatistics Center of the
Regional Medical Program
March 1970 to 1973

Associate Professor:
Department of Preventive Medicine
University of Maryland
1970 to present

Associate Professor of Epidemiology
Johns Hopkins School of Hygiene & Public Health
July 1, 1969 to present

Instructor in Department of Preventive Medicine:
University of Maryland
1967-1969

Training Fellowship in Public Health:
Johns Hopkins School of Hygiene & Public Health
1962-1964

Assistant Professor of Epidemiology:
Johns Hopkins School of Hygiene & Public Health
1964-1969

Instructor in Epidemiology
Johns Hopkins School of Hygiene & Public Health
1959-1964

Pediatrician Out-Patient Department:
Johns Hopkins Hospital
1957 to present

Research Assistant in Epidemiology:
Johns Hopkins School of Hygiene & Public Health
1957-1959

Assistant Resident in Pediatrics:
Johns Hopkins Hospital
1956-1957

Intern in Pediatrics
Johns Hopkins Hospital
1955-1956

Research Assistant
Johns Hopkins School of Medicine
1955

CURRICULA VITAE

CATEGORY II TEAM

MONS 025527

CURRICULUM VITAE

Alvito Peter Alvares, Ph.D.

Personal:

Born: December 25, 1935: Bombay, India
Citizenship: U.S.A.
Married: two children

Education:

University of Bombay, India, 1951-1958
B.Sc. Degree: Major in Chemistry; Minor in Physics, 1955
B.Sc.(Tech) Degree: in Chemical Technology, 1957
University of Detroit, 1958-1960:
M.S. Degree: Major in Biochemistry; Minor in Chemistry, 1961
University of Chicago, 1960-1965
Ph.D. Degree; Pharmacology, 1966

Present Address

Department of Pharmacology
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, Maryland 20816
Telephone: (202) 295-3226

Appointments:

1. Post-doctoral Fellow: Department of Pharmacology, University of Minnesota Medical School, Minneapolis, Minn. 1965-1967.

2. Senior Research Biochemist: Wellcome Research Laboratories, Burroughs Wellcome and Co., Tuckahoe, N.Y. 1967-1970.

3. Research Associate: The Rockefeller University, New York, N.Y. 1970-1971.

4. Assistant Professor: The Rockefeller University, New York, N.Y. 1971-1973.

5. Assistant Professor: Department of Pharmacology, Cornell University Medical College, New York, N.Y. 1972-1973.

6. Adjunct Associate-Professor: Department of Pharmacology, Cornell University Medical College, New York, N.Y. 1973-1977.

7. Associate Professor: The Rockefeller University, New York, N.Y. 1973-1977.

8. Adjunct Professor: The Rockefeller University, New York, N.Y. 1977-1978.

9. Associate Professor: Department of Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, Maryland. 1977-1978.

10. Professor: Department of Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, Maryland. 1978-present.

B. Awards:

Irma T. Hirschl Scholar, 1974-1978
National Institutes of Health Career Development Award

C. Professional Societies:

Sigma Xi
American Association for the Advancement of Science
New York Academy of Sciences
American Society of Pharmacology and Experimental Therapeutics
American Society of Biological Chemists
American Society for Clinical Pharmacology and Therapeutics
Toxicology Section, International Union of Pharmacology (IUPHAR)
Society of Toxicology

D. Medical School and University Activities:

1. Lectures in Medical Pharmacology Course
2. Minicourse in Toxicology for 2nd year medical students
3. Graduate Student Advisory Committee
4. Member: Faculty Senate, 1978-80
5. Chairman: Grievance Committee, Faculty Senate, 1979-80
6. Member: Research Proposal Merit Review Committee, 1979-82.
7. Member: Biohazards, Controlled Substances, and Dangerous Materials Committee, 1981-84.

E. Graduate Students and Theses:

Julie L. Eiseman. "Alterations in heme metabolism induced by gold." 1979.

F. Memberships:

1. Member, Steering Committee, Biochemical Pharmacology Discussion Group, New York Academy of Sciences, 1975-1977.

2. Ad hoc reviewer for Biochemical Pharmacology, Molecular Pharmacology, Life Sciences, Science, Clinical Pharmacology and Therapeutics, and Journal of Pharmacology and Experimental Therapeutics.

3. Member, Workgroup of the National Commission on Digestive Diseases, 1977-1978.

4. Member, Editorial Boards:

Clinical Pharmacology and Therapeutics
Pharmacology
Journal of Environmental Pathology and Toxicology

MONS 025529

C. Participant (Invited Speaker)

1. First International Symposium in Microsomes and Drug Oxidations, Bethesda, Maryland, 1968.

2. International Symposium on Drug Tolerance, Addiction, Abuse and Methadone Treatment, New Orleans, Louisiana, 1971.

3. Second International Symposium on Microsomes and Drug Oxidations, Stanford, California, 1972.

4. IUB Symposium: Reaction Mechanisms of Cytochrome P-450 and Related Enzymes, Stockholm, Sweden, 1973.

5. Upjohn Conference on Hypnotics and Sedatives, Kalamazoo, Michigan, 1974.

6. European Society of Pediatric Endocrinology, Annual Meeting, Berlin, West Germany, 1975.

7. Third International Symposium on Microsomes and Drug Oxidations, Berlin, West Germany, 1976.

8. Gordon Research Conference - Drug Metabolism, Plymouth, New Hampshire, 1976.

9. Fourth Deer Lodge Conference on Clinical Pharmacology, Flathead Lake Lodge, Montana, 1976.

10. Gordon Research Conference - Toxicology, Kimball Union Academy, New Hampshire, 1977.

11. Symposium on Drug Disposition in Man, Sarasota, Florida, 1977.

12. Symposium on Influence of Nutritional Factors on Toxicology, International Congress of Pharmacology, Paris, France, 1978.

13. Symposium on Assessment of Drug Metabolism in Man, Bonnemoa, France, 1978.

14. International Conference on Critical Current Issues in Environmental Health Hazards, Tel-Aviv, Israel, 1979.

15. Seventh European Workshop in Drug Metabolism, Zurich, Switzerland, 1980.

16. Workshop on the Combined Effects of Xenobiotics, National Research Council, Ottawa, Canada, 1981.

17. Gordon Conference on Food and Nutrition, 1982.

MONS 025530

PUBLICATIONS:

McKusick VA, Murray GE, Peeler RC, Webb CM: Musical murmurs, Bull of Johns Hopkins Hospital 97:136, 1955

Price WH, Matanoski GM, Morrison D, Prewer A, Wagner G: The fractionation of seromucoids from human serum. Bull of Johns Hopkins Hosp. 108:227, 1961

Price WH, Matanoski GM, Prewer A, Rector L: Seromucoid fraction patterns of individuals with pneumonia or leukemia. J General Physiology 45-205, 1962

Matanoski GM, Price WH, Ferencz C: Epidemiology of streptococcal infections in rheumatic and non-rheumatic families. I. Objectives, plan of study, and comparative frequency of streptococcal isolations. Amer. J. Epid. 87:179-189, 1968

Matanoski GM, Price WH, Ferencz C: Epidemiology of streptococcal infections in rheumatic and non-rheumatic families. II. The inter-relationship of streptococcal infections to age, family transmission and type of Group A. Amer. J. Epid. 87:190-206, 1968

Matanoski GM, Price WH, Ferencz C: Epidemiology of streptococcal infections in rheumatic and non-rheumatic families. III. Comparison of the immune response to streptococcal infections in the two populations. Amer. J. Epid. 87:207-225, 1968

Matanoski GM, Price WH, Ferencz C: Epidemiology of streptococcal infections in rheumatic and non-rheumatic families. IV. The effect of tonsillectomy on streptococcal infections. Amer. J. Epid. 87:226-236. 1968

Matanoski GM: The role of the tonsils in streptococcal infections: A comparison of tonsillectomized children and sibling controls. Amer. J. Epid. 95:278-291, 1972

Matanoski GM, Seltser R, Sartwell PE, Diamond EL, Elliott EA: Changing trends in mortality of specialists and U.S. white males. Proceedings and abstracts of papers presented at the seventh annual meeting of the Society for Epidemiologic Research, Berkeley, California, June 19-22, 1974

Ringelberg ML, Matanoski GM, Kimball AW: Dental caries-experience in three generations of families. Journal of Public Health Dent 34:3, pages 174-180, summer 1974

Matanoski GM, Seltser R, Sartwell PE, Diamond EL, Elliott EA: The current mortality rates of radiologists and other physician specialists: Deaths from all causes and cancer. Amer. J. Epid. 101:3, 188-198, March 1975

Matanoski GM, Seltser R, Sartwell PE, Diamond EL, Elliott EA: The current mortality rates of radiologists and other physician specialists: Specific causes of death. Amer. J. Epid. 101:3, 199-210, March 1975

Matanoski GM, Sartwell PE, Elliott EA: Letter: Hodgkin's disease mortality among physicians. Lancet 1:926, 1975

Matanoski GM, Landau E, Elliott E: Epidemiology Studies - Pilot Study of Cancer Mortality Near a Chemical Plant and Other Industries in Baltimore, U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, D.C. 20460, May 1976, Final Report

Matanoski GM, Henderson MM, Stine OC, Courpas C, Hepner R, Walker S: The effectiveness of phonocardioscan screening for the detection of heart disease in school-age children. AJP 67:7, 609-611, July 1977

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Kaszuba AL, Matanoski GM, Gibson G: Evaluation of the Emergency Department as a Site for Hypertension Screening. JACEP 7:2, pages 51-58, February 1978

Mak H, Flynn JPG, Matanoski GM: Do Administrative Guidelines Modify the Application and Clinical Benefit of Home Oxygen? Abstract. American Review of Respiratory Disease, Supplement 119-4, April 1979

H. Areas of Scientific Interest:

(a) Factors influencing the metabolism and action of drugs, environmental chemicals and carcinogens.

(b) Interactions between nutritional factors and drug metabolism.

(c) Biochemical and toxicological effects of environmental chemicals and carcinogens.

(d) Heavy metal toxicity.

(e) Effects of foreign chemicals on heme biosynthesis and heme metabolism.

(f) Microsomal hemoproteins: differences in composition and turnover rates; regulation by drugs, chlorinated hydrocarbons and carcinogens.

ALVITO PETER ALVARES

List of Publications:

1. Alvares, A. P.: Utilization of wastes and by-products of the fatty oil industry. Bombay Technologist, 8: 1-4, 1957.

2. Harber, L. H., A. P. Alvares, A. I. Jacobson and W. J. Visek: Effect of barbituric acid and chlortetracycline upon growth, ammonia concentration and urease activity on the gastrointestinal tract of chicks. Journal of Nutrition, 80: 1-5, 1963.

3. Alvares, A. P., L. H. Harber and W. J. Visek: Effect of barbituric acid, chlortetracycline and carbohydrates upon growth and gastrointestinal urease activity of chicks. Journal of Nutrition, 82: 93-98, 1964.

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5. Hendrickson, R. F., A. P. Alvares and W. J. Visek: Effects of chlortetracycline and isoniazid on body weight gain and intestinal urea hydrolysis of rats. Journal of Nutrition, 84: 65-70 1964.

6. Kabara, Jon J., A. P. Alvares, C. Riegel and J. T. McLaughlin: Brain cholesterol X: Effect of scheduling on the sterol lowering capability of methylphenidate (Ritalin). Proceedings of the Society of Experimental Biology and Medicine, 120: 37-41, 1965.

7. Anders, M. W., A. P. Alvares, and G. J. Mannering: Inhibition of drug metabolism. II: Metabolites of 2-diethylaminoethyl 2,2-diphenylvalerate HCl (SKF 525-A). Molecular Pharmacology, 2: 328-334, 1966.

8. Alvares, A. P., G. R. Schilling, W. Levin and R. Kuntzman: Studies on the induction of CO-binding pigments in liver microsomes by phenobarbital and 3-methylcholanthrene. Biochemical and Biophysical Research Communications, 29: 521-526, 1967.

9. Alvares, A. P., G. R. Schilling and R. Kuntzman: Differences in the kinetics of benzpyrene hydroxylation by hepatic drug-metabolizing enzymes from phenobarbital and 3-methylcholanthrene-treated rats. Biochemical and Biophysical Research Communications, 30: 500-505, 1968.

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Matanoski GM, Seltser R, Sartwell PE, Diamond E, Elliott E: Risks of Radiologists Over Saven Decades. Abstract presented at SER Meeting, New Haven, Connecticut, 1979

Matanoski GM, Payton AJ: A Cohort Study of Cancer Mortality in Virologists. Abstract presented at the First Annual NIOSH Scientific Symposium 1978. Toxicological & Carcinogenic Health Hazards in the Workplace. Pathotox publishers, 1979

Sandler DP, Matanoski GM, Comstock GW: Health Consequences of Nasopharyngeal Radium Irradiation. Abstract presented at SER meeting, New Haven, Connecticut, June 1979. Amer. J. Epid. 110:3, page 358, September 1979

Matanoski GM, Landau E, Tonascia J, Lazar C, Elliott EA, McEnroe W, Keating R, Seifter J: Lung Cancer/Mortality in Proximity to a Pesticide Plant. EPA 560/11-80-013 (Epidemiology Studies), U.S. Environmental Protection Agency, Washington, D.C., March 1980 (an interim report)

Mak H, Flynn JPG, Matanoski GM: Do Clinical Guidelines Modify the Application and Benefit of Home Oxygen? Maryland State Medical Journal by the Medical and Chirurgical Faculty of the State of Maryland, Baltimore, Maryland, March 1980

Ferencz C, Matanoski GM, Wilson PD, Rubin JD, Neill CA, Gutberlet R: Maternal Hormone Therapy and Congenital Heart Disease. Teratology 21:2, 225-239, April 1980

Massey RM, Crochetiere CA, Matanoski GM: Hematologic Values in Benzene Exposed Workers. Journal of Environmental Pathology and Toxicology 5:2. 515-521, Pathotox, January 1981

Matanoski GM, Billings CE, Levine MS, Lees PJ, Elliott EA: Investigation of Health Hazards in the Painting Trades Industry Report. Unpublished report to NIOSH, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland, January 1980

Matanoski GM, West S: Occupation and Environmental Exposures and the Risk of Congenital Heart Defects. Abstract presented at SER Meeting, Minneapolis, Minnesota, June 1980

Alter MJ, Gerety RJ, Sampliner RE, Smallwood L, Tabor E, Matanoski GM, Nathanson N: Community Acquired Non-A- Non-B Hepatitis. Abstract presented at SER Meeting, Minneapolis, Minnesota, June 1980

Sandler D, Matanoski GM, Comstock G, Mitchell T: Health Consequences of the Nasopharyngeal Radium Exposure. Symposium on Biologic Effects. Imaging Techniques and Dosimetry of Ionizing Radiation. HHS Publication (FDA) 80-8126

Sandler DP, Comstock GW, Matanoski GM: Neoplasms Following Low-Dose Radium Irradiation of the Nasopharynx. Submitted to JNCI, September 1980

Some Metals and Metalic Compounds. International Agency for Research on Cancer Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 23, Julliet, 1980

Matanoski GM: Risk of Cancer Associated with Occupational Exposure in Radiologists and Other Radiation Workers. Proceedings of the 1980 International Symposium on Cancer, September 14-18, 1980. Cancer - Achievements, Challenges and Prospects for the 1980s. Volume 1:241-254, Grune and Stratton, 1981

Matanoski GM, Landau E, Tonascia J, Lazar C, Elliott EA, McEnroe W, King K: Cancer Mortality in an Industrial Area of Baltimore. Environmental Research 25:8-28, 1981

Matanoski GM, Elliott EA: Bladder Cancer Epidemiology. Epidemiologic Reviews Vol. 3: 1981 (In Press)

CONSULTANT ACTIVITIES:

Periodontal Diseases Advisory Committee, National Institute of Dental Research, January 1975-June 30, 1978

Subcommittee on Adult Health, Medical and Chirurgical Faculty of the State of Maryland, September 1975-June 1978

Program Development Board, American Public Health Association, 1977-1978

Food and Drug Administration Biometric and Epidemiological Methodology Advisory Committee, Bureau of Drugs, HEW Rockville, Maryland, November 1978-January 1978

Air Quality Control Advisory Council, Maryland State Department of Mental Hygiene, March 1978-present

Technical Panel on Environmental Hazards, American Public Health Association, 1978-1981

Center for Disease Control, Beryllium Meeting, Atlanta, Georgia, October 1978

Central Maryland Health Systems, Chairman, Technical Advisory Group on Maternal & Child Health, November 1978-1979

Craniofacial Anomalies Program, NIDR, HEW, December 1978

Symposium on Potentiation of Immune Response to Vaccines, NIAID, NIH, February 1979

U.S. Army Environmental Hygiene Agency, Residency Advisory Committee, Edgewood Arsenal, Maryland, 1978-present

Food and Drug Administration, Anesthetic & Life Support Drugs Advisory Committee, March 1979-1982

Human Health Studies Program, Division of Biometric and Environmental Research, Dept. of Energy

Special Committee: Consultant to prepare a special report for HEW Secretary Califano - Review experimental and epidemiological data on the carcinogenicity of beryllium. Center for Disease Control, Atlanta, Georgia, October 9, 1978

CONSULTANT AND MEMBER:

Science Projection Paper Committee, CSR, Inc.
Public Meeting - A Proposed Federal Radiation Research Agenda -
Held in the Jack Masur Auditorium, Clinical Center, NIH,
Bethesda, Maryland, March 10-11, 1980

Member ofthe Preventive Medicine and Public Health Test Committee
of the National Board of Medical Examiners, 1980-1984

Member of the International Agency for Research on Cancer (IARC)
Working Group on the Evaluation of the Carcinogenic Risk of Chemicals
to Humans: Some Metals. World Health Organization, Lyon, France,
October 23-30, 1979

Member of the AUA Review Committee for the Radiological and Environmental
Research Division, Argonne National Laboratory, July 1, 1980-June 30, 1983

Participant in the 1980 International Symposium on Cancer presented by
Sloan-Kettering Cancer Center with the American Cancer Society and the
National Cancer Institute, New York, New York
Conference entitled: "Cancer 1980: Achievements, Challenges, Prospects"
Dr. Matanoski Lecture: "Risk of Cancer Associated with Occupational
Exposure in Radiologists and Other Radiation Workers"
September 14-18, 1980

Participant and discussant in the joint U.S.A.-Commision of the European
Countries Seminar on Ambient and Biological Monitoring, Luxembourg,
December 8-12, 1980

Member of the Medical Radiation Advisory Committee, Bureau of Radiological
Health, 1981-

PROFESSIONAL SOCIETIES:

American Association for the Advancement of Science
American Public Health Association
New York Academy of Sciences
Society for Epidemiological Research
International Epidemiological Association
Association of Teachers of Preventive Medicine
American College of Preventive Medicine

RESEARCH INTERESTS:

Cancer risks from occupational and environmental exposures to radiation and other agents; evaluation of health programs; family-based population studies; dental disease; especially oral cancer and the role of immunology in periodontal disease; rheumatic fever and streptococcal infections; infant mortality and congenital malformations.

CURRENT RESEARCH:

Epidemiology of infant mortality and congenital malformations; survival rates following diagnosis of oral cancer-relation to type; factors associated with risk of oral cancer; physician mortality in relation to radiation exposure; cancer mortality in virologists and veterinarians; occupational risk from exposure to dyes and synthetic rubber; health hazards from paint application; etiological factors in multiple myeloma; environmental risks from exposure to arsenic; the effects of exposure to low-levels of radiation in a population of shipyard workers.

10. Alvares, A. P., G. Schilling, W. Levin and R. Kuntzman: Alteration of the microsomal hemoprotein by 3-methylcholanthrene: Effects of ethionine and actinomycin D. Journal of Pharmacology and Experimental Therapeutics, 163: 417-424, 1968.

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12. Kuntzman, R., W. Levin, G. Schilling and A. P. Alvares: The effects of 3-methylcholanthrene and phenobarbital on liver microsomal hemoproteins and on the hydroxylation of benzpyrene. In Microsomes and Drug Oxidations, Academic Press, New York, 349-363, 1969.

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14. Alvares, A. P., G. Schilling, A. Garbut and R. Kuntzman: Studies on the hydroxylation of 3,4-benzpyrene by hepatic microsomes: Effect of albumin on the rate of hydroxylation of 3,4-benzpyrene. Biochemical Pharmacology, 19: 1449-1455, 1970.

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19. Alvares, A. P., G. Schilling, and R. Kuntzman: Alteration in the microsomal hemoprotein and the kinetics of 3,4-benzpyrene hydroxylase induced by 3-methylcholanthrene: Time course study and effects of puromycin. Life Sciences, 10: 129-136, 1971.

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20. Kuntzman, R., A. P. Alvares and W. Levin: Effects of inducers of liver microsomal enzymes on the composition of microsomal hemoprotein. Advances in Cytopharmacology, Vol. I, Eds. F. Clementi and B. Ceccarelli, Raven Press, N. Y., pps. 241-248, 1971.

21. Alvares, A. P., G. Schilling, W. Levin and R. Kuntzman: Inability of substrates to alter the carbon monoxide and ethyl isocyanide difference spectra of microsomal hemoprotein. Journal of Pharmacology and Experimental Therapeutics, 176: 1-10, 1971.

22. Mitani, F., A. P. Alvares, S. Sasa and A. Kappas: Preparation and properties of a solubilized form of cytochrome P-450 from chick embryo liver microsomes. Molecular Pharmacology, 7: 280-292, 1971.

23. Levin, W., R. Kuntzman, A. P. Alvares and A. H. Conney: Chromatography of radioactive microsomal hemoproteins on diethylaminoethyl cellulose. Molecular Pharmacology, 7: 500-510, 1971.

24. Mitani, F., R. Winchester, A. P. Alvares, A. Poland and A. Kappas: Interaction of cytochrome P-450 with antibodies raised against a solubilized P-450 preparation from hepatic microsomes. Molecular Pharmacology, 7: 689-696, 1971.

25. Alvares, A. P. and A. Kappas: Influence of phenobarbital on the metabolism and analgesic effect of methadone in rats. Journal of Laboratory and Clinical Medicine, 79: 439-454, 1972.

26. Levin, W., A. H. Conney, A. P. Alvares, I. Merkatz and A. Kappas: Induction of benzo(a)pyrene hydroxylase in human skin. Science, 176: 419-420, 1972.

27. Alvares, A. P. and A. Kappas: The influence of phenobarbital on the in vitro and in vivo metabolism of methadone in rats. In Drug Addiction: Experimental Pharmacology, Vol. 1, Futura Publishing Co., Mt. Kisco, N. Y., pps. 191-198, 1972.

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30. Bickers, D. R., L. C. Harber, A. Kappas and A. P. Alvares: Polychlorinated biphenyls: Comparative effects of high and low chlorine-containing Aroclors on hepatic mixed function oxidase. Research Communications in Chemical Pathology and Pharmacology, 1: 505-512, 1972.

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39. Alvares, A. P., D. R. Bickers and A. Kappas: Induction of drug-metabolizing enzymes and aryl hydrocarbon hydroxylase by microscope immersion oil. Life Sciences, 14: 853-860, 1974.

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51. Alvares, A. P., K. E. Anderson, A. H. Conney and A. Kappas: Interactions between nutritional factors and drug biotransformations in man. Proceedings of the National Academy of Sciences, 73: 2501-2504, 1976.

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59. Anderson, K. E., A. Fischbein, D. Kostenbaum, S. Sassa, A. P. Alvares and A. Kappas: Plumbism from airborne lead in a firing range: An unusual exposure to a toxic heavy metal. The American Journal of Medicine, 63: 306-312, 1977.

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61. Kappas, A., A. P. Alvares, K. E. Anderson, W. A. Garland, E. J. Pantuck and A. H. Conney: The regulation of human drug metabolism by nutritional factors. In Proceedings of the Third International Symposium on Microsomes and Drug Oxidations, Pergamon Press, N. Y. 703-708, 1977.

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65. Alvares, A. P. and A. Kappas: Heterogeneity of cytochrome P-450s induced by polychlorinated biphenyls. Journal of Biological Chemistry, 252: 6373-6378, 1977.

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68. Kappas, A., A. P. Alvares, K. E. Anderson, E. J. Pantuck, C. B. Pantuck, R. Chang and A. H. Conney: Effect of charcoal-broiled beef on antipyrine and theophylline metabolism. Clinical Pharmacology and Therapeutics, 23: 445-450, 1978.

69. Fischbein, A., S. M. Baum, B. Davidov, A. P. Alvares, S. Sassa, A. Kappas, J. Rindinger, W. W. Blumberg and I. J. Selikoff: Lead hazard among isomerchers dismantling an elevated subway line in New York City. N. Y. State Journal of Medicine, 78: 1250-1259, 1978.

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75. Sasse, S., A. Kappas, S. E. Bernstein and A. P. Alvares: Heme biosynthesis and drug metabolism in mice with hereditary hemolytic anemia: Heme oxygenase induction as an adaptive response for maintaining cytochrome P-450 in chronic hemolysis. Journal of Biological Chemistry, 254: 729-735, 1979.

76. Alvares, A. P. and A. Kappas: Lead and polychlorinated biphenyls: Effects of heme and drug metabolism. In proceedings of the Symposium on Drug Disposition in Man, Drug Metabolism Reviews, 10: 91-108, 1979.

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87. Eiseman, J. L., J. von B. and A. P. Alvares: The effect of honeybee (*Apis Mellifera*) venom on the course of adjuvant-induced arthritis and depression of drug metabolism in the rat. Biochemical Pharmacology, in press.

88. Alvares, A. P., T. -H. Ueng and J. L. Eiseman: Polychlorinated biphenyls inducible monooxygenases in rabbits and mice: Species and organ specificities. Life Sciences, in press.

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June 9, [illegible]

CURRICULUM VITAE

NAME:	Philip E. Enterline		
BIRTHDATE:	4/25/21		
BIRTHPLACE	Kittanning, PA		
CITIZENSHIP:	U.S.A.		
SOCIAL SECURITY NUMBER:	181-14-5618		
BUSINESS ADDRESS:	A315 Crabtree Hall, GSPH 130 DeSoto Street Pittsburgh, PA 15261	TELEPHONE:	412/624-3013
HOME ADDRESS:	37 St. Clair Drive Pittsburgh, PA 15228	TELEPHONE:	412/343-1330

EDUCATION AND TRAINING

Undergraduate

1938-42	Westminster College	BBA (1942)	Economics

Graduate

1948-54	American University	MA (1954)	Statistics
1955-60	American University	Ph.D. (1960)	Demography (Dr. Frank Lorimer

APPOINTMENTS AND POSITIONS

Academic

1960-65	American University	Professorial Lecturer
1965-67	McGill University	Professor of Medical Statistics
1967 - date	University of Pittsburgh	Professor of Biostatistics
1975	University of Michigan	Faculty, Summer Session on Health Care Organization

Non-Academic Positions

1942-45	U.S. Army
1945-50	U.S. Public Health Service Statistician

1950-54	U.S. Public Health Service	Asst. Chief Program Analysis Section Tuberculosis and Chronic Diseases
1954-59	"	Chief Statistician Heart Disease Control Program
1959-61	"	Chief, Morbidity and Health Statistics Branch, Public Health Methods
1961-65	"	Chief, Biometrics and Social Studies Branch, Occupational Health

MEMBERSHIP in PROFESSIONAL ORGANIZATIONS

1946 - present	American Public Health Association
1946 - present	American Statistical Association (Treasurer Pgh. Chapter 1972-74 Council Member 1971-73)
1968 - present	International Epidemiological Association
1973 - present	Society for Occupational and Environmental Health

HONORS

1955	Fellow, American Public Health Association
1972	Elected Fellow, American Statistical Association
1977	Pittsburgh Statistician of the Year
1957	HEW Departmental Superior Service Award
1957	HEW Departmental Nominee - Arthur S. Flemming Award for Ten Most Outstanding Young Men in Government
1958	Pi Gamma Mu (National Social Science Honor Society)
1979-81	Member, Editorial Board, American Review of Respiratory Disease

PROFESSIONAL ACTIVITIES

Teaching (current)

Biostatistics 211	Principles of Statistical Reasoning
Biostatistics 216	Introduction to Sampling
Biostatistics 219	Vital and Medical Care Statistics

Research and Training (1967 - date)

Grants and Contracts

Years Federal Grants	Title	Source	Amount
1968-74	Training in Public Health Statistics	NIH	$158,181
1972-75	Training in Industrial Biostatistics	NIOSH	$161,406
1971-75	Training in Medical Care Statistics	NCHSR	$274,376
1969-76	Study of the Effects of National Health Insurance in Quebec	NCHSR	$746,532
1976-77	Planning Grant on Childhood Lead Poisoning	NIH	$ 71,790
1977-81	Cancer in Arsenic Exposed Populations	NCI	$315,870

Non Federal Contracts

1973-80	Health of Workers in Mineral Wool and Fibrous Glass Manufacturing	TIMA	$305,559
1976-80	Mortality of Nickel Workers Huntington, W. Va.	HUNT. ALLOYS	$108,551
1975-	Surveillance of Health of Chemical Workers Deer Park Texas	SHELL OIL	$ 58,604
1981-	Mortality Among Smelter Workers	SERA	$450,377
1981-82	Cross-Sectional Study of Pulmonary Function in Alcoa Arkansas Workers	ALCOA	$ 34,586

Other Non-Federal -- $46,602

2. **Other Research and Training Related Activities**

1960-65	Panel Member, U.S. Board of Civil Service Examiners (Statistician)
1966-70	Health Services Research Study Section, HSMHA
1967-date	Health Advisory Committee, National Bureau for Economic Research
1967-72	Advisory Fellow, Mellon Institute and Industrial Hygiene Foundation

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1970-72	Health Services Demonstrations Study Section, HSMA
1972-75	National Advisory Food and Drug Committee, FDA
1972-74	Panel on Chromium, Committee on Biological Effects of Atmospheric Pollutants, National Academy of Sciences
1974-76	Chairman, Advisory Committee on Longitudinal Study of Submariners, U. S. Navy
1975-79	Pulmonary Diseases Advisory Committee, NHLBI
1979-80	Task Force on the Epidemiology of Respiratory Disease, NHLBI Chairman, Committee on Occupational Agents
1979-	Literature Reviewer-Epidemiology-J. of Occupational Medicine
1979-	Associate Director, Center for Environmental Epidemiology

Service (current)

1. Departmental: Chairman (1976-date)

2. School: Member, Dean's Cabinet

3. Local and State: Grants Review Committee, Pennsylvania Coal Workers Respiratory Disease Program

PUBLICATIONS

1. Refereed Articles

Enterline, Philip E., and Sauer, Herbert I: Community-wide X-ray surveys, VI, Records and Reports. Pub. Health Rep. 66:1613-1624. (December 7, 1951).

Enterline, Philip E: Group Chest X-ray Examinations and the Tuberculosis Death Rate. Pub. Health Rep. 67:762-766 (Aug. 1952).

Payne, Howard M., Enterline, Philip E., and Houck, Julia: A Study of the Positive Roentgenographic Findings for 1948 Washington Mass Survey. Am. Rev. Tbc. 66:548-566 (Nov. 1951).

Bowman, Walter M., and Enterline, Philip E: Delayed Blood Sugar Determinations--Evaluation of a Blood Preservative. Pub. Health Rep. 69:240-246 (March 1954).

Anderson, Robert J., Enterline, Philip E., and Turner, Otis D.: Undetected Tuberculosis in Various Economic Groups. Am. Rev. Tbc. 70:593-600 (Oct. 1954).

Anderson, Robert J., Enterline, Philip E., Hill, Rank J., and Roberts, Jean: An Evaluation of Tuberculosis Detection by Chest X-ray Surveys. Pub. Health Rep. 69:1053-1060 (Nov. 1954).

Kurlander, Arnold B., Hill, Elizabeth , and Enterline, Philip E: An Evaluation of Some Commonly Used Screening Tests for Heart Disease and Hypertension. J. Chr. Dis. 2:427-439 (Oct. 1955).

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:nterline, Philip E., and Stewart, William H: Geographic Patterns in Deaths rom Coronary Heart Disease. Pub. Health Rep. 71:849-855 (Sept. 1956).

;tewart, William H., and Enterline, Philip E: Ecology and Coronary Heart Disease. J. Chr. Dis. 6:86-89 (July 1957).

Brodeur, Armand E., Baker, James P., and Enterline, Philip E: Abnormalities seen on Chest Photofluorograms and Diagnosable Heart Disease. Am. J. Roent. Rad. Ther., and Nuc. Med. 78:226-233 (Aug. 1957).

Enterline, Philip E., and Kordan, Bernard: A Controlled Evaluation of Mass Surveys of Tuberculosis and Heart Disease. Pub. Health Rep. 73:867-875 (Oct. 1958).

Enterline, Philip E., and Capt, Katherine G: A Validation of Information Provided by Household Respondents in Health Surveys. Am. J. Pub. Health 49:205-212 (Feb. 1959).

Zubal, William J., Lewis, Robert H., Enterline, Philip E., Painter, Robert C., Nelson, Lloyd S., Fawcett, Robert M., Meredith, Alla P., and Peterson, Beatrice: A Short-Term Community Study of the Epidemiology of Coronary Heart Disease. Am. J. Pub. Health 49:1930-2039 (Dec. 1959).

Sauer, Herbert I., and Enterline, Philip E: Are Geographic Variations in Death Rates for the Cardiovascular Diseases Real? J. Chr. Dis. 10:513-524 (Dec. 1959).

Enterline, Philip E., Rikli, Arthur E., Sauer, Herbert I., and Hyman, Morton: Death Rates for Coronary Heart Diseases in Metropolitan and Other Areas. Pub. Health Rep. 75:759-766 (Aug. 1960).

Meredith, Alla P., Enterline, Philip E., Peterson, Beatrice, and Pehover, Jean C: An Epidemiologic Diet Study in North Dakota. J. Am. Dietet. Assoc. 37:339-343 (Oct. 1960).

Enterline, Philip E., and Stewart, William H: Estimated Morbidity in the United States based on Monthly Labor Force Report. Pub. Health Rep. 75: 1151-1160 (Dec. 1960).

Enterline, Philip E: Causes of Death Responsible for Recent Increases in Sex Mortality Differentials in the United States. Milbank Mem. Fund Quart. 39:312-328 (April 1961).

Enterline, Philip E: Work Loss Due to Illness in Selected Occupations and Industries. J. Occup. Med. 3:405-411 (Sept. 1961).

Stewart, William H., and Enterline, Philip E: Effects of the National Service on Physicians Utilization and Health in England and Wales. New England J. of Med. 165:1187-1194 (Dec. 1961).

Enterline, Philip E., and Stewart, William H: Health Program Requirements to Offset Effects on Levels of Living. Am. J. Pub. Health. 52:401-409 (March 1962).

Cooper, W. Clark, Enterline, Philip E., and Worden, Eloise T: Estimating Occupational Disease Hazards Through Medical Care Plans. Pub. Health Rep. 77:1065-1070 (Dec. 1962).

Enterline, Philip E., and McKiever, Margaret P: Differential Mortality From Lung Cancer by Occupation. J. Occup. Med. 5:283-290 (June 1963).

Syme, S. Leonard, Hyman, Merton J., and Enterline, Philip E: Some Social and Cultural Factors Associated with the Occurrence of Coronary Heart Disease. J. Chr. Dis. 17:277-289 (1964).

Enterline, Philip E: Sick Absence for Men and Women by Marital Status. AMA Arch. Environ. Health. 8:466-470 (March 1964).

Enterline, Philip E: Mortality Rates Among Coal Miners. Am. J. Public Health. 54:758-768 (May 1964).

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Syme, S. Leonard, Hyman, Merton M., and Enterline, P.E.: Sociocultural Factors and Coronary Heart Disease. Sociological Inq. Vol. 34, No. 1, (Winter, 1964).

Syme, S. Leonard, Hyman, Merton M., Enterline, Philip E: Cultural Mobility and the Occurrence of Coronary Heart Disease. J. of Health and Human Behavior Vol. 6 (Winter, 1965).

Ashford, J.R., Enterline, Philip E: Radiologic Classification of the Pneumoconioses. Arch. of Environ. Hlth. Vol. 12, (March 1966).

Enterline, Philip E: Social Causes of Sick Absence. Arch. of Environ. Hlth. Vol. 12, (April, 1966).

Enterline, Philip E: The Effects of Occupation on Chronic Respiratory Disease. Arch. Environ. Hlth. Vol. 14, 189-200 (Jan. 1967).

Enterline, Philip E. and Lainhart, W.S.: The Relationship Between Coal Mining and Chronic Nonspecific Respiratory Disease. Am. J. of Pub. Health Vol. 57, No. 3, 484-493 (March 1967).

Enterline, Philip E. and Kendrick, Mildred A: Asbestos-Dust Exposures at Various Levels and Mortality. Arch. Environ. Hlth. Vol. 15, 181-186 (Aug. 1967).

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Herman, B. and Enterline, Philip E: Lung Cancer Among the Jews and Non-Jews of Pittsburgh. Amer. J. of Epid. Vol. 91, No. 4, 355-367 (April 1970).

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Enterline, Philip E., DeCoufle, Pierre, and Henderson, Vivian: Mortality in Relation to Occupational Exposure in the Asbestos Industry. J. Occup. Med. Vol. 14, No. 12 (Dec. 1972).

Enterline, Philip E., DeCoufle, P. and Henderson, V: Respiratory Cancer in Relation to Occupational Exposures Among Retired Asbestos Workers. Brit. J. Industr. Med., Vol. 30, 162-166 (1973).

Enterline, Philip E., McDonald, J.C., McDonald, A.D., and Salter, V: The Effects of "Free" Medical Care on the Practice of Medicine - The Quebec Experience. New England J. of Med. 228:1152-1155 (May 31, 1973).

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Henderson, V., and Enterline, P.E.: An Unusual Mortality Experience in Cotton Textile Workers. J. Occup. Med., Vol. 15, No. 9 (September 1973).

Enterline, P.E., Salter, V., McDonald, A.D., and McDonald, J.C.: The Distribution of Medical Services Before and After "Free" Medical Care--The Quebec Experience. New England J. Of Med. 189:1174-1178 (Nov. 1973).

Enterline, P. E. and Henderson V: Type of Asbestos and Respiratory Cancer in the Asbestos Industry. Arch. Environ. Hlth., Vol. 24 (Nov. 1973).

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Enterline, Philip E: Respiratory Cancer Among Chromate Workers. J. Occup. Med., Vol. 16:523 (Aug. 1974).

Enterline, Philip E. and Henderson, V: Mortality and Morbidity Experience of Retired Fibrous Glass Workers. Arch. of Environ. Hlth., Vol. 30 (March 1975).

McDonald, A.D., McDonald, J.C. Salter, V. and Enterline, P.E.: Effects of Quebec Medicare on Physician Consultation for Selected Symptoms. New Eng. J. of Med. 291:649-652 (Sept. 26) 1974.

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Pinto, S., Enterline, Philip E., Henderson, V., and Varner, Michael, O: Mortality Experience in Relation to a Measured Arsenic Trioxide Exposure. Environmental Health Perspectives, Vol. 19:127-130 (Aug. 1977).

McDonald, J.C., McDonald, A.D., and Enterline, P.E.: Some Effects of Medicare in Quebec (Etudes sur l'assurance-maladie due Quebec) Sociologie et Societes, IX, 1, pp. 56-75 (Spring 1977).

Ricci, E., Enterline, P.E., Henderson, V: "Contacts with Pharmacists before and After "Free" Medical Care — the Quebec Experience," Medical Care, Vol. 16, No. 3, March 1978.

Pinto, S., Henderson, V. and Enterline, P.: Mortality Experience of Arsenic Exposed Workers. Arch. of Environ. Hlth. pp. 325-331, Nov/Dec. 1978.

Marsh, G. and P.E. Enterline: A Method for Verifying the Completeness of Cohorts Used in Occupational Mortality Studies. J. of Occup. Med., Vol. 21: 10, pp. 665-670, October 1979.

Enterline, P.E.: Attributability in the Face of Uncertainty. CHEST. Vol. 78, p. 377S-379S, Supplment August 1980.

2. Proceedings

Enterline, Philip E: A Controlled Evaluation of Casefinding by Chest X-ray. Proceedings of the National Tuberculosis Association (May 1957).

Enterline, Philip E: Trends and Variations in Sick Absence in the United States, Proceedings of the Second Int'l Conf. on Sick Abs. Statistics. Amsterdam, The Netherlands (April 22, 1965).

Enterline, Philip E: Mortality Among Asbestos Products Workers in the United States. Annals of the N.Y. Acad. of Sci. Vol. 132 (Dec. 1965).

Enterline, Philip E: The Statistician in Epidemiologic Research. The Proceedings of the Canadian Assoc. of Teachers of Soc. and Prev. Med., Annual Meeting. (June 3 and 4, 1966).

Enterline, Philip E: Asbestos Dust Increments and Mortality from Two Diseases. Proceedings of the Second Int'l Conf. on Biological Effects of Asbestos. Dresden, Germany, (April 1968).

Enterline, Philip E: Recent Developments in Sick Absence Statistics. Transactions of the 33rd Meeting of the Industrial Hygiene Foundation of America, Inc. (Oct. 1968).

Enterline, Philip E: Statistical Studies of U.S. Asbestos Products Workers. Proceedings of Fibrous Dust Seminar - Mellon Institute, Pittsburgh, PA (Nov. 22, 1968).

Enterline, Philip E., Salter, Vera, McDonald, A.D., and McDonald, J.C.: Doctor Visits in Various Income Groups Prior to Canadian Medicare. Proceedings of the VI Conf. of the Int'l Epidemiological Association. Primosten, Yugoslavia, (Aug. 1971).

McDonald, J.D., McDonald, A.D., Steinmets, H., Enterline, P. and Salter, V: Work of Physicians in Montreal. Proceedings of the VI Conf. of the Int'l Epidemiological Association. Primosten, Yugoslavia (Aug. 1971).

Enterline, Philip E. and Weill, H: Asbestosis in Asbestos Cement Workers. Proceedings of the IARC Working Group to Assess the Biological Effects of Asbestos. Lyon, France (Oct. 1972).

Enterline, Philip E: A Review of Mortality Data for American Coal Miners. Annals of the N.Y. Acad. of Sci., Vol. 200 (Dec. 19, 1972).

Enterline, P.E.: Proceedings of the Third Annual Industry-Government Conference Asbestos Information Association of North America. (Sept. 8-9, 1976) pp. 176.

Enterline, P.E.: Proceedings of the Interdepartmental Worker's Compensation Task Force Conference on Occupational Diseases and Workers Compensation, U.S. Government Printing Office. (1976) pp. 13-15.

Enterline, P.E., Pinto, S., and Henderson, V.: Cancer Among Arsenic Exposed Workers in a Copper Smelter. Proceedings of the Air Pollution Control Association, Macon, Nov. 8-9, 1976.

Enterline, P.E.: Epidemiology in Studies of Occupational Health. Proceedings of the Annual AMA Congress on Occupational Health, September 30, 1977.

Enterline, P.E.: Epidemiological Methods for Establishing Dose-Response Relationships in Asbestos-Dust Related Diseases. Proceedings of the Asbestos Symposium, Johannesburg, South Africa, October 4, 1977.

Enterline, P.E.: Epidemiologic Methods in Industry. Proceedings of the IPAI Health Protection Seminar, Copenhagen, Denmark, June 29, 1977.

Enterline, P.E. and Marsh, G.M.: Environmental and Mortality of Workers from a Fibrous Glass Plant. Proceedings of the Society for Occupational and Environmental Health, Washington, DC, December 6, 1977.

Enterline, P.E. and G. Marsh: Environment and Mortality of Workers from a Fibrous Glass Plant. In Dusts and Diseases, 1979.

Enterline, P.E.: Some observations on Geographic Variations in Mortality. Proceedings of the 13th Annual Conference on Trace Substances in Environmental Health, Columbia, Missouri, June 5, 1979, pp. 19-27.

Enterline, P.E.: Asbestos and Health Panel Remarks, 4th Industry and Government Conference, Asbestos Information Association, Sept. 19-20, 1979, Arlington, VA.

Enterline, P.E. and G. Marsh: Mortality of Workers in the Man-Made Mineral Fiber Industry, Proceedings of the Symposium on the Biological Effects of Mineral Fibers, IARC, Lyon, France, September 25-27, 1979.

Enterline, P.E.: Sorting Out Multiple Causal Factors in Individual Cases, Proceedings of the Society for Occupational and Environmental Health, Washington, DC, December 4, 1979.

Henderson, V. and P.E. Enterline: Asbestos Exposure: Factors Associated with Excess Cancer and Respiratory Disease Mortality. Annals of NY Academy of Sciences, Vol. 33, pp. 117-126, December 14, 1979.

Enterline, P.E.: Extrapolation from Occupational Studies--A Substitute for Environmental Epidemiology, Proceedings of the First Annual Symposium on Environmental Epidemiology, Pittsburgh, PA., April 28, 1980.

Enterline, P.E.: Use of the National Death Index in Occupational Epidemiology, Proceedings of the Public Health Conference on Records and Statistics, August 5, 1980.

Enterline, P.E. and G. Marsh: Mortality Among Workers in a Nickel Refinery and Manufacturing Plant in West Virginia, USA. Proceedings of the 2nd International Nickel Conference on Environmental and Occupational Toxicology of Nickel, Swansea Wales, United Kingdom, September 3, 1980.

Enterline, P.E.: Proportion of Cancer Due to Exposure to Asbestos. Proceedings of the Conference on the Quantification of Occupational Cancer, Banbury Center, Cold Spring Harbor Laboratory, March 30, 1981.

Enterline, P.E.: Epidemiologic Basis for the Asbestos Standard. Proceedings of the Second Annual Symposium on Environmental Epidemiology. Pittsburgh, PA April 28, 1981.

Enterline, P.E. and G.M. Marsh: Missing Records in Occupational Disease Epidemiology. Proceedings of the 1981 American Occuational Health Conference, Atlanta, GA April 29, 1981.

3. Abstracts

Enterline, P.E.: Factors Associated with Geographic Differences in Deaths from Coronary Heart Disease. Circulation 14 (Nov. 1956).

Syme, S. Leonard, Hyman, Merton M., and Enterline, Philip E: Some Social and Cultural Factors Associated with the Incidence of Coronary Heart Disease. Circulation. (Oc. 1961).

Enterline, Philip E. and Manos, Nicholas E: Sex Differentials in Mortality in England and Wales and in the United States. Population Index (July 1963).

4. Other

Enterline, Philip E.: Rewarding the Sick. (Editorial) J. of Amer. Medical Assoc. Vol. 196, No. 5, (May 2, 1966).

Enterline, Philip E: Asbestos and Public Health (Editorial). J. of Amer. Medical Association, Vol. 201, No. 12, 146-147 (Sept. 18, 1967).

Enterline, Philip E.: (Member of Committee) Standards for Epidemiologic Surveys in Chronic Respiratory Disease. National Tuberculosis and Respiratory Disease Association. New York (1969).

Lainhart, W.S., Doyle, H.N., Enterline, Philip E., Henschel, A., and Kendrick, M.A.: Pneumoconiosis in Appalachian Bituminous Coal Miners. U. S. Dept. of Health, Education, and Welfare, Pub. Hlth. Service, Publ. No. 2000, (1969).

Enterline, Philip E. and Jacobsen, M.: "Epidemiology" in Medicine in the Mining Industries. Heinemann Medical Books, London, 1972 (J. Regan Ed.)

Enterline, P.E.: "Effects of Chromium Compounds on Human Health" in report on Chromium prepared by the National Research Council, National Academy of Sciences, Washington, D.C., 1974.

Enterline, P.E.: (Editorial) Asbestos and Cancer: The International Lag. Am. Rev. of Resp. Dis., Vol. 118:975-978 (December 1978).

Enterline, P.E., McDonald, A. and McDonald, J.: Some effects of Quebec Health Insurance. NCHSR Research Digest Series, DHEW Pub. No. (PHS) 79-3328, January 1979.

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CURRICULUM VITAE

Name: Frank G. Standaert

Home Address: 8205 Stone Trail Drive
Bethesda, Maryland 20817

Business Address: 3900 Reservoir Road, N.W.
Washington, D.C. 20007

Business Telephone: (202) 625-7635

Birthdate: November 12, 1929

Birthplace: Paterson, New Jersey

Citizenship: U.S.A.

Marital Status: Married, 3 sons

Education:

Harvard College, 1947-1951, A.B. (cum laude), Chemistry
Cornell University Medical College, 1951-1955, M.D.

Appointments and Positions:

Academic:

The Johns Hopkins Hospital
Interne (medicine) 1955-1956

Cornell University Medical College
Research Fellow, 1956-1957
Instructor in Pharmacology, 1958-1960
Assistant Professor of Pharmacology, 1960-1964
Associate Professor of Pharmacology, 1964-1967

Georgetown University Schools of Medicine and Dentistry
Schering Foundation Professor and Chairman of Pharmacology, 1967-

The Murray and Leonie Guggenheim Dental Clinic
Lecturer to the staff, 1960-1967

Naval Medical Research Institute, Bethesda, Maryland
Guest Scientist, 1967-1970

Walter Reed Army Institute of Dental Research
Consultant-lecturer, 1968-1972

Naval Dental School
Consultant-lecturer, 1970-1971

Appointments and Positions (Continued):

U. S. Government:

National Institutes of Health
Pharmacology and Endocrinology Fellowship Review Committee, 1968-1971
Neurological Disorders Program Project Review Committee, 1971-1975; Chairman 1973-1975
Pharmacology Toxicology Program Project Review Committee, 1976-1980; Chairman, 1977-1980
Fogarty International Fellowship Review Committee, 1975, 1976, 1979 (Chairman), 1981 (Chairman)
Biotechnology Resources Review Committee, 1981-
NINCDS Committee to review Antiepileptic Drug Development Program, 1981-1982

Veteran's Administration
Merit Review Board, Neurobiology, 1974-1977
Chairman, 1976-1977
Consultant, 1977

Congress of the United States
Commission on the Federal Drug Approval Process 1981-

Federal Trade Commission
Consultant 1971-1974; 1978

Occupational Safety and Health Administration
Consultant 1974

Private:

National Research Council
Committee on Toxicology, 1971-1977
Panel on Anticholinesterase Chemicals, 1981-
Division of Biology and Agriculture, Representative from American Society for Pharmacology and Experimental Therapy, 1967-1977
Safe Drinking Water Committee (consultant) 1976
Pesticide Information Review & Evaluation Committee 1977-1981
Committee on Military Environmental Problems, (Chairman) 1980-1981
Committee on Recommendations for U. S. Army Basic Scientific Research 1981-

American Heart Association
National Capital Affiliate
High School Research Committee, 1970-1972
Chairman, 1971-1972
Research Committee, 1972-1977
Board of Directors, 1972-1978
Middle Atlantic Regional Heart Committee
Research Review and Certification Subcommittee, 1979-1981

U.S. Pharmacopeial Convention, 1970-

Exxon Health Research, Board of Scientific Advisors, 1981-

Professional Societies:

American Society for Pharmacology and Experimental Therapeutics
Committee on Intersociety Relations 1966-1968
Representative to Div. of Biol. and Agriculture, NAS-NRC, 1968-1977
Representative to Publications Committee of Federation of American Societies for Experimental Biology, 1970-1975
Educational and Professional Affairs Committee, 1971-1974; 1979-
Subcommittee on Graduate Convocation Program, Chairman 1972-1974
Program Committee (ad hoc member), 1968-
Ad Hoc Committee on Teaching of Pharmacology, 1970-1971
Task Force in Support of Training and Research, 1973-1975
Secretary-Treasurer, 1976-1977
Committee for Liaison with Society of Toxicology (Chairman) 1976-1978
Long Range Planning Committee, 1979- ; (Chairman) 1979-1981

Federation of American Societies for Experimental Biology
Publications Committee, 1970-1974, Chairman, 1971-1974
Life Sciences Research Office-Panel for evaluation of health hazards of irradiated beef 1977-1978.
Long Range Planning Group, 1980
Treasurer Elect 1981

Association for Medical School Pharmacology, 1969-
Councillor, 1974-1975
Secretary, 1975-1976

Society of Toxicology
Committee on Ethics of Animal and Human Experimentation (Co-Chairman, 1974-1978)
Toxicology-80's Commission, 1979

Sigma Xi 1960-
Vice President, Cornell Medical subchapter, 1966-1967
Executive Committee, Georgetown chapter, 1970-1973

The New York State Society for Medical Research
Vice President, 1968
Vice President and Treasurer, 1966-1967

Editorial Positions:

The Journal of Pharmacology and Experimental Therapeutics
Editorial Board, 1966-1971
Field Editor, Neuropharmacology, 1971-1978
Guest Field Editor, 1978-

Pharmacology for Physicians (now called Rational Drug Therapy)
Editorial Board, 1966-1971

Science; Anesthesiology (ad hoc)

Fellowships and Awards:

U.S.P.H.S. Career Development Awardee, 1961-1965, 1966-1967
Golden Apple Award, 1968

Military Service:

U. S. Navy, 1957-1959, Lt. (M.C.) U.S.N.R., Stationed at Naval Medical Research Institute, Bethesda, Maryland

Professional Societies:

American Association of Dental Schools
American Association for Laboratory Animal Science
American Association of University Professors
American Medical Association (Faculty Affiliate)
American Society for Clinical Pharmacology and Therapeutics
American Society for Pharmacology and Experimental Therapeutics
Association of Dental Pharmacology and Therapeutics Teachers
Association for Medical School Pharmacology
Drug Information Association
The Harvey Society
New York Academic of Sciences
Sigma Xi
Society for Experimental Biology and Medicine
Society for Neuroscience
Society of Toxicology
The Peripatetic Society

Professional Licenses:

District of Columbia
Maryland
New York

Publications:

See appended list

BIBLIOGRAPHY

FRANK G. STANDAERT

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5. Barr, N.L., B.E. Shepp, M. Yarczower and F.G. Standaert: Physiologic responses to stressful stratosphere flights. J. Aviat. Med. 30: 334-343, 1959.

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9. Standaert, F.G., S.L. Friess and R.O. Doty: Comparative ganglion-blocking potencies of the geometric isomers of two cyclic 1,2-amino-alcohols. J. Med. Chem. 1: 459-466, 1959.

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12. Friess, S.L., F.G. Standaert, E.R. Whitcomb, R.F. Nigrelli, J.D. Chanely and Harry Sobotka: Some pharmacologic properties of holothurin A, a glycosidic mixture from the sea cucumber. Ann. N.Y. Acad. Sci. 90: 893-901, 1960.

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13. Friess, S.L., L.J. Reber, W.C. Thommesen, L.J. Greenbaum, F.G. Standaert, and W.V. Hudak: Toxicological properties and stereo-chemical configuration in derivatives of the tropanol series. Toxicol. Appl. Pharmacol. 2: 574-588, 1960.

14. Friess, S.L., L.J. Greenbaum, F.G. Standaert and W.C. Thommesen: Central activity evoked in the cat by cistransisomers of 1,2-aminocyclohexanol derivatives. Toxicol. Appl. Pharmacol. 3: 638-653, 1961.

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18. Standaert, F.G.: The action of d-tubocurarine on the motor nerve terminal. J. Pharmacol. Exp. Ther. 143: 181-186, 1964.

19. Standaert, F.G.: The mechanisms of post-tetanic potentiation in cat soleus and gastrocnemius muscles. J. Gen. Physiol. 47: 987-1001, 1964.

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21. Riker, W.F., Jr. and F.G. Standaert: The action of facilitatory drugs and acetylcholine on neuromuscular transmission. Ann. N.Y. Acad. Sci. 135: 163-178, 1966.

22. Standaert, F.G., B. Levitt and J. Roberts: Antagonism of digitalis arrhythmia by pronethalol--a neural phenomenon? Nature 210: 742, 1966.

23. Raines, A. and F.G. Standaert: Pre- and post-junctional effects of diphenylhydantoin at the cat soleus neuromuscular junction. J. Pharmacol. Exp. Ther. 153: 361-366, 1966.

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26. Roberts, J., B. Levitt and F.G. Standaert: Autonomic nervous system control of cardiac rhythm. Nature 214: 912, 1967.

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27. Standaert, F.G. and W.F. Riker: The consequences of cholinergic drug actions on motor nerve terminals. Ann. N.Y. Acad. Sci. 144: 517-533, 1967.

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41. Raines, A., B. Levitt, F.G. Standaert and Y.J. Sohn: The influence of sympathetic nervous activity on the antiarrhythmic efficacy of diphenyl. hydantoin. European J. Pharmacol. 11: 293-297, 1970.

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54. Dretchen, K.L., F.G. Standaert and A. Raines: Effects of phenytoin on the cyclic nucleotide system in the motor nerve terminal. Epilepsia. 18(3): 337-342, 1977.

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ABSTRACTS

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2. Standaert, F.G.: Mechanism of post-tetanic potentiation (PTP) in cat slow and fast muscles. Fed. Proc. 22: 309, 1963.

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6. Sohn, Y.J., A. Raines, F.G. Standaert and B. Levitt: Antiarrhythmic properties of sodium 5,5-diphenyl-2-thiohydantoin (DPTH). The Pharmacologist 10: 221, 1968.

7. Gillis, R.A. and F.G. Standaert: Effect of carotid sinus and vagal nerve section on some cardiovascular rsponses induced by ouabain. The Pharmacologist 10: 220, 1968.

8. Detwiler, P. and F.G. Standaert: The action of gerwine monoacetate (GMA) on cat soleus muscles and nerves. Fed. Proc. 28: 699, 1969.

9. Gillis, R.A., B. Levitt, A. Raines, Y.J. Sohn and F.G. Standaert: Effect of ouabain on sympathetic, vagus and phrenic nerve activity. The Pharmacologist 11: 244, 1969.

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17. Skirboll, L.R., L. Baizer, M. Iadarola, F.G. Standaert, V.H. Morgenroth, III and K.L. Dretchen: The effects of calcium, magnesium, lanthanum tetraethylammonium and aminopyridines on the cyclic nucleotide system in the motor nerve terminal. Fed. Proc. 36: 976, 1976.

18. Standaert, F.G.: Structure, function and pharmacology of motor nerve terminals. In American Society of Anesthesiology: Workshop on neuromuscular junction--a comprehensive review. Ed. J. Savarese; Boston, March, 1977.

19. Curley, W.H., K.A. Scappaticci, R. McGee, K.L. Dretchen, and F.G. Standaert: Cyclic AMP phosphodiesterase from cat sciatic nerve. Fed. Proc. 38: 272, 1979.

20. Dretchen, K.L., R.A. Howard, F.G. Standaert and C.S. Rabe: Differential effects of acetylcholine and edrophonium on motor nerve endings. Soc. Neurosci. Abst. 5: 479, 1979.

21. Curley, W.H., K.L. Dretchen and F.G. Standaert: Inhibition by Physostigmine of Neural cAMP Phosphodiesterase. Fed. Proc. 39: 410, 1980.

22. Standaert, F.G.: Neuromuscular Transmission - What is a cholinergic receptor? Lectures Amer. Soc. Anesthesia, 133-1 to 133-4, 1980.

23. Day, N.S., Dretchen, K.L. and Standaert, F.G.: Comparison of Norcuron and Pancuronium on Neuromuscular Transmission. Fed. Proc. 141: 260, 1981.

24. Dretchen, K.L. and Standaert, F.G.: Cyclic nucleotides and antimyasthenic drugs. N.Y. Acad. Sci. (In Press)

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CURRICULUM VITAE

John Arlen Thomas

[redacted]FICE ADDRESS: Department of Pharmacology and Toxicology
West Virginia University Medical Center
Morgantown, West Virginia 26506
Telephone: (304) 293-5249

[redacted]ME ADDRESS: 661 Valley View Street
Morgantown, West Virginia 26505
Telephone: (304) 599-1429

[redacted]RN: La Crosse, Wisconsin
April 6, 1933

[redacted]UCATION: La Crosse Public School, La Crosse, Wisconsin 1938-1950
University of Wisconsin-La Crosse, La Crosse, Wisconsin 1951-1953; 1955-1956
State University of Iowa, Iowa City, Iowa 1956-1961

[redacted]ADEMIC DEGREES: B.S., University of Wisconsin, 1956
M.A., State University of Iowa, 1958
Ph.D., State University of Iowa, 1961

[redacted]RITAL STATUS: Married (1957): one son - DOB June 12, 1962;
one daughter - DOB May 31, 1964

[redacted]LITARY SERVICE: Non-commissioned Officer (Sergeant)
U.S. Army - 1953-1955

[redacted]ICENSES AND [redacted]RTIFICATES: American Registry of Physical Therapists-State University of Iowa-1957 (inactive)
American Academy of Toxicologic Sciences - Diplomate, 1982-1985

MONS 025569

HONORS AND PROFESSIONAL RECOGNITION:

Dean's Lists, University of Wisconsin - La Crosse
Gamma Alpha, Science Honorary, University of Iowa
Pre-doctoral Fellowships, University of Iowa
Foreign Travel Award, American Society for Pharmacology and Experimental Therapeutics Mexico City, Mexico; San Paulo, Brazil, 1966
Chairman, Endocrine Pharmacology, American Society for Pharmacology and Experimental Therapeutics (University of Minnesota, 1968)
Chairman, Endocrine Pharmacology, Federation of American Society for Experimental Biology (Atlantic City, N.J.) 1971
Co-Chairman, Liver Microsomal Enzymes, Society for Toxicology (New York, New York) 1973
Visiting Professor and Senior Research Advisor, Faculty of Medicine, University of Ottawa, Ontario, Canada 1971
McLaughlin Award - Outstanding Teaching Award, West Virginia University School of Medicine (Shared Award) 1971
Adjunct Professor, Department of Allied Health Sciences, Kent State University 1975-present
Outstanding Teaching Award 1973-1974 West Virginia University
Co-Chairman, Endocrine Pharmacology, American Society for Pharmacology and Experimental Therapeutics (University of Montreal, 1974)
Co-Chairman, Endocrine Pharmacology, American Society for Pharmacology and Experimental Therapeutics (University of California, 1975)
U.S. Environmental Protection Agency - Certificate of Scientific Service, 1977
McLaughlin Awards - Outstanding Teaching Award, West Virginia University School of Medicine, (Shared Award), 1977
National Academy of Science Travel Award, XII International Cancer Congress, Buenos Aires, Argentina, 1978
Co-Organizer, Epidemiology of Toxicology, ASPET/SOT Joint Meeting, (University of Texas, 1978)
Maurice O. Graff Distinguished Alumni Award (University of Wisconsin-La Crosse), 1978
Co-Organizer, N.I.E.H.S. - sponsored Target Organ Toxicity: The Endocrines Symposium, West Virginia University, 1980
Organizer, ASPET/SOT - Sponsored Symposium, "Innovating Models in Teratogenicity" (University of Louisville), 1982

MONS 025570

RESEARCH APPOINTMENTS:

Research Associate, State University of Iowa, 1958-1959
Visiting Senior Scientist - Travenol Laboratories, Chicago, Illinois - 1982

TEACHING ASSISTANTSHIPS AND ACADEMIC APPOINTMENTS:

Teaching Assistant, Department of Physiology, School of Medicine, State University of Iowa, 1960
Instructor, Department of Physiology, School of Medicine, State University of Iowa,1961
Assistant Professor, Department of Pharmacology, University of Virginia School of Medicine, 1961-1964
Associate Professor, Department of Physiology-Pharmacology, Creighton University, School of Medicine, 1964-1967
Associate Professor, Department of Pharmacology, West Virginia University School of Medicine, 1967-1969
Visiting Professor and Acting Chairman, Department of Pharmacology, Pahlavi University School of Medicine, Shiraz, Iran, 1970
Professor, Department of Pharmacology and Toxicology, West Virginia University School of Medicine, 1970-present

ADMINISTRATIVE EXPERIENCE AND CURRENT RESPONSIBILITIES:

Associate Dean of Administration, West Virginia University School of Medicine, 1973-present
Assistant Dean of Administration, West Virginia University School of Medicine, 1973-1975
American Association of Medical Colleges Executive Development Seminar Program, 1976,(M.I.T. Sloan School of Management)
Fiscal Officer, West Virginia University School of Medicine, 1973-present
Promotion and Tenure, West Virginia University School of Medicine,1973-present
Chief Grants and Contracts Officer, West University School of Medicine,1973-present
Affirmative Action Liaison, West Virginia University School of Medicine,1973-present
Academic Review, West Virginia University School of Medicine, 1973-present
Biomedical Research Grant Support Officer, West Virginia University School of Medicine, 1973-present
Facilities and Scheduling, West Virginia University School of Medicine 1973-present

RESEARCH ACTIVITIES AND INTERESTS:

Co-Investigator, National Cancer Institute, (Prostate Cancer) 1970-present
Endocrine Pharmacology/Physiology
Reproductive System Toxicity
Drug-Hormone Interactions
Heavy Metal Toxicity (Zinc Metabolism)
Pesticide Toxicity
Gonadal Toxicants
Anti-androgenic Agents
Phthalate Acid Esters

ORGANIZATIONS:

American Society for Pharmacology and Experimental Therapeutics
Endocrine Society
Society of Toxicology
Western Pharmacology Society
Sigma XI
American School Health Association, elected Fellow, 1971
National Society for Medical Research
West Virginia Association of Academic Deans
Association of American Medical Colleges-representative

PRESENT COMMITTEES:

Executive Faculty Committee, 1973
Medical School Promotions Committee - 1973 - ex-officio
Medical School Admissions Committee - 1973 - ex-officio
Building Committee for Basic Sciences - Chairman, 1973 -
Medical Center Planning Committee - Chairman, 1974 -
Educational Program Committee, 1973 -
Learning Resources Committee, 1974 -
Senior Banquet Committee, 1974 -
Association of American Medical Colleges - Planning Coordinator, 1973 -
Faculty Council - School of Dentistry - 1976 -
Medical Student Financial Aids Committee - 1977 -
American Society for Pharmacology and Experimental Therapeutics - Committee on Environmental Pharmacology, 1973 -
Computer Users Committee 1978 -
Medical School-Hospital Liaison to Student Body Committee, 1978 -
Dissertation Committees, 1968 -
Post-doctoral Training Grant (Endocrinology) 1977 -
NSF Committee to Stimulate Competitive Research in West Virginia, Chairman, 1978 -
W.V.U. Medical Center Biohazards Committee, Chairman 1980 -

SELECTED LIST OF PAST AND PRESENT CONSULTANTSHIPS AND ADVISORY ROLES:

H.E.W. - Health Manpower Branch, Region III
Environmental Protection Agency
National Cancer Institute Committee on Carcinogenesis
University Park Press, Baltimore, Maryland
Mason Research Institute, Worchester, Mass.
ASHA-PMA Lecturer on Drug Abuse
Encyclopedia Britannica
Ad Hoc Reviewer - Journal of Animal Science
Editorial Board - Journal of Toxicology and Applied Pharmacology 1973-1981
Clinical Pharmacology - Texas Allergy Research Foundation
Baxter-Travenol Laboratories - Chicago, Illinois
World Health Organization - Narcotic Division
Ad Hoc Reviewer - Science
Ad Hoc Reviewer - American J. School Health
Ad Hoc Reviewer - American J. Physiology
Ad Hoc Reviewer - Journal of National Cancer Institute
Clement Associates, Inc. Scientific Regulatory Consultants, Washington, D.C.
Editorial Board, Technomic Publishing Company (Health Science Division) Westport,CT
National Institute Arthritis, Metabolic, and Digestive Diseases
Union Carbide Corporation, South Charleston, W.Va.
American Public Health Association
Urban & Schwarzenberg Medical Publishers, Baltimore, Maryland
National Science Foundation-Regulatory Biology Program
Editorial Board, J. Toxicology and Environmental Health
Editorial Board, Perspectives in Toxicology
Raven Press, New York, New York
Professional Consultants in Occupational Health, Inc.,Washington, D.C.
Ad Hoc Reviewer - Proceedings Society Experimental Biology and Medicine
Ad Hoc Reviewer - Andrology
National Toxicology Program (NTP) Board of Scientific Counselors
Exxon Corporation, Newark, N.J.
Syntex Research (Division of Syntex[USA], Inc.), Palo Alto, California
Ad Hoc Reviewer - National Prostatic Cancer Project

SELECTED LIST OF PAST COMMITTEES AND OFFICES (CHRONOLOGICAL):

President - Virginia Academy of Sciences, Medical Sciences, 1964
Secretary - Virginia Academy of Sciences, Medical Sciences, 1962-1963
Research Fellowship Committee, University of Virginia, 1962-1964
Secretary-Treasurer, Society of Sigma xI-Creighton University, 1965-1967
Secretary, Society of Sigma xI - West Virginia University 1969
Curriculum Committee, West Virginia University School of Medicine, 1967-1969
Faculty Senate (WVU), 1969-1971; 1973-1976
Faculty Senate Committee (WVU) on Membership and Constituencies, 1970-1971
Medical School Promotions Committee (WVU), 1969-1973; Chairman 1970-1973
Medical School Admissions Committee (WVU), 1969-1973; Vice Chairman 1970-1973
Pre-Medical Advisory Group (WVU), 1970-1979
Basic Science Administrator for West Virginia University Comprehensive Cancer Center
Director of Graduate Studies in Pharmacology (WVU) 1967-1973
President's (West Virginia University) Task Force Committee on North Central Accreditation, 1972-1974
President's Ad Hoc Council for West Virginia University Research and Graduate Education, 1972-1974
Co-Director, USPHS Training Grant in Pharmacology, 1967-1973
Medical Center Long Range Planning Committee (WVU), 1968-1974
American School Health Association Committee on Drug Abuse, 1970-1975
Faculty Promotions and Tenure Committee (WVU School of Pharmacy) 1972-1974
Graduate Faculty, Kent State University, 1975
Board of Examiners, University of Madras, India
Board of Examinars, University of Ottawa, Canada
Search Committee for University Comptroller (WVU) Chairman, 1978
Research Strategy Committee (WVU), Chairman, 1977-1978
By-Laws Committee, West Virginia University School of Medicine, 1978

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Selected List of Past Committees and Offices (Chronological):

Faculty of Reproductive Physiology, Institute of Biological Sciences, West Virginia University 1967
Radiation and Isotope Committee, 1968
Cancer Fellowship and Research Committee, 1968
Faculty Promotions and Tenure Committee - Department of Pharmacology, 1970-1978
Inter-Disciplinary Advisory Committee - Master's Program in Nursing, 1972-1974
University Energy Committee, 1977-1979
Executive Committee of the Gerontology Center 1978-1980
Thesis Committees, 1968

MONS 025575

PUBLICATIONS (including 123 research papers/books/chapters/reviews; 9 [illegible] tapes/films/media; 104 abstracts):

Glucose Tolerance in Rheumatoid Arthritis, J.A. Thomas, and W.O.Paul, Clinical Chemistry 6: 556, 1956 (Abstract).

Effect of 2450 Megacycle Microwaves in Dogs, Rats and Larvae of Common Fruit Fly, G.O. Searle et.al., Biol. Effects of Microwave Radiation 1: 187, 1961.

Carbohydrate Metabolism in Patients with Rheumatoid Arthritis as Determined by Oral and IV Glucose Tolerance. J.A. Thomas, M.A. Thesis, State University of Iowa, 1958.

Effect of Microwave Irradiation on Spermatogenesis and Accessory Sex Organs in the Male Albino Rat. J.A. Thomas, Doctoral Dissertation, State University of Iowa, 1961. Dissertation Abstracts 25: 107, 1961 (Abstract).

The Effects of Microwave Irradiation on Spermatogenesis and Accesory Sex Organs in the Male Albino Rat. J.A. Thomas, and J.D. Thompson, Federation Proceedings 20: 401, 1961 (Abstract).

Alterations in Glucagon Response in Alloxan Diabetic Orchidectomized Rats by 17-ethyl-19-nortestosterone and Estradiol Benzoate. J.A. Thomas, Federation Proceedings 21: 199, 1962 (Abstract).

Effect of 17-ethyl-19-nortestosterone on Blood Glucose in the Alloxan Diabetic Rat. J.A. Thomas, Virginia Journal of Science 13: 293, 1962 (Abstract).

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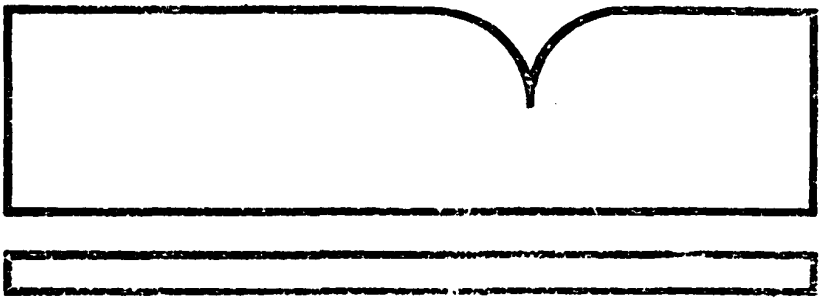

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THIRD ANNUAL REPORT ON

CARCINOGENS

DECEMBER 1982

Pursuant to Section 301(b) (4)
of the Public Health Service Act
as Amended by Section 262, PL 95-622

Prepared by the National Toxicology Program

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service

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EXECUTIVE SUMMARY

The Third Annual Report on Carcinogens, prepared by the National Toxicology Program (NTP), U.S. Public Health Service, is issued by the Secretary of the Department of Health and Human Services (DHHS), pursuant to Public Law 95-622 of November 9, 1978.* This law requires the Secretary to publish an Annual Report which contains "a list of all substances (i) which either are known to be carcinogens or which may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;...." Annual Reports should also provide available information on the nature of exposures, the estimated number of persons exposed, and the extent to which the implementation of Federal regulations decreases the risk to public health from exposure to these substances.

For the purpose of this Report, "known carcinogens" are defined as those substances for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer. Substances "which may reasonably be anticipated to be carcinogens" are defined as those for which there is a limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

Substances in the above categories, for which exposure of persons residing in the United States has been demonstrated, are included in the Report. Also included are some substances which have been banned, or the use of which has been restricted, because people previously exposed are potentially at risk, or because some of these substances still remain in the environment. The Third Annual Report does not contain all known or reasonably anticipated carcinogens. Additional substances with identified carcinogenic properties will be included in the subsequent Annual Reports.

Several problems are encountered in developing the information required for the Annual Reports on Carcinogens. Estimating the number of people exposed to a substance and identifying the nature, route, and intensity of exposure are difficult tasks. It is often impossible to obtain accurate production volumes and use patterns for most chemicals. The information that is being collected by the U.S. Environmental Protection Agency under the Toxic Substances Control Act, at least that part which is public record, may assist in obtaining more accurate exposure estimates in the future. In addition, the forthcoming National Occupational Exposure Survey** will provide new information on the extent and degree of exposure for different substances and manufacturing processes.

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* Section 262, Paragraph (4).

** An update of the National Occupational Hazard Survey conducted from 1972 to 1974 by the Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH).

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Perhaps the hardest task in preparing this Report is to evaluate the effectiveness of Federal regulations in decreasing the risk to public health. One reason is that virtually all Federal laws concerned with reducing risk have been enacted within the last 15 years. Thus, given the relatively long period between exposure to a carcinogen and the onset of disease, the extent to which the regulations implemented during these 15 years have reduced the risk remains unknown. Another reason is that reliable information on past exposures which could be used as a baseline for estimating future risk reduction is generally not available. Nonetheless, decreasing exposure should be considered as reducing carcinogenic risk even if the reduction cannot be quantified at present.

The Third Annual Report lists 117 agents. Included are the entries from the Second Annual Report and 28 additional substances or groups of substances. The new entries were chosen from those designated by the Agencies participating in the preparation of the Report,* from those tested within the National Toxicology Program and the National Cancer Institute Carcinogenesis Bioassay Program,** or from those evaluated by the International Agency for Research on Cancer (IARC), a part of the World Health Organization (WHO), located in Lyon, France.

Of the 117 entries, nineteen substances or groups of substances and three technological processes are listed as "known carcinogens":

- 4-Aminobiphenyl
- Arsenic and certain arsenic compounds
- Asbestos
- Auramine manufacture
- Benzene
- Benzidine
- N,N-Bis(2-chlorethyl)-2-naphthylamine (Chlornaphazine)
- Bis(chloromethyl)ether and technical grade chloromethyl methyl ether
- Chlorambucil
- Chromium and certain chromium compounds
- Coke oven emissions
- Cyclophosphamide
- Diethylstilbestrol
- Hematite underground mining
- Isopropyl alcohol manufacture (strong-acid process)
- Melphalan
- Mustard gas
- 2-Naphthylamine
- Nickel refining
- Soots, tars, and mineral oils
- Thorium dioxide
- Vinyl chloride

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* CDC/NIOSH, Consumer Product Safety Commission (CPSC), U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Institutes of Health/National Cancer Institute (NIH/NCI), National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS), National Institutes of Health/National Library of Medicine (NIH/NLM), and U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA).

** Now part of NTP/NIEHS.

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Ninety-five substances or groups of substances are included because they "may reasonably be anticipated to be carcinogens." Nickel appears in both lists because occupational exposure associated with nickel refining is known to be carcinogenic although specific substances which may be responsible for the carcinogenesis in humans have not yet been identified; and elemental nickel and certain nickel compounds may reasonably be anticipated to be carcinogens.

For each substance or technological process, there is a summary description including a synopsis of the evidence that explains inclusion in this Report. This is followed by a collation of regulatory information received from the participating Agencies.

Among the 117 entries, two are natural substances which are not used or produced commercially: aflatoxins and cycasin. Two are food or cosmetic additives: saccharin and safrole. Safrole has been banned for most uses. The use of saccharin has been continued by Congressional mandate.

Twelve pesticides are listed: amitrole; Aramite®; arsenical pesticides; 1,2-dibromo-3-chloropropane; hexachlorobenzene; Kepone®; lindane and other hexachlorocyclohexane isomers; mirex; nitrofen; sulfallate; toxaphene; and 2,4,6-trichlorophenol. Most of these substances have been banned or limited in use.

There are 15 therapeutic substances: N,N-bis(2-chloroethyl)-2-naphthylamine; chlorambucil; cyclophosphamide; diethylstilbestrol; iron dextran complex; melphalan; oxymetholone; phenacetin; phenazopyridine hydrochloride; phenytoin; procarbazine; reserpine; selenium sulfide; streptozotocin; and tris(1-aziridinyl)phosphine sulfide. Two of these substances are no longer produced or used in the United States: N,N-bis-(2-chloroethyl)-2-naphthylamine and streptozotocin. Six are anticancer agents: chlorambucil, cyclophosphamide, diethylstilbestrol, melphalan, procarbazine, and tris(1-aziridinyl)phosphine sulfide.

The remaining 83 substances may be classified as various industrial chemicals and by-products (25); dyes, dye intermediates, and pigments (19); combustion products (13); solvents (6); metals and metal compounds occurring in mining, extraction, and refining processes (6); analytical and research chemicals (5); and chemicals used for miscellaneous purposes (9).

The three occupational exposures known to be carcinogenic are those associated with the manufacture of auramine, the underground mining of hematite, and the manufacture of isopropyl alcohol by the strong acid process.

Scientific knowledge and judgment play important roles in grading the available evidence of carcinogenicity as sufficient, limited, or inadequate. Similarly, in all but one category of substances, regulatory action is an interpretation by the regulators of their Congressional mandates. The sole exception is the deliberate addition of additives and colors to foods. The

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Delaney clause in the Food Additives Amendment of 1958 to the Federal Food, Drug, and Cosmetic Act requires that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals;...."*

Requests to DHHS for conducting research, testing for carcinogenicity or providing information on the effects of standards or regulations on public health are included in the Report as received; this is required in clause (i), subparagraph (4)(D) of Section 262.

Appendix A is an index of synonyms and trade names to identify substances known under a variety of different names. Appendix B contains a glossary of frequently used terms, a list of commonly used acronyms, and some common units of measurement. Appendix C lists the substances, group of substances, and technological processes contained in the Report and tabulates the synonyms and trade names for each of them. Appendix D is a list of participating Agencies and their staff who collaborated in the preparation of the Third Annual Report, and Appendix E contains a cumulative index to the Annual Reports on Carcinogens.

Corrections or suggestions, as well as any additional information that the reader may have should be sent to the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Summaries of this Report may be obtained from the Public Information Office, National Toxicology Program, B2-04, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Copies of the complete report are available for a fee from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161. Request number PB 83-135855 should be indicated.

* So far only two substances have been banned on the basis of the Delaney clause: Flectol H in 1967 and chloraniline in 1969. According to the FDA, both substances were used to make adhesives for food packaging material.

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INTRODUCTION

Cancer is the second most common cause of death in the United States. One in every four Americans will suffer from cancer sometime during their lifetime; one in every five will die from cancer. In 1979, more than 400,000 Americans died of cancer.[1] In addition to the physical and emotional suffering caused by cancer, this disease may cost the Nation as much as $30 billion each year in lost production and income, medical expenses, and research resources. For these reasons, the American public is concerned about cancer and cancer hazards, especially about ways to prevent the occurrence or decrease the incidence of cancers.

Contrary to popular belief, cancer is not one but many diseases which may have different causes. Most scientists now consider that about one-third to two-thirds of all cancers are associated with the environment in which we live and work. In this context, the environment is understood as "anything that interacts with humans, including substances eaten, drunk, and smoked, natural and medical radiation, workplace exposures, drugs, aspects of sexual behavior, and substances in air, water, and soil."[2] Some cultural and behavioral patterns, apart from defined habits of smoking and alcohol consumption, may significantly influence the development of tumors in the gastrointestinal tract, breast, uterus, and prostate. These aspects of social environment, personal behavior, and habits are sometimes called "lifestyle." Although we rarely know the environmental factors and conditions which are responsible for the development of specific cancers, in some cases we are beginning to have some understanding. Most cancers that are associated with the environment should be avoidable, at least potentially.

Development of cancer also depends on "host factors." Host factors are attributes of human organisms associated with individual differences in the risk of developing a specified cancer. A host factor may be associated with reduced risk of a cancer, not only with increased risk.[3] Examples of host factors are immunological and endocrine functions, nutritional status, genetic constitution, age, and sex.[4]

As Americans have become more and more concerned about the environment and cancer, they have repeatedly asked the Federal Government to clarify what is known about cancer-causing substances. The public wants to know and should know which substances are regarded as cancer hazards in the work place and in the general environment and how well we are protected from exposure to these substances.

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Section 262 of Public Law 95-622 of November 9, 1978* reflects the requests for this information. Paragraph (4) of this section stipulates that the "Secretary shall publish an annual report which contains

"(A) a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;

"(B) information concerning the nature of such exposure and the estimated number of persons exposed to such substances;

"(C) a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency; and (ii) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance; and

"(D) a description of (i) each request received during the year involved -

"(I) from a Federal agency outside the Department of Health, Education and Welfare for the Secretary, or

"(II) from an entity within the Department of Health, Education and Welfare to any other entity within the Department,

to conduct research into, or testing for, the carcinogenicity of substances to provide information described in clause (ii) of subparagraph (C), and (ii) how the Secretary and each such other entity, respectively, have responded to each request."

Annual Reports on Carcinogens are issued in response to these requirements. These reports discuss substances or technological processes which are known to be carcinogens or which may reasonably be anticipated to be carcinogens; they contain information received from Federal agencies participating in the preparation of the Reports.

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* Community Mental Health Centers Act, Amendments.

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Participants

Within the Department of Health and Human Services, the responsibility for preparing these annual reports has been delegated to the National Toxicology Program.* Other agencies participating in this effort are:

Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH)

Consumer Product Safety Commission (CPSC)

U.S. Environmental Protection Agency (EPA)

Food and Drug Administration (FDA)

National Institutes of Health/National Cancer Institute (NIH/NCI)

National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS)

National Institutes of Health/National Library of Medicine (NIH/NLM)

U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA)

Four of these agencies -- CPSC, EPA, FDA, and OSHA -- are responsible for regulating hazardous substances and limiting the exposure to and use of such substances.

Identifying Carcinogens

For many years Government research agencies, industries, universities, and other research organizations have studied various substances to ascertain those which might cause cancer. Other Federal agencies have been developing information on exposure and potential hazards and making rules and regulations to control substances which have been identified as carcinogens.

The largest single national testing effort, the National Cancer Institute's Carcinogenesis Testing Program, has now become a part of NTP/NIEHS. The NCI Clearinghouse on Environmental Carcinogens, consisting of a panel of experts from governmental and non-governmental institutions, has reviewed the NCI testing results, and an analysis of results of NCI carcinogenesis bioassays of 190 chemicals has recently been published.[5] The Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors, augmented by an *ad hoc* panel of experts in chemical carcinogenesis, has now replaced the NCI Clearinghouse as the body of non-government experts conducting peer reviews of the NTP carcinogenesis bioassay results.

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* DHHS agencies participating in NTP are NIH/NCI; NIH/NIEHS; FDA/National Center for Toxicological Research (FDA/NCTR); and CDC/NIOSH.

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Many of the substances listed in the Third Annual Report on Carcinogens have been chosen from the "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" published by the International Agency for Research on Cancer (IARC) in Lyon, France.* Each monograph is the product of an individual working group of experts in chemical carcinogenesis and related fields. The experts evaluate the data for each substance included in a monograph. The evaluation is based on the published information available at the time the working group meets. A joint IARC/WHO ad hoc Working Group met in October 1977 to review and revise the criteria for judging the adequacy of available data. The terms 'sufficient evidence' and 'limited evidence' of carcinogenicity used in these criteria refer only to the amount and adequacy of the available evidence and not to the potency of carcinogenic effect or the mechanisms involved. An updated version of these criteria is included in each IARC Monograph Volume. The IARC Monograph Supplement 4 contains re-evaluations by an ad hoc working group of all chemicals, industrial processes and occupational exposures for which some data on carcinogenicity in humans are available either in the first 29 volumes of monographs or in other subsequent publications.[6]

A direct comparison of the IARC evaluations[6] and the evaluation of NCI/NTP bioassay results[5] cannot be made because different criteria were used to assess the evidence; but these criteria can be related.[2] Such evaluations involve a component of personal judgment. In some cases the available evidence may be assessed differently depending on the criteria used and the composition of the group of experts.

Clause (i) in subparagraph (A)(4) of Section 262 requires "a list of all substances which are either known to be carcinogens or may reasonably be anticipated to be carcinogens." For the purpose of this report, the two categories in the law -- known to be carcinogens and reasonably anticipated to be carcinogens -- relate to the IARC criteria for the degree of evidence[6] as follows:

1. Known to be carcinogens:

   There is "sufficient evidence of carcinogenicity" from studies in humans "which indicates a causal relationship between the agent and human cancer."

2. Reasonably anticipated to be carcinogens:

   A. There is "limited evidence of carcinogenicity" from studies in humans, "which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded." or

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* The IARC address is: 150, cours Albert-Thomas, 69372 Lyon Cedex 2. France. WHO/IARC Publications may be obtained from WHO Publications Centre USA, 49 Sheridan Avenue, Albany, New York 12210.

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B. There is "sufficient evidence of carcinogenicity" from studies in experimental animals "which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data concerning dose response effects, as well as information on mutagenicity or chemical structure."

Most of the substances contained in this Annual Report can be identified chemically. Some carcinogens occur naturally, some are produced when materials are burned, and others are present in raw materials, or in intermediate and final products of industries. In some cases only the exposure associated with a specific technological or manufacturing process, occupation, or industry can be related to an increased incidence of cancer in humans, but the substances responsible cannot be identified. Examples of such processes are the underground mining of hematite and the strong-acid process for the manufacture of isopropyl alcohol.

Human and Animal Studies

Some understanding of the human and animal studies used for identifying carcinogens is necessary to clarify what is meant by the words "known" and "reasonably anticipated." The strongest evidence for a relationship between exposure to a suspected substance and cancer in humans comes from epidemiological studies. Although we have adequate epidemiological evidence only for a few carcinogens, we think the patterns seen in these studies show how other animal carcinogens might affect humans. Epidemiological investigations give the best information on cancer-causing agents, but such studies of groups of individuals do have shortcomings. They may require observations over a long time because the latent period between initial exposure and cancer occurrence may be up to 20-30 years. Intentional, long-term exposures of human groups are, of course, unacceptable. As an alternative, scientists make educated predictions about the effects in humans, based on the effects observed in studies with experimental animals.

Although test animals may respond differently from humans, experience has shown that almost all known human carcinogens also cause cancer in experimental animals if adequately tested.* This finding is understandable since cancer begins in individual cells and all mammalian cells are comparable in structure and function. The basic premise of experimental carcinogenesis research is that substances that produce cancer in rodents and other experimental animals may affect human cells in the same way.

* The evidence for carcinogenicity in experimental animals of arsenic compounds is still regarded as inadequate, and the evidence for benzene is at present limited.[6]

Relatively large doses of chemicals are used in animal studies to make up for the small number of experimental animals exposed, as compared to the size of human populations. Animal tests are costly, take years to complete, and are often difficult to interpret in terms of human carcinogenic risk. They are nevertheless, the best testing tool we have. No animal test can prove beyond doubt that a substance will or will not cause cancer in humans. Even "sufficient evidence" of carcinogenicity in experimental animals may prove not to be definitive. But if we are to prevent cancer, we cannot wait 20 to 30 years to obtain a definitive evidence of harm to human health. Therefore, substances which show "sufficient evidence" of cancer causation in experimental animals are considered as reasonably anticipated human carcinogens.

Inclusion of Substances

The Third Annual Report contains substances, groups of substances and technological processes which were listed in the Second Annual Report. Where necessary, the information has been updated. The Third Annual Report presents information on 28 additional substances. Each has been chosen either from substances tested by the NCI Carcinogenesis Testing Program or the National Toxicology Program (NTP); from designations of the participating agencies, or from substances evaluated by the IARC working groups. Other substances from the same sources will be added to the subsequent Annual Reports.

Section IIIA of the Third Annual Report lists all the substances and technological processes included. The list is divided into two sublists. One contains substances, groups of substances, or technological processes known to be carcinogens (22 entries). The other list of 95 entries includes substances or groups of substances which may reasonably be anticipated to be carcinogenic. Nickel appears in both sublists because the nickel refining process is known to be carcinogenic, whereas elemental nickel and certain nickel compounds may reasonably be anticipated to be carcinogens.

Section IIIB contains a brief description of each substance or technological process together with a summary of evidence for its carcinogenicity. References to the original papers on experimental or epidemiological studies, which can be found in the IARC Monographs or in the NCI and NTP bioassay reports, have not been included in the Third Annual Report.

A substance not listed in this Annual Report may still be a known carcinogen or a reasonably anticipated carcinogen. More substances than those included may potentially present a carcinogenic risk to persons living in the United States. These substances will be incorporated into subsequent Annual Reports as resources permit. Some chemicals will be introduced as a result of testing performed by industry in response to EPA's requests under the Toxic Substances Control Act. The National Toxicology Program will also play a role in providing new information for these reports as further test results become available.

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Ionizing radiation, ultraviolet radiation (including sunlight), tobacco, alcoholic beverages, and some viruses are known or suspected to be carcinogens. They have not been included in this Report because ionizing radiation is discussed thoroughly in a General Accounting Office report,[7] and a recent Surgeon General's report[8] reviews the overwhelming relationship between tobacco and cancer. Several publications issued by the National Cancer Institute[9] explain the relationship of alcoholic beverages, ultraviolet radiation, and viruses to cancer.

Estimating Exposure

According to clause (ii) of subparagraph (4)(A), this Report is required to include those substances "to which a significant number of people residing in the United States are exposed." Substances to which only a few people are exposed are not included for the most part. Yet some substances which have been banned or restricted in use are contained in the Report (e.g., safrole, arsenical pesticides, mirex) either because people who were previously exposed remain potentially at risk, or because these substances are still present in the environment.

Subparagraph (4)(B) requires that the Annual Reports provide "information concerning the nature of such exposure and the estimated number of persons exposed to such substances." The determination of the number of people exposed and the route, intensity, and duration of such exposure for each substance remains a formidable task. This Report attempts to respond to these questions, and wherever adequate answers could be obtained, they are included in Section IIIB. Exposure to carcinogens can occur anywhere. Some carcinogens have always been present in the environment, and their amount varies, depending on geographical location and other environmental conditions. Every year human activities may add more carcinogens to the ambient air, water, food, soil, and occupational environment. Although scientists attempt to estimate the amount of carcinogens present in and added to the environment, there is no reliable way to predict who is exposed to what carcinogen and when exposure occurs. Also, since human populations are always exposed to many chemicals at the same time, this may modify the effects of a specific exposure either by multiplying (synergism) or reducing its action (antagonism).

If exposure is linked to a specific habit such as smoking, a specific use such as medical diagnosis or treatment, or a restricted environment such as the work place, our ability to estimate exposure improves, and in some cases the size of population segments involved can be estimated. Production and use data may also help estimate exposure, but this information may not be publicly available for many substances, and where it is, it may be out-dated or even contradictory.

The National Occupational Hazard Survey (NOHS), conducted by CDC/NIOSH from 1972 to 1974, gave information on the number of workers exposed and on some broader aspects of occupational exposure. The forthcoming National Occupational Exposure Survey (a repeat of NOHS) should yield valuable information with respect to more recent exposures. Subsequent Annual Reports on Carcinogens will explore this and other available data bases, and their strengths and limitations.

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Regulatory Status

Subparagraph (4)(C) of Section 262 also requires "a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency;...." The Third Annual Report responds to this requirement by appending to the description of each substance in Section IIIB a summary of federal regulations as submitted by the participating agencies. Some of these standards and regulations have been enacted for reasons other than the carcinogenicity of the substance, for instance, to prevent other adverse health effects or to improve the environmental quality or food quality. Solid or liquid wastes or wastes discharged into the air may contain carcinogens, yet these may be regulated as toxic substances or hazardous pollutants and not specifically as carcinogens. But if these regulations reduce exposure to carcinogens, then the carcinogenic risk posed by such substances will also decrease.

Estimating Risk Reduction

Clause (ii) in subparagraph (4)(C) requires a statement identifying "for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance;...." This requires quantified information on the amount of protection from cancer the public receives from established Federal standards.

Estimating the amount of health protection is perhaps the most difficult task in preparing the Annual Reports. One reason is that most Federal laws concerned with reducing carcinogenic risk have been enacted within the last 15 years. Given the long period between the initial exposure to a carcinogen and the onset of disease, it is still too early to evaluate how much Federal standards and other regulations have decreased the risk to public health. Another reason is that information on past exposure levels, which could serve as a baseline for estimating future risk reduction, often is not available or accurate.

The risk -- the likelihood of developing cancer -- depends on the intensity, route, and duration of exposure to a carcinogen. Individuals may respond differently to similar exposures, depending on host factors such as age, sex, nutritional status, overall health and inherited characteristics. Only in a few instances, where studies of long-term human exposures and cancer incidence in restricted environments are available, can risk be estimated with confidence.

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The regulation of asbestos in the work place provides a good example. In 1969, under the Walsh-Healy Act which then regulated only the firms with Government contracts, the standard for permissible exposure was 12 fibers of asbestos per cubic centimeter (cc) of air. Under the Occupational Safety and Health Act, this standard was reduced to 5 fibers/cc in 1972 and to 2 fibers/cc in 1976. On April 17, 1980, a joint NIOSH-OSHA Working Group recommended the elimination of all non-essential uses of asbestos and the implementation of a public health program to reduce human exposures. The high risk to workers exposed prior to 1969 is well known. The actual data on exposure levels in the '40s, '50s, and '60s are fragmentary, although exposure levels were undoubtedly unacceptably high by today's standards. Mesothelioma (primarily an asbestos-induced cancer) and lung and other cancers, the incidence of which is increased by exposure to asbestos, generally take 20-40 years or more to develop and become apparent. For these reasons, we will not know until early in the next century to what extent the series of exposure reductions in the '70s have reduced the cancer risk to those persons exposed to asbestos.

One possible way to provide quantitative estimates of risk reduction might be to assume that the carcinogenic risk is directly proportional to exposure. This approach also supposes that data on past and present exposure levels are available, or that conditions in all work places are in compliance with regulations. However, information supporting these assumptions is only rarely obtainable. Nevertheless, it is reasonable and prudent to accept that the reduction of exposure, for any reason, particularly to substances shown to be carcinogenic in experimental animals, will decrease the incidence of cancer. This is the basis of current regulatory policies which aimed to lower human exposure to cancer-causing substances and thereby improve public health. For a more detailed discussion of the issues involved, see the previously cited report to Congress on the assessment of technologies for determining cancer risks from the environment.[2]

Requests for Research, Testing, and Information

The last requirement of subparagraph (4)(D) is

"a description of (I) each request received during the year involved -

"(I) from a Federal Agency outside the Department of Health, Education and Welfare for the Secretary, or

"(II) from an entity within the Department of Health, Education, and Welfare to any other entity within the Department, to conduct research into, or testing for, the carcinogenicity of substances or to provide information described in clause (i) of subparagraph (C), and (ii) how the Secretary and each other entity, respectively, have responded to each such request."

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Section IV of the Report provides a list of such requests as received from the participating agencies. The inclusion of a substance in this table does not imply that it is a known or reasonably anticipated carcinogen.

Appendixes

Appendix A is an index of synonyms and trade names of substances included in the Third Annual Report. Appendix B contains a glossary of frequently used terms, acronyms and units of measurement. Appendix C lists in alphabetical order the substances, groups of substances, and technological processes included, and the synonyms and trade names for each of them. Appendix D is a list of participating agencies and their staff members who collaborated in preparing the Third Annual Report. Appendix E is a cumulative index to the Annual Reports on carcinogens.

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III. SUBSTANCES LISTED

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LIST OF SUBSTANCES*

a. Substances or groups of substances, and technological or manufacturing processes that are known to be carcinogenic**

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4-Aminobiphenyl	31
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Asbestos	47
Auramine manufacture	52
Benzene	57
Benzidine	60
N,N-bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)	69
Bis(chloromethyl)ether and technical grade chloromethyl methyl ether	71
Chlorambucil	83
Chromium and certain chromium compounds	88
Coke oven emissions	95
Cyclophosphamide	102
Diethylstilbestrol	137
Hematite underground mining	161
Isopropyl alcohol manufacture (strong-acid process)	174
Melphalan	184
Mustard gas	195
2-Naphthylamine	197
Nickel refining	198
Soots, tars, and mineral oils	266
Thorium dioxide	277
Vinyl chloride	292

b. Substances or groups of substances that may be reasonably anticipated to be carcinogens**

2-Acetylaminofluorene	21
Acrylonitrile	23

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* An alphabetized list of substances, their synonyms, and their trade names appears in Appendix A. The synonyms and trade names for each substance included are listed in Appendix C.

** For the purpose of this Report, "known carcinogens" are defined as those substances for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer. Substances "which may reasonably be anticipated to be carcinogens" are defined as those for which there is a limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

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Benzo(b)fluoranthene	62
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Beryllium and certain beryllium compounds	66
Cadmium and certain cadmium compounds	75
Carbon tetrachloride	80
Chloroform	85
p-Cresidine	97
Cupferron	99
Cycasin	101
2,4-Diaminoanisole sulfate	104
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Dibenz(a,h)acridine	108
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Dibenz(a,h)anthracene	112
7H-Dibenzo(c,g)carbazole	114
Dibenzo(a,h)pyrene	116
Dibenzo(a,i)pyrene	118
1,2-Dibromo-3-chloropropane	120
1,2-Dibromoethane	123
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Hexachlorobenzene	162
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MONS 025620

B. Individual Substances

MONS 025621

2-ACETYLAMINOFLUORENE

Incorporation of this compound into the feed caused increased incidences of malignant tumors in a variety of organs in the rat.[1] Long-term studies in which mice were given 2-acetylaminofluorene (AAF) in the diet showed increased incidences of liver and urinary bladder cancers.[2]

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[1]Wilson, N.H., F. DeEds, and A.J. Cos. The Toxicity and Carcinogenic Activity of 2-Acetylaminofluorene. Cancer Research. Vol. 1, 1941, pp. 595-60d.

[2]Staffa, J.A., and M.A. Mehlman (eds.). Innovations in Cancer Risk Assessment (ED_{01} study): Proceedings of a Symposium. Journal of Environmental Pathology and Toxicology. Vol. 3, 1980, pp. 1-246.

AAF was intended for use as a pesticide, but this chemical was never marketed because it was found to be carcinogenic in experimental animals.

AAF is used as a positive control by biochemists and technicians engaged in the study of liver enzymes and of the carcinogenicity and mutagenicity of aromatic amines. These research persons may be exposed to AAF.

AAF is distributed by several companies that deal in specialty chemicals. EPA reported one producer in one region (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). Information obtained from the distributors indicates that AAF is imported from Europe. A typical chemical distributor keeps approximately 10 lb of AAF in stock. The chemical is usually sold in 1-, 5-, or 25-g quantities. Based on this information, it is estimated that the total U.S. usage is less than 20 lb per year.

Human exposure to AAF may occur through inhalation and skin absorption. The occupations at greatest risk to AAF exposure are organic chemists, chemical stockroom workers, and biomedical researchers. Although neither NIOSH nor OSHA has estimated the number of U.S. workers exposed to AAF, perhaps fewer than 1000 workers in 200 laboratories may come in contact with this animal carcinogen.

Because AAF is an animal carcinogen, on February 11, 1974, OSHA promulgated a standard for this chemical designating protective clothing, hygiene procedures for workers, and special engineering requirements for the manufacture or processing of AAF.

MONS 025622

2-Acetylaminofluorene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. Un known use in consumer products. (CPSC)		
RCRA, 3001 3004: Listed as a hazardous constituent of waste. Wastes known to contain this chemical are subject to handling and report/recordkeeping requirements.. Promulgated 5/19/80. The Carcinogen Assessment Group at EPA has included this chemical on its list of carcinogens. As a result of this listing, this chemical is regulated under the Resource Conservation and Recovery Act's hazardous waste disposal rule. The Office of Planning and Management is developing a chapter in EPA's Occupational Safety Manual stipulating handling procedures for chemicals posing carcinogenic hazards, including carcinogenicity to users. This chemical is included. (EPA)		40 CFR 261.33 (EPA)
Protective clothing, respirator, hygiene, training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1014 (OSHA)

MONS 025623

ACRYLONITRILE

There is sufficient evidence for the carcinogenicity of acrylonitrile (AN) in experimental animals; the evidence of carcinogenicity in humans is limited.[1] Acrylonitrile was carcinogenic in rats where administered by gavage and in drinking water, or by inhalation.[1,2]

An epidemiological study of workers potentially exposed to acrylonitrile and observed for 20 years or more showed an increased incidence of cancers of the lung, large intestine and prostate. The mortality from lung cancer was also increased. Another similar study of persons occupationally exposed to acrylonitrile and followed for 10 years or more also indicated an increased incidence of cancers of the stomach, colon, brain and respiratory tract.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 19. Lyon, France: IARC, 1979, pp. 73-133.

AN is a reactive chemical that is commercially important because it polymerizes readily. It is a volatile liquid, soluble in water and in most common organic solvents.

AN is used extensively in manufacturing of synthetic fibers, resins, plastics, elastomers, and rubber for a variety of consumer goods such as textiles, dinnerware, food containers, toys, luggage, automotive parts, small appliances, and telephones. In 1976, about 48 percent of the AN was used to produce acrylic and modacrylic fibers; 21 percent to produce acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins; 19 percent to produce nitrile elastomers and latexes such as butadiene acrylonitrile copolymers; and 12 percent to produce adiponitrile, an intermediate used in nylon production.

AN has been produced in the United States since 1940. NIOSH has reported that approximately 1.5 billion lb of AN are now manufactured annually.

Exposure to AN can occur during manufacture and production. The compound is volatile, and exposure occurs primarily through vapor inhalation and skin absorption. OSHA estimated that approximately 278,000 persons are potentially exposed to AN. These persons work as acrylic resin makers; organic chemical synthesizers; pesticide workers; rubber, synthetic fiber, and textile makers.

MONS 025624

According to the Consumer Product Safety Commission in 1980, direct consumer exposure to AN through consumer product use is low, because there is little migration of the monomer from such products. The levels of AN in consumer products are estimated to be less than 1 ppm in acrylic and modacrylic fibers, 30-50 ppm in ABS copolymers, 15 ppm in SAN copolymers, and 0-750 ppm in nitrile rubber and latex goods. The presence of AN, even as a trace contaminant, may be cause for concern; however, data describing the actual levels of residual in finished products and the potential for consumer exposure and uptake are currently lacking. The extent of exposure to AN of the general population through air emissions from production, manufacture, bulk storage, and waste disposal has not been determined. However, a 1977 report cited that total AN air emissions are 2.2 percent of total production.

During 1978, EPA declared AN a hazardous substance based on the reported acute toxic effects. As a result, EPA promulgated hazardous spill regulations in 1979 under the Clean Water Act, establishing reportable quantities of 100 lb for AN. The EPA Carcinogen Assessment Group included AN on its list of carcinogens. Because AN is an animal carcinogen, EPA proposed in 1980 to reduce the reportable quantity of AN to 10 lb. Under the Resource Conservation and Recovery Act, EPA regulates waste products, off-specification batches, and spill residues in excess of 2200 lb AN.

FDA and OSHA have also regulated AN. During 1977, FDA banned the use of AN copolymers for beverage containers and proposed to limit AN migration from other food-contact materials to 50 ppb. During 1979, FDA was asked to review the ban, and this has been a continuing effort. In 1983, the FDA intends to review all AN regulations and bring them into alignment with current carcinogenicity data. This review will include an advisory opinion and subsequently a proposal for use of a new type of container that limits AN migration. In addition, OSHA enacted regulations in 1978 to reduce worker exposure to AN by establishing a standard of 2 ppm (4.5 mg/m^3) as a time-weighted average. This standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No regulatory plans at present. (CPSC)		
CWA, 311: Hazardous spill regulation establishing reportable quantity (100 lb. 45.4 kg) and imposing reporting requirements. Promulgated 6/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipment of the chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.33
Proposal to reduce reportable quantity to 10 lb (4.54 kg), proposed 7/9/80.	Based on carcinogenicity.	45 FR 133, p. 46094
FIFRA, 3: Classified for restricted use. 2/9/78.	Accident history of acute effects. (EPA)	40 CFR 162.31
FIFRA, 6: Voluntary cancellation of product registration by three producers, 6/15/78, and two subsequent dates in 1978.		43 FR 26310 (first notice)
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates acrylonitrile as a hazardous constituent of waste and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CAA: Exposure assessment completed 8/79. Technology assessment in progress.		BAQPS, personal communication, 10/80 (EPA)
See Carcinogen Assessment Group statement for 2-acetylaminofluorene. (EPA)		
Bureau of Foods; FFDCA:	To eliminate or minimize exposure to acrylonitrile consumer through migration into food. (FDA)	
June 1976: Regulation published interim listing of acrylonitrile copolymers.		
November 1976: Report received showing positive results in teratology studies.		
January 1977: Interim report on 2-year rat feeding study showed a strong tumorigenic response.		
March 1977: Stay of beverage bottle regulations published. Additionally, a proposal to limit acrylonitrile migration from food-contact articles other than beverage bottles to 50 ppb was published.		
March 1977: U.S. Court of Appeals set aside the FDA stay of the beverage container regulations and held a public hearing.		
June 1977: Public hearing on acrylonitrile.		

(Continued)

MONS 025626

Acrylonitrile (Concluded)

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
August 1977: Administrative law judge upheld FDA position on acrylonitrile beverage containers. November 1977: Appeal of Commissioner's decision. November 1979: The court upheld the revocation of the acrylonitrile bottle regulations and remanded to FDA the issue of new bottles with lower residual acrylonitrile monomer levels as well as the issue of the safety of all other acrylonitrile copolymers. As a part of the opinion, the court also upheld the Commissioner's right to decide that certain levels of substances were too trivial to be considered under the food additive provisions of the FDACA. FDA Bureau of Medical Devices; FDACA: to regulation of medical device uses. Amount of migration is not known. (FDA)		
PEL: 2 ppm 8-hr TWA; 10 ppm 15-min TWA ceiling. No skin or eye contact with liquid acrylonitrile. Additional Regulations: Protective clothing, hygiene, training, and medical surveillance requirements for workers; respirator requirements where engineering and work practice controls not sufficient or feasible; monitoring requirements; housekeeping and waste disposal requirements; sign requirements for regulating areas; labeling requirements for containers. (OSHA)	Regulatory History: 1952: Welsh-Healy, 20 ppm maximum allowable concentration. August 27, 1971: OSHA Takeover Standard--skin, 20 ppm 45 mg/m³ 8-hr TWA. January 17, 1978: Emergency Temporary Standards--2 ppm 8-hr TWA; 10 ppm 15-min TWA ceiling; no skin or eye contact. November 2, 1978: Final Standard--current level effective. (OSHA)	29 CFR 1910.1045 (OSHA)

MONS 025627

AFLATOXINS

There is sufficient evidence for the carcinogenicity of aflatoxins in experimental animals. The evidence of carcinogenicity in humans is limited.[1] Aflatoxins were carcinogenic in mice, rats, fish, ducks, marmosets, tree shrews, and monkeys by several routes of administration (including oral), producing mainly cancers of the liver, colon, and kidney.[2]

Epidemiological studies have shown a positive correlation between the average dietary concentrations of aflatoxins and the incidence of primary liver cancer. No studies have been carried out that could link an increased risk of liver cancer to actual aflatoxin intake in individuals.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 10. Lyon, France: IARC, 1976, pp. 51-72.

Aflatoxins are a group of toxic metabolites produced by certain types of fungi. They are intensely fluorescent in ultraviolet light and slightly soluble in water.

Aflatoxins are not commercially manufactured; they are naturally occurring contaminants that are formed by fungi on food during conditions of high temperature and high humidity.

Human exposure to aflatoxins occurs through ingestion of contaminated food. Grains, peanuts, tree nuts, and cottonseed meal are among the more common foods on which these fungi grow. Meat, eggs, milk, and other edible products from animals that consume aflatoxin-contaminated feed are additional sources of potential exposure. Americans consume an estimated 0.15 to 0.50 μg of aflatoxins daily.

Under the Resource Conservation and Recovery Act, 3001-3004, EPA regulates aflatoxins as a hazardous constituent of waste. In addition, the EPA Carcinogen Assessment Group considered aflatoxins to be carcinogenic. The FDA has established enforcement levels of 0.5 ppb in milk and 20 ppb for other food products.

MONS 025628

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Listed as a hazardous constituent of waste. Wastes known to contain any aflatoxin are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. Because aflatoxins are naturally occurring contaminants, EPA has a limited regulatory authority over these substances. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)
Aflatoxins were found to be unavoidable contaminants in foods. Enforcement action levels of 20 ppb (total B_1, B_2, G_1, G_2) for all products and 0.5 ppb aflatoxin M_1 in milk are in effect. (FDA)	Holds human exposure to lowest practicable level. (FDA)	Compliance Policy Manual Guide Numbers 7106.10, 7112.02, 7112.07, 7112.02, 7112.07, 7112.08, 7120.26, 7126.33 (FDA)

MONS 025629

2-AMINOANTHRAQUINONE

Technical grade 2-aminoanthraquinone (impurities unspecified), administered in the feed, was carcinogenic in male Fischer 344 rats, causing a combination of hepatocellular carcinomas and neoplastic nodules of the liver. The compound was also carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes and malignant hematopoietic lymphomas in females.[1] An IARC working group considered that the evidence for the carcinogenicity in experimental animals of the material tested was limited.[2] In view of another evaluation of NCI bioassay results, the evidence can be considered as sufficient.[3]

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[1]National Cancer Institute. Bioassay of 2-Aminoanthraquinone for Possible Carcinogenicity. Technical Report Series No. 144. DHEW Publication No. (NIH) 78-1399. Bethesda, Maryland, 1978.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 191-98.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

2-Aminoanthraquinone (AAQ), an aromatic amine, is insoluble in water and soluble in alcohol.

AAQ is used as an intermediate in the industrial synthesis of anthraquinone dyes. It is the precursor of five dyes and one pigment, including Colour Index Vat Blues 4, 6, 12, and 24; Vat Yellow 1; and Pigment Blue 22.

Production in 1971 was 200,000 lb for AAQ and its salts. Imports in 1974 were 375,000 lb. EPA reported five producers and importers of AAQ between 1975 and 1977 (Toxic Substances Control Act, Chemical Substance Inventory, Initial Inventory, 1979, public record). Production of AAQ was not reported to the U.S. International Trade Commission in 1979-1980. Data from NCI indicated that imports through principal U.S. customs districts in 1980 were only 250 lb. The 1982 Directory of Chemical Producers indicates that only one U.S. company now produces AAQ and its salt. Recent production figures for AAQ are considered proprietary and are not available.

MONS 025630

Human exposure to AAQ is principally through inhalation and skin contact. Because AAQ is used on a commercial scale solely by the dye industry, the potential for exposure to the compound is greatest for workers at dye manufacturing facilities. However, no additional data are available on the number of facilities using AAQ.

The National Occupational Hazard Survey in 1974 made no estimate of the potential occupational exposure to AAQ (NIOSH). However, the Consumer Product Safety Commission staff believes that trace amounts of unreacted AAQ may possibly be present in some dyes based on this chemical and in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on experience with other dyes derived from aromatic amines. Data are not available on the actual levels of impurities in the final product, the potential for consumer exposure, and the uptake.

1-Aminoanthraquinone

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
Because of its low production volume, 1-aminoanthraquinone is of low regulatory priority to EPA. It may be considered as the dyes and pigments industry is studied. (EPA)		

MONS 025631

4-AMINOBIPHENYL

There is sufficient evidence for the carcinogenicity of 4-aminobiphenyl both in humans and in experimental animals.[1] 4-Aminobiphenyl is carcinogenic in mice, rats, rabbits and dogs after oral administration, producing principally cancer of the urinary bladder.[2]

Epidemiological studies, which are confined to one series of workers occupationally exposed to commercial 4-aminobiphenyl, show a high incidence of bladder cancer.[1-3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1979, p. 22.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: IARC, 1972, pp. 74-79.
[3]Melamed, M.R. Diagnostic Cytology of Urinary Tract Carcinoma. European Journal of Cancer. Vol. 8, 1972, pp. 287-92.

4-Aminobiphenyl is an aromatic amine that is slightly soluble in water. Although formerly used as a rubber antioxidant, this compound has no current commercial use in the United States. Nor is there evidence of any current commercial production. For 1975-77, EPA reported only one producer in one region, according to the Toxic Substances Control Act (TSCA), Chemical Substances Inventory, 1979, public record.

4-Aminobiphenyl has been used as a research chemical and as a reagent for the detection of sulfates. The compound also occurs as a contaminant in 2-aminobiphenyl.

2-Aminobiphenyl, a chemical closely related to 4-aminobiphenyl, is used in the manufacture of dyes. According to OSHA, approximately 130 workers are potentially exposed to 4-aminobiphenyl during the production of 2-aminobiphenyl.

EPA regulates 4-aminobiphenyl under the Resource Conservation and Recovery Act as a hazardous constituent of waste and under TSCA. The EPA Carcinogen Assessment Group lists 4-aminobiphenyl as a carcinogen. In February 1974, OSHA issued a final standard requiring use of exhaust fans, protective clothing, and respirators; prohibiting operation in open vessels; and requiring control of plant contamination.

MONS 025632

In 1980, the Consumer Product Safety Commission preliminarily determined that 4-aminobiphenyl was not present in consumer products under its jurisdiction. The Commission subsequently requested (45 FR 61344) public comment to verify the accuracy of their information, and no comments were received. Pending the receipt of new information, the Commission plans no action on 4-aminobiphenyl.

4-Aminobiphenyl

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products. (CPSC)		
OCAA, 1001-1004: Listed as a hazardous constituent of waste. Wastes known to contain 4-aminobiphenyl are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261 11
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. Also applies to diphenylamine.		45 FR 42, 9, 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, respirator, hygiene, training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/78: Emergency Temporary Standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1011 (OSHA)

MONS 025633

1-AMINO-2-METHYLANTHRAQUINONE

Technical-grade 1-amino-2-methylanthraquinone (impurities unspecified), administered in the feed, was carcinogenic in Fischer 344 rats, inducing hepatocellular carcinomas in rats of both sexes, and kidney tumors (such as tubular-cell adenomas and adenocarcinomas) in males. The compound was carcinogenic in female B6C3F1 mice, producing an increased combined incidence of hepatocellular carcinomas and neoplastic nodules.[1] An IARC working group considered that the evidence for the carcinogenicity in experimental animals of the material tested was limited,[2] but in view of another evaluation of NCI bioassay results, the evidence can be considered as sufficient.[3]

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[1]National Cancer Institute. Bioassay of 1-Amino-2-methylanthraquinone for Possible Carcinogenicity. Technical Report Series No. 111. DHEW Publication No. (NIH) 78-1366. Washington, D.C., 1978.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 199-204.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

1-Amino-2-methylanthraquinone is an aromatic amine that is insoluble in water and soluble in ethanol, acetone, and benzene.

1-Amino-2-methylanthraquinone is used almost exclusively as a dye intermediate for the production of a variety of anthraquinone dyes. The Society of Dyers and Colourists in 1971 reported that it can be used as a dye for a variety of synthetic fibers, especially acetates, as well as wool, sheepskins, furs, and surface dyeing of thermoplastics. None of the dyes that can be prepared from it are presently produced in commercial quantities.

1-Amino-2-methylanthraquinone had been produced commercially in the United States since 1948, but production was last reported by one company in 1970. Imports through the principal U.S. customs districts were only 260 lb when last reported in 1972. A recent study by the Consumer Product Safety Commission (CPSC) staff indicated that 1-amino-2-methylanthraquinone was no longer either regularly produced in commercial quantities or imported. However, in their inventory of chemicals in commerce (1979, public record), EPA reported two importers in one region. The amount of the imports was not reported.

MONS 025634

According to NCI, no evidence was available to indicate that 1-amino-2-methylanthraquinone was either produced commercially or imported in the United States. -Domestic production was not reported to the U.S. International Trade Commission for 1979-1980.

Human exposure to 1-amino-2-methylanthraquinone is principally through inhalation of vapors. The potential for exposure is greatest among workers engaged in the dyeing of textiles. The National Occupational Hazard Survey of 1974 contains no information on 1-amino-2-methylanthraquinone, but does estimate that 6400 workers may have been exposed to anthraquinone dyes. 1-Amino-2-methylanthraquinone is not presently used in consumer products according to the CPSC.

EPA has proposed regulation of 1-amino-2-methylanthraquinone under the Toxic Substances Control Act, 8(a), reporting rule, which would provide detailed production and marketing data.

1-Amino-2-methylanthraquinone

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 3/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with the risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13ooo (EPA)

MONS 025635

AMITROLE

There is sufficient evidence of the carcinogenicity of amitrole in experimental animals; the evidence of carcinogenicity in humans is considered inadequate.[1]

Amitrole was carcinogenic in several strains of mice and rats, producing thyroid and liver tumors following administration in drinking water, diet, or by stomach tube, or subcutaneous injection.

Railroad workers who were exposed to amitrole and other herbicides showed a slight excess of cancer when all sites were considered together. Because the workers were exposed to several different herbicides, no conclusions could be made regarding the carcinogenicity of amitrole alone.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France; IARC, 1974, pp. 31-43.

Amitrole, a herbicide also known as aminotriazole, is soluble in water and very soluble in ethanol. Amitrole is formulated into soluble powders, liquids, and aerosols.

The major use for amitrole in the United States has been as a herbicide, but this use is now limited to noncrop applications.

Amitrole was first patented for use in the United States in 1954. Current domestic production is limited to approximately 4000 lb/yr. No reports are available on current imports, but 893,000 lb were imported in the first 9 months of 1973.

The potential for exposure to amitrole exists in its manufacture and application as a herbicide. According to NIOSH, an estimated 83 persons have been exposed to amitrole during its production, but no data are available on the number of people who may be exposed during its application or on the exposure levels in the general population.

After application, amitrole will persist in soil for several weeks and in water for more than 200 days.

MONS 025636

The use of amitrole on croplands was canceled in 1971, and EPA's Office of Pesticide Programs does not permit any residues on any food or feed crop. Under the Resource Conservation and Recovery Act, EPA also regulates the use and production of amitrole. In addition, EPA is reviewing amitrole under the Federal Insecticide, Fungicide, and Rodenticide Act to determine if further regulation may be warranted.

Amitrole

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80. Also lists amitrole as a hazardous constituent of waste subject to some requirements. FIFRA, 6: Under review to determine if additional regulation may be warranted. This study was triggered by the finding of carcinogenicity. No target for completion. Canceled for use on croplands, July 1971. See Carcinogen Assessment Group statement under 2-acetylaminofluorene: (EPA)		40 CFR 261.11, 261.33 (EPA)

MONS 025637

o-ANISIDINE AND o-ANISIDINE HYDROCHLORIDE

There is sufficient evidence for the carcinogenicity of o-anisidine in experimental animals.[1,2] o-Anisidine hydrochloride, given in the diet, was carcinogenic in Fischer 344 rats and B6C3F1 mice, inducing transitional-cell carcinomas or papillomas of the bladder in animals of both sexes and transitional-cell carcinomas of the pelvis and the kidney, and follicular-cell tumors of the thyroid in male rats.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 63-77.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[3]National Cancer Institute. Bioassay of o-Anisidine Hydrochloride for Possible Carcinogenicity. Technical Report Series No. 89. DHEW Publication No. (NIH) 78-1339. Bethesda, Maryland, 1978.

o-Anisidine, a derivative of aniline, is volatile with steam; practically insoluble in water; and miscible with alcohol, ether, acetone, and benzene.

o-Anisidine hydrochloride, reported to be used in the manufacture of dyes, is a possible ingredient in permanent oxidation hair dyes. Chloro, nitro, alkyl, and aryl derivates of o-anisidine are also used in the synthesis of azo dyes. Consumer Product Safety Commission (CPSC) staff members were unable to find any suppliers for this dye intermediate. However, the Chemical Buyer's Directory and the 1982 Chemical Week Buyer's Guide list 12 suppliers for o-anisidine.

Production of o-anisidine hydrochloride was not reported to the U.S. International Trade Commission (USITC) in 1980, although production was reported in 1979 by one producer, indicating an annual production greater than 5000 lb. Imports of o-anisidine and its meta and para isomers for 1979 were reported to the USITC as 3.2 million lb. Imports of o-anisidine through principal U.S. customs districts in 1980 were 2.4 million lb (NCI). No data are available on the importation of o-anisidine hydrochloride.

o-Anisidine hydrochloride was not reported in the Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record.

MONS 025638

If o-anisidine is used in the manufacture of dyes, the CPSC staff stated that residual traces of o-anisidine may possibly be present in some of these dyes and in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on experience with other dyes derived from aromatic amines. No data are available on the actual levels of o-anisidine in the final product. The National Occupational Hazard Survey in 1974 made no estimate of potential worker exposure to o-anisidine hydrochloride (NIOSH); however, it estimated that approximately 1800 workers were potentially at risk of exposure to anisidine derivatives.

OSHA adopted a permissible exposure level of 0.5 mg/m^3 time-weighted average, and noted a potential for skin absorption.

o-Anisidine and o-Anisidine Hydrochloride

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
Because of small production volumes, o-anisidine and o-anisidine hydrochloride are of low regulatory priority to EPA. They may be considered as the dyes and pigments industry is studied. (EPA)		
PEL: 0.5 mg/m^3 TWA (contains o,p-isomers). Potential for skin absorption noted. (Standard adopted for toxic effects other than cancer.) (OSHA)	Regulatory History: 1968: Noise-Hazard, 0.5 mg/m^3 TWA. 8/27/71: OSHA Carcinogen Standard--current list effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025639

ARAMITE^{R}

There is sufficient evidence for the carcinogenicity of Aramite^{R} in experimental animals.[1] Aramite^{R} was carcinogenic to several strains of rats and to the dog when administered in the diet. It produced liver tumors in the rat and carcinomas of the gall bladder and biliary ducts in the dog.[2]

Aramite^{R} was tested in several strains of mice by dietary administration and produced a significant increase of hepatomas in males of one strain.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 5. Lyon, France: IARC, 1974, pp. 39-46.

Aramite^{R} is the proprietary name for an organic aromatic compound that is insoluble in water but miscible with most organic solvents.

Aramite^{R} was previously registered for use as a pesticide on 39 crops, 20 of which were fruits and nuts, but in 1970, its use was restricted to postharvest application on fruit trees (EPA).

The single producer of Aramite^{R} ceased production in 1975, prior to the 1977 voluntary cancellations of registrations by all distributors. Aramite^{R} is probably not available in the United States. Although actual production volumes are not known, this pesticide was not widely used. For example, only 20,000 lb were used on fruit and nuts grown in California in 1971. By 1977, only 135 lb of the formulated product were available on the U.S. market, according to EPA.

No data are available on the number of workers who were actually or potentially exposed to Aramite^{R} during its manufacture and formulation. Nor are estimates available on direct consumer exposure to the pesticide through consumption of contaminated fruit and nut crops. Regulatory action has now eliminated the potential for exposure of the general public.

EPA regulates Aramite^{R} under the Federal Insecticide, Fungicide, and Rodenticide Act and the Resource Conservation and Recovery Act. The significant regulatory action was a voluntary cancellation of the active ingredient registration by the sole producer in 1975. One formulator holding remaining stockpiles was permitted to sell them through December 1977.

MONS 025640

Arsenic[a]

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
FIFRA, §: Voluntary cancellations of registrations by all producers, 6/13/77.	One formulator was permitted to distribute 135 lb of finished product prior to 12/31/77. No tamper available. (EPA)	42 FR, p. 60908
RCRA, 3001-3004: Designates Arsenic[a] as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025641

ARSENIC AND CERTAIN ARSENIC COMPOUNDS

Information on the carcinogenicity of arsenic compounds in experimental animals is considered inadequate for evaluation.[1] There is sufficient evidence that skin cancer in humans is causally associated with exposure to inorganic arsenic compounds in drugs, drinking water, and the occupational environment. The risk of lung cancer was increased 4 to 12 times in certain smelter workers who inhaled high levels of arsenic trioxide. However, the influence of other constituents of the working environment cannot be excluded in these studies. Case reports have suggested an association between exposure to arsenic compounds and blood dyscrasias and liver tumors.[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 23. Lyon, France: 1980, pp. 39-141.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: 1982.

Arsenic is an element that is used as many compounds including arsenic trioxide, arsenic pentoxide, sodium arsenate, and sodium arsenite; all of these forms are soluble in water. Arsenic trioxide, referred to as white arsenic, is the source for 97 percent of all arsenic products. Pentavalent organic arsenicals are used for animal drugs.

Elemental arsenic and arsenic compounds are used in pesticides, glass, ceramics, paints, dyes, and the preservation of hides. Arsenic occurs naturally in a number of ores and in food. The chemical form of arsenic in food has not been clearly established. Metabolically, it behaves as a pentavalent organic arsenical.

Approximately 70 million lb of arsenic and inorganic arsenic compounds are produced in the United States. Over 95 percent of the arsenic produced is a byproduct of copper and lead ore smelting. About 13.5 million lb of arsenic are imported, primarily as arsenic trioxide. EPA reported one producer of potassium arsenite in one region (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record).

MONS 025642

Industrial workers may be exposed to arsenic and its compounds during manufacturing and processing operations. An estimated 545,000 workers are potentially exposed. Higher-than-average worker exposure occurs during the smelting of arsenic-containing ores and during pesticide application.

Direct consumer exposure to arsenic and arsenic compounds may occur in the consumption of foods. The FDA estimates that food provides an intake of approximately 0.02 mg/day/person. Trace levels of arsenic have been reported in the tissues of livestock that were administered arsenic drugs and feed additives. Consumer exposure to arsenic may occur through the consumption of contaminated drinking water. EPA has established interim regulations to minimize exposure risks.

The general population may be exposed to arsenic compounds through air emissions from pesticide manufacturing facilities, cotton gins, glass manufacturing operations, and other sources. EPA estimated total environmental emissions to be 9000 tons.

The Consumer Product Safety Commission reports that a small number of arsenic compounds are used extensively as wood preservatives. In 1978, approximately 63.5 million cubic feet of wood products, which include lumber, timber, playground equipment, and fence posts, were treated with arsenicals. A large portion of the total products treated was lumber used for residential construction, such as decks, patios, greenhouses, and housing foundations. The CPSC staff is coordinating efforts with the EPA staff to assess the need for controls on consumer use of treated wood.

EPA, FDA, and OSHA have regulated the use of arsenic and its compounds. The EPA limits arsenic in drinking water to a maximum level of 0.05 mg/l. The Agency established effluent guidelines controlling the environmental release of such compounds for certain industrial categories. EPA issued a Rebuttable Presumption Against Registration for 11 inorganic arsenic pesticide products and regulates arsenic under the Resource Conservation and Recovery Act. FDA has set tolerances for residues of arsenic-containing pesticides in fruits and vegetables (0.35-7 mg/kg), field crops (cotton, 0.7-2.8 mg/kg), and livestock (cattle and horses, 0.7-2.7 mg/kg). OSHA promulgated a final standard in 1978 limiting occupational exposure to inorganic arsenic compounds to 10 mg/m^3. The PEL of 0.5 mg/m^3 for organic arsenic as an 8-hour time-weighted average was adopted by OSHA in 1971. In addition, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

MONS 025643

REGULATIONS

Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
Arsenic: EC&T coordinating efforts with EPA TSCA/FIFRA staff to assess need for controls for consumer uses of wood-treated lumber. (CPSC)		
CWA, 301: Effluent guidelines for certain industrial categories address arsenic.	Control established through conditions in NPDES permits. Carcinogenicity was a direct factor in establishing guidelines.	40 CFR 418, 421, 429, 430 (portions)
CWA, 304(a): Water quality criteria document published in final, 11/28/80.		45 FR 231, p. 79318
CAA, 112: Inorganic arsenic listed for NESHAP, 6/5/80.	Chronic toxicity, including potential carcinogenicity.	45 FR, p. 37886
First regulation would have affected two primary copper smelters, one of which closed permanently in 8/80. The second is voluntarily complying with the controls that would have been proposed for the source.	EPA is monitoring compliance and efficacy of the controls before determining if the results should be codified.	OAQPS, personal communication, 4/82
	Other sources are being evaluated to determine if NESHAPs should be set for them. This determination and a ranking, if deemed appropriate, should be completed by 1982.	OAQPS, personal communication, 4/82
	New York State has sued EPA for not having proposed NESHAPs for inorganic arsenic. No hearing date has been set.	OAQPS, personal communication, 4/82
CAA, 110: New source performance standards for smelters are being studied for revision. No target completion date has been set.	Would normally apply to new or expanded/remodeled facilities. Could be extended to all sources under a special provision of existing CAA.	OAQPS, personal communication, 4/82
RCRA, 3001-3004: Designated as a toxic waste. Requires testing to determine presence of arsenic. Wastes containing arsenic are subject to handling and reporting/recordkeeping requirements. Promulgated 5/19/80.	Concentration triggering compliance requirements, 5.0 mg/l.	40 CFR 261.24
SDWA, 1412: Primary drinking water regulation. Promulgated 12/24/75.	Establishes maximum contaminant level of 0.05 mg/l. Does not address carcinogenicity. Under review for possible revision.	40 CFR 141.11
SDWA, 1412: Revision of drinking water maximum contaminant level scheduled for proposal by 8/83.	Existing maximum contaminant level of 0.05 mg/l remains in force. Chronic toxicity, including carcinogenicity, is under review and will be considered. (EPA)	ODW, Memorandum, 10/81 (EPA)
TSCA: Under continuing assessment to determine if other controls may be needed.		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

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REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Arsenic: (Concluded) FDA, Bureau of Foods and Bureau of Veterinary Medicine, FDA'A: None of the regulated arsenic compounds are those that have been associated with occupational cancer. There are extensive toxicity studies on arsenicals used as pet drugs. None have shown any carcinogenic potential. (FDA)	Withdrawal requirements for meat-producing animals exposed to arsenicals should ensure that the levels are similar to normal background levels for arsenicals. (FDA)	Both organic and inorganic arsenics are regulated under CFR 21 558.60, 500.62, 500.170, 500.930, 193.336, 540.335 (FDA)
PEL: 0.5 mg/m³ 8-hr TWA as arsenic (organic); 10 ug/m³ 8-hr TWA (inorganic). No skin or eye contact with arsenic trichloride or liquid or particulate inorganic arsenic that is likely to cause skin or eye irritation.	Regulatory History: 1942: Value-ceiling, 0.5 mg/m³ maximum allowable concentration. 8/27/71: OSHA Takeover Standard--current limit effective.	29 CFR 1910.1000 (organic arsenic)
Protective clothing, respirator, hygiene training, and medical surveillance requirements for workers, monitoring requirements, housekeeping requirements, sign requirements for regulated areas, labeling requirements for containers. (OSHA)	6/30/78: Final Standard--current limit effective. (OSHA)	29 CFR 1910.1018 (inorganic arsenic) (OSHA)
Arsenic Trioxide CWA, 311: Hazardous spill regulation establishing reportable quantity (5000 lb, 2270 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping of chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13
FIFRA: Ban on use of formulations containing more than 1.5 percent arsenic trioxide in households and grazing areas. 8/68.	Some reduction in use.	Written notice to registrants
FIFRA, b: Voluntary cancellation by producers of three products. 9/13/77.	Minimal reduction in use.	42 FR 177, p. 45944
FIFRA, 6: RPAR issued regarding 11 inorganic arsenical pesticides. 10/18/78.	Uses other than as a wood preservative are still under consideration for regulation. (EPA)	43 FR 202, p. 48267
RCRA, 3001-3004: Substitute waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designated as a hazardous constituent of waste. Wastes known to contain arsenic trioxide are subject to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)

(Continued)

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REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Potassium Arsenate:		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 3/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.13
RCRA, 3001-3004: Arsenical compounds not otherwise specified are listed as hazardous constituents of waste. Wastes known to contain any of these are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)
Sodium Arsenate:		
CWA, 311: Hazardous spill regulations establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13
FIFRA, 6: RPAR issued regarding 11 inorganic arsenical pesticides, 10/10/78.	Proposed determination to development will address uses other than as a wood preservative. (EPA)	43 FR 202, p. 48267
RCRA, 3001-3004: Arsenical compounds not otherwise specified are listed as hazardous constituents of wastes. Wastes known to contain any of these are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)
Sodium Arsenite:		
CWA, 311: Hazardous spill regulations establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity.	40 CFR 117.3, 117.13
FIFRA: Ban on use of formulations containing more than 2 percent of sod. m arsenite in households or on grazing area, 8/80.	Some reduction in use.	Written notice to all affected registrants
FIFRA, 6: Registrations of two products voluntarily canceled by producers, 3/8/77.		
FIFRA, 6: RPAR issued regarding 11 inorganic arsenical pesticides, 10/10/78.	Determined not to be a wood preservative, but is under consideration for regulation.	43 FR 202, p. 48267

(Continued)

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REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Sodium Arsenite: (Concluded) RCRA, 3001-3004: Arsenical compounds not otherwise specified are listed as hazardous constituents of waste. Wastes known to contain any of these are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11
TSCA, 8(a): Reporting rule requiring process and use data. Proposed 2/29/80.		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		45 FR 42, p. 13646 (EPA)
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)
Arsenic Pentoxide: CWA, 311: Hazardous spill regulation establishing reportable quantity (5000 lb, 227C kg) and labeling requirements. Promulgated 8/29/.	Not based on carcinogenicity.	40 CFR 1.7.3, 117.13
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste. Wastes known to contain arsenic pentoxide are subject to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
FIFRA, 3: Classification for restricted use as a wood preservative, 2/19/81. Proposed.	Oncogenicity, mutagenicity, and teratogenicity. Would reduce user/worker exposure.	46 FR, p. 13020
FIFRA, 6: RPAR issued regarding 11 inorganic arsenical pesticides, 10/10/78.	Proposed determination in development will address uses other than as a wood preservative. (EPA)	43 FR 202, p. 48267 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)
Calcium Arsenate, Calcium Arsenite, [illegible] Arsenate, Lead Arsenate, and Potassium Arsenite: RCRA, 3001-3004: Arsenic compounds not otherwise specified are listed as hazardous constituents of waste. Wastes known to contain any of these are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025647

ASBESTOS

There is sufficient evidence for the carcinogenicity of asbestos both in humans and in experimental animals.[1]

All types of commercial asbestus fibers that have been tested are carcinogenic in mice, rats, hamsters and rabbits, producing mesotheliomas and lung carcinomas after inhalation, and after intrapleural, intratracheal and intraperitoneal administration.[2]

Occupational exposure to chrysotile, amosite, anthophyllite, and mixtures containing crocidolite has resulted in a high incidence of lung cancer. A predominantly tremolitic material mixed with anthophyllite and small amounts of chrysotile has also caused an increased incidence of lung cancer. Pleural and peritoneal mesotheliomas have been observed after occupational exposure to crocidolite, amosite and chrysotile asbestos. Gastrointestinal tract cancers were increased in groups exposed occupationally to amosite, chrysotile or mixed fibers containing crocidolite. An excess of cancer of the larynx was also observed in exposed workers. Mesotheliomas have occurred in individuals living in the neighborhood of asbestos factories and crocidolite mines, and in persons living with asbestos workers. Both cigarette smoking and occupational exposure to asbestos fibers increase lung cancer incidence independently. When present together, they act multiplicatively.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: 1979.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 14. Lyon, France: 1977, pp. 1-106.

Asbestos is the generic name of a class of natural fibrous silicates. There are four commercially important forms: chrysotile, amosite, anthophyllite, and crocidolite. Chrysotile represented 94 percent of U.S. consumption in 1974.

Asbestos is currently used in more than 5000 products, some of which are roofing, thermal and electrical insulation, cement pipe and sheet, flooring, gaskets, friction materials, coatings, plastics, textiles, and paper products.

Total production of asbestos in 1976 was estimated at 250 million lb; 1979 production was reported to be 200 million lb. Some producers are developing suitable substitutes for asbestos, and production is expected to decline in the 1980s.

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Human exposure to asbestos is primarily through inhalation or ingestion of fibers. Asbestos may occur as a contaminant of food or beverages that come in contact with materials such as adhesives and repeatedly used polyester-resin, rubber, and phenolic-resin molded plastic articles. FDA is aware that asbestos might be used in dental filling material, especially temporary cements. Exposure to asbestos in dental filling materials is assumed to be very low to virtually nil. Asbestos is so widely used that the entire population is exposed to some degree. Worker exposure has been a concern in the mining and milling of asbestos, during the manufacture of all asbestos products, and in the construction and shipbuilding industries. OSHA reported that about 2.5 million workers are estimated to have some exposure to asbestos.

The general population is exposed to asbestos fibers from air, beverages, drinking water, food, pharmaceutical and dental preparations, and asbestos-containing consumer products. Families of asbestos workers have been exposed to high fiber levels through contaminated clothing brought home for laundering.

Asbestos fibers are released into the environment from the natural occurrence of asbestos in the earth and as a result of wear and deterioration of asbestos products. Asbestos minerals are emitted into the atmosphere and water systems from the mining and milling of asbestos ores. Applications of asbestos materials to buildings and vehicle brake linings account for a significant amount of emissions to the atmosphere. The demolition of buildings with asbestos insulation or fireproofing can cause high atmospheric concentrations for relatively short periods of time. The disposal of mining and building material wastes in landfills also increases the distribution of asbestos into the environment, but no estimates of the quantity of material released in this manner are available.

The 1977 banning by the Consumer Product Safety Commission (CPSC) of asbestos in patching compounds and in gas fireplaces prevented additional exposure of several million consumers who were exposed to asbestos from these sources. U.S. manufacturers of hand-held dryers cooperated with CPSC by voluntarily ceasing to use asbestos liners. This voluntary program resulted in the repair by manufacturers of 2 million dryers. CPSC has published advance notice of proposed rulemaking stating an intent to further regulate the uses of asbestos. The Commission will convene a Chronic Hazard Advisory Panel to assess the carcinogenicity, mutagenicity, and teratogenicity of asbestos and, if feasible, estimate the probable harm to human health that will result from exposure to asbestos. The panel will meet for the first time in January 1983. A report is expected from the panel in early summer 1983. Studies in progress are looking at asbestos release from products; another study in progress is examining asbestos substitutes. EPA proposed an asbestos water quality criteria document for the protection of human health in October 1979. EPA regulates asbestos under the Clean Air Act, the Clean Water Act, and the Resource Conservation and Recovery Act, and proposes to do so under the Toxic Substances Control Act. A voluntary EPA program is removing or encapsulating sources of asbestos release in school buildings.

MONS 025649

EPA published advance notices of proposed rulemaking that stated an intent to further regulate the uses of asbestos. FDA action concerning asbestos (and talc) restricted the utilization of asbestos filters in the manufacture of parenteral drugs and parenteral drug ingredients. FDA has taken no action to date with regard to asbestos in food, because there is no evidence that the ingestion of small amounts of asbestos found in food poses any human health risk. The OSHA standard for asbestos fibers permitted in the workplace is two fibers/cc of air for fibers longer than 5 μm. In addition, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

In April 1980, a NIOSH/OSHA work group reviewed the most recent scientific information and recommended that a new standard for asbestos be promulgated. Recommendations included reduction of the current environmental limit and elimination of nonessential asbestos exposures with substitution of less hazardous alternatives.

MONS 025650

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Ban in effect on general-use garments (1972) containing asbestos.	Essentially eliminated that type of exposure.	1600 CFR 1500.17 (a)(7)
Voluntary recall of hair dryers.	(1979) 1.5 million units returned.	
Advance notice of proposed rulemaking describing proposed approach of seeking elimination of all nonessential uses of asbestos in consumer products from which asbestos fibers are released during use.		FR 44, p. 60056
Ban (1978) on patching compounds and gas log emberizing materials containing respirable free asbestos.	Between 1 and 3 million persons had been exposed to patching compounds; no subsequent exposures.	1600 CFR 1304
	0.5 - 1.0 x 10^6 persons exposed to emberizing materials; no additional exposures. (CPSC)	
Staff developing proposal to ban asbestos paper for consumer use. (CPSC)		1600 CFR 1306 (CPSC)
CAA, 112: NESHAP addressing several industrial categories. Promulgated 4/6/73 and 10/14/75.	Some reduction in emissions largely through engineering and practice controls. Numerical limits were not set because of the absence of reliable and economically feasible analytical methods.	40 CFR 61.20-60.25
CWA, 301: Effluent guidelines for the asbestos industry and for asbestos mining/milling operations. Promulgated 2/20/74, 2/11/75, and 10/16/75.	Control through NPDES permit conditions. Asbestos is not directly addressed. Control of suspended solids would afford a degree of control over asbestos.	40 CFR 427, 436.70
CWA, 304(a): water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
TSCA, 6: Voluntary program of abatement of asbestos in schools, published 3/30/79.	High interest in acting to encapsulate or replace asbestos-containing materials.	44 FR 54, p. 17791
ANPR seeking comments on regulation of several sources, published 10/17/79. Issued in conjunction with CPSC. Hearings ongoing.		44 FR 202, p. 60056
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 3000 kg to handling and record/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, 6a and Department of Education-Asbestos School Hazard Detection and Control Act of 1980.		
Proposed rule requiring state plans to inspect schools for friable asbestos, and authorizing grants and loans to cover 50 percent of the cost of inspection and control.	Ties to NESHAP and OSHA rules released to asbestos. Stipulates compliance during control activities. (EPA)	45 CFR 180, p. 61950 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 025651

Asbestos (Concluded)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
FDA Bureau of Foods, FD&CA: Most permitted uses approved + on asbestos, was not known to be implicated as a carcinogen. At present there are no GP's available to estimate the levels of migration of asbestos into foods from the regulated uses. It is assumed that under good manufacturing practice, there will be "virtually nil or de minimis" migration of asbestos into human foods. FDA Bureau of Medical Devices, FD&CA: No regulatory history and no regulations issued to date. (FDA)	Further reductions would require new estimates of how much asbestos is actually getting into food and development of sensitive detection methods. Increased awareness of products with asbestos achieved by inclusion in Medical Devices Inventory. (FDA)	21 CFR 175.105, 177.2420, 177.2410, 177.2600 (FDA)
PEL: 2 fibers/cc > 5 um in length, 8-hr TWA. 10 fibers/cc > 5 um in length, ceiling. Medical surveillance requirements for workers; monitoring requirements; housekeeping and waste disposal requirements; protective clothing, respirator, and change room requirements in areas where engineering and work practice controls are not sufficient to lower asbestos to permissible levels; sign requirements for regulated areas. (OSHA)	Regulatory history: 1971 Walsh-Healy: 5 mppcf maximum allowable concentration. 6/1/71: OSHA Takeover Standards--Tremolite 20 mppcf or (20 mg/m^3)/(%SiO$_2$) 8-hr TWA; amosites 12 fibers/cc > 5 um in length or 2 mppcf 8-hr TWA. 12/7/71: Emergency Temporary Standards--5 fibers/cc > 5 um in length 8-hr TWA; 10 fibers/cc > 5 um in length, ceiling, no visible for up to 15 min/hr, 5 hr/day. 1/11/72: Standard coverage expanded to include ship repairing, shipbuilding, shipbreaking, and longshore workers. 7/7/72: Revised Standards--5 fibers/cc > 5 um in length, 8-hr TWA; 10 fibers/cc > 5 um in length, ceiling. 7/1/76: Final Standard--current limit effective. (OSHA)	29 CFR 1910.1001 (OSHA)

MONS 025652

AURAMINE AND THE MANUFACTURE OF AURAMINE

There is sufficient evidence that the manufacture of auramine is carcinogenic in humans. The evidence for the carcinogenicity of technical grade auramine in humans and in experimental animals is considered as limited.[1]

When given in the diet, commercial auramine of unknown purity was tumorigenic in two strains of mice and in Wistar rats after oral administration, producing liver tumors, and after subcutaneous injection in rats, producing local sarcomas.[1]

The manufacture of auramine (which also involves exposure to other chemicals) is judged to be causally associated with increased incidence of bladder cancer. The actual carcinogenic compound(s) has not been specified precisely.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: 1972, pp. 69-73.

Auramine (Basic Yellow 2), an aromatic amine, appears as yellow leaves or needles, which are insoluble in water.

Auramine (hydrochloride salt) is used industrially as a dye or dye intermediate for coloring inks, textiles, wool, paper, and leather. According to 1979 U.S. International Trade Commission data, auramine was not domestically produced; however, 165,000 lb were imported.

Human exposure to auramine occurs principally through skin absorption or vapor inhalation. Approximately 3000 workers in the textile, paper, and leather industries may be exposed to auramine. Low-level dermal exposure to the consumer may occur but would be limited to any migration of auramine from fabric, leather, or paper goods.

Auramine is regulated by the EPA under the Resource Conservation and Recovery Act. NIOSH is currently preparing a special hazard review for auramine and the manufacture of auramine.

MONS 025653

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Based on toxicologic and genomic evaluation conducted in 1981 and 1982, staff recommendations will be presented in FY83. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-spec'fication batches, and spill residues in excess of 1000 kg to handling and report/record-keeping requirements. Also, listed as a hazardous constituent of waste. Wastes known to contain acrylonitrile are subject to the same requirements. Promulgated 1/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See the Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
NIOSH Special Hazard Review in preparation. (NIOSH)		

MONS 025654

BENZ(a)ANTHRACENE

There is sufficient evidence of the carcinogenicity of benz(a)-anthracene (BA) in experimental animals.[1] BA given by several routes of administration has proved to be carcinogenic in the mouse. It produced hepatomas and lung adenomas following repeated oral administration to young mice. In a parallel experiment with methylcholanthrene, the carcinogenic effect upon the liver and lung was similar for the two compounds at the same dose level. In the same experiment, BA did not produce tumors of the gastrointestinal tract, whereas methyl-cholanthrene induced them consistently.[2]

BA is a complete carcinogen for the mouse skin. The fact that the tumor yield was higher when using a dodecane solution than with toluene is related to the co-carcinogenic effect of dodecane. Benzo(a)pyrene given at a lower dose level produced more skin tumors with a shorter latency period than did BA. BA is also an initiator of skin carcinogenesis in mice.[2]

BA produced tumors in mice following subcutaneous injections. Fifty ug BA was the lowest dose tested, and it was effective in newborn and in adult animals. It produced bladder tumors in mice following implantation.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1976, pp. 45-68.

BA belongs to the class of chemicals known as polycyclic aromatic hydrocarbons (PAHs), which are formed under geothermal conditions leading to coal and petroleum and as a result of incomplete combustion. BA is slightly soluble in water and soluble in most organic solvents, except alcohol.

BA is a contaminant and does not have any reported commercial use or application, although one producer did report the substance for the Toxic Substances Control Act Inventory.

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BA has been reported present in cigarette smoke condensate, automobile exhaust gas, soot, and emissions from coal and gas works and electric plants. BA also occurs in the aromatic fraction of mineral oil, commercial solvents, waxes, petrolatum, creosote, coal tar, petroleum asphalt, and coal tar pitch. Microgram quantities of BA can be found in various foods such as charcoal broiled, barbecued, or smoked meats and fish; certain vegetables and vegetable oils; and roasted coffee and coffee powders.

Human subjects are exposed to BA through either inhalation or ingestion. Workers at facilities with likely exposure to fumes from burning or heating of organic materials have a potential for exposure to BA. Consumers can be exposed to this chemical through ingestion of various foods, with concentrations of 100 ug/kg in some instances. Cigarette smoke condensate has quantities of BA that range from 0.03 to 4.6 ug/g.

BA is found in the atmosphere at levels that vary with geographical features and climate. These values can range from up to 136 ug/1000 m^3 in summer to 361 ug/1000 m^3 in winter. Drinking water samples may contain up to 23 ng/l BA, and surface waters have been found to contain 4-185 ng/l. The soil near industrial centers has been shown to contain as much as 390 ug/kg of BA, whereas soil near highways can have levels of up to 1500 ug/kg, and areas polluted with coal tar pitch can reach levels of 2500 mg/kg.

The Carcinogen Assessment Group at EPA lists BA as a carcinogen, and the water quality criteria for PAHs apply by inference to BA. There have been few attempts to develop exposure standards for PAHs either individually or as a class; however, NIOSH has recommended a workplace standard for coal tar products of 0.1 mg/m^3 as a time-weighted average for a 10-hour workshift in a 40-hour workweek. OSHA indirectly limits exposure to BA by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour period as a time-weighted average.

MONS 025656

Benzo[a]anthracene

REGULATI S

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.33, 261.33
CWA, 304(a): Water quality criteria published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate.		45 FR 231, p. 79318
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/27/80.	Would, if promulgated, permit a basis for estimating exposure. (EPA)	45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
PEL: 0.2 mg/m³ 8-hr TWA [coal tar pitch volatiles] [limited coverage]. (OSHA)	Regulatory History: 6/21/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 025657

BENZENE

The evidence that benzene is carcinogenic in experimental animals is limited.[1] Administered by stomach tube to rats, benzene increased the incidence of Zymbal gland carcinomas. An increased incidence of lymphoid tumors occurred in male mice exposed to benzene by inhalation. In similar studies with another strain of mice and with rats, no leukemic response was observed.[2]

There is sufficient evidence that benzene is carcinogenic to man.[1] Several case reports as well as an epidemiological case control study establish a relationship between benzene exposure and leukemia. Two cohort studies showed an increased incidence of acute nonlymphocytic leukemia in workers exposed to benzene. There has been an additional report of a large number of leukemia cases (most of which were acute nonlymphocytic) among a group of workers exposed to benzene.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: 1982, pp. 93-148.

Benzene, a volatile, colorless, flammable liquid, is a major raw material of the chemical industry.

Benzene is used extensively as a solvent in the chemical and drug industries, as a starting material and intermediate in the synthesis of numerous chemicals, and as a gasoline additive. Eighty percent of the benzene is consumed in the production of ethylbenzene, cumene, and cyclohexane.

Benzene is domestically produced in the United States in over 50 locations, and in 1979, approximately 12 billion lb were produced. An additional 1.6 billion lb were imported, whereas exports were 1.3 million lb. Benzene is expected to remain one of the industry's most important chemicals. Increasing market demands are forecast at approximately 5 percent annually.

An estimated 3 million workers may be exposed to benzene. Exposure may occur during the production of benzene or during the use of substances containing the chemical as an ingredient or contaminant. Human exposure to benzene is primarily through inhalation of the vapor or through skin absorption.

MONS 025658

Due to the ubiquitous nature of benzene, over 75 percent of the population has probably been exposed to this chemical. In 1976, an estimated 1.3 billion lb of benzene were released into the atmosphere from 132 million stationary and mobile sources. This included an estimated 240 million lb/yr from the production, transport, storage, and use of benzene; 1 billion lb/yr from the refueling and operation of motor vehicles; and 22 million lb/yr from oil spills. It has been estimated that 800,000 persons may be exposed to benzene from coke oven emissions at levels greater than 0.1 ppm; 5 million persons from petroleum refinery emissions at levels of 0.1-1.0 ppm.

Information on the levels of benzene in the atmosphere is limited. Ambient monitoring data indicate that levels of benzene range from 1 ppb to 100 ppb. The highest values were reported in metropolitan areas and may be due to exhausts from motor vehicles. Benzene has been identified in drinking water and in subsurface water at concentrations to 10 ppm. Benzene occurs in fruits, fish, vegetables, nuts, dairy products, beverages, and eggs. The National Cancer Institute estimated that an individual could ingest up to 250 ug/day.

In May 1981, the Consumer Product Safety Commission (CPSC) withdrew its proposed ban of consumer products, except for gasoline and laboratory reagents, which contained benzene as an intentional ingredient or as a contaminant at 0.1 percent or greater by volume. The decision to withdraw the rulemaking was based on CPSC findings that benzene is no longer used as an intentional ingredient in consumer products and that the contaminant levels remaining in certain consumer products are unlikely to result in significant consumer exposure to benzene vapor. A labeling regulation, established in 1962 for products containing more than 5 percent benzene, and a 1977 safety packaging requirement for paint solvents and thinners containing 10 percent or more of petroleum distillates, such as benzene, remains in effect.

In 1977, EPA listed benzene as a hazardous air pollutant under Section 112 of the Clean Air Act. Emission standards for ethylbenzene-styrene plants, benzene storage and fugitive emissions, and coke byproduct plants were being assessed by EPA during 1980-81; and a standard for maleic anhydride production was proposed in 1980. EPA also regulates benzene under the Clean Water Act; the Federal Insecticide, Fungicide, and Rodenticide Act; and the Resource Conservation and Recovery Act.

OSHA's 1971 standard limited benzene to 10 ppm in the air for an 8-hour time-weighted average (TWA). This was lowered in 1977 by an emergency temporary standard to a 1 ppm TWA with a maximum of 5 ppm for 15 minutes. A final standard establishing a permissible exposure limit (PEL) of 1 ppm 8-hour TWA with a 5 ppm upper level limited to 15 minutes has been overturned by the U.S. Supreme Court. Subsequent to this Supreme Court action, the OSHA regulation has reverted to a 10 ppm 8-hour TWA PEL.

MONS 025659

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
1978: Proposed ban under CPSA of benzene as an intentional ingredient in consumer products and products containing 0.1 percent or more by volume of benzene as a contaminant. Action withdrawn in 1981.	No known intentional use of benzene in consumer products. Perhaps as a result of proposed ban, 400,000-800,000 persons are no longer exposed.	46 FR, p. 27910
Under FHSA, household products containing 1 percent or more benzene by weight must bear cautionary labeling.	Difficult to assess the effectiveness of labeling.	1500 CFR 1500.14 (a)(3), (b)(3)
Safety packaging required under PPPA for prepackaged liquid solvents that contain 10 percent or more petroleum distillates, both as benzene, by weight and have viscosity less than 300 SUS at 100° F. (CPSC)	Not based on carcinogenicity. Overall safety packaging effectiveness estimated 25 percent over 3-year period--not able to assess poisoning reduction from benzene products per se. (CPSC)	1600 CFR 1700.14 (a)(15) (CPSC)
CAA, 112: Benzene listed for NESHAP development, 6/8/77. NESHAP for benzene emissions from maleic anhydride production facilities proposed 6/18/80. NESHAP for ethylbenzene-styrene production facilities. NESHAP to address benzene emissions from other industrial sources in development.	Would establish numerical emission limits and provide guidance on means to achieve them. Scheduled for proposal between early 1981 and mid-1982.	42 FR 110, p. 29332 47 FR, p. 26660
CAA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipment of chemicals and should result in reduction of accidental exposure.	40 CFR 117.3, 117.13
FIFRA, 6: Voluntary cancellation of registrations of products containing benzene as an active ingredient are being processed.	Based on hematopoietic effects, oncogenicity, and mutagenicity. Would affect all but one producer. (EPA)	OPP, SPRD Status Report, 12/81
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also listed as a hazardous constituent of waste. Wastes known to contain benzene are subject to the same requirements. Promulgated 5/19/80. See the Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
Regulatory Authority: FD&CA, 201(T). (FDA)	Action pending completion of contaminants policy. (FDA)	
REL: 10 ppm 8-hr TWA, 25 ppm ceiling, 50 ppm maximum peak for 10 min in any 8-hr period. (OSHA)	Regulatory History: 6/27/71: OSHA Takeover Standard--10 ppm 8-hr TWA. 5/21/77: Emergency Temporary Standard--1 ppm 8-hr TWA, 5 ppm 15-min TWA ceiling. 2/10/78: Revised standard promulgated. 7/2/80: U.S. Supreme Court reverted standard to 10 ppm 8-hr TWA. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025660

BENZIDINE

There is sufficient evidence that benzidine is carcinogenic in experimental animals after oral and subcutaneous administration, producing liver tumors in mice and hamsters; liver, mammary and Zymbal's gland tumors in rats; and bladder cancers in dogs.[1,2]

There is sufficient evidence that benzidine is carcinogenic to humans.[1,2] Case reports and followup studies of workers provide sufficient evidence that occupational exposure to benzidine is causally associated with an increased risk of bladder cancer.[1] The causal association is strengthened by data which suggest that the incidence of this cancer in workers decreased after a reduction in industrial exposure.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: IARC, 1982, pp. 149-83.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

Benzidine, an aromatic amine slightly soluble in cold water, has been used for over 60 years as an intermediate in the production of azo dyes, sulfur dyes, fast color salts, naphthols, and other dyeing compounds. More than 250 benzidine-based* dyes have been reported. However, the general use of benzidine has fallen dramatically because of its carcinogenicity.

Benzidine was formerly produced in the United States at levels of many millions of pounds per year. In 1977, U.S. production of benzidine-based dyes was reported as 1.4 million lb; 76,300 lb were imported. The annual production of benzidine is now about 500 lb.

Human exposure to benzidine is primarily through inhalation or skin absorption. NIOSH has estimated that 700 workers may be directly exposed. OSHA has estimated that about 2200 workers are potentially exposed to benzidine.

In the fall of 1980, CPSC instructed its staff to collect additional economic and toxicological data in order to propose a ban on the use of benzidine-based dyes in direct consumer dye products. Studies are in progress to assess the dermal penetration of benzidine congener dyes and their respective bases. Economic studies are also in progress.

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* Benzidine-based means that the chemical structure of benzidine is included as part of a larger molecule, even though the method of synthesis may not require the use of benzidine as a starting material.

MONS 025661

Residual levels or trace impurities of benzidine may be present in benzidine-derived dyes and pigments and in the final consumer product. The presence of this known carcinogen, even as a trace contaminant, is a cause for concern.— Available data show that benzidine residuals in benzidine dyes range from 1 to 270 ppm.

EPA controls benzidine through both the 1977 toxic pollutant effluent standards and the water quality criteria proposed in October 1979. The OSHA standard restricts the use of benzidine in open vessels and requires protective clothing, engineering controls, and medical surveillance of workers.

Benzidine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Toxicological and economic studies are in progress. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste. Wastes known to contain benzidine are subject to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CWA, 311: Hazardous spill regulation establishing reportable quantity (10 lb. 4.54 kg) and imposing reporting requirements. Promulgated 6/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.33
CWA, 307(a): Toxic pollutant effluent standards.	Manufacture has dropped considerably since 1977 promulgation.	40 CFR 129.104
CWA, 304: Water quality criteria. Published in final form, 11/28/80.		FR 45.231, p. 79318 (EPA)
Sev Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, respirator, hygiene, training and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1010 (OSHA)

MONS 025662

BENZO(b)FLUORANTHENE

There is sufficient evidence for the carcinogenicity of benzo(b)-fluoranthene (B(b)F) in experimental animals.[1] B(b)F has produced skin tumors in mice following repeated skin paintings. The lowest carcinogenic dose for the mouse skin was at least ten times higher than that of benzo(a)pyrene. B(b)F is also an initiator of skin carcinogenesis in mice and produces local sarcomas after subcutaneous injection. It has not been tested by other routes in the mouse or in other species.[2] The isomer of B(B)F, benzo(J)fluoranthene, has limited evidence of carcinogenicity in experimental animals.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 69-90.

B(b)F is a polycyclic aromatic hydrocarbon (PAH). This compound may be used as a research chemical.

There is no commercial production reported for this substance. However, this compound is formed as a result of incomplete combustion of organic substances and is found in coke oven emissions and coal tar. No data are available on the amounts generated.

Human exposure is primarily through inhalation of smoke from the incomplete combustion of organic compounds. B(b)F has been detected in mg/kg quantities of particulates in air, coal tar, soot, automobile exhaust, road dust, and sewage water. It has been detected in cigarette smoke condensates, soil, drinking water, rivers and lakes, and food in microgram quantities.

EPA has designated B(b)F as a carcinogen and regulates the compound under the Resource Conservation and Recovery Act. In order to minimize the risk of workplace exposure to PAHs, OSHA promulgated an exposure standard of 150 $\mu g/m^3$ (8-hour time-weighted average) for coke oven emissions; NIOSH has recommended a workplace standard of 100 $\mu g/m^3$ (10-hour time-weighted average) for coal tar products (coal tar, creosote, and coal tar pitch). OSHA has indirectly limited exposure to B(b)F by requiring that occupational exposure to coal tar pitch volatiles not exceed, as a time-weighted average, 0.2 mg/m^3 over an 8-hour period.

MONS 025663

Benzo(b)fluoranthene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CWA, 304(a): Water quality criteria for PAHs published in final form, 11/28/80. Total PAHs addressed; no indicator nor surrogate.		45 FR 22... p. 79318
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.33 (EPA)
PEL: 0.2 mg/m³ 8-hr TWA (coal tar pitch volatiles) [limited coverage]. (OSHA)	Regulatory History: 6/27/71: OSHA Takeover Standard--current limits effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 025664

BENZO(a)PYRENE

There is sufficient evidence for the carcinogenicity of benzo(a)-pyrene (B(a)P) in experimental animals.[1] B(a)P has produced tumors in all of the nine species for which data are reported following different administrations including oral, skin, and intratracheal routes. It has both a local and a systemic carcinogenic effect. In subhuman primates, there is convincing evidence of the ability of B(a)P to produce local sarcomas following repeated subcutaneous injections and lung carcinomas following intratracheal instillation. It is also an initiator of skin carcinogenesis in mice, and it is carcinogenic in single-dose experiments and following prenatal exposure.

In skin carcinogenesis studies in mice, B(a)P was consistently found to produce more tumors in a shorter period of time than did other polycyclic aromatic hydrocarbons, with the possible exception of dibenzo(a,h)acridine (DB(a,h)A). In a dose-response study involving subcutaneous injection in mice, the minimal dose at which carcinogenicity was detected was higher for B(a)P than for DB(a,h)A and for 3-methyl cholanthrene. The latent periods were shorter for B(a)P, however, than for DB(a,h)A. In studies using intratracheal administration, B(a)P appeared to be less effective than 7H-dibenzo(c,g)carbazole in the hamster.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 91-136.

B(a)P is a polycyclic aromatic hydrocarbon (PAH); it is not commercially produced. One chemical company manufacturers B(a)P, and several specialty chemical companies distribute it for research purposes in quantities from 100 mg to 5 g.

B(a)P also occurs as a product of combustion. An estimated 1.8 million lb/yr are released from stationary sources. Ninety-six percent of this amount comes from coal refuse piles, outcrops, abandoned coal mines, residential external combustion of bituminous coal, coke manufacture, and residential external combustion of anthracite coal.

Human exposure can occur from the presence of B(a)P in polluted air, in some foods, and in the occupational environment. The number of persons exposed is not known. Persons working at airports, in tarring operations, in refuse incinerator operations, in power plants, and in coke manufacturing

MONS 025665

operations may be exposed to higher B(a)P levels than the general population. Scientists involved in cancer research or in sampling toxic materials may also be occupationally exposed. The general population may be exposed to B(a)P from air pollution, cigarette smoke, and food sources. B(a)P has been detected in cigarette smoke at levels ranging from 0.2 to 12.2 ug/100 cigarettes. B(a)P has also been detected in foods at low levels ranging from 0.1 to 50 ppb.

On October 18, 1978, EPA issued a notice of Rebuttable Presumption Against Registration for coal tar, creosote, or neutral oils. B(a)P is one of many constituents in these products. The EPA Carcinogen Assessment Group has designated B(a)P as a carcinogen, and EPA regulates the compound under the Resource Conservation and Recovery Act. Under the Clean Air Act, B(a)P is considered both a surrogate for particulate organic matter and an indicator of coke oven emissions. Water quality criteria for the protection of human health address total PAHs. OSHA indirectly limits exposure to B(a)P by requiring that occupational exposure to cual tar pitch volatiles not exceed a time-weighted average of 0.2 mg/m^3 over an 8-hour period.

Benzo(a)pyrene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CWA, 304(a): Water quality criteria for PAH published in final form, 11/2/80. Total PAH addressed, no surrogate nor indicator.		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates benzo(a)pyrene as a hazardous constituent of waste, and subjects wastes shown to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring use and process data, published 2/29/80.		45 FR 42, p. 13646
CAA: EPA has been working to determine what controls over both PAH and coke emissions may be appropriate. Benzo(a)pyrene has been the surrogate for polycyclic organic matter, and is an indicator in the assessments of coke oven emissions. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		DAQPS, personal communication, 8/80 (EPA)
PEL: 0.2 mg/m^3 8-hr TWA (coal tar pitch volatiles) (limited coverage). (OSHA)	Regulatory History: 8/21/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 025666

BERYLLIUM AND CERTAIN BERYLLIUM COMPOUNDS

There is limited evidence for the carcinogenicity of beryllium in humans, and sufficient evidence of carcinogenicity of some beryllium compounds in experimental animals.[1]

Beryllium compounds were carcinogenic in rats, rabbits and monkeys. Beryllium metal, beryllium-aluminum alloy, beryl ore, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium sulfate (or its tetrahydrate) and beryllium oxide, all produced lung tumors in rats exposed by inhalation or intratracheally. Beryllium oxide and beryllium sulfate produced lung tumors in monkeys after intrabronchial implantation or inhalation. Beryllium metal, beryllium carbonate, beryllium oxide, beryllium phosphate, beryllium silicate and zinc beryllium silicate all produced osteosarcomas in rabbits following intravenous and/or intramedullary administration.[2]

Four early epidemiological studies and three recent ones of occupational exposure to beryllium were considered to provide limited evidence that exposure to beryllium may lead to human lung cancer. The data for most of the studies were derived from two beryllium plants and from the Beryllium Case Registry. Although 55 new cases of beryllium disease were registered between 1973 and 1977, no further data were available on the incidence of lung cancer. An analysis of the pathology of the 47 lung cancers noted in one study confirmed the post-mortem diagnosis of lung cancer in 32 of the 37 cases available for review. Of the 47 cases, 21 were noted to have been smokers, but the smoking histories of the other cases were not given.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 23. Lyon, France: IARC, 1979, pp. 143-204.

Beryllium and its compounds are widely distributed in nature. Beryllium compounds of commercial importance include beryllium oxide, beryllium sulfate, and beryl.

MONS 025667

Beryllium is used extensively in the manufacturing of electrical components, chemicals, ceramics, and X-ray tubes. A number of alloys are produced in which beryllium is added to yield greater tensile strength, electrical conductivity, and resistance to corrosion and fatigue. The metal is used as a neutron reflector in high-flux test reactors.

Beryllium has been produced commercially in the United States since the 1940s. In 1979, two companies were reported to produce beryllium in unknown amounts. The Toxic Substances Control Act (TSCA), Chemical Substance Inventory (public record) reported six producers and importers in 1977, with production of 74,000 lb. Imports for 1978 were approximately 1400 lb. Beryllium oxide has been produced commercially in the United States since 1958. In 1978, only minor amounts were produced by one producer. In 1977, EPA reported that 406,000 lb were produced domestically. Eleven other beryllium compounds are produced in small quantities.

Human exposure occurs mainly through inhalation of beryllium dust or fumes. OSHA has estimated that approximately 25,000 workers are exposed to beryllium. Among these are beryllium ore miners, beryllium alloy makers and fabricators, phosphor manufacturers, ceramic workers, missile technicians, nuclear reactor workers, electric and electronic equipment workers, and jewelers.

The major source of beryllium exposure of the general population is through the burning of coal. Approximately 250,000 lb of beryllium is released from coal- and oil-fired burners. EPA has estimated the total release of beryllium to the atmosphere from point sources is 5500 lb per year. The principal emissions are from beryllium-copper alloy production. Approximately 721,000 persons living within 12.5 miles (20 km) of point sources are exposed to small amounts of beryllium (median concentration, 0.005 $\mu g/m^3$). Small concentrations of beryllium have been reported in drinking water supplies and in food.

In 1973, EPA promulgated a National Emissions Standard for Hazardous Air Pollutants (NESHAP) for extraction and production sites for beryllium and for beryllium oxide and beryllium rocket-motor firing. In 1980, EPA published a water quality criteria document for beryllium for the protection of human health. In 1980, the Agency established regulations under the Resource Conservation and Recovery Act for wastes known to contain beryllium and beryllium compounds. These regulations were based on the inclusion of beryllium and its compounds in the EPA Carcinogen Assessment Group's list of chemical carcinogens. The Agency does not plan to regulate beryllium in drinking water under the Safe Drinking Water Act, but EPA has proposed a rule under TSCA requesting production and other data.

Current OSHA standards for limiting exposure to workers are a 2 $\mu g/m^3$, time-weighted average, a 5 $\mu g/m^3$ ceiling, and 25 $\mu g/m^3$ maximum peak for 30 minutes. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 025668

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CAA, 112: NESHAP promulgated for extraction and production sites for beryllium and beryllium oxide, and beryllium rocket-motor firing, 4/6/73.	Under continuing assessment to determine efficacy of existing rule; source assessment complete, 5/80.	40 CFR 61.30 et seq.; 61.40 et seq.
CWA, 304(a): Water quality criteria for dissociated beryllium. Published in final form, 11/28/80.		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects wastes known to contain beryllium and beryllium compounds to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.10
Subjects beryllium 0.01 as waste products; also subjects off-specification batches and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, 8(a): Proposed rule requesting production and other data (beryllium sulfate).		45 FR 42, p. 13646
SDWA: EPA does not plan to regulate beryllium in drinking water because of reports that it is not absorbed by the gastrointestinal system.		ODW, personal communication, 8/80
A standard of 2 $\mu g/m^3$ was adopted by the industry in 1949, and has "usually been met" since the early 1950s.		OHRS draft criteria document, 3/79 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
PEL: 2 $\mu g/m^3$ 8-hr TWA; 5 $\mu g/m^3$ ceiling; 25 $\mu g/m^3$ maximum peak for 30 min. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 6/27/71: OSHA Takeover Standards--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025669

N,N-BIS(2-CHLOROETHYL)-2-NAPHTHYLAMINE (CHLORNAPHAZINE)

There is sufficient evidence of the carcinogenicity of N,N-bis-(2-chloroethyl)-2-naphthylamine (chlornaphazine) in humans, and limited evidence in experimental animals.[1] N,N-bis(2-chloroethyl)-2-naphthylamine produced lung tumors in mice following intraperitoneal injection, and local sarcomas in rats after subcutaneous administration.[2]

The administration of chlornaphazine together with radioactive phosphorus (^{32}P-sodium phosphate) caused bladder cancer in 10 of 61 patients treated for polycythemia vera. In 46 patients treated with ^{32}P-sodium phosphate alone, no cases of bladder cancer were found.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 119-24.

This antineoplastic drug, sparingly soluble in water, is a nitrogen mustard. The drug is commonly called chlornaphazine.

Chlornaphazine is neither produced nor used commercially in the United States, although it has been used in other countries in the treatment of leukemia and related cancers. The drug now has no wide therapeutic application.

The EPA Carcinogen Assessment Group has included this chemical on its list of carcinogens. Under the Resource Conservation and Recovery Act, EPA requires that the use, handling, or disposal of wastes containing this substance be subject to special reporting and recordkeeping requirements. The FDA reported that N,N-bis(2-chloroethyl)-2-naphthylamine is not an approved drug for therapeutic use.

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N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling report/recordkeeping requirements. Also designates N,N-Bis(2-chloroethyl)-2-naphthylamine as a hazardous constituent of wastes, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA reports that N,N-Bis(2-chloroethyl)-2-naphthylamine is not an approved drug. (FDA)		

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BIS(CHLOROMETHYL)ETHER AND TECHNICAL GRADE CHLOROMETHYL METHYL ETHER

There is sufficient evidence for the carcinogenicity of these substances both in experimental animals and in humans.[1] Bis(chloromethyl)ether (BCME) produced tumors at the site of application in mice after administration by inhalation, skin application or subcutaneous injection, and in rats after inhalation and subcutaneous administration. Technical grade chloromethyl methyl ether (CMME) (which is almost always contaminated with BCME) produced local sarcomas in mice after subcutaneous administration, and was also an initiator of skin tumors.[1,2]

Two studies of workers exposed to BCME and technical grade CMME showed an increased risk of lung cancer, mainly oat-cell carcinoma. Two subsequent studies have shown a positive association between atypical cells in bronchial excretions (abnormal pulmonary cytology) and exposure to BCME which was not related to cigarette smoking. Several studies have demonstrated a significant excess of lung cancer among BCME- or CMME-exposed workers which was directly related to intensity and duration of exposure. Oat-cell carcinoma was the predominant histological type of lung cancer. The excess respiratory cancer mortality was most marked in workers under 55 years of age. The evaluation of CMME alone is complicated by the presence of 1 percent to 8 percent of BCME as a contaminant.[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1979, pp. 26-27.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 239-45.

Both BCME and CMME are water-soluble, colorless liquids.

BCME and CMME are used in the synthesis of other chemicals and in the manufacture of plastics and ion exchange resins. Domestic production of BCME by one producer is estimated by EPA to be 550,000 lb annually. BCME has been primarily used in the United States as a chemical intermediate. There are currently four producers of CMME in the United States, but the amount produced has not been reported. Technical grades of CMME are contaminated with 1 to 8 percent BCME.

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The main route of exposure to BCME and CMME is through inhalation, and less likely through skin absorption. Potential sources of human exposure to BCME and CMME exist primarily for workers, such as organic chemical synthesizers, ion exchange resin makers, laboratory workers, and polymer makers. No estimates of the number of workers exposed are available. Very low incidental exposure might occur due to metabolites of some dental materials regulated by the FDA.

Environmental exposure through water pollution is small because both chemicals rapidly decompose in water. However, the breakdown in air is less rapid. BCME can be formed whenever formaldehyde, water, and hydrogen chloride vapors are mixed at room temperature even in low concentrations.

The EPA regulates BCME under the Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). BCME was deleted from the CWA hazardous substance list due to its extremely short life in water and the absence of data indicating it is a water pollution problem. RCRA lists BCME as a hazardous constituent of waste. The EPA primarily addresses BCME, although assessments are in progress regarding additional regulations for CMME in water and air. OSHA issued an emergency temporary standard covering both chemicals in 1973 and a final standard in 1974. This standard prohibits the operation in open vessels and requires exhaust fans, protective clothing and devices, and warning signs and labels.

The Consumer Product Safety Commission (CPSC) staff preliminarily determined in 1980 that BCME and CMME were not present in consumer products under CPSC jurisdiction. The Commission subsequently requested (45 FR 61344) public comment to verify the accuracy of its information. No comments were received on these chemicals. Pending the receipt of new information, the Commission plans no action on BCME or CMME.

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Dichloromethyl ether

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products. (CPSC)		
CWA, 304(a): Water quality criteria published in final form, 11/28/80 (BCME and two other chloroethyl ethers).		45 FR 231, p. 79318
CWA, 307: Delisted from hazardous substance list, 2/4/81.	Extremely short life in water and absence of data indicating BCME to be a water pollution problem. (EPA)	46 FR, p. 10723
RCRA, 3001-3006: Listed as a hazardous constituent of waste. Wastes known to contain BCME are subject to handling and report/record-keeping requirements. Promulgated 5/19/80.		40 CFR 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Medical Devices, FD&CA: No regulations promulgated by FDA-BMD. (FDA)	Possible presence in dental restorative materials is listed, but exposure is considered incidental). (FDA)	
Protective clothing, respirator, hygiene, training and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: (Emergency Temporary Standards-- protective clothing and hygiene requirements for workers; open-vessel operations restricted; engineering requirements. (OSHA)	29 CFR 1910.1000 (OSHA)

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REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates CMME as a hazardous constituent of waste and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13536 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Medical Devices, FD&CA: No regulations promulgated by FDA-BMD. (FDA)		
Protective clothing, respirator, hygiene, training and medical surveillance requirements for workers; exhaust fan requirements, open-vessel operations prohibited; contamination control requirements for areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers; open-vessel operations restricted; engineering requirements. 2/22/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1006 (OSHA)

MONS 025675

CADMIUM AND CERTAIN CADMIUM COMPOUNDS

The evidence for the carcinogenicity of cadmium and certain cadmium compounds in experimental animals is sufficient; the evidence of carcinogenicity in humans is limited.[1]

Cadmium chloride, oxide, sulfate, and sulfide are carcinogenic in rats, causing local sarcomas after subcutaneous injection. Cadmium powder and cadmium sulfide produce local sarcomas in rats following intramuscular administration. Cadmium chloride and cadmium sulfate produce testicular tumors in mice and rats following subcutaneous administration.[1]

Studies have suggested that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate, respiratory, and genitourinary cancers in humans.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. Lyon, France: IARC, 1976, pp. 39-74.

Cadmium and certain cadmium compounds are widely used commercially in electroplating, alloys, soldering, plastic stabilizers, batteries, fungicides, and in phosphors and pigments for television tubes, inks, artists' colors, glass, ceramics, textiles, and paper.

The 1980 domestic production of cadmium and eight high-volume cadmium compounds was approximately 17 million lb, whereas an additional 2 million lb were imported. Cadmium oxide accounts for approximately 10 million lb (about 60 percent) of the total domestic production. An estimated 4-5 million lb/yr are used exclusively for jewelry and silversmithing. Plastic stabilizers utilize approximately 2 million lb/yr of cadmium and cadmium compounds.

Human exposure to cadmium and certain cadmium compounds occurs through inhalation and ingestion. OSHA estimates that 360,000 workers are potentially exposed to cadmium and its compounds. The entire population is exposed to low levels of cadmium in the diet because of the entry of cadmium into the food chain as a result of its natural occurrence. Tobacco smokers are exposed to an estimated 1.7 ug/cigarette. Cadmium is present in relatively low amounts in the earth's crust; as a component of zinc ores, cadmium may be released into the environment around smelters.

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The Consumer Product Safety Commission (CPSC) investigated the potential consumer hazard presented by materials painted with cadmium-containing inks. No cadmium was found in inks used in printed products. The CPSC staff indicates there is little cadmium found in other printed consumer products. The EPA has regulated cadmium and its compounds under the Clean Water Act (CWA), the Resource Conservation and Recovery Act, the Safe Drinking Water Act (SDWA), and the Toxic Substances Control Act; regulation is planned or proposed under the Clean Air Act. Under the CWA, water quality criteria for the protection of human health have been published that are identical to SDWA standards of 10 ug/l. The EPA has issued a Rebuttable Presumption Against Registration of cadmium-containing pesticides, but final action has not been taken. The Carcinogen Assessment Group includes cadmium oxide, cadmium sulfide, and cadmium sulfate on its list of potential carcinogens. The FDA limits leaching from pottery and enamel to 0.5 ug/ml of leaching solution for pottery (flatware) and small hollowware (0.25 ug/ml of leaching solution for large hollowware). The OSHA has adopted permissible exposure limits of 0.1 mg/m^3 as an 8-hour time-weighted average for fumes, 0.3 mg/m^3 as a ceiling for fumes, 0.2 mg/m^3 as an 8-hour time-weighted average for dust, and 0.6 mg/m^3 as a ceiling for dust. This standard was adopted by OSHA for toxic effects other than cancer. NIOSH has recommended a standard for cadmium and all cadmium compounds of 40 ug/m^3 as a time-weighted average, and 200 ug/m^3 as a 15-minute ceiling.

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REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
FY81 investigation of materials printed with cadmium-containing inks. FY82--no current action. (CPSC)		
CWA, 301: Effluent guidelines for certain industrial categories address cadmium. Promulgated 4/8/74, 4/24/75, 11/6/75. Proposed 9/7/79; pretreatment portion promulgated.	Control established through enforcement of conditions of NPDES permits. Carcinogenicity was not considered in establishing guidelines.	40 CFR 413, 421, 440 (portions) 44 FR 179, p. 2
CWA, 304(a): Water quality criteria published in final form, 11/28/80.	Protection of human health (general toxicity) 10 ug/l.	45 FR 231, p. 79318
CWA, 307(a): Toxic pollutant effluent standards were proposed in 1973, but never promulgated.	Difficulty in identifying sources to extent required by law was cited in the 6/76 deferral.	OWRS, personal communication, 4/79
CWA, 311: Hazardous spill regulation establishing reportable quantity (100 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. Addresses cadmium acetate, cadmium chloride.	40 CFR 117.3, 117.13
RCRA, 3001-3004: Designated as a toxic waste. Requires testing to determine presence. Wastes containing cadmium are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.	Concentration triggering compliance with requirements: 1.0 mg/l.	40 CFR 261.24
Designated as a hazardous constituent of waste (cadmium compounds, not otherwise specified).		40 CFR 261.11
RCRA, 4004: Prohibition on open burning, use on food cropland, or open dumping of municipal sludges designated hazardous. (CWA, 405, also authority.) Promulgated 9/13/79.	Prohibition on cropland use specifically addresses cadmium.	40 CFR 257
CWA, 405: Limitation for concentrations of cadmium and other toxic substances in sludges intended for use as soil conditioners under study.	On hold pending development of a policy regarding sludge; considering treatability and costs relevant to toxics therein.	OSW, personal communication, 4/82
SDWA, 1412: Revision of drinking water maximum contaminant level scheduled for proposal by 6/83.	Existing maximum contaminant level is 0.01 mg/l. Chronic toxicity, including possible carcinogenicity, will be addressed.	40 CFR 141.11 OSW, memorandum, 9/81
FIFRA, 6: OPAR issued addressing registered pesticides containing cadmium, 10/26/77.	Addresses cadmium carbonate and cadmium chloride. Proposed determination in development.	42 FR 206, p. 56874

(Continued)

MONS 025678

Cadmium and Certain Cadmium Compounds (Continued)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CAA: Under assessment to determine if airborne cadmium presents a risk warranting regulation. Risk assessments are in varying stages of review.		OAQPS, personal communication, 9/80
TSCA, 8(a): Reporting rule requiring process and use data proposed.	Addresses cadmium oxide and cadmium sulfate.	45 FR 42, p. 13646 (EPA)
TSCA: Under review to determine if additional regulatory action may be warranted. No target for determination established.		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Includes cadmium sulfide and cadmium sulfate. (EPA)	
FDA Bureau of Foods, FD&CA: Cadmium is an unavoidable contaminant present at low levels in most foods. Cadmium is not a permitted food or food additive.	Limits leaching solutions from pottery and enamel to 0.5 mg. (FDA)	CFR 21 7437.02 (FDA)
FDA Bureau of Medical Devices, FD&CA: No regulatory action at present until a position is clarified on the use of colors in medical devices.		
Initiated a collaborative study with industry, state, and university labs involved in food sample analyses to evaluate a dry-ash anodic stripping voltammetry method for detecting cadmium (lead can also be determined through this method) in March 1981.		
Participated in an international, collaborative "hot-leach study" on leachable cadmium from cookware. Final results of this study will be presented at the fall meeting of the Association of Official Analytical Chemists.		
Participated in an international survey--"An International Assessment of Cadmium Pollution" in March 1981. The study was carried out by the Monitoring and Assessment Research Center, Chelsea College, University of London.		

(Continued)

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REGULATIONS

Regulations and Other Action.	Effect of Regulations; Other Comments	Citation of Regulation
Colorado State University and the Denver Metropolitan Sewage Disposal District no. 1 have completed a joint contract study funded by EPA and FDA to evaluate the impact on cattle of incorporating sewage sludge into cattle feed. A final report was prepared. Survey and monitoring of grocery products for the presence of cadmium through the Total Diet Program continues. (FDA)		
PEL: 0.1 mg/m^3 8-hr TWA (fumes), 0.3 mg/m^3 ceiling (fumes), 0.2 mg/m^3 8-hr TWA (dust), 0.6 mg/m^3 ceiling (dust). (OSHA)	Regulatory History: 1951: Walsh-Healy, 0.1 mg/m^3 maximum allowable concentration. 8/27/71: OSHA Takeover Standard--current limit effective. [Standard adopted for toxic effects other than cancer.] (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025680

CARBON TETRACHLORIDE

There is sufficient evidence for the carcinogenicity of carbon tetrachloride (CCl_4) in experimental animals; the evidence of carcinogenicity in humans is inadequate.[1]

Carbon tetrachloride is carcinogenic to mice and rats, producing liver tumors after administration by various routes. It also produced liver tumors in trout and hamsters following oral administration.[2]

Three case reports describe liver tumors associated with cirrhosis in humans exposed to carbon tetrachloride. A mortality study of laundry and drycleaning workers exposed to a variety of solvents suggested an excess of respiratory cancers, liver tumors, and leukemia.[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1976, pp. 371-99.

CCl_4 is a colorless, highly volatile liquid with a strong ethereal odor similar to chloroform. The chemical mixes sparingly with water.

Most of the CCl_4 produced is used for the manufacture of Freons 11 and 12, but it is also used in industrial degreasing operations as a general solvent and as a grain fumigant.

The EPA reported 1977 domestic production as 410 million lb/yr and imports as 4 million lb/yr (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). In 1979, nearly 730 million lb were manufactured; 5.4 million lb were imported; and 85 million lb were exported, which indicates a 100 percent increase in exports since 1978. Market reports for 1979 indicate a 5-10 percent decrease in consumption as a result of discontinued uses, such as for drycleaning and fire extinguishers. Because of the increasing concern about the general toxicity of CCl_4, a downward trend of consumption will probably continue.

Human exposure can occur by inhalation of fumes or skin absorption. Approximately 4500 workers are exposed during production processes, and 52,000 more workers are exposed during industrial use and consumption of the chemical. OSHA estimated that 3.4 million workers could be exposed to CCl_4 directly or indirectly. Under the authority of the Hazardous Substances Act, the Consumer Product Safety Commission has banned CCl_4 and CCl_4-mixtures

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as hazardous substances. This ban excludes unavoidable manufacturing residues of CCl_4 in other chemicals that do not, during use, result in an air concentration of > 10 ppm. The compound could be ingested as a contaminant of foods that were either fumigated with CCl_4 or ingested in water contaminated with CCl_4 (reported concentrations of 0.2-18 ppm). When used as a fumigant on stored grain, residue levels can range from 3.0 to 72 mg/kg. CCl_4 may also be ingested as a contaminant of the chlorine used in treating drinking water. CCl_4 has been found in human tissues in concentrations of 1-13 ppm.

An estimated 5 million lb/yr of CCl_4 are emitted during manufacture and processing, and approximately 60 million lb/yr are released as solvent emissions. The amount of CCl_4 emitted to the environment indicates that a large proportion of the general population has been exposed. EPA estimated that 8 million people living within 12.5 miles of manufacturing sites are exposed to average levels of 0.5 ug/m^3, with peaks of 1580 ug/m^3. CCl_4 has been found in 10 percent of 113 surveyed public water systems at mean concentrations ranging from 2.4 to 6.4 ug/l; in 45 percent of surface water supplies; and in 25 percent of groundwater samples, at concentrations of 0.001-0.40 mg/l. Estimates indicate that 19 million people might be exposed to CCl_4 through ambient air, 20 million through contaminated drinking water, and 2 million through contaminated soil or landfills.

The EPA has regulated disposal and related handling of CCl_4 under the Resource Conservation and Recovery Act, and effluents and spills under the Clean Water Act. The World Health Organization recommends that no detectable residue (limit, 0.01 ppm) be allowed on food or feed, but permits 50 mg/kg on cooked cereals. Under the Federal Hazardous Substances Act, FDA banned the use of CCl_4 in all products except where it was an unavoidable byproduct, which would not yield ambient levels greater than 10 ppm. OSHA has adopted a permissible exposure level in the workplace of 10 ppm as an 8-hour time-weighted average, a 25-ppm ceiling, and a 200-ppm maximum peak for 5 minutes in any 4-hour period. This standard was adopted by OSHA for toxic effects other than cancer.

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REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Consumer use banned except for manufacturing residues. (CPSC)		16 CFR 1500.17(a)(2) (CPSC)
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/record-keeping requirements. Promulgated 5/19/80. Also designated as a hazardous constituent of waste. Wastes known to contain CCl_4 are subject to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb) and imposing reporting requirements. Promulgated 6/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals, and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13
Proposed to reduce reportable quantity to 1000 lb, 7/25/80.	Based on carcinogenicity.	45 FR 133, p. 46006
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CAA: Exposure assessment completed. Under consideration for possible regulation. No completion date scheduled.		Document, 5/80 for OAQPS
SDWA, 1412: NAPS reporting volatile organics published, 3/4/81.	Seeks comments regarding establishment of of maximum contaminant level, issuance of guidance, and other courses of action. Notice discusses risk estimates and other factors.	47 FR 43, p. 9380
FIFRA, 6: RPAR issued 10/16/80.	Based on oncogenicity; renal and hepatotoxicity. Comment period closed, 11/24/80. Comment review and risk/benefit assessment in progress.	45 FR, p. 68634
FAO/WHO recommendation that no detectable residues be permitted on any food or feed, but permits up to 50 mg/kg in canned cereal products. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Detection limit in food/feed 0.01 ppm. (EPA)	1975, cited by OPP and OAPS (EPA)
FDA under the authority of FHSA banned the use of CCl_4 in all products except where it was an unavoidable by-product, which would not yield content levels greater than 10 ppm. (FDA)		
PEL: 10 ppm 8-hr TWA; 25 ppm ceiling; 200 ppm maximum peak for 5 min in any 4-hr period. (OSHA)	Regulatory History: Walsh-Healy, 50 ppm maximum allowable concentration. 5/27/71: OSHA Takeover Standard--current limit effective. (Standard adopted for toxic effects other than cancer.) (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025683

CHLORAMBUCIL

There is sufficient evidence of carcinogenicity of chlorambucil both in humans and in experimental animals.[1] Chlorambucil is carcinogenic in rats and mice following intraperitoneal injection, producing lymphomas in rats, and lymphosarcomas, ovarian tumors, and lung tumors in mice.[1]

Excesses of acute leukemia were reported in a number of epidemiological studies of people treated with chlorambucil, either alone or in combination with other therapies, for both non-malignant and malignant diseases. Other cancers have also been associated with the use of chlorambucil and other agents. An excess of acute leukemia in association with chlorambucil was seen in a further study in which 431 previously untreated patients with polycythemia vera were given phlebotomy alone or chlorambucil with phlebotomy, and followed for a mean of 6.5 years. Of the 26 cases of acute leukemia that occurred, 16 were in the group receiving chlorambucil. The risk increased with increasing dose and time of treatment.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 26. Lyon, France: IARC, 1981, pp. 115-36.

Chlorambucil, a drug used to treat cancer, is a derivative of nitrogen mustard. This drug is primarily used as an antineoplastic agent for the treatment of lymphocytic leukemia, malignant lymphomas, follicular lymphoma, and Hodgkin's disease. The treatments are not curative, but they do produce some marked remissions. Chlorambucil has also been tested for treatment of chronic hepatitis and rheumatoid arthritis and for use as an insect chemosterilant.

All of the chlorambucil used in this country is imported from the United Kingdom. No data are available on the quantity imported, but the FDA reported that 6.4 million prescriptions were dispensed by retail pharmacies in 1980. Exposure in the United States would be limited to workers formulating the tablets or to patients receiving the drug.

The Carcinogen Assessment Group includes this chemical on its list of carcinogens. Therefore, the EPA regulates chlorambucil under the Resource Conservation and Recovery Act. The FDA approved chlorambucil for use as a prescription drug in 1969, noting restrictive approved clinical use for the treatment of chronic lymphocytic leukemia, malignant lymphomas, and Hodgkin's disease.

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Chlorambucil

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-Acut: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chlorambucil as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/82. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Drugs, FD&CA: Regulated as an approved prescription drug. Approved for use 9/30/53. (FDA)	Limits use to treatment of indicated treatments of chronic lymphocytic leukemia, malignant lymphomas, and Hodgkin's disease. As with other potent antineoplastic agents, the likelihood of these drugs being carcinogenic is not surprising; and their clinical usage recognize that risk by restrictive approved clinical indications. (FDA)	CFR 21, Subchapter D (FDA)

MONS 025685

CHLOROFORM

There is sufficient evidence for the carcinogenicity of chloroform in experimental animals.[1] Chloroform was tested in three experiments in mice and in one in rats by oral administration. It produced hepatomas and hepatocellular carcinomas in mice (gavage of a solution in olive oil), malignant kidney tumors in male rats, and tumors of the thyroid in female rats. In another series of experiments in male mice, chloroform administered orally (gavage in toothpaste or in arachis oil) produced benign and malignant kidney tumors.[1,2]

[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 401-27.

Chloroform is a highly volatile liquid that is slightly soluble in water. It is used primarily as an intermediate in the manufacture of fluorocarbon compounds, dyes, drugs, and pesticides; as a solvent in the extraction and purification of some antibiotics, vitamins, and flavors; as an industrial solvent in photography and drycleaning; and as a heat transfer medium. Its use as an anesthetic has been largely discontinued. At least one grain fumigant mixture contains chloroform with carbon disulfide, and it has been formulated with other ingredients for screw worm control on animals. The consumption pattern for 1974 was as follows: 51 percent for fluorocarbon refrigerants, 24 percent for plastics, and 25 percent for other uses.

During 1971-78, 230-350 million lb of chloroform were produced in the United States. Domestic production in 1977 was reported by EPA (public record) as 176 million lb and imports as 4 million lb. U.S. exports were estimated at 20 million lb in 1977. The annual growth rate for production was forecast at 7 percent.

The wide industrial use of chloroform potentially exposes 360,000 workers (OSHA). Chemists and support workers as well as hospital workers are believed to be at a higher risk than the general population.

Chloroform has been detected in the atmosphere at < 0.05-7.3 μg/m3 (< 0.01-15 ppb); in water at < 0.1-311 μg/l; in foodstuff at 50 ppm; in aquatic life at 7-1040 μg/kg (56-1040 μg/kg--molluskx; 7-851 μg/kg--fish) (dry weight); and in human tissue samples at 1-68 μg/kg of wet tissue.

MONS 025686

EPA criteria and promulgated regulations include (1) general rules for regulating hazardous spills, (2) water quality criteria document for the protection of human health and assessment regarding carcinogenicity, (3) restriction of use as a pesticide under the Rebuttable Presumption Against Registration, (4) regulations regarding handling and disposal of chloroform production waste material, and (5) the Safe Drinking Water Act in which EPA has promulgated a regulation (1980) regarding the removal of chloroform from drinking water and established a maximum contaminant level of 100 µg/l. Chloroform was banned by FDA from use in food, drugs, and cosmetics on June 29, 1976. Prior to being banned, chloroform had been approved for use in cough preparations, liniments, toothpastes, cosmetics, and toothache drops. OSHA adopted a ceiling level of 50 ppm (240 mg/m^3) for any 10-minute period. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 025687

Chloroform

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity (5000 lb, 2270 kg) and imposing reporting requirement. Promulgated 8/29/79.	Not based on carcinogenicity.	40 CFR 117.3, 117.13
A proposal to reduce reportable quantity to 100 lb (45.4 kg), 7/9/80.	Based on carcinogenicity.	45 FR 133, p. 46094
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chloroform as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
SDWA: Regulation regarding removal of chloroform and some other trihalomethanes. Promulgated 11/29/79. Establishes technology-based maximum contaminant level of 100 ug/l.		40 CFR 141.12
FIFRA, 6: RPAR issued 4/6/76.	Based on oncogenicity. Comment period closed, 7/23/76. Comment review and risk/benefit assessment continuing. (EPA)	41 FR, p. 14000 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Drugs, FD,C&A: Regulations promulgated which removed chloroform after 7/29/76 from drugs and cosmetics that had added chloroform as an ingredient. FDA Bureau of Foods: No specific regulations or tolerances for dietary exposure, which results from the presence of chloroform as a natural constituent of foods. (FDA)	To prevent the addition of chloroform to foods, thus completely eliminating risk. (FDA)	
PEL: 50 ppm (240 mg/m³) ceiling. [Standard adopted for acute effects other than cancer.] (OSHA)	Regulatory History: 1962: Ceiling, 100 ppm maximum allowable concentration. OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025688

CHROMIUM AND CERTAIN CHROMIUM COMPOUNDS

There is sufficient evidence for the carcinogenicity of chromium and certain chromium compounds both in humans and experimental animals.[1]

Calcium chromate is carcinogenic in rats when given by several routes, producing tumors at the sites of administration. Lead chromate, sintered calcium chromate, zinc chromate, strontium chromate, sintered chromium trioxide, lead chromate oxide and cobalt-chromium alloy produce sarcomas at the sites of their subcutaneous, intramuscular and/or intrapleural administration in rats; lead chromate also produced renal carcinomas following its intramuscular administration in rats.[2]

There is sufficient evidence for increased incidence of lung cancer among workers in the chromate-producing industry and possibly also among chromium platers and chromium alloy workers. There is also a suggestion of increased incidence of cancers at other sites. However, the chromium compounds responsible cannot be specified.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 23. Lyon, France: IARC, 1980, pp. 205-323.

Chromium is a steel-gray, lustrous metal. Chromium and its compounds are used in metal alloys such as stainless steel; as protective coatings on metal; on magnetic tapes; and as pigments for paints, cement, paper, rubber, composition floor covering, and other materials. These compounds are also used as oxidants in organic chemical synthesis, in photomechanical processing, in industrial water treatment, and in medicine as an astringent and antiseptic.

The aggregate 1980 domestic production of chromium and 10 important chromium compounds was over 752 million lb. Approximately 102 million lb were imported in 1980. Sodium dichromate is the highest volume chemical of all chromium compounds. Its domestic production in 1980 was approximately 554 million lb, and imports totaled approximately 71 million lb.

MONS 025689

Chromium (in the form of unidentified chromium compounds) is widely distributed in air, water, soil, and food. In trace amounts, the trivalent form may be an essential ingredient in our diet. The entire population is thus exposed to some of these compounds, but the levels of exposure vary. Hexavalent chromium compounds are of greater health concern than trivalent compounds; however, hexavalent compounds are readily reduced to trivalent forms in the presence of organic matter. The National Occupational Hazard Survey has estimated that 2.5 million workers are exposed to chromium and its compounds.

The Consumer Product Safety Commission (CPSC) staff is investigating the potential hazard to consumers from materials printed with chromium-containing inks. Although chromium was found in some inks used in printed products, the levels found in the final product did not warrant further activity. The CPSC staff indicated that there was little chromium found in other printed consumer products. The EPA has regulated chromium and its compounds under the Clean Water Act, the Resource Conservation and Recovery Act, and the Toxic Substances Control Act. The EPA maximum level permitted in drinking water is 0.05 mg/l (Safe Drinking Water Act, 1412). The EPA Carcinogen Assessment Group has included 10 chromium compounds on its list of carcinogens. NIOSH recommends respiratory devices, protective clothing, proper housekeeping, and training for persons potentially exposed to hexavalent chromium compounds. OSHA has adopted an 8-hour TWA exposure limit of 0.5 mg/m^3 for soluble chromium compounds and 1 mg/m^3 for chromium metal and insoluble compounds as an 8-hour time-weighted average. For chromic acid and chromates, the permissible exposure limit is 0.1 mg/m^3 ceiling. NIOSH recommends exposure limits of 1 ug/m^3 for carcinogenic hexavalent chromium compounds, 25 ug/m^3 as an 8-hour time-weighted average, and 50 ug/m^3 ceiling for other hexavalent chromium compounds.

MONS 025690

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
Chromium:		
CWA, 304: Effluent guidelines for certain industrial categories address chromium. Proposals for additional categories: 7/2, 9/7, 10/19, and 12/21/79. Pretreatment part of one category. Promulgated 9/7/79.	Establishes control through NPDES permits. Carcinogenicity was not addressed in setting guidelines, although the generally higher risks associated with hexavalent chromium were considered.	40 CFR 409, 413, 415, 419, 420, 423, 424, 425, 426, 429 (portions)
	Proposed guidelines for textiles and leather tanning and finishing item. Will seek comments on possible revisions of proposals in 12/80. All four are targeted for promulgation during mid- or late 1981.	44 FR 120, p. 38745 44 FR 175, p. 2 44 FR 230, p. 62204 44 FR 247, p. 75926
CWA, 304(a): Water quality criteria published in final form, 11/28/80.	The health-based criterion is general toxicity (trivalent 130 ug/l; hexavalent 50 ug/l).	45 FR 231, p. 79318
RCRA, 3001-3004: Designated as hazardous constituent of waste (chromium and compounds, not otherwise specified). Requires testing to determine presence of chromium. Wastes known to contain chromium are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.	Concentration triggering compliance requirements is 5.0 mg/l.	40 CFR 261.11
SDWA, 1412: Primary drinking water standard. Promulgated 12/24/75.	Existing maximum contaminant level is 0.05 mg/l, total chromium. Chronic toxicity and carcinogenicity of hexavalent chromium was considered in setting this level.	40 CFR 141.11
TSCA: Assessment completed, 5/79.	Problems not being addressed were determined to be workplace related. (EPA)	OTS, personal communication, 8/79 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Foods: No specific regulations or tolerances for dietary exposure. No action has been taken on chromium as a carcinogen because the data available are not adequate to assess its carcinogenicity through dietary exposure.	Not applicable for dietary sources. Regulated uses are based on an assumption that "all" migration of chromium will occur.	Regulated under 21 CFR 175.105 for sanitizers; 21 CFR 177.2600 for rubber products; and 21 CFR 176.180 for paper and paperboard in contact with dry food. (FDA)
FDA Bureau of Medical Devices; FDDCA: No regulations have been promulgated. Testing the carcinogenic potential of chromium salts liberated by corrosion has been suggested to MCI. (FDA)	Hexavalent compounds have not been regulated for use. (FDA)	

(Continued)

MONS 025691

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Chromium: (Continued) PEL: 0.1 mg/m³ ceiling (chromic acid and chromates); 0.5 mg/m³ 8-hr TWA (soluble chromic or chromous salts); 1 mg/m³ 8-hr TWA (metal and insoluble salts). (OSHA)	Regulatory History: 1943: Voln-mealy, 0.1 mg/m³ maximum allowable concentrations (chromic ac'd and chromates). 6/27/71: OSHA Takeover Standard--current limits effective. (OSHA)	29 CFR 1910.1000 (OSHA)
Calcium Chromate: See RCRA, 3001-3004, under chromium. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA) See recommended standard for chromium (VI). (NIOSH) See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Chromium Acetate: CAA, 311: hazardous spill regulation establishing quantity (1000 lb, 454 kg) and reporting requirements (8/30/79). See RCRA, 3001-3004 under chromium. (EPA)	Based on aquatic toxicity. Fosters greater care in handling and shipping chemicals. (EPA)	40 CFR 117.3, 117.12 (EPA)
Chromium Carbonate: FY81 evaluation of consumer exposure to chromium from printed materials. FY82 evaluation of exposure to chromium from nonprinted consumer products. (CPSC) See RCRA, 3001-3004, under chromium. (EPA)		
Barium Chromate: See RCRA, 3001-3004. See the Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 025692

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Chromic Oxide:		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See RCRA, 3001-3004, under chromium. (EPA)		
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Chromium Phosphate:		
See RCRA, 3001-3004. (EPA)		
Chromium Trioxide:		
See RCRA, 3001-3004, under chromium.		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Lead Chromate:		
See RCRA, 3001-3004, under chromium.		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Potassium Chromate:		
See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation quantity [1000 lb., 454 kg] and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.13
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)

(Continued)

MONS 025693

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Potassium Dichromate:		
See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation quantity (1000 lb, 454 kg) toxicity reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reductions of accidental exposures.	40 CFR 117.*, 117.13 (EPA)
CWA, 301: Effluent guidelines address manufacture of potassium and sodium dichromate. Promulgated 3/12/74; amended subsequently.	Control of chromium through NPDES permits. (EPA)	40 CFR 415.120, 415.126, 415.170, 415.176
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Sodium Chromate:		
See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	CFR 117.3, 117.13
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Sodium Dichromate:		
See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13 (EPA)
CWA, 306: Effluent guidelines address manufacture of potassium and sodium dichromate. Promulgated 3/12/74; amended subsequently.	Control of chromium through NPDES permits. (EPA)	40 CFR 415.120, 415.126, 415.170, 415.176 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 025694

Chromium and Certain Chromium Compounds (Concluded)

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Sodium Dichromate: (Continued) See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Strontium Chromate: See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/80.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.13
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 42, p. 13646 (EPA)
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Zinc Chromate Hydroxide: See RCRA, 3001-3004, under chromium.	Although this compound is not believed to be commercially available in the United States, knowledge that it is present in waste would afford a degree of control over it. (EPA)	
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025695

COKE OVEN EMISSIONS

The overwhelming scientific evidence supports the finding that coke oven emissions are carcinogenic. This finding rests on epidemiological surveys as well as animal studies and chemical analyses of coke oven emissions. Coke oven workers have an increased risk of developing cancer of the lung and urinary tract. In addition, observations on animals and of human populations have shown that skin tumors can be induced by the products of coal combustion and distillation. Chemical analyses of coke oven emissions reveal the presence of a large number of known carcinogens as well as several agents known to enhance the effect of chemical carcinogens especially on the respiratory tract.[1]

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[1]Occupational Safety and Health Administration: Exposure to Coke Oven Emissions. Federal Register. Vol. 41(206), 1976, pp. 46742-90.

Coke oven emissions are a complex mixture of coal and coke particles, various vapors, gases, and tars that include polycyclic aromatic hydrocarbons. OSHA defines these emissions as the benzene-soluble fraction of total particulate matter present during the destructive distillation or carbonization of coal for the production of coke. Polycyclic aromatic hydrocarbons generally constitute about 2-3 percent of the total particulates and 3-6 percent of the benzene-soluble fraction.

According to the Bureau of Mines, 64 domestic plants operated about 13,000 coke ovens in 1970. Most of the coke produced in this country is used in the extraction of metals from their ores, especially iron. As a raw material, coke is used in the synthesis of calcium carbide and in the manufacture of graphite and electrodes.

Workers and those living in industrial areas where coke oven emissions occur have a high risk of exposure. Oven-charging operations and leakage around poorly sealed coke oven doors are the major sources of gaseous emissions from byproduct ovens. OSHA estimated that 10,000 coke oven workers are exposed to these emissions. Worker exposures to the benzene-soluble fraction were reported in air sampling studies to range from 0.40 mg/m^3 to 3.0 mg/m^3.

The OSHA standard for coke oven emissions, which was promulgated in 1977, established a permissible exposure limit of 150 $\mu g/m^3$ averaged over any 8-hour period. Under this standard, specific engineering and work practice control requirements became effective in January 1980.

MONS 025696

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CAA: Coke oven emissions are under assessment to determine if regulations are warranted and feasible.		OAQPS, personal communication, 6/80. (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Addresses PAH constituent. (EPA)	
PEL: 150 mg/m³ 8-hr TWA. Additional Regulation: Protective clothing, training, and medical surveillance requirements for workers; respirator requirements where engineering and work-practice controls not sufficient or feasible; monitoring requirements; specific engineering-control requirements for charging and coking operations; specific work-practice control requirements for charging, coking, pushing, and maintenance and repair operation; sign requirements for regulated areas and areas where respirators required; labeling requirements for containers of contaminated clothing. (OSHA)	Regulatory History: 1969: Walsh-Healy, 0.2 mg/m³ maximum allowable concentration of coal tar pitch volatiles. 6/27/71: OSHA Takeover Standard--0.2 mg/m³, 8-hr TWA for coal tar pitch volatiles. 1/23/77: Final Standard--effective. 1/20/80: Specific engineering and work-practice control requirements effective. (OSHA)	29 CFR 1910.1029 (OSHA)

MONS 025697

p-CRESIDINE

When administered in the diet, p-cresidine was carcinogenic to Fischer 344 rats, causing increased incidences of carcinomas and papillomas of the urinary bladder in both sexes, increased incidences of olfactory neuroblastomas in both sexes, and of liver tumors in males. p-Cresidine was also carcinogenic in B6C3F1 mice, causing carcinomas of the urinary bladders in both sexes and hepatocellular carcinomas in females.[1]

[1]National Cancer Institute. Bioassay of p-Cresidine for Possible Carcinogenicity. CAS No. 120-71-8. Technical Report Series No. 142. DHHS Publication No. (NIH) 78-1394. Bethesda, Maryland, 1979.

p-Cresidine is an aromatic amine that is insoluble in water but very soluble in organic solvents.

p-Cresidine appears to be used solely as an intermediate in the production of various azo dyes and pigments, including 11 dyes that are produced commercially in the United States.

The average annual production is not known, but one manufacturer has reported a production of about 590,000 lb during 1971-76. The EPA in 1977 reported 14 manufacturers and/or importers.

Human exposure to p-cresidine occurs primarily through inhalation of vapors or skin absorption of liquids, and this exposure is believed to be limited to workers in dye-production facilities. The Consumer Product Safety Commission stated that residual levels or trace impurities of p-cresidine may possibly be present in some dyes based on this chemical and in the final consumer product. The presence of p-cresidine, even as a trace contaminant, may be cause for concern. But no data are available describing the actual levels of impurities in the final product, the potential for consumer exposure, and the potential uptake.

Under the Toxic Substances Control Act, EPA has proposed a rule to require data reporting on the process and the use of p-cresidine. p-Cresidine is not currently regulated under the Food, Drug, and Cosmetic Act (FD&CA). The chemical is a potential contaminant in the FD&CA Red 40 (Allura Red), however, and regulatory action is pending.

MONS 025698

p-Cresidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 42, p. 13646 (EPA)
Not currently regulated under FHSCA. Regulation is pending due to its potential to contaminate FDSCA food -0. (FDA)		

MONS 025699

CUPFERRON

Cupferron, given in the diet, was carcinogenic to Fischer 344 rats, causing hemangiosarcomas, hepatocellular carcinomas, and squamous-cell carcinomas of the forestomach in males and females, as well as carcinomas of the auditory sebaceous gland in females. The chemical was also carcinogenic to B6C3F1 mice, causing hemangiosarcomas in males; and hepatocellular carcinomas, carcinomas of the auditory sebaceous gland, a combination of hemangiosarcomas and hemangiomas, and adenomas of the Harderian gland in females.[1]

[1]National Cancer Institute. Bioassay of Cupferron for Possible Carcinogenicity. Technical Report Series No. 100. DHEW Publication No. (NIH) 78-1350. Bethesda, Maryland, 1978.

Cupferron, a laboratory chemical, is a crystalline solid that is very soluble in water and alcohol. This compound is an N-nitrosohydroxylamine derivative.

Cupferron is used to separate tin from zinc, and copper and iron from other metals. Cupferron also finds application as a quantitative reagent for vanadates and titanium and for the colorimetric determination of aluminum.

EPA has indicated that two companies currently produce cupferron in two regions. Domestic production has been estimated as 37,000 lb. Imports were not reported (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The 1980 production of cupferron was reported to the U.S. International Trade Commission as greater than 5000 lb.

Human exposure to cupferron occurs mainly through ingestion or inhalation of the dust from the dry salt. Skin absorption is a secondary route of exposure. The potential for exposure appears to be greatest for those engaged in analytical or research studies involving use of the chemical. Workers may also be exposed to the compound during manufacturing processes.

The National Occupational Hazard Survey in 1974 estimated that 4000 workers were potentially exposed to cupferron.

Cupferron is currently proposed for regulation by EPA under the TSCA, 8(a), reporting rule, which would provide detailed production and marketing data.

MONS 025700

Cupferron

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 025701

CYCASIN

There is sufficient evidence for the carcinogenicity of cycasin in experimental animals.[1] Cycasin was carcinogenic in five animal species, inducing tumors in several organs. When administered in the diet, it was carcinogenic to the rat, guinea-pig and fish. Administered by gavage, it was carcinogenic to the hamster. It was also active in single-dose experiments and following prenatal exposure. The carcinogenicity of its metabolite, methylazoxymethanol, has been demonstrated in the rat and hamster and that of a closely related synthetic substance, methylazoxymethanol acetate, in the rat.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: IARC, 1972, pp. 157-63.

Cycasin occurs naturally in the seeds, roots, and leaves of cycad plants, which are found in the tropical and subtropical regions of the world. Nuts from the cycads are used to make chips, flour, and starch.

Cycasin is not produced or used commercially. The major potential exposure is the ingestion of the foods containing cycasin. It is estimated that about 50-55 percent of the inhabitants of Guam are potentially exposed (50,000-60,000 persons) to cycasin. Wastewater from the preparation of the cycad nuts contains large amounts of cycasin and represents a potential secondary exposure source.

The EPA regulates cycasin under the Resource Conservation and Recovery Act. Cycasin is designated as a hazardous constituent of waste, and wastes known to contain it are subject to handling and report/recordkeeping requirements.

Cycasin

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Designates cycasin as a hazardous constituent of waste, and subjects wastes known to contain it, to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025702

CYCLOPHOSPHAMIDE

There is sufficient evidence for the carcinogenicity of cyclophosphamide both in humans and in experimental animals.[1] Cyclophosphamide was carcinogenic in rats following administration in drinking water and intravenous injection, and in mice following subcutaneous injection. Dosages were comparable to those used in clinical practice. The chemical produced benign and malignant tumors at various sites, including bladder tumors in the rat.[2]

Five epidemiological studies are available in which persons treated with cyclophosphamide for a variety of medical conditions were compared with similarly afflicted controls. These studies consistently demonstrate an excess of various neoplasms and leukemias in the treated groups, although the number in all five studies was small.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 26. Lyon, France: IARC, 1981, pp. 165-202.

Cyclophosphamide, a chemical related to the nitrogen mustards, is a widely used synthetic antineoplastic drug that is soluble in water.

Cyclophosphamide is used in the treatment of malignant lymphoma, multiple myeloma, leukemias, and other malignant diseases. Cyclophosphamide has been tested as an insect chemosterilant and for use in the chemical shearing of sheep.

Cyclophosphamide is not produced in the United States. It is produced in the Federal Republic of Germany and exported to the United States where one company has formulated and marketed the drug since 1959. U.S. sales are approximately 1300 lb annually.

The FDA estimates that 200,000-300,000 patients per year are treated with cyclophosphamide, which is administered orally and through injection. The adult dosage is usually 1-5 mg/kg of body weight daily or 10-15 mg/kg administered intravenously every 7-10 days.

MONS 025703

The FDA requires an insert in the drug package to warn of secondary malignancies that may occur several years after treatment with cyclophosphamide has ended. The FDA is investigating the use of cyclophosphamide in nonmalignant diseases. EPA regulates this chemical under the Resource Conservation and Recovery Act.

Cyclophosphamide

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPCS)		
RCRA, 3001,-3004: Designated as a hazardous constituent of waste. Any w ..e known to contain cyclophosphamide is subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)
FDA Bureau of Drugs, FDACA: Prescription drug use for treatment of neoplasias. The package has clear warning of the induction of secondary malignancies that may occur several years after treatment has been discontinued. (FDA)	The physician is provided with information required for a benefit versus risk assessment on each patient. Use in nonmalignant diseases is investigational but could allow exposure of very young children, young adults, and adults to doses that might induce future malignancies. More stringent regulation of physicians re this danger may be advisable. (FDA)	C/R 21, Subchapter D (FDA)

MONS 025704

2,4-DIAMINOANISOLE SULFATE

There is sufficient evidence for the carcinogenicity of 2,4-diaminoanisole sulfate in experimental animals.[1,2] In Fischer 344 rats, dietary administration of the technical-grade 2,4-diaminoanisole sulfate increased the incidence of malignant tumors of the skin and the associated glands, and of malignant thyroid tumors in each sex. In B6C3F1 mice, dietary administration of 2,4-diaminoanisole sulfate induced thyroid tumors in each sex. Fischer 344 female rats exposed in the feed to technical-grade 2,4-diaminoanisole sulfate developed tumors of the thyroid, mammary, clitoral, and pituitary glands.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 191-98.

[3]National Cancer Institute. Bioassay of 2,4-Diaminoanisole Sulfate for Possible Carcinogenicity. Technical Report Series No. 84. DHEW Publication No. (NIH) 78-1334. Bethesda, Maryland, 1978.

2,4-Diaminoanisole sulfate (2,4-DAA sulfate) is a phenylenediamine derivative that is soluble in water and ethanol.

The principal use of 2,4-DAA sulfate is as a component of oxidation ("permanent") hair- and fur-dye formulations. Approximately three-quarters of the hair-dye formulations in 1978 contained 2,4-DAA or 2,4-DAA sulfate. These two compounds are also used as intermediates for the production of C.I. Basic Brown 2, used to dye furs, acrylic fibers, cotton, wool, nylon, polyester, leather, suede, and as an ingredient of shoe polishes. The Consumer Product Safety Commission (CPSC) reported that currently the chemical is not used in consumer products under CPSC jurisdiction. It is, however, used as a component of cosmetic products under FDA jurisdiction.

Commercial production of 2,4-DAA sulfate was first reported in 1967 to the U.S. Tariff Commission. The estimated annual domestic usage of this compound in 1977 was 30,000 lb. The CPSC indicated that 2,4-DAA sulfate is no longer produced in commercial quantities or imported. However, EPA has reported two producers and importers of 2,4-DAA sulfate. No domestic production data were available. Imports of 2,4-DAA sulfate were estimated as 350 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). NCI stated that production of 2,4-DAA sulfate was not

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reported to the U.S. International Trade Commission for 1979-1980; however, the 1982 Directory of Chemical Producers indicates that one U.S. company currently produces the chemical. The one company listed stated they no longer produce this chemical on a regular basis according to the information received by the CPSC.

Human exposure to 2,4-DAA sulfate may occur through skin absorption at chemical- and dye-production facilities. Dermal contact also occurs for persons using hair dyes containing 2,4-DAA sulfate. The maximum concentration of the compound in hair-dye preparations is about 1.5 percent. The National Occupational Hazard Survey in 1974 made no estimate of the potential worker exposure to 2,4-DAA sulfate (NIOSH). However, the survey estimated 7200 exposures for 2,4-DAA. NCI states that substantial exposure of the population to 2,4-DAA sulfate is questionable.

Under 21 CFR 740.18, FDA regulates 2,4-DAA sulfate as a component of hair dyes. Under 44 FR 5952, FDA requires a warning label on cosmetic products containing 2,4-DAA sulfate. However, a September 1980 court decision stayed the FDA regulation, pending a determination of the potential human health risk from dermal exposure to this compound. FDA is continuing its consideration of the matter.

2,4-Diaminoanisole Sulfate

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
2,4-Diaminoanisole sulfate is produced in small enough quantities that it is of low priority regulatory interest to EPA. (EPA)		
Regulated as a cosmetic ingredient product, as coal-tar hair dyes pose a risk of cancer.		21 CFR 740.18
A warning label required on cosmetic products containing chemical, but this regulation was stayed in a 9/22/80 court decision. (FDA)		44 FR, p. 5952 (Stayed, pending determination by FDA of risk from dermal exposure.) (FDA)

MONS 025706

2,4-DIAMINOTOLUENE

There is sufficient evidence for the carcinogenicity of 2,4-diaminotoluene in experimental animals.[1] 2,4-Diaminotoluene was carcinogenic in rats after administration in the diet, producing hepatocellular carcinomas, and after subcutaneous injection, inducing local sarcomas.[2] In another bioassay, 2,4-diaminotoluene administered in the feed of F344 rats induced hepatocellular carcinomas or neoplastic nodules in both males and females and carcinomas or adenomas of the mammary gland in females. The test chemical also produced hepatocellular carcinomas in female B6C3F1 mice.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 16. Lyon, France: IARC, 1978, pp. 83-95.

[3]National Cancer Institute. Bioassay of 2,4-Diaminotoluene for Possible Carcinogenicity. Technical Report Series No. 162. DHEW Publication No. (NIH) 79-1718. Bethesda, Maryland, 1979.

2,4-Diaminotoluene is a water-soluble crystalline solid.

Most of the 2,4-diaminotoluene is used as an intermediate to produce toluene diisocyanate, which is used in the production of polyurethane. Small amounts are used in the production of dyes for textiles, leathers, furs, wood, and biological stains. 2,4-Diaminotoluene is used in hair-dye formulations, but FDA has specific labeling requirements. 2,4-Diaminotoluene may be formed on hydrolysis of toluene diisocyanate-based polyurethanes (e.g., polyurethane adhesives).

2,4-Diaminotoluene has been produced commercially in the United States for over 50 years. Approximately 14 companies currently produce and import this chemical. Domestic production for 1980 has been estimated at 216 million lb. Imports in 1980 were approximately 4000 lb. Domestic production has increased 800 percent since 1967, with only 1978 production showing a decline.

Human exposure to 2,4-diaminotoluene occurs by skin contact and less frequently by inhalation. Despite a long high-volume production history, there are no data available on the number of people exposed during the production or use of 2,4-diaminotoluene. More than 99 percent of the 2,4-diaminotoluene produced in the United States is used captively to produce toluene diisocyanate, usually at the same site; hence, exposure potential is minimized. Air emissions from production are believed to be insignificant. Water solubility of 2,4-diaminotoluene may contaminate industrial wastewater discharges and result in exposure of the general population.

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The Consumer Product Safety Commission staff stated that it is possible that residual traces of 2,4-diaminotoluene are present in some dyes based on this chemical, and in the final consumer product. The presence of 2,4-diaminotoluene, even as a trace contaminant, may be a cause for concern. However, data describing the actual levels of impurities in the final product and the potential for consumer exposure are currently lacking. The EPA regulates toluenediamine (isomers not specified) under the Resource Conservation and Recovery Act.

2,4-Diaminotoluene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues of toluenediamine (isomers) not specified) in excess of 1000 kg to hazardous and reporting/recordkeeping requirements. Designates toluenediamine as a hazardous constituent of waste. (EPA)	Based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
Regulatory Authority: FD&CA 601(a). (FDA)	Coal tar hair dyes may not be considered adulterated under the Act as long as they bear appropriate warning labels. (FDA)	

MONS 025708

There is sufficient evidence of the carcinogenicity of dibenz-(a,h)acridine (DB(a,h)AC) in experimental animals.[1] In mice, painting with DB(a,h)AC induced skin tumors. Subcutaneous administration to mice induced local sarcomas and increased the incidence of lung tumors. Intravenous administration increased the incidence of multiple lung tumors.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 247-53.

DB(a,h)AC belongs to a class of organic chemicals known as heterocyclic compounds.

The compound has limited application but it may be used in biochemical and cancer research. DB(a,h)AC has been detected in air pollution emitted from coal combustion, petroleum refineries, incinerators, and automobile exhausts. No commercial production has ever been reported.

Based on the occurrence of this compound in polluted air, widespread inhalation exposure appears likely for both the occupational and the general population.

The monitoring of several air pollution sources has detected DB(a,h)AC levels of 17 mg/1000 m^3 in domestic coal combustion stack effluents, < 0.12 mg/1000 m^3 in petroleum refinery incinerator effluents, and 0.01 mg/1000 m^3 in air polluted by coal-tar pitch. DB(a,h)AC occurs in cigarette smoke condensate at concentrations up to 0.01 ug/100 cigarettes.

EPA regulates DB(a,h)AC under the Resource Conservation and Recovery Act and the Clean Water Act. OSHA indirectly limits exposure to DB(a,h)AC by requiring that occupational exposure to coal-tar pitch volatiles not exceed a time-weighted average of 0.2 mg/m^3 over an 8-hour period.

MONS 025709

Dibenz(a,h)acridine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CWA, 304(a): Water quality criteria for PAHs published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate.		45 FR 23:1, p. 79318
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements unless exempted by EPA. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogenic Assessment Group statement under 2-acetylaminofluorene. (EPA)		
PEL: 0.2 mg/m³ 8-hr TWA (coal tar pitch volatiles) (limited coverage). (OSHA)	Regulatory History: 6/11/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1[illegible]. 1910.1002 (OSHA)

MONS 025710

DIBENZ[a,j]ACRIDINE

The evidence of carcinogenicity of dibenz[a,j]acridine (DB[a,j]AC) in experimental animals is considered sufficient.[1] DB[a,j]AC induced skin tumors in mice following topical application and produced local sarcomas at the highest dose tested following subcutaneous administration. It increased the incidence of lung tumors after subcutaneous administration.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 254-59.

DB[a,j]AC is a heterocyclic organic compound.

DB[a,j]AC is used in biochemical and toxicological research. No commercial production of this chemical for other purposes has been reported. Based on the environmental occurrence of DB[a,j]AC, there is a potential of inhalation exposure for the general population.

DB[a,j]AC has been detected in air pollutants from coal combustion and petroleum refinery incinerators, from automobile exhausts, and from cigarette smoke. DB[a,j]AC occurs in domestic coal combustion stack effluents at concentrations of 2 mg/1000 m^3, in petroleum refinery incinerator effluents at concentrations of 0.15 to 1.8 mg/1000 m^3, and in air polluted by coal-tar pitch at a concentration of 0.001 mg/1000 m^3. DB[a,j]AC also occurs in cigarette smoke condensate at levels of 0.27 ug/100 cigarettes and in motor exhaust at levels up to 300 ug/kg. In addition, trace amounts have been detected in the average U.S. urban atmosphere.

Both EPA and OSHA regulate DB[a,j]AC. The EPA regulates it under the Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). Under the CWA, EPA has published a water quality criteria document for the protection of human health for PAHs, and under RCRA, EPA has designated DB[a,j]AC a hazardous constituent of waste. OSHA has indirectly limited exposure to DB[a,j]AC by requiring that occupational exposure to coal tar pitch volatiles not exceed a time-weighted average of 0.2 mg/m^3 over an 8-hour period.

MONS 025711

Dibenz[a,j]acridine

REGULATION		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CWA, 304(a): Water quality criteria for PAHs published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate.		45 FR 231, p. 79318
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and reporting/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement for 7-acetylmethylbenzene. (EPA)		
PEL: 0.2 mg/m³ 8-hr TWA (coal tar pitch volatiles) (listed coverage). (OSHA)	Regulatory History: 6/21/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 025712

DIBENZ(a,h)ANTHRACENE

There is sufficient evidence of the carcinogenicity of dibenz-(a,h)anthracene (DB(a,h)A) in experimental animals.[1] DB(a,h)A has produced tumors by different routes of administration in mice, rats, guinea pigs, frogs, pigeons and chickens. It has both local and systemic carcinogenic effects. On oral administration in food, it produced tumors of the forestomach in the mouse; intratracheal administration to hamsters produced lung tumors. In repeated mouse skin painting (in several mouse strains), DB(a,h)A and benzo(a)pyrene (B(a)P) appeared to be equally effective. In a dose-response study (with C3H mice) on subcutaneous carcinogenicity with DB(a,h)A, B(a)P and 3-methylcholanthrene (MC), DB(a,h)A was shown to be effective at a lower dose than that effective for B(a)P or for MC; its latent period, however, was longer. DB(a,h)A induced local sarcomas and increased the incidence of lung adenomas following a single subcutaneous injection in newborn mice at dose levels which were ineffective with MC.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 178-96.

DB(a,h)A is a member of the class of chemicals known as polycyclic aromatic hydrocarbons (PAHs), which are formed as a result of incomplete combustion of organic compounds.

There is no reported commercial application for this compound. DB(a,h)A occurs in cigarette smoke condensate; gasoline engine exhaust; soot; smoke; coke and coal tars; various smoked, barbecued, or charcoal-broiled meats and fish; and certain vegetables and vegetable oils. EPA lists one producer for DB(a,h)A, but there are no data on its production.

Exposure to this chemical would occur through inhalation or ingestion. Workers near burning or energy-producing operations are more likely to be exposed to DB(a,h)A than the general public. The highest concentrations of DB(a,h)A have been reported in airborne soot and in coal tar containing 64-705 mg/1000 m^3 and 230 mg/kg, respectively.

DB(a,h)A has a widespread presence in the environment, particularly in ambient air, but it is also found in soils and water. Therefore, a large segment of the population could be potentially exposed to DB(a,h)A from environmental sources as well as from foods and cigarette smoke.

MONS 025713

There have been few attempts to develop exposure standards for PAHs, either individually or as a class. However, NIOSH has recommended a workplace standard for coal tar products of 0.1 mg/m^3 as a time-weighted average for a 10-hour shift in a 40-hour workweek. OSHA indirectly limits exposure to DB(a,h)A by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour period as a time-weighted average. EPA regulates DB(a,h)A under the Resource Conservation and Recovery Act, and has proposed a reporting rule requiring process and use data under TSCA, 8(a).

Dibenz(a,h)anthracene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
CWA, 304(a): Water quality criteria for PAHs published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate.		45 FR 231, p. 79318
RCRA, 3281-3004: Subjects waste products, off-specification batches, and spill residues in excess of 100lb to be handling and report/recordkeeping requirements. Also designates this compound as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11
TSCA, 8(a): Proposed reporting rule requiring use data, published 2/19/80. See Carcinogen Assessment Group statement for 2-acetylaminofluorene (EPA)	Would, if promulgated, permit a basis for estimating exposure. (EPA)	45 FR 12, p. 13646 (EPA)
PEL: 0.2 mg/m^3 8-hr TWA (coal tar pitch volatiles) [limited coverage]. (OSHA)	Regulatory History: 6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025714

7H-DIBENZO(c,g)CARBAZOLE

There is sufficient evidence of the carcinogenicity of 7H-dibenzo(c,g)carbazole (7H-DB(c,g)C) in experimental animals.[1] 7H-DB(c,g)C was shown to be carcinogenic in the mouse, rat, hamster, and possibly in the dog. It had both a local and a systemic carcinogenic effect. Following oral administration to the mouse, forestomach tumors and hepatomas occurred; intratracheal administration to hamsters produced tumors of the respiratory tract. In comparison with benzo(a)-pyrene, 7H-DB(c,g)C appears to be a stronger respiratory tract carcinogen for the hamster.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 260-68.

7H-DB(c,g)C is a member of the class of organic chemicals known as heterocyclic compounds. This chemical is soluble in most organic solvents.

7H-DB(c,g)C may be formed by incomplete combustion and has been found in cigarette tar in concentrations of 0.07 µg/100 cigarettes. It is produced as a research chemical.

No case reports or epidemiologic studies have been made on human exposure to 7H-DB(C,g)C. But because this chemical has been detected in cigarettes, some persons, especially smokers, may be exposed.

EPA regulates 7H-DB(c,g)C under the Resource Conservation and Recovery Act. In addition, OSHA indirectly limits exposure to 7H-DB(c,g)C by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour time-weighted average.

MONS 025715

7H-Dibenzo[c,g]carbazole

REGULATIONS

Regulations and Other Actions	Effect of Regulation; Other Comments	Citation of Regulation
CWA, 304(a): Water quality criteria for PAHs published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate.		45 FR 2311, p. 79316
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and reporting/recordkeeping requirements unless exempted by EPA. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylamin.fluorene. (EPA)	Regulation based on reports of chronic hazard. (EPA)	40 CFR 261.11 (EPA)
PEL: 0.2 mg/m³ 8-hr TWA (coal tar pitch volatiles) [limited coverage]. (OSHA)	Regulatory History: 6/21/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 025716

DIBENZO(a,h)PYRENE

There is sufficient evidence for the carcinogenicity of dibenzo-(a,h)pyrene (DB(a,h)P) in experimental animals.[1] Carcinogenic effects of DB(a,h)P were demonstrated following repeated skin painting in mice and injections in mice and rats. In the skin painting experiment, DB(a,h)P was less active than benzo(a)pyrene.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 207-14.

DB(a,h)P is a polycyclic aromatic hydrocarbon (PAH) that is insoluble in water.

DB(a,h)P is not deliberately produced; it is a combustion product. The occurrence of DB(a,h)P in the environment is not well documented; however, it has been detected in minute amounts in coal tar pitch, engine exhaust, and in cigarette tar.

In 1974, the National Occupational Hazard Survey estimated that approximately 210,000 workers were exposed to PAHs from asphalt volatiles, coal tar pitch volatiles, and coke oven emissions, all of which may contain DB(a,h)P. An unspecified additional number of workers may be exposed to DB(a,h)P in the products of combustion from fuel oil, diesel fuel, kerosene, and wood.

The EPA has included DB(a,h)P on the Carcinogen Assessment Group list of carcinogens, and EPA regulates this chemical under the hazardous waste disposal rule of the Resource Conservation and Recovery Act. OSHA indirectly limits exposure to DB(a,h)P by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour period as a time-weighted average.

MONS 025717

Dibenzo(a,h)pyrene

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CWA, 304(a)1: Water quality criteria for polynuclear aromatic hydrocarbons published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate.		45 FR 231, p. 79318
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements unless exempted by EPA. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Regulation based on reports of chronic hazard. (EPA)	40 CFR 261.11 (EPA)
PEL: 0.2 mg/m^3 8-hour TWA (coal tar pitch volatiles) (limited coverage). (OSHA)	Regulatory History: 5/1/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 025718

DIBENZO(a,i)PYRENE

There is sufficient evidence of the carcinogenicity of dibenzo-(a,i)pyrene (DB(a,i)P) in experimental animals.[1] Subcutaneous injections of DB(a,i)P resulted in a rapid appearance of local sarcomas in the hamster and the mouse. The smallest single dose which produced sarcomas in mice was 50 ug. Repeated skin application in mice was also effective, but DB(a,i)P was less active than benzo(a)pyrene.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 215-23.

DB(a,i)P is a polycyclic aromatic hydrocarbon (PAH) that is insoluble in water.

DB(a,i)P is not commercially produced but is found as a combustion product. DB(a,i)P is the byproduct of poorly controlled combustion encountered in coal or refuse burning, in the exhaust of diesel-powered vehicles, and in coke oven emissions. It has also been detected in tobacco smoke at concentrations of 0.002-0.27 ug/100 cigarettes and in smoked foods.

In 1974, the National Occupational Hazard Survey estimated that about 210,000 workers were exposed to PAHs from asphalt and coal tar pitch volatiles and from coke oven emissions, all of which contain DB(a,i)P.

The EPA has included DB(a,i)P on the Carcinogen Assessment Group list of carcinogens. Under the Resource Conservation and Recovery Act, this chemical has been included in the hazardous waste disposal rule. OSHA indirectly limits exposure to DB(a,i)P by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour period as a time-weighted average.

MONS 025719

Dibenzo(a,i)pyrene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates dibenzo(a,i)pyrene as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
CWA, 304(a): Water quality criteria document for polynuclear aromatic hydrocarbons published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		45 FR 231, p. 79318 (EPA)
PEL: 0.2 mg/m^3 8-hr TWA [coal tar pitch volatiles] [limited coverage]. (OSHA)	Regulatory History: 6/21/71. OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 025720

There is sufficient evidence for the carcinogenicity of 1,2-dibromo-3-chloropropane (DBCP) in experimental animals.[1] DBCP administered in corn oil by gavage to Osborne-Mendel rats and B6C3F1 mice was carcinogenic, producing squamous-cell carcinomas of the forestomach in both sexes and carcinomas of the mammary gland in female rats.[2] In an inhalation experiment, DBCP was carcinogenic in male and female F344 rats, inducing increased incidence of nasal cavity tumors and tumors of the tongue in both sexes, and cortical adenomas in the adrenal gland of females.[3] DBCP was also carcinogenic in B6C3F1 mice of both sexes, producing increased incidence of nasal cavity tumors and lung tumors.[4]

[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 83-86.
[3]National Toxicology Program. Carcinogenesis Bioassay of 1,2-Dibromo-3-Chloropropane (Cas No. 96-12-8) in F344 Rats and B6C3F1 Mice (Inhalation Study). Technical Report Series No. 206. NIH Publication No. 82-1762. NTP, Research Triangle Park, N.C., and Bethesda, Maryland, 1982.
[4]National Cancer Institute. Bioassay of Dibromochloropropane for Possible Carcinogenicity. Technical Report Series No. 28. DHEW Publication No. (NIH) 78-828. Bethesda, Maryland, 1978.

DBCP is a dark amber to oark brown liquid that is slightly soluble in water.

DBCP has been registered by EPA as a soil fumigant to control nematodes during plant growth that include field crops, vegetables, fruits and nuts, greenhouse and nursery crops, and turf. In 1974, U.S. farmers used 9.8 million lb of DBCP on crops. In 1977, 831,000 lb were used in California alone, mostly on grapes and tomatoes. The Agency, however, suspended all registrations of end-use products during 1977, except for use on pineapples in Hawaii.

DBCP was first produced commercially in the United States in 1955. The annual production estimated during 1974 and 1975 was 18-20 million lb. In 1979, EPA prohibited the sale, distribution, or movement of DBCP in commerce for all suspended uses. No data are currently available on the amount of DBCP produced in the United States nor in existing stockpiles.

MONS 025721

Human exposure to DBCP can occur by inhalation and skin contact, primarily during the pesticide's manufacture, formulation, and storage. According to OSHA, approximately 17,500 workers have been exposed to the chemical. Pesticide applicators as well as farm workers were the high risk exposure groups during formulation and application. Exposure of the general population through soil is considered negligible because DBCP is moderately volatile and is degraded in moist soil. According to a 1977 EPA report, human dietary exposure to DBCP was estimated to be in the range of 2.2 to 61.0 x 10^{-6} mg/kg/day. The chemical has been detected in carrots (0.009-1.5 mg/kg) and in radishes (0.03-0.194 mg/kg) that were treated with DBCP.

On October 29, 1979, the EPA suspended, unconditionally, all DBCP-containing products for end uses except for use on pineapples in Hawaii. It further issued a notice of intent to cancel unconditionally all remaining end uses of all registered DBCP-containing pesticide products. The FDA established maximum residue levels of 1.5 mg/l in raw milk and 0.05 mg/kg in all other raw agricultural commodities. The current OSHA standard for DBCP established in April 1978 is 1 ppb (0.01 mg/m^3) as an 8-hour time-weighted average permissible exposure limit for workers. In addition, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

MONS 025722

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current activity. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
FIFRA, 6: Notice of intent to cancel all uses and suspension order affecting all uses except on pineapples in Hawaii, published 10/29/79. Final action after OPAR, except for hearings now in progress.	An estimated 2000 cancers/year could result from use of DBCP as registered and without cancellation action. Two major producers had discontinued pesticide production and recalled supplies in August 1977.	44 FR, p. 65135
FIFRA, 3: Classifies remaining use as restricted.	Based on oncogenicity and reproductive effects. Minimizes exposure to users. (EPA)	44 FR, p. 60135
RCRA, 3004-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates DBCP as a hazardous constituent of waste, and subjects waste known to contain it to the same requirements. Promulgated 6/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting requirement for submission of use and related data, published 2/19/80.		45 FR 42, p. 13644 (EPA)
See Carcinogen Assessment Group statement under 1-acetylaminofluorene. (EPA)		
PEL: 1 ppb, 8-hr TWA airborne concentration. No skin or eye contact.	Regulatory History: 5/4/77: Emergency Temporary Standards--10 ppb 8-hr TWA; 50 ppb, 15-min TWA ceiling.	29 CFR 1910.1044 (OSHA)
Preventive cleaning, respirator, hygiene, training, and medical surveillance requirements for workers; monitoring requirements; recordkeeping and waste disposal requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	6/17/78: Final Standard--current limit effective. (OSHA)	

MONS 025723

1,2-DIBROMOETHANE

There is sufficient evidence for the carcinogenicity of 1,2-dibromoethane (ethylene dibromide, EDB) in experimental animals. The evidence of carcinogenicity in humans is inadequate.[1]

When administered by gavage in corn oil, 1,2-dibromoethane (technical grade) was carcinogenic to Osborne-Mendel rats, inducing squamous-cell carcinomas of the forestomach in both sexes, hepatocellular carcinomas in females and hemangiosarcomas in males. The compound induced squamous-cell carcinomas of the forestomach and alveolar/bronchiolar adenomas in B6C3F1 mice of both sexes.[2] When inhaled, EDB was carcinogenic in male and female F344 rats, increasing the incidence of nasal cavity tumors and tumors of the circulatory system. EDB also increased the incidence of lung tumors in both sexes of B6C3F1 mice.[3] Topical application to mice produced tumors of the skin, lung and forestomach.[1]

There was only one epidemiological study of carcinogenic effects of occupational exposure to EDB; it did not produce adequate information.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982, pp. 124-126.

[2]National Cancer Institute. Bioassay of 1,2-Dibromoethane for Possible Carcinogenicity. Technical Report Series No. 86. U.S. Department of Health, Education, and Welfare. Bethesda, Maryland, 1978.

[3]National Toxicology Program. Carcinogenesis Bioassay of 1,2-Dibromoethane (CAS no. 106-93-4) in F344 Rats and B6C3F1 Mice (Inhalation Study). Technical Report Series No. 210. U.S. Department of Health and Human Services. National Institutes of Health (NIH Publication 82-1766, NTP-80-28). Research Triangle Park, North Carolina, and Bethesda, Maryland, 1982.

EDB, an industrial chemical, is a good solvent for resins, gums, waxes, and many organic chemicals; however, its major use (85 percent) is as an additive in leaded gasoline, where it scavenges lead oxide residues from the combustion chambers of gasoline engines. Other uses are in fumigants; in agricultural insecticide formulations; and in the production of certain dyes, drugs, and vinyl bromide.

MONS 025724

Production of EDB was first reported in the United States in 1923. EPA indicated in 1977 that about 300 million lb of EDB were produced annually (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). Estimated exports were 99 million lb in 1973. Imports in 1976 were reported as less than 3000 lb. Demand for EDB is expected to fall sharply because of the decline in the consumption of gasoline lead additives.

Human exposure is primarily through inhalation, ingestion, or skin absorption. NIOSH has estimated that approximately 9000 employees at production facilities are potentially exposed to ethylene dibromide. OSHA has estimated that 218,000 workers are potentially exposed in processes using this compound. The National Occupational Hazard Survey (1974) indicated that 126,000 workers may be exposed. In addition to these potential industrial exposures, NIOSH (1977) estimated that 650,000 gas station attendants may have a potential risk of exposure.

Emission concentrations of ethylene dibromide were monitored at a bulk transfer site at levels of 0.2-17 $\mu g/m^3$. An EPA study (1975) measured levels of 90-115 $\mu g/m^3$ for one ethylene dibromide production facility. Emission samples taken adjacent to gas stations and traffic arteries contained 0.07-0.11 $\mu g/m^3$.

Between 13 and 15 million lb are applied annually to soil as a pesticide, and it can be assumed that as a result of this application the chemical enters the environment through leaching. Concentrations of 0.2-31 $\mu g/l$ were measured in raw water, and finished water contained concentrations of 0.2-6 $\mu g/l$. NIOSH (1978) estimated that 304,000 lb/yr were released to the atmosphere from all sources. The low vapor pressure and rather high water solubility of the compound tend to promote its environmental presence in air, water, and soil. However, with a half-life in the atmosphere of 45 days and 5-10 days in water, no appreciable environmental accumulation would be expected.

The EPA has regulated ethylene dibromide under the Resource Conservation and Recovery Act and the Clean Water Act; and the Agency has issued a notice of Rebuttable Presumption Against Registration (1977) under the Federal Insecticide, Fungicide, and Rodenticide Act, and is considering regulation under the Clean Air Act. In 1971, OSHA adopted a permissible exposure limit of 20 ppm as an 8-hour time-weighted average, a 30 ppm ceiling, and 50 ppm maximum peak for 5 minutes in an 8-hour time period. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 025725

1,2-Dibromoethane

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSA jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/record/keeping requirements. Promulgated 5/19/80.		40 CFR 261.33
FIFRA, 6: RPAR issued 12/14/77.	Comments have been reviewed. Remaining use is as a soil fumigant (1985); proposed restricted use, 12/10/80.	42 FR, p. 63134 45 FR, p. 81506
CWA, 311: Hazardous spill regulation establishes reportable quantity (1000 lb, 454 kg) and imposes reporting requirements, 3/30/79.	Based on aquatic toxicity. Fosters greater care in handling and shipping chemicals. (EPA)	40 CFR 117.3, 117.13
CAA: Under assessment to determine if sources pose a hazard sufficient to warrant control.		OAQPS, personal communication, 8/80
FAO/WHO: Recommended that no detectable residues be allowed on foods. Detection limit cited as being 1 ppm. (EPA)		FAO/WHO: Evaluation of the Hazard to Consumers Resulting from the Use of Fumigants in the Protection of Food, 1965 (EPA)
PEL: 20 ppm 8-hr TWA, 30 ppm ceiling, 50 ppm maximum peak for 5 min in an 8-hr time period. (Standard adopted for toxic effects other than cancer.) (OSHA)	Regulatory History: 6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025726

3,3'-DICHLOROBENZIDINE

There is sufficient evidence for the carcinogenicity of 3,3'-dichlorobenzidine (DCB) in experimental animals. The evidence of carcinogenicity in humans is inadequate.[1]

3,3'-Dichlorobenzidine was carcinogenic in rats, hamsters, and dogs. In rats it produced tumors of the skin, mammary gland, Zymbal gland and hematopoietic tissues following administration in the diet or subcutaneous injection. In mice it produced liver cell tumors and leukemias following dietary and transplacental exposure, respectively. In dogs and hamsters, it produced malignant tumors of the liver and bladder following administration in the diet.[1,2]

In three retrospective epidemiological studies, no bladder tumors were reported in men occupationally exposed to dichlorobenzidine, but the studies were of insufficient quality to permit confident exclusion of carcinogenicity.

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: IARC, 1982, pp. 239-56.

DCB is used commercially in the United States primarily as a base (3,3'-dichlorobenzidine) and as a salt (3,3'-dichlorobenzidine dihydrochloride). Both are essentially insoluble in cold water.

The major uses of DCB are in the manufacture of pigments for printing ink, textiles, and plastics, and as a curing agent for solid urethane plastics.

DCB has been produced commercially in the United States since 1938. An estimated 5 million lb of DCB (base and salt) were produced in 1972. No production data are available after 1972. According to estimates from the U.S. International Trade Commission, 208,000 lb of DCB were imported into the United States in 1979.

Human exposure to DCB occurs through inhalation and probably through percutaneous absorption, primarily during industrial operations. NIOSH estimated in 1974 that 1100 people were exposed to DCB. However, no data are available on the number of workers exposed to DCB during manufacturing, processing, storing and handling, and repackaging operations.

MONS 025727

According to the EPA in 1980, there are limited data on the presence of DCB in the environment. The Agency did, however, report that a survey detected DCB levels of 0.13-3.0 mg/l at one DCB production waste disposal site.

CPSC staff has stated that residual levels or trace impurities of DCB may be present both in DCB-based dyes and pigments and in the final consumer products. The presence of this potential carcinogen, even as a trace contaminant, is cause for concern. However, no data are available to describe the actual levels of impurities in the final product, the potential for consumer exposure, and the potential uptake.

EPA regulates DCB under the Toxic Substances Control Act (TSCA), the Clean Water Act (CWA), and the Resource Conservation and Recovery Act. Under the CWA, the Agency has published a water quality criteria document for the protection of human health (1980). Under TSCA, the Agency conducted a pre-regulatory assessment of DCB based on its suspected carcinogenicity. Waste disposal guidelines were promulgated May 19, 1980, for DCB. Although the FDA has classified DCB as a carcinogen, no regulatory guidelines have been enacted by the Agency. OSHA also regulates this carcinogen. The standard includes requirements for personal protective equipment, training, medical surveillance, signs, labeling, and engineering controls.

MONS 025728

Dicyclopentadiene and 3,3'-Dichlorobenzidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
OCRA, 2001-2004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80. Also designates 3,3'-dichlorobenzidine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements.		40 CFR 261.11, 261.33
CWA, 304(a): Water quality criteria published in final form, 11/28/80. (Heading indicates 3,3'-dichlorobenzidine; text does not specify isomer.)		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation designating reportable quantity (10 lb, 4.54 kg) proposed 7/25/80 (no isomer specified).	Based on carcinogenicity. (EPA)	45 FR 133, p. 46096 (EPA)
TSCA, 8(a): Proposed reporting rule requiring use and process data, published 2/29/80 (3,3'-dichlorobenzidine).		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, respirator, hygiene, training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/SC/73: Emergency temporary standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Current regulations effective. (OSHA)	29 CFR 1910.1007 (OSHA)

MONS 025729

1,2-DICHLOROETHANE

There is sufficient evidence that 1,2-dichloroethane is carcinogenic in experimental animals.[1,2] 1,2-Dichloroethane (technical grade) was tested in one experiment in mice and in one in rats by gavage in corn oil. In B6C3F1 mice, it produced benign and malignant tumors of the lung and malignant lymphomas in animals of both sexes, hepatocellular carcinomas in males and mammary, and uterine adenocarcinomas in females. In Osborne-Mendel rats, it produced carcinomas of the forestomach in male animals, benign and malignant mammary tumors in females, and hemangiosarcomas in animals of both sexes.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 429-44.

[3]National Cancer Institute. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity. Technical Report Series No. 55. DHEW Publication No. (NIH) 78-1361. Bethesda, Maryland, 1978.

1,2-Dichloroethane, commonly known as ethylene dichloride (EDC), is a chlorinated hydrocarbon that is sparingly soluble in water.

EDC is primarily used as a component of leaded fuel and as an intermediate in the production of vinyl chloride, trichloroethane, trichloroethylene, perchloroethylene, vinylidene chloride, and ethyleneamines. Other minor uses are as an insect fumigant for stored grains and mushroom houses; as a soil fumigant in peach and apple orchards; as a cleaner for upholstery and carpets; as a solvent in textile cleaning and metal degreasing; as a dispersant for plastics and elastomers such as synthetic rubber; as an ore flotation compound; and as an extractant in certain food processes.

Commercial production of EDC was first reported in the United States in 1922. The average annual U.S. production between 1973 and 1976 was reported at 10 billion lb. In 1976, approximately 7.2 billion lb were produced, 420 million lb were exported, and negligible amounts were believed to be imported. Current production estimates are not available.

MONS 025730

Human exposure to EDC can occur through skin absorption, inhalation, or ingestion. According to NIOSH, as many as 2 million workers, including those employed in chemical manufacturing and processing industries, may have been exposed to EDC. The population at large may also be exposed through the use of EDC in food, gasoline, and agriculture. EPA reported that EDC was identified at concentrations of 1-90 ppb in 53 of 204 surface water samples taken near heavily industrialized areas across the United States.

EPA regulates EDC under the Clean Water Act and has assessments in progress under the authority of the Clean Air Act; the Safe Drinking Water Act; the Federal Insecticide, Fungicide, and Rodenticide Act; and the Toxic Substances Control Act. The FDA, Bureau of Foods, under the Food, Drug, and Cosmetics Act, has labeled EDC as an animal carcinogen. Through regulations and other actions, FDA is eliminating EDC residues in foods. OSHA has adopted permissible exposure levels of 50 ppm (200 mg/m^3) as an 8-hour time-weighted average, 100 ppm ceiling, 200 ppm maximum peak concentration for 5 minutes in any 3-hour period. OSHA adopted this standard for toxic effects other than cancer.

MONS 025731

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Preliminary economic and toxicologic review complete. Disposition recommendations to be made in FY83. (CPSC)		
CWA, 311: Hazardous spill regulation establishing reportable quantity and reporting requirements. Promulgated 1/29/79. Proposal to reduce reportable quantity.	Carcinogenicity-based proposal	40 CFR 117
SDWA, 304(a). Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
FIFRA, 3: Data call-in issued regarding chronic effects. Letter sent to all registrants of record, 7/2/81.	Teratogenicity and reproductive effects data deemed inadequate in light of current registration requirements.	Not published in FR
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 100 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste and subjects waste known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CAA, 109, 130, 112: Assessment of sources and exposure completed 5/80. Regulatory action anticipated during FY84.	Based on chronic toxicity.	OAQPS, personal communication, 9/81
OSHA, 1412: ANPR regarding 1,2-dichloroethane and five other volatile organics published, 3/4/81. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Based on chronic effects, including carcinogenicity reviewed in draft. Criteria document completed 8/81. (EPA)	47 FR, p. 9280 (EPA)
FDA Bureau of Foods, FD&CA: The compound has been issued an animal carcinogen, and the Agency has initiated revocation of the regulations. (FDA)	To eliminate residues of 1,2-dichloroethane in foods. (FDA)	21 CFR 173.220, 173.315(a)(3) 173.710, 173.840 (FDA)
PEL: 50 ppm 8-hr TWA, 100 ppm ceiling, 200 ppm maximum peak for 5 min in any 3-hr period. [Standard accepted for toxic effects other than cancer.] (OSHA)	Regulatory history: 1962: Halon-body, 75 ppm maximum allowable concentrations. 8/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025732

DIEPOXYBUTANE

There is sufficient evidence for the carcinogenicity of diepoxybutane in experimental animals.[1] Two forms of 1,2:3,4-diepoxybutane (DL and meso) were carcinogenic in mice by skin application. Both compounds produced squamous-cell skin carcinomas. The D,L-racemate also produced local sarcomas in mice and rats by subcutaneous injection.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. Lyon, France: IARC, 1975, pp. 115-23.

Diepoxybutane (DEB) is a highly reactive industrial chemical. DEB exists in four isomeric forms (D-, L-, DL, and meso), which differ in some of their chemical and physical properties.

DEB is primarily used in research and experimental work, as a curing agent for polymers, as a crosslinking agent for textile fabrics, and in preventing microbial spoilage in substances. DEB is also used commercially as mixed stereoisomers and as individual isomers in the preparation of erythritol and other pharmaceuticals.

Annual production volumes are small. EPA indicated that 350 lb of 1,2:3,4-diepoxybutane (isomeric forms not specified) were imported by one importer (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). According to HCI, DEB apparently was not imported or produced commercially in the United States in 1979-1980.

Human exposure to DEB is principally through inhalation and skin absorption. The National Occupational Hazard Survey in 1974 made no estimate of worker exposure to DEB. No consumer product use of this chemical was found.

EPA regulates DEB under the Resource Conservation and Recovery Act. Regulation is also proposed under the TSCA, 8(a), reporting rule that would preview detailed production and marketing data.

MONS 025733

Diisopropylbutane

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Pr. current action. (CPSC)		
PCRA, 3001-3004: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 7/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 025734

DI(2-ETHYLHEXYL)PHTHALATE

There is sufficient evidence for the carcinogenicity of di(2-ethylhexyl)phthalate in experimental animals.[1,2] Di(2-ethylhexyl)phthalate, given in the diet, was carcinogenic to Fischer 344 rats and B6C3F1 mice, producing increased incidence of hepatocellular carcinomas in female rats, and male and female mice; and an increased incidence of hepatocellular carcinomas or neoplastic nodules in male rats.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: IARC, 1982, pp. 269-85.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[3]National Toxicology Program. Carcinogenesis Bioassay of Di(2-ethylhexyl)phthalate in F344 Rats and B6C3F1 Mice (Feed Study). Technical Report Series No. 217. DHHS Publication No. (NIH) 82-1773. Research Triangle Park, North Carolina, 1982.

Di(2-ethylhexyl)phthalate (DEHP) is easily soluble in body fluids, e.g., saliva and plasma.

DEHP is most commonly used as an additive to polyvinyl chloride resins for fabricating flexible products. Polyvinyl chloride polymers plasticized with DEHP are used in many types of products such as teething rings, pacifiers, soft squeeze toys, and balls; in vinyl upholstery, tablecloths, shower curtains, and raincoats; and in many other products (CPSC, EPA). DEHP is also used in adhesives, in resins and polymeric coatings, in components of paper and paperboard, in defoaming agents, in enclosures for food containers, in animal glue, in surface lubricants, and in flexible devices for administering parenteral solutions (FDA).

DEHP is used in the manufacturing of vinyl gloves used for medical examinations and surgery. Approximately 500 million pairs of these vinyl gloves are produced annually. Three million flexible bags for iv fluids and an additional 8 million medical products both containing DEHP are used annually by physicians and hospitals.

DEHP was patented in 1933 and became commercially available in the 1940s. The Society of Plastics reported 302 million lb of DEHP was consumed in the United States during 1980. Approximately 400 million lb of DEHP are produced annually.

MONS 025735

EPA reported 18 producers and importers in five regions, with domestic production of 278 million lb and imports of 1100 lb (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). NCI estimated 1980 production of DEHP as 257 million lb.

The entire population can potentially be exposed to this widely used phthalate. Exposure depends on the amount of DEHP that is volatilized from vinyl products such as upholstery in automobiles, and on the ease with which DEHP is extracted from products into water or saliva. The human exposure estimate from all sources of ingestion is 5.8 mg/day. The FDA is currently reviewing the data to determine if a human health hazard occurs from DEHP used in food contact items. Large-volume parenteral formulations are packaged in flexible containers made from polyvinyl chloride that contains DEHP as a plasticizer. Parenteral solutions are administered intravenously. The concentration of DEHP in replenishers (fluids, nutrients, electrolytes) is estimated to be less than 5 ppm. An individual weighing 70 kg and receiving 3 liters of a replenisher per day gets less than 0.3 mg DEHP/kg/day. Individuals undergoing peritoneal dialysis are exposed to larger amounts of DEHP. But because of losses in the dialysis effluent, not all DEHP in the solutions is absorbed. Pharmaceutical manufacturers, aware of the possible carcinogenic risk from DEHP exposures, either are shifting to other flexible plastics that require no plasticizer or are replacing DEHP in polyvinyl chloride with other plasticizers (FDA). The National Occupational Hazard Survey in 1974 estimated that 612,000 workers were potentially exposed to DEHP (NIOSH).

DEHP is known to be widely distributed in the environment, having been detected in various forms of marine life, in soil samples, and in both animal and human tissues. The average estimated concentration of 1 ug/l in surface waters is 2 to 3 times below the levels that cause harmful effects in aquatic organisms. DEHP is biodegradable; however, it tends to partition into sediment where it is relatively persistent. Indirect human exposure to DEHP may occur through contamination of drinking water and aquatic organisms, which lead to contamination in the food chain. The leaching of DEHP from plastic articles placed in landfills is also a potential source of exposure.

EPA regulates DEHP under the Resource Conservation and Recovery Act. Regulation has been proposed under the Toxic Substances Control Act, 8(a). FDA regulates DEHP as an indirect food additive. OSHA has set a permissible exposure level of 2 ppm or 12 mg/m^3 time-weighted average for phthalic anhydride. DEHP is the subject of a NIOSH Special Hazard Review because of a 1980 NTP test in which DEHP was carcinogenic to rats and mice. Additional concern over DEHP is due to its use for respirator leak testing. NIOSH submitted to OSHA the preliminary hazard review in September 1981. This hazard review was part of OSHA's rulemaking to amend the respirator test provisions of the lead standard.

MONS 025736

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Promulgate project in progress. Studies to determine release of DEHP from infants'/children's products in progress. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues to excess of 1,000 kg to manifesting and reporting/recordkeeping requirements. Also designates chemical a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
Regulated as an indirect food additive. (FDA)		21 CFR 175.105, .300, .380 21 CFR 176.170, .210, .1010 21 CFR 177.1210, .1400 21 CFR 178.3120, .3910 21 CFR 181.27 (FDA)
PEL: 2 ppm (12 mg/m³) TWA (phthalic anhydride). [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1968: Walsh-Healy, 2 ppm (12 mg/m³) TWA. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025737

DIETHYLSTILBESTROL

There is sufficient evidence for the carcinogenicity of diethylstilbestrol (DES) both in humans and in experimental animals.[1] Diethylstilbestrol, administered in several ways, was carcinogenic in mice, rats, hamsters, frogs, and squirrel monkeys, producing tumors principally in the estrogen-responsive tissues.[2]

Diethylstilbestrol causes clear-cell carcinoma of the vagina in females exposed in utero. The evidence for an association with other human cancers is either limited (endometrium) or inadequate (breast, ovary).[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 21. Lyon, France: IARC, 1979, pp. 173-231.

DES is a synthetic hormone that is practically insoluble in water but soluble in ethanol, chloroform, diethyl ether, and certain oils.

DES had been used extensively as a growth promoter for cattle and sheep and as a treatment for estrogen-deficiency disorders in veterinary medicine. In humans DES has been used to prevent spontaneous abortions; to treat symptoms associated with menopause, menstrual disorders, postpartum breast engorgement, primary ovarian failure, and advanced breast cancer; and to treat advanced prostate cancers in males.

U.S. production of DES was first reported in 1941, but only one U.S. company now reports production of an undisclosed amount of DES. Production data were last reported in 1952, when 3960 lb were produced. Imports in 1976 were 13,000 lb.

Most exposure to DES occurs as a result of its oral administration as a drug. OSHA has estimated that 4000 workers are exposed during DES manufacture or product formulation. An estimated 500,000 patients each year are treated with DES. They are mostly males who are treated for neoplastic disease. Dosages range from to 1 to 15 mg/day. When DES was used as a growth promoter for sheep and cattle, the entire population could have been exposed to low levels of less than 10 ppb.

MONS 025738

The EPA Carcinogen Assessment Group has included DES on its list of carcinogens. In addition, EPA regulates DES under the hazardous waste disposal rule of the Resource Conservation and Recovery Act. FDA requires product labeling to state that DES is contraindicated for use during pregnancy. FDA passed a regulation in 1977 requiring a package insert to inform patients of the risks involved in taking DES, and the FDA further requires special labeling to inform physicians of the risk associated with administering estrogens. In 1979, the FDA revoked all use of DES in food-producing animals. The Court of Appeals upheld the Commissioner's decision to revoke the use of DES in all food-producing animals on November 24, 1980, and the motion to reconsider was denied on December 24, 1980.

Diethylstilbestrol

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known exposure to consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates diethylstilbestrol as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirement. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Foods, FD&CA: Because DES has been shown to be a carcinogen in animals and has been associated with carcinogenesis in humans, a regulation was published in the Federal Register on 7/6/79, to revoke all use of DES in food-producing animals. On 8/3/79, a stay of the effective date for revoking DES until 11/1/79, was published in the Federal Register. The Court of Appeals upheld the Commissioner's decision to revoke the use of DES on 11/24/80; and the motion to reconsider was denied on 12/24/80. There is presently no legal use of DES in food-producing animals.	Congress's removed the risk of continuous exposure to DES as a residue in meat and meat products.	44 FR, p. 39387
In late 1940s and early 1950s DES was prescribed extensively for threatened abortion. This use continued as epidemiology studies demonstrated DES to be ineffective in preventing abortion outcomes. In 1971, further epidemiologic data proved a relationship between DES intrauterine exposure and clear-cell adenocarcinoma of the vagina of female offspring. FDA has always required product labeling to state that DES is contraindicated for use in pregnancy. Dispensing an estrogen patient package insert with each new prescription became a regulation in 1977. Special estrogen labeling, FDA Bureau of Drugs; FD&CA. (FDA)	The use of DES in pregnant women is listed as contraindicated. Special patient package inserts and physician estrogen labeling information is required by regulation. The use of such educational material will inform both the patient and the doctor of the risks associated with DES. (FDA)	CFR 21, Subchapter D (FDA)

MONS 025739

3,3'-DIMETHOXYBENZIDINE

There is sufficient evidence for the carcinogenicity of 3,3'-dimethoxybenzidine (o-dianisidine) in experimental animals.[1] 3,3'-Dimethoxybenzidine administered by stomach tube was carcinogenic in rats, producing tumors at various sites, including intestinal, skin and Zymbal's gland carcinomas. The findings in hamsters exposed to o-dianisidine in the feed also suggest carcinogenicity.[2]

The evidence for the carcinogenicity of o-dianisidine in humans is inadequate.[1] Most of the workers exposed to this substance were also exposed to related amines, such as benzidine, which are strongly associated with urinary bladder cancer in humans.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 41-47.

3,3'-Dimethoxybenzidine (DMOB) (o-dianisidine), an aromatic amine, is slightly soluble in water and soluble in most organic solvents and lipids.

DMOB or its dihydrochloride is used principally as a chemical intermediate for the production of azo dyes. The Society of Dyers and Colourists reported the production of 89 dyes using DMOB as an intermediate in 1971. About 30 percent of DMOB is used as a chemical intermediate in the production of o-dianisidine diisocyanate (3,3'-dimethoxy-4,4'-diisocyanate-biphenyl) that is used in adhesive systems and also as a component of polyurethane elastomers and resins. DMOB is used as a dye itself for leather, paper, plastics, rubber, and textiles. DMOB has also been used in the detection of metals, thiocyanates, and nitrites.

DMOB has been produced commercially for at least 50 years. Current production figures are not available. In 1979, only one company produced DMOB, and production statistics were confidential. In 1978, the U.S. International Trade Commission (USITC) reported 3.9 million lb of DMOB produced and 86,000 lb imported. In 1979, USITC reported 77,000 lb of DMOB and 615,000 lb of DMOB dihydrochloride imported. Production of DMOB was not reported to the USITC in 1980; however, production of the hydrochloride salt was indicated in 1979 by two producers, which implied an annual production of more than 10,000 lb. Imports of DMOB through principal U.S. customs districts in 1980 were 20,000 lb; imports of DMOB hydrochloride were 642,000 lb.

MONS 025740

Human exposure to DMOB is possible through inhalation of dye particles from equipment vent systems and through skin absorption from the finished dye product, textile processing, mixing operations, or packaging processes. Workers potentially exposed to DMOB are dye makers and o-dianisidine diisocyanate production workers. However, current dye production processes for DMOB and dyes made from DMOB are generally closed systems with minimal risk to workers. The National Occupational Hazard Survey in 1974 estimated that 200 workers were potentially exposed to DMOB.

DMOB-based dyes and pigments are metabolized to DMOB. The CPSC staff is concerned that dyes and pigments based on DMOB contain residual levels or trace impurities of DMOB in the parts-per-million range and that traces may be present in the final consumer product. At present, no data exist on the actual quantities present in the final consumer product. A study is now in progress on the dermal penetration of DMOB and DMOB dyes.

In late 1980, CPSC instructed its staff to collect data in order to propose a ban on the use of DMOB-based dyes in mass-merchandised consumer dye products. EPA regulates DMOB under the Resource Conservation and Recovery Act. EPA has also proposed regulation under the Toxic Substances Control Act, 8(a), reporting rule that would provide detailed production and marketing data.

3,3'-Dimethoxybenzidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
A study is in progress on the dermal penetration of DMOB and DMOB dyes. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity of the chemical. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 025741

4-DIMETHYLAMINOAZOBENZENE

There is sufficient evidence of carcinogenicity of 4-dimethylaminoazobenzene (DAB) in experimental animals.[1] DAB was carcinogenic in rats, producing liver tumors after administration by several routes (subcutaneous injection, diet, gavage), and in dogs, producing bladder tumors when administered in the diet.[2]

DAB has also been tested by subcutaneous injection in mice, and the results are suggestive of local and hepatic carcinogenicity. Treatment of newborn animals produced liver tumors and lung adenomas in mice. Skin-painting with DAB produced epidermal tumors in rats but not in mice.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 8. Lyon, France: IARC, 1975, pp. 125-46.

4-Dimethylaminoazobenzene (DAB), an aromatic azo compound, is insoluble in water and soluble in strong mineral acids and oils.

DAB is used for coloring polishes and other wax products, polystyrene, soap, and as a chemical indicator.

No current production or import data on DAB are available. Large-scale production in the United States was first reported in 1914. DAB was one of a group of at least 20 colors for which individual production data were not available, but whose U.S. production as a group totaled 1 million lb in 1974

Human exposure to DAB can occur either through inhalation or through skin absorption. OSHA has estimated that 2500 workers were exposed to DAB.

EPA regulates DAB under the Resource Conservation and Recovery Act, and has proposed a reporting rule requiring process and use data under TSCA, 8(a). In 1974, OSHA promulgated standards for DAB based on its carcinogenicity. The standards require protective clothing and hygiene procedures for workers and engineering control measures for the manufacturing and processing of the chemical.

MONS 025742

4-Dimethylaminoazobenzene

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Toxicologic and economic assessment in FY82. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and record/recordkeeping requirements. Also designates DAB as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, Sec': Reporting rule requiring process and use data, proposed 2/29/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		45 FR 42, p. 13646 (EPA)
5/'/73: Emergency Temporary Standard: Protective clothing, respirator, hygiene, training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 2/11/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1015 (OSHA)

MONS 025743

3,3'-DIMETHYLBENZIDINE

The available test results are considered to provide sufficient evidence for the carcinogenicity of 3,3'-dimethylbenzidine in experimental animals.[1] Commercial 3,3'-dimethylbenzidine (o-tolidine) when given to the rat by subcutaneous injection caused mainly Zymbal's gland carcinomas, but mammary and forestomach tumors, and miscellaneous tumors at other sites were also present. A gastric intubation experiment with rats produced mammary carcinomas, but the result is of doubtful significance because of the small number of animals involved. In feeding experiments, the commercial product did not produce tumors in hamsters. Other experiments verified 3,3'-dimethylbenzidine as a systemic carcinogen producing multiple site tumors when given subcutaneously to the rat.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: IARC, 1972, pp. 87-91.

3,3'-Dimethylbenzidine (DMB) (o-tolidine), an aromatic amine, is a white to reddish crystalline powder that is slightly soluble in water and highly soluble in ethanol, ethyl ether, and dilute acids.

Over 75 percent of DMB is used as a dye and as an intermediate in the production of dyestuffs and pigments. According to the Society of Dyers and Colourists, more than 95 dyes are derived from DMB. Approximately 20 percent of DMB is used in the production of polyurethane-based high-strength elastomers, coatings, and rigid plastics. DMB has also been used in small quantities in chlorine test kits by water companies and swimming pool owners and in test tapes in clinical laboratories.

The major company producing DMB ceased production in 1978; its annual production average was approximately 200,000 lb. EPA reported five producers and importers during the 1975-1977 period (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). Imports appear to be the only source of DMB at present. The U.S. International Trade Commission (USITC) reported that approximately 3.5 million lb of DMB and 240,000 lb of its hydrochloride were imported during 1979. In 1980, more than 5000 lb of DMB hydrochloride were reported to the USITC (NCI).

MONS 025744

Workers potentially exposed to DMB include dye makers, repackagers of DMB end dyes, workers in toluene-diisocyanate production, and clinical and analytical chemistry laboratory personnel. Workers in a variety of occupations may be exposed to small quantities of DMB used for analytical purposes, among them water and sewage plant attendants, chemical test tape or kit makers, and swimming pool service representatives. NIOSH in 1978 estimated that fewer than 100 employees were exposed to large quantities of DMB in the United States, but as many as 200,000 may be exposed to small quantities. The National Occupational Hazard Survey in 1974 estimated that 420 workers were potentially exposed to DMB.

DMB-based dyes and pigments are metabolized to DMB in vivo. Residual levels of DMB may also be present in DMB-based dyes and pigments and in the final consumer products. Available data indicate that such contaminants occur in the parts-per-million range. The Consumer Product Safety Commission (CPSC) has instructed its staff to collect additional data to propose a ban on the use of DMB-based dyes in mass-merchandised consumer dye products. DMB is present in swimming pool water test kits. Each kit contains 0.5-1 percent DMB. Exposure is through dermal absorption or through ingestion if the test solutions are emptied back into the pool.

DMB used in swimming pool test kits is currently being evaluated by CPSC. Data are being collected on the dermal absorption of DMB and on DMB-based dyes. EPA regulates DMB under the Resource Conservation and Recovery Act.

3,3'-Dimethylbenzidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Use in swimming pool test kits is currently being evaluated. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and record/reporting requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. (EPA)	Regulation based on chronic toxicity of chemical. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)

MONS 025745

DIMETHYLCARBAMOYL CHLORIDE

There is sufficient evidence for the carcinogenicity of dimethylcarbamoyl chloride in experimental animals.[1] Dimethylcarbamoyl chloride is carcinogenic in mice, producing local carcinomas after application to the skin and local sarcomas after subcutaneous or intraperitoneal injection.[2]

A study of humans exposed to dimethylcarbamoyl chloride is considered inadequate.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 12. Lyon, France: IARC, 1976, pp. 77-84.

Dimethylcarbamoyl chloride (DMCC) is a colorless liquid that rapidly hydrolyzes in water.

DMCC is used as a chemical intermediate in the production of pharmaceuticals, pesticides, rocket fuel, and in dye synthesis. The pharmaceuticals (neostigmine bromide, neostigmine methylsulfate, and pyridostigmine bromide) are used in the treatment of myasthenia gravis. The three U.S. registered pesticides derived from DMCC are known by the trade names, Tandex^{R}, Dimetilan^{R}, and Pirimor^{R}.

Production data are limited; however, the Toxic Substances Control Act (TSCA), Chemical Substance Inventory (1979) reported that there were four producers in 1977 (no production data on public record) and approximately 400 lb imported annually.

Limited human exposure is restricted to chemical workers, pesticide formulators, dye makers, and pharmaceutical workers. OSHA estimated that 200 workers are exposed to DMCC, primarily through inhalation. DMCC has been found at levels up to 6 ppm during the production of phthaloyl chlorides. It is possible that levels of exposure might be higher in facilities in which the chemical is used for further synthesis. When DMCC is used as a dye intermediate, exposure can occur from residue in the product and the migration of the chemical from the product.

The Consumer Product Safety Commission staff stated that residual levels or trace impurities of DMCC might be present in the final consumer product. The presence of this potential carcinogen, even as a trace contaminant, is cause for concern. However, data describing the actual levels of impurities in the final product and the potential for consumer exposure and uptake are currently lacking. The EPA has regulated DMCC as a carcinogen under the Resource Conservation and Recovery Act and has proposed a reporting rule under the TSCA, 8(a).

MONS 025746

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates dimethylcarbamoyl chloride as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025747

DIMETHYL SULFATE

There is sufficient evidence for the carcinogenicity of dimethyl sulfate in experimental animals, but the evidence in humans is considered as inadequate.[1]

Dimethyl sulfate was carcinogenic in BD rats after inhalation or subcutaneous injection, producing mainly local tumors, and after prenatal exposure, producing tumors of the nervous system.[2]

Four cases of bronchial carcinomas have been reported in men occupationally exposed to dimethyl sulfate.[2] One case of pulmonary carcinoma in a man exposed to dimethyl sulfate and other chemicals, and one case of choroidal melanoma in a man exposed six years to dimethyl sulfate have also been reported.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 271-76.

Dimethyl sulfate is an industrial chemical that is soluble in water. It is used mainly as an alkylating agent for converting compounds such as phenols, amines, and thiols to the corresponding methyl derivatives. It is also used as a component of polyurethane base adhesives.

Dimethyl sulfate was first produced commercially in the United States in 1920. There are 12 producers and importers with a combined domestic production of approximately 48 million lb/yr. No data on imports or exports are available.

Human exposure occurs by inhalation of the vapors or by skin absorption of the liquid at the sites where the chemical is produced or where its derivatives are formulated. NIOSH has reported that 1250 workers are potentially exposed to dimethyl sulfate. OSHA estimated 3900 workers are potentially exposed.

Environmental sources of dimethyl sulfate are primarily from the production losses to air and water. The chemical has been found in the wastewater streams and air emissions from plants where it was made or used. The hydrolysis of dimethyl sulfate in water is rapid; its transfer from water to air is not likely to occur.

MONS 025748

The EPA's Carcinogen Assessment Group has included this chemical on its list of carcinogens. The EPA regulates dimethyl sulfate under the Resource Conservation and Recovery Act and proposes to require reporting under the Toxic Substances Control Act. The FDA regulates this substance under the Food, Drug, and Cosmetic Act as an optional component of polyurethane base adhesives. There is no expected migration of this chemical to food under conditions of use specified in the adhesive regulation. OSHA has adopted limits for the concentration of dimethyl sulfate in the workplace as 1 ppm (5 mg/m^3) in an 8-hour time-weighted average. This standard was adopted by OSHA for toxic effects other than cancer.

Dimethyl Sulfate

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Designates dimethyl sulfate as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 7/29/80.		45 FR 42, p. 13646 (EPA)
See the Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Regulatory Authority: FDCA; FR 11/16/77. (FDA)		21 CFR 175.105 (FDA)
PEL: 1 ppm (5 mg/m^3) 8-hour TWA. Potential for skin absorption noted. [Standard denote: for toxic effect: other than cancer.] (OSHA)	Regulatory History: 1954: Walsh-Healy; 1 ppm maximum allowable concentration. 6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025749

There is sufficient evidence for the carcinogenicity of 1,4-dioxane in experimental animals.[1] 1,4-Dioxane administered in drinking water is carcinogenic in rats and guinea pigs. It produced malignant tumors of the nasal cavity and liver in rats and tumors of the liver and gall bladder in guinea pigs. It was also active as a promoter in a two-stage skin carcinogenesis study in mice.[2]

[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC. 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. Lyon, France: IARC, 1976, pp. 247-56.

1,4-Dioxane is a highly volatile liquid that is flammable and moderately explosive.

1,4-Dioxane is used as a stabilizer for chlorinated degreasing solvents and as a solvent for lacquers, plastics, varnishes, paints, dyes, fats, greases, waxes, and resins. The chemical can occur as a contaminant in certain consumer products, and as a byproduct of reactions based on condensing ethylene oxide (EtO) or ethylene glycol.

The first commercial production of dioxane in the United States occurred in 1951. The EPA reported that 13 producers and importers account for 7.7 million lb of domestic production and approximately 800,000 lb of imports. No significant change in the estimated trends for U.S. production and sales of dioxane is forecast.

Exposure to dioxane is primarily through inhalation of the vapors, but the chemical is also readily absorbed through the skin. Exposure in industry occurs when dioxane vapors are released from degreasing operations and from spent solvents. Additional workers involved with shipping operations, primarily by rail and truck, may be exposed to dioxane through leakage from bulk loading lines.

According to the Consumer Product Safety Commission (CPSC), consumers may be exposed to residual levels of 1,4-dioxane formed during the manufacture of detergents, shampoos, surfactants, and certain pharmaceuticals. CPSC has stated that the presence of 1,4-dioxane even as a trace contaminant is cause for concern. However, no data are available on the actual levels of impurities in final products or on the potential for consumer exposure and uptake.

MONS 025750

The National Occupational Hazard Survey in 1974 estimated that 334,000 workers were potentially exposed to dioxane, 100,000 of whom were exposed as a result of dioxane contamination of 1,1,1-trichloroethane. Estimates from OSHA, however, indicated that 466,000 workers were potentially exposed.

Because dioxane is volatile and infinitely soluble in water, there is a large potential for its presence in the environment. Emissions to the atmosphere can occur where it is manufactured and used, and improperly disposed spent solvents can contaminate ground and surface waters.

The EPA regulates dioxane through the Resource Conservation and Recovery Act. The FDA has undertaken a survey of 1,4-dioxane contamination of raw materials and products. OSHA has adopted a permissible exposure limit of 100 ppm or 360 mg/m^3 as an 8-hour time-weighted average in the workplace for dioxane. This standard was adopted by OSHA for toxic effects other than cancer.

1,4-Dioxane

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 3000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, Sec. 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Foods, FD&CA: Proposed action pending; may propose to minimize its exposure.		21 CFR 175.105 (FDA)
Regulatory Authority: FD&CA 601(a). (FDA)	Survey of raw materials and product contamination under way. (FDA)	
PEL: 100 ppm (360 mg/m^3) 8-hr TWA. Potential for skin absorption noted. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1972: Walsh-Healy, 100 ppm maximum allowable concentration. 6/17/71: OSHA Takeover Standards--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025751

DIRECT BLACK 38

There is sufficient evidence that commercial Direct Black 38 is carcinogenic to experimental animals.[1] In a thirteen-week feeding study Direct Black 38 (technical grade) was carcinogenic in male and female Fischer 344 rats, inducing hepatocellular carcinomas and neoplastic nodules in the liver. The test dye was not carcinogenic to B6C3F1 mice under the same test conditions.[2]

In a recent occupational hazard review,[3] it was concluded that all benzidine-based dyes, including Direct Black 38, regardless of their physical state or proportion in the mixture, should be recognized as potential human carcinogens.

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]National Cancer Institute. Thirteen-Week Subchronic Toxicity Studies of Direct Blue 6, Direct Black 38, and Direct Brown 95 Dyes. Technical Report Series No. 108. DHEW Publication No. (NIH) 78-1358. Bethesda, Maryland, 1978.

[3]National Institute of Occupational Safety and Health. Special Occupational Hazard Review for Benzidine-Based Dyes. Washington, D.C.: U.S. Government Printing Office, 1980.

Direct Black 38 is a water-soluble azo dye derived from benzidine. It is usually sold as a dry powder.

Direct Black 38 is possibly being used to dye fabric, leather, cotton, cellulosic materials, and paper; these are then used in consumer products. The chemical may be used by artists (CPSC, EPA). The FDA has indicated that although Direct Black 38 is identified in the literature as a hair-dye component, it is currently not used by the cosmetic industry.

U.S. manufacturers of consumer dye products stated that they have discontinued the use of benzidine-based dyes. EPA reported six producers and importers of Direct Black 38 in one region, with domestic production of 4 million lb and imports of 370,000 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). U.S. production of Direct Black 38 was reported to the U.S. International Trade Commission for 1980 as greater than 5000 lb.

MONS 025752

In view of a health hazard alert issued in December 1980 by OSHA, which cautioned workers and employers of the carcinogenic effect of benzidine-derived Direct Black 38, new nonbenzidine Direct Black dyes have been developed and used successfully in commercial applications by the paper and leather industry during the past year. These nonbenzidine dyes were developed with the hope of replacing benzidine-based dyes throughout industry.

Human exposure to Direct Black 38 may occur through inhalation, skin absorption, and unintentional ingestion. Consumer exposure to Direct Black 38 depends upon the ability of the dye to migrate out of consumer products and either penetrate the skin or degrade prior to penetrating the skin. No additional data quantifying the rate of migration or degradation of this dye are currently available. In the general population, unspecified exposure levels to Direct Black 38 are thought to occur through the use of textile dyed products and retail packaged dyes for home dyeing and school use. The National Occupational Hazard Survey in 1974 estimated that approximately 16,000 workers were potentially exposed to Direct Black 38. The population exposed consisted of dyers of leather, plastics, cotton, wool, and silks, along with makers of aqueous inks, biological stains, typewriter ribbons, and wood stains.

In late 1980, CPSC directed its staff to collect additional scientific and economic data in order to propose a ban on the use of all benzidine congener dyes in consumer dye products. Currently CPSC is studying the skin penetration of benzidine congener dyes and the presence of these dyes in textile, leather, and paper consumer products. EPA is currently proposing regulation of Direct Black 38 under the TSCA, 8(a), reporting rule that would provide detailed production and marketing data. FDA does not regulate the cosmetic use of Direct Black 38, but was petitioned to approve Direct Black 38 for use as indirect food additives, i.e., as dyes for paper and paperboard products. In 1979, the petition was withdrawn. NIOSH reported that Direct Black 38 was the subject of a November 1979 Special Hazard Review and recommended stringent work practices, material replacement, and other measures applied to carcinogens. The Special Hazard Review was based on an April 1978 joint NCI/NIOSH recommendation.

MONS 025753

Direct Block 38

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CPSC is currently studying the skin penetration of benzidine congener dyes and the presence of these dyes in textile, leather, and paper consumer products. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
NIOSH recommended stringent work practices, material replacement, and use of other protective measures applicable to carcinogens. (NIOSH)		Special Hazard Review, 1979 (NIOSH)

MONS 025754

DIRECT BLUE 6

There is sufficient evidence for the carcinogenicity of Direct Blue 6 (technical grade) in experimental animals.[1] In a thirteen-week feeding study Direct Blue 6 dye (technical grade) was carcinogenic to male and female Fischer 344 rats, inducing hepatocellular carcinomas and neoplastic nodules in the liver. The test dye was not carcinogenic to B6C3F1 mice under the same test conditions.[2]

In a recent occupational hazard review,[3] it was concluded that all benzidine-based dyes, including Direct Blue 6, regardless of their physical state or proportion in the mixture should be recognized as potential human carcinogens.

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]National Cancer Institute. Thirteen-Week Suochronic Toxicity Studies of Direct Blue 6, Direct Black 38, and Direct Brown 95 Dyes. Technical Report Series No. 108. DHEW Publication No. (NIH) 78-1358. Bethesda, Maryland, 1979.

[3]National Institute of Occupational Safety and Health. Special Occupational Hazard Review for Benzidine-Based Dyes. Washington, D.C.: U.S. Government Printing Office, 1980.

Direct Blue 6 is a water-soluble azo dye derived from benzidine. It is sold as a dry powder for commercial use and as a component in retail packaged dyes.

Direct Blue 6 may still be used by artists. It is potentially used to dye fabric, leather, cotton, cellulosic materials, and paper; these are then used in consumer products (CPSC, EPA). The FDA has indicated that although Direct Blue 6 has been identified in the literature as a hair dye component, it is not presently used by the cosmetic industry.

In 1978, 61,000 lb of Direct Blue 6 were produced in the United States and 220 lb were imported.

All three manufacturers of consumer dye products stated that they have discontinued the use of benzidine-based dyes (CPSC). In their initial inventory of domestic producers and users of chemicals, EPA reported five producers and importers of Direct Blue 6 in one region, with a total domestic production of 75,000 lb and imports of 4000 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). Production of Direct Blue 6 was not reported to the U.S. International Trade Commission in 1980; however,

MONS 025755

production was reported in 1979 by one producer, which implied an annual production of more than 5000 lb. The producer currently produces direct dyes; but it is unknown whether the company actually ceased the production of this particular direct dye or simply did not produce it in 1990.

Human exposure to Direct Blue 6 may occur through inhalation, skin absorption, and to a lesser extent, unintentional ingestion, when the dye is in the press cake or dry powder form. The primary source for exposure to Direct Blue 6 is at the production site. The initial production step is in a closed system. However, other production operations, such as filter press, drying, and blending, may be performed in the open and, therefore may afford a greater potential for worker exposure. The general population may be exposed to Direct Blue 6 through the use of retail packaged dyes containing this benzidine-based dye.

Consumer exposure to Direct Blue 6 depends upon the ability of the dye to migrate out of the consumer product and either penetrate the skin or break down prior to penetrating the skin. No additional data are currently available. The National Occupational Hazard Survey in 1974 estimated that 1300 workers were potentially at risk of exposure to Direct Blue 6.

In the late 1980s, the CPSC directed the staff to collect additional scientific and economic data in order to propose a ban on the use of all benzidine congener dyes in consumer products. CPSC is now studying the skin penetration of benzidine congener dyes and the presence of these dyes in textile, leather, and paper consumer products. EPA is currently proposing a reporting rule for Direct Blue 6 under TSCA, 8(a). FDA, which does not regulate the cosmetic use of Direct Blue 6, was petitioned to approve this chemical, among others, for use as an indirect food additive, i.e., as a dye for paper and paperboard products. In 1979, the petition was withdrawn. NIOSH has reported that Direct Blue 6 was the subject of a November 1979 Special Hazard Review. NIOSH recommended stringent work practices, material replacement, and treatment of these substances as carcinogens. The Special Hazard Review was based on an April 1978 joint NCI/NIOSH recommendation.

Direct Blue 6

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CPSC is currently studying the skin penetration of benzidine congener dyes and the presence of these dyes in textile, leather, and paper consumer products. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/88. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	46 FR, p. 13646 (EPA)
NIOSH recommended stringent work practices, material replacement, and other protective measures applicable to carcinogens. (NIOSH)		Special Hazard Review, 1979 (NIOSH)

MONS 025756

ETHYLENE THIOUREA

There is sufficient evidence for the carcinogenicity of ethylene thiourea (ETU) in experimental animals.[1] ETU given in the diet to rats produced thyroid carcinomas.[2,3] Increased incidence of liver-cell tumors was reported in two strains of mice following oral administration of ETU (gavage initially, then diet).[4]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]Graham, S.L., W.H. Hansen, K.J. Davis, and C.H. Perry. Effects of One-Year Administration of Ethylene Thiourea Upon the Thyroid of the Rat. J. Agric. Food Chem. Vol. 21, 1973, pp. 324-29.

[3]Gak, J.C., C. Graillot, D. Fournier, R. Truhaut, and B. Radenen. Differences in Susceptibility of Hamsters and Rats to the Effects of Long-Term Administration of Ethylene Thiourea. Eur. J. Toxicol. Environ. Hyg. Vol. 9, 1976, pp. 303-12.

[4]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France: IARC, 1974, pp. 45-52.

Ethylene thiourea is a water soluble chemical, available in the United States as a solid powder and as an oil dispersion.

ETU has been widely used in the United States since 1948 as an accelerator in the vulcanization of various elastomers, including neoprene (polychloroprene) and polyacrylate rubber. Although the curing of these rubbers converts most of the ETU to other compounds, trace amounts are still present in the cured products. Neoprene is used almost exclusively in industrial applications such as automotive parts, wire and cable production, construction, and adhesives. Consumer products containing neoprene include shoes and closures for containers (e.g., aerosol dispensers). The EPA has reported additional uses of ETU as an intermediate in the manufacture of antioxidants, insecticides, fungicides, dyes, pharmaceuticals, and synthetic resins, and as a constituent of electroplating baths.

ETU is a manufacturing, processing, and metabolic product of the ethylenebisdithiocarbamate group of fungicides such as maneb, manco_eb, metiram, and zineb. ETU appears as a stable residue on fruit and vegetable crops that have been treated with ethylenebisdithiocarbamate fungicides. Studies have revealed that ETU is present in 28 different ethylenebisdithiocarbamate commercial products.

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Commercial production was first reported in the United States in 1951. Domestic production reported by EPA (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record) was 375,000 lb by seven producers in four regions. U.S. production greater than 1000 lb was reported to the U.S. International Trade Commission in 1980 (NCI). ETU is distributed and available from most major chemical companies in small as well as bulk quantities. No data are available on current levels of imports or exports.

The National Occupational Hazard Survey in 1974 estimated that 68,000 workers were potentially exposed to ETU. The major routes of exposure are skin contact and inhalation. NIOSH estimated that 3500 workers are exposed to ETU in the manufacture of fabricated rubber products.

In October 1978, ETU was the subject of a NIOSH Special Hazard Review. NIOSH considered carcinogenic and teratogenic effects in recommending that worker exposure be minimized by using an encapsulated form of the substance in the workplace.

EPA currently regulates ETU under the Resource Conservation and Recovery Act and is proposing regulation under the TSCA, 8(a), reporting rule. FDA has prohibited the use of ETU in food.

Ethylene thiourea

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Under evaluation. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
FDA has prohibited the use of ethylene thiourea in food. (FDA)		21 CFR 189 (FDA)
NIOSH considered carcinogenic and teratogenic effects in recommending that worker exposure be minimized by using an encapsulated form of the substance in the workplace. (NIOSH)		Special Hazard Review, 1978 (NIOSH)

MONS 025758

FORMALDEHYDE

There is sufficient evidence for the carcinogenicity of formaldehyde in experimental animals.[1]

Formaldehyde was tested for carcinogenicity by inhalation exposure in two strains of rats and one strain of mice. A significant incidence of squamous-cell carcinomas of the nasal cavity was induced in both strains of rats but not in mice. Another study in mice and one in hamsters by inhalation exposure, one in rats by subcutaneous administration, and one in rabbits by exposure of the oral mucosa were considered inadequate for evaluation. Levels of formaldehyde that caused nasal tumors also caused acute degeneration, necrosis, inflammation and increased cell replication in the nasal mucosa of rats and mice following inhalation exposure.[1,2]

The available epidemiological studies do not provide adequate evidence for assessing the carcinogenicity of formaldehyde in man.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: IARC, 1982, pp. 345-89.

Formaldehyde (HCHO) is a colorless, pungent irritant gas that is water soluble and most frequently marketed as 37-56 percent aqueous solutions, commonly known as formalin. The solutions are usually stabilized with 10-15 percent methanol to prevent polymerization.

HCHO is a high-volume chemical of which 65-70 percent is used for the production of phenolic, urea, melamine, and acetal resins with wide usage in the construction, automotive, and appliance industries. HCHO also has many uses in products such as textiles, embalming fluids, fungicides, bactericides, air fresheners, cosmetics, medicinals, and toothpastes.

Sixteen companies currently produce HCHO at 53 plants in the United States. Production levels for 1980 have been estimated as 6 billion lb, while 1979 estimates were 6.5 billion lb. Imports and exports in 1980 were reported as 10.2 million and 15.6 million lb, respectively. In 1978, market analysts forecasted an average growth rate of 0-3 percent through the early 1980s; however, some analysts predict production decreases of 5-30 percent.

MONS 025759

Human exposure to HCHO is principally through inhalation and skin absorption or less frequently by ingestion. Most of the HCHO production in the United States is from methanol in closed automated process systems. The exposure potential during transportation and storage is likely to be minimal. Estimated emission levels from production plants range from 0.0004 to 2500 ug/m^3, with a median exposure of 0.01 ug/m^3. EPA estimates that 27.7 million people living within 12.5 miles of point sources may be exposed to low levels. NIOSH estimates that 8000 workers are potentially exposed to HCHO during direct production. In addition, pathologists and histology technicians represent a high exposure group. In 1974, the National Occupational Hazard Survey estimated that 57,000 full-time and 1.7 million part-time employees may have been exposed to HCHO, and OSHA estimated the number of workers exposed as 2.6 million.

Most consumers are exposed to formaldehyde through its use in construction materials, wood products, textiles, home furnishings, paper, cosmetics, and pharmaceuticals. The ambient air levels in the United States, ranging from about 0.001 ppm to 0.030 ppm, expose the entire population of 230 million. Two subpopulations have been identified as having particularly high potential for HCHO exposure: 2.2 million residents of mobile homes containing particle board and plywood have an average exposure of 0.4 ppm HCHO, and 1.7 million persons living in conventional homes insulated with urea-formaldehyde foam have a potential average exposure of 0.12 ppm. Inadvertant production of formaldehyde from combustion sources also may contribute to these exposures. An estimated 159 million persons are potentially exposed to ambient air concentrations at maximum levels of 0.25 ug/m^3 of HCHO. Automobiles alone emit 610 million lb of HCHO each year. HCHO has a short half-life in air because it is degraded by photochemical processes. HCHO is also unstable in water, and no effluent data are available.

The Consumer Product Safety Commission (CPSC) requires labeling, to warn that formaldehyde is a strong sensitizer, on household products containing 1 percent or more of formaldehyde. Under the authority of Section 8 of the Consumer Product Safety Act, the CPSC banned the use of urea-formaldehyde foam insulation in residences and schools (16 CFR Part 1304, Vol. 47 #64, April 2, 1982, pp. 14366-421). The Commission is currently studying the off-gassing of formaldehyde from other products, the bioavailability and dermal penetration of formaldehyde from textiles, and the sensitizing capability of formaldehyde. EPA also regulates HCHO under the Clean Water Act, the Resource Conservation and Recovery Act (RCRA), and the Clean Air Act. The RCRA regulations are not based on carcinogenicity; however, they encourage greater care in handling and shipping of HCHO and should result in a reduction of accidental exposures. OSHA adopted permissible exposure levels of 3 ppm as an 8-hour time-weighted average, 5 ppm ceiling, and 10 ppm maximum peak concentration for 30 minutes in an 8-hour period. This standard was adopted by OSHA for toxic effects other than cancer.

Actions initiated by FDA and EPA are presently under assessment to determine what additional regulatory course, if any, should be taken.

MONS 025760

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Regulatory Authority: CPSA/FHSA		1600 CFR 1500.13(e)
FHSA: Any product containing 1 percent formaldehyde has to be labeled as a strong sensitizer.		
Final ban on the use of urea-formaldehyde foam insulation in schools and residences. (CPSC)	An increased risk of cancer of up to 1.8 additional cases from every 10,000 additional houses insulated with urea-formaldehyde will be eliminated. (CPSC)	16 CFR Part 1209, Vol. 47 #64, pp. 14366-14421, 4/2/82 (CPSC)
CWA 311: Hazardous spill regulation designating reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping of chemicals, and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.13
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CAA: Assessment of sources and exposures completed 9/80. Continuing assessment to determine regulatory course, if any.		OAQPS, personal communication, 9/80 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Regulatory Authority: FD&CA 601(a).	Coordinating effort through IRLG. (FDA)	21 CFR 175.105, 102.99, 173.340, 176.215, 176.3120, 175.210, 175.300, 175.320, 175.3e0, 176.170, 177.1210, 176.180, 177.2410, 177.2800, 573.460
In March 1982 the FDA announced the availability of safety and effectiveness data that could be used to support a new drug application in aquaculture. (FDA)		47 FR 15411, 4/9/82 (FDA)
PEL: 3 ppm 8-hr TWA, 5 ppm ceiling, 10 ppm maximum peak, 30 min in an 8-hr period. [Standard intended for toxic effects other than cancer. (OSHA)	Regulatory History: 1951: Walsh-Healy, 3 ppm maximum allowable concentration. 8/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025761

HEMATITE UNDERGROUND MINING

There is sufficient evidence for the carcinogenicity to humans of underground hematite mining (with exposure to radon).[1]

No carcinogenic effects were observed in mice, hamsters, or guinea-pigs given ferric oxide intratracheally.[2]

Underground hematite miners have a high incidence of lung cancer, whereas surface hematite miners do not. It is not known whether this excess risk may be due to hematite; to radon (a known lung carcinogen); to inhalation of ferric oxide or silica; or to a combination of these or other factors. Some studies of metal workers exposed to ferric oxide dusts have shown an increased incidence of lung cancer, while other studies have not.[1,2] The influence of factors in the workplace other than ferric oxide cannot be eliminated.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: IARC, 1972, pp. 29-39.

Human exposure to hematite from underground hematite mining is principally through inhalation and/or ingestion of dust. No estimates are available concerning the number of underground miners exposed.

The EPA views hematite mining as being primarily within the jurisdiction of the Mine Safety and Health Administration of the U.S. Department of Labor. Some EPA guidelines address the ferric ore mining, milling, and refining categories but do not specifically address underground hematite mining. It is unlikely that EPA will assume further jurisdiction.

Hematite Underground Mining

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Hematite mining is viewed by EPA as primarily within the jurisdiction of MSHA (extraction and milling) or OSHA (iron production). Some effluent guidelines address the ferric ore mining, milling, and refining but do not address hematite mining per se. In view of the indication that the primary cancer risk is to workers, it is unlikely that EPA will assume further jurisdiction. (EPA)		

MONS 025762

HEXACHLOROBENZENE

There is sufficient evidence for the carcinogenicity of hexachlorobenzene in experimental animals.[1] Hexachlorobenzene (HCB) was tested by dietary administration in mice, hamsters and rats (one experiment with each species). In Swiss mice, HCB produced liver-cell tumors in animals of both sexes. In Syrian golden hamsters, HCB produced hepatomas, liver hemangioendotheliomas and thyroid adenomas in both sexes.[2] Female Agus and MRC Wistar rats fed hexachlorobenzene in their diet developed liver-cell tumors.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 155-78.
[3]Smith, A.G., and J.R. Cabral. Liver-Cell Tumors in Rats Fed Hexachlorobenzene. Cancer Lett. Vol. 11, 1980, pp. 169-72.

Hexachlorobenzene (HCB) is an industrial chemical and a byproduct from many chemical and pesticide manufacturing processes. HCB technical-grade formulations include wettable powders, liquids, and dust.

HCB's principal use in the United States has been as a fungicide to control wheat bunt and smut fungi on other grains. HCB has also been used as a chemical intermediate in dye manufacture and synthesis of other organic chemicals and as a wood preservative.

HCB is formed as an impurity during the synthesis of several herbicides and pesticides, including the herbicide dimethyltetrachloroterephthalic acid (DCPA), which may contain 10-14 percent HCB, and the pesticide pentachloronitrobenzene (PCNB), which may contain 1-6 percent HCB. HCB is used as an intermediate in the production of pentachlorophenol (PCP), a widely used herbicide and fungicide. PCP may contain up to 13 percent impurities, part of which consist of residual HCB.

Commercial production of HCB in the United States was first reported in 1933. Production of HCB in the United States ended in 1976. In the period between 1975 and 1977, there were three producers and importers in three regions, with a domestic production of 3.7 million lb and imports of 3800 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). NCI reported that HCB is not now imported or produced commercially in the United States. Approximately 8.5 million lb of HCB wastes are produced annually by 14 industries surveyed as sources of HCB wastes.

MONS 025763

The production and use of HCB as a fungicide over the past several decades, and its occurrence as a byproduct in the manufacture of other chemicals, indicate that widespread human exposure occurs in both occupational and nonoccupational settings. Exposure to HCB may occur as a result of its presence in wastes from pesticide manufacture. Contamination of the ground and of grazing cattle around dumps and along roads where the waste is trucked has occurred. The National Occupational Hazard Survey in 1974 estimated that 4400 workers were potentially exposed to HCB. Occupations where the potential for human exposure exists include fungicide workers, organic chemical synthesizers, synthetic rubber producers, seed disinfecters, pesticide producers, and wood preservers. The EPA's monitoring of human adipose tissue collected across the United States has shown that approximately 95 percent of the population has trace residues of HCB.

HCB residues have been detected in soil, wildlife, fish, and food samples collected worldwide. In the Total Diet Program of the FDA, HCB was detected in food composites in 30 cities at levels of 0.006 to 0.040 mg/kg. The average daily intake of humans in 1973 and 1974 has been calculated to be 0.04 ug/day and 0.07 ug/day, respectively.

HCB was detected in most river water residues (2 ng/l to 90 ng/l) and soil residues ranging from traces to 1700 ng/kg near industrialized regions of the United States. HCB is a toxicological and environmental concern due to its bioaccumulation and persistence. HCB is insoluble in water and under most environmental conditions has a very low rate of degradation.

EPA has recommended an upper limit of 0.5 ppm HCB in fatty tissues of cattle, pigs, and sheep, but has not promulgated a tolerance. EPA regulates HCB under the Clean Water Act, 304 and 311, and the Resource Conservation and Recovery Act. In addition, a reporting regulation is proposed under TSCA, 8(a).

MONS 025764

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action; under evaluation. (CPSC)		
CWA, 304: Water quality criteria published in final form, 11/28/80.		45 FR, p. 79318
CWA, 311: Hazardous spill regulation establishes reportable quantity 1 lb, 3.454 (g) and imposes reporting requirement. Promulgated 6/29/79.	Regulation based on aquatic toxicity. Fosters greater care in handling and shipping of chemicals.	40 CFR 117.3, 117.13
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity of chemical. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 025765

HYDRAZINE AND HYDRAZINE SULFATE

There is sufficient evidence for the carcinogenicity of hydrazine in experimental animals.[1] Hydrazine administered by gavage, mainly as hydrazine sulfate, produced a high incidence of multiple pulmonary adenomas and adenocarcinomas, and hepatomas and hepatocarcinomas in mice of several strains. Low-level inhalation exposure to hydrazine produced lung tumors in mice, albeit in a small number of animals.[2] Intraperitoneal injection to several strains of mice of hydrazine in physiological saline produced sarcomas of the mediastinum, leukemias and lung tumors. Administration of hydrazine sulfate by gavage to Cb/Se rats caused lung adenomas and adenocarcinomas, liver adenocarcinomas and mammary fibroadenomas.[3]

Two reports on cancer mortality of workers exposed to hydrazine have been published some years ago but the evidence provided is considered as inadequate.[3]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] McEwen, J.D., E.E. McConnel, and K.C. Back. The Effect of a Six Month Chronic Level Inhalation Exposure to Hydrazine on Animals. L-Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio. AMRL-FR-74-125, Paper No. 16. Distributed by National Technical Information Service. U.S. Department of Commerce, Springfield, Virginia. /D-A-011865. 1974.

[3] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 127-36.

Hydrazine and hydrazine sulfate are both highly soluble in water.

Hydrazine is used primarily as a chemical intermediate and as a rocket fuel. The chemical has been used commercially as an oxygen scavenger in water boiler and heating systems. Hydrazine is used as an intermediate in the production of agricultural chemicals, spandex fibers, and antioxidants; as a polymerization catalyst; as a blowing agent; as a scavenger for gases; for plating metals on glass and plastics; and in fuel cells, solder fluxes, and photographic developers. Hydrazine sulfate is used in refining rare metals, as an antioxidant in soldering flux for light metals, in analytical tests for blood, as a biocide for fungi and molds, and in the preparation of hydrazine hydrate.

MONS 025766

Hydrazine is a suspect contaminant of liquid formulations of isoniazide, a drug used in treating tuberculosis. FDA is investigating the magnitude of the problem to ensure that the contamination of isoniazide is kept to the lowest detectable limit. Hydrazine sulfate has been investigated as an adjunct to antineoplastic drug treatment, although extensive use is not foreseeable. Its carcinogenic potential does not necessarily preclude use for this purpose; many antineoplastic agents are carcinogenic.

EPA has estimated 17 producers and importers of hydrazine in four regions, with domestic production of 7.4 million lb and imports of 444,000 lb. Ten producers and importers of hydrazine sulfate were listed in the Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record; domestic production was reported as 562,000 lb; imports were not reported. Production of hydrazine was not reported to the U.S. International Trade Commission in 1979-1980. The 1982 Directory of Chemical Producers, however, indicates that three U.S. companies now produce hydrazine in commercial quantities.

The National Occupational Hazard Survey in 1974 estimated that about 11,000 workers were potentially exposed to hydrazine.

The environmental fate of hydrazine and its derivatives is largely unknown. All the simple hydrazine derivatives are polar, nonvolatile, and soluble in water. The use of hydrazine in boiler water treatment might result in its occurrence in discharged waste, but it would rapidly react with oxygen.

There is no known presence of hydrazine in consumer products. The possible route of human exposure to hydrazine is ingestion of trace residues in processed foods. Steam in contact with food must contain no hydrazine (21 CFR 173.310 (d)). In 1979, FDA proposed to revoke the use of hydrazine as a boiler water additive for boilers in contact with food. Final action is pending. The EPA regulates hydrazine under the Resource Conservation and Recovery Act. Hydrazine was the subject of a June 1978 NIOSH Criteria Document that considered a variety of serious health effects and recommended a reduction of the OSHA permissible exposure limit from 1 ppm (1.3 mg/m^3) time-weighted average to 0.04 mg/m^3 ceiling.

MONS 025767

REGULATIONS

Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. (EPA)	Regulation based on chronic toxicity of chemical. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
Regulated as a secondary direct food additive for use in boiler water. Use is limited to zero content in steam in contact with food. (FDA)		21 CFR 173.310 21 CFR 173.310(d) (FDA)
PEL: 1 ppm (1.3 mg/m^3). Potential for skin absorption noted. [Standard accepted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1980: Walsh-Healy, 1 ppm (1.3 mg/m^3) TWA. (OSHA)	29 CFR 1910.1000 (OSHA)
NIOSH recommended a reduction of the OSHA PEL from 1.3 mg/m^3 TWA to 0.04 mg/m^3 ceiling. (NIOSH)		Criteria Document, 1978 (NIOSH)

MONS 025768

HYDRAZOBENZENE

The evidence for the carcinogenicity in experimental animals can be considered sufficient for hydrazobenzene.[1,2] When administered in the feed, hydrazobenzene was carcinogenic to Fischer 344 rats of both sexes, causing increased incidences of hepatocellular carcinoma and Zymbal's gland squamous-cell neoplasms in male rats; and neoplastic nodules of the liver, and mammary adenocarcinomas in female rats. Hydrazobenzene was also carcinogenic to female B6C3F1 mice, causing an increased incidence of hepatocellular carcinomas. The compound was not carcinogenic to male mice.[1]

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[1]National Cancer Institute. Bioassay of Hydrazobenzene for Possible Carcinogenicity. Technical Report Series No. 92. DHHS Publication No. (NIH) 78-1342. Bethesda, Maryland, 1978.

[2]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Hydrazobenzene is insoluble in water but soluble in ethanol and ethers. The chemical name for hydrazobenzene is 1,2-diphenylhydrazine.

Hydrazobenzene finds its major use in the dye manufacturing industry as the precursor of the important dye intermediate benzidine, a potent carcinogen. The chemical is also used as an intermediate in the production of phenylbutazone, which is used in the treatment of rheumatoid arthritis and related conditions.

There are seven producers and importers of this chemical, with an annual domestic production of 373,000 lb and an annual import of 135,000 lb. Additional unknown quantities are produced at dye manufacturing facilities by the reduction of nitrobenzene to hydrazobenzene, prior to its rearrangement to benzidine.

The potential for exposure to hydrazobenzene is greatest for workers in the dye industry, although workers in the pharmaceutical industry may also be exposed. The primary route of exposure is through ingestion or inhalation of the chemical. There are no data for the numbers of persons exposed or possible levels of exposure, because there are no reliable estimates for its occurrence as an intermediate in the production of benzidine. Because of the importance of benzidine, the potential for exposure to its precursor, hydrazobenzene, probably involves many workers.

MONS 025769

The EPA has published a water quality criteria document for the protection of human health and has proposed a rule under the Toxic Substances Control Act that would require the reporting of data concerning the processing and use of hydrazobenzene. Hydrazobenzene is regulated under the Resource Conservation and Recovery Act, based on chronic toxicity.

Hydrazobenzene

REGULATIONS

Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
No current action. (CPSC)		
CWA 311: Hazardous spill regulation designating reportable quantity as 100 lb (45.4 kg), proposed 7/8/80. (Lumer of diphenylhydrazine not specified.	Based on carcinogenicity.	45 FR 133, p. 46094
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1200 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80.	Based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 42, p. 13640 (EPA)

MONS 025770

INDENO(1,2,3-cd)PYRENE

There is sufficient evidence of the carcinogenicity of this compound in experimental animals. Indeno(1,2,3-cd)pyrene (IP) was shown to be a complete carcinogen and an initiator of skin carcinogenesis in the mouse (Swiss-albino HA/ICR/Mil). It produced local sarcomas in XVIInc/Z male mice after subcutaneous injection. It seems to be of lower potency as a skin carcinogen than benzo(a)pyrene.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 229-37.

IP is a polycyclic aromatic hydrocarbon (PAH). Although reported for the Toxic Substances Control Act Inventory, IP is not commercially manufactured, and no use data are available. This compound is widely found as a byproduct of poorly controlled combustion that occurs in refuse burning, coal furnaces, diesel-powered vehicles, forest fires, and coke ovens. IP has been measured in soot at 15 mg/kg, in coal tar pitch at 7300-8300 mg/kg, and in petroleum asphalt at 1 mg/kg. It has also been isolated in smoke from cigarettes at concentrations ranging from 0.4 ug to 2.0 ug/cigarette. Fresh sausages contained 0.3 ug/kg, and low levels (0.9-1.6 ug/kg) have been detected in edible oils.

The 1974 National Occupational Hazard Survey has estimated that about 210,000 workers were exposed to PAHs found in asphalt, coal-tar and pitch volatiles, and coke oven emissions, all of which contain IP. An unspecified number of workers may be exposed to IP in the byproducts of combustion from fuel oil, diesel fuel, kerosene, and wood.

The EPA has included IP on the Carcinogen Assessment Group list of carcinogens. EPA regulates IP under the Resource Conservation and Recovery Act. Under the Toxic Substances Control Act, 8(a), EPA is proposing the reporting of process and use data, and under the Clean Water Act the Agency published a water quality criteria for the protection of human health.

MONS 025771

Indeno-1,2,3-cdlpyrene

REGULATIONS		
Regulations and Other Actions	Effect of Regulation; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification watches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates this compound as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data published 2/29/80.	Would, if promulgated, permit a basis for estimating exposure.	45 FR 42, p. 13646
See Carcinogen Assessment Group statement under 2-acetylaminofluorene.		
CWA, 304(a): Water quality criteria published in final form, 11/28/80. (EPA)		45 FR 231, p. 79318 (EPA)

MONS 025772

IRON DEXTRAN COMPLEX

There is sufficient evidence for the carcinogenicity of iron dextran complex in experimental animals; the evidence of carcinogenicity in humans is inadequate.[1]

Iron dextran complex was carcinogenic to mice and rats after subcutaneous or intramuscular injection, producing local tumors.[2]

There have been case reports of sarcomas in human subjects associated with injections of iron dextran. The tumors appeared at the probable site of injections, and the similarity of the local effect in humans and animals was noted.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 2. Lyon, France: IARC, 1973, pp. 161-78.

Iron dextran is a complex of ferric hydroxide with dextran. Dextrans are polysaccharides produced by bacterial action on sucrose.

Iron dextran complex is used for parenteral treatment of iron-deficiency anemia in humans and baby pigs. The product for human use is a sterile, dark-brown colloidal solution in saline. The products designed for animal use are more concentrated.

The iron dextran complex was introduced in the United States in 1957. There is no record of current U.S. production, although it is known to be produced by two manufacturers. Iron dextran is available as two prescription items, Chromagen-D and Imferon. In 1980, 30,000 prescriptions were dispensed by pharmacies. The therapeutic dose for humans is 1-5 ml (50-250 mg iron) daily by deep intramuscular injection. Use is advised solely for those patients who have not responded to oral administration of iron. Clear warning of potential injection-site sarcoma is included with the physician's package insert.

The EPA has classified iron dextran as a hazardous waste constituent and regulates environmental release under the Resource Conservation and Recovery Act. The FDA approved iron dextran in 1974 and regulates this substance as a drug under the Federal Food, Drug, and Cosmetic Act.

MONS 025773

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
NO current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste. Wastes known to contain iron dextran are subject to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
Regulatory Authority: FD&CA. Bureau of Drugs and Bureau of Veterinary Medicine regulated as an approved prescription drug. (FDA)	Use limited to iron deficiency that does not respond to oral treatments. Clear warning of potential injection-site problems is included in physician package insert. (FDA)	40 FR, p. 13958 41 FR, p. 6868 42 FR, p. 53956 21 CFR 522.1192, 522.1193 (FDA)

MONS 025774

ISOPROPYL ALCOHOL MANUFACTURING (STRONG ACID PROCESS)

There is sufficient evidence that the manufacture of isopropyl alcohol (strong acid process) is carcinogenic in humans.[1] An increased incidence of cancer of the paranasal sinuses was observed in workers in factories manufacturing isopropyl alcohol by the strong-acid process. The risk of laryngeal cancer may also have been elevated. It is not clear which substances are responsible (diisopropyl sulfate, isopropyl oils, or other chemicals).[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 15. Lyon, France: IARC, 1977, pp. 223-43.

Commercial isopropyl alcohol, a water-soluble alcohol, has been produced in the United States since 1921.

There are several industrial processes for the manufacture of isopropyl alcohol. One process using strong sulfuric acid leaves a residue composed of a mixture of many organic chemicals including isopropyl oils. No figures are available on the quantities of isopropyl oils formed during the manufacture of isopropyl alcohol through the strong acid process; newer processes have been replacing the strong acid method. The EPA reports annual production of isopropyl alcohol to be approximately 750 million lb. The amount of isopropyl oils produced is unknown. Diethyl sulfate, as well as isopropyl oils, have been suggested as a potential causative agent for the increased incidence of cancer in workers manufacturing isopropyl alcohol by the strong acid process.

Approximately 50 percent of the isopropyl alcohol is used in acetone production. Additional commercial uses are as a solvent, as a chemical intermediate, and in pharmaceutical and cosmetic formulations.

Human exposure is primarily through inhalation during the manufacture of isopropyl alcohol. NIOSH estimates that about 141,000 employees may be exposed to isopropyl alcohol in the United States. The EPA has no data to indicate that isopropyl oils are present in effluents, emissions, or wastes from production facilities.

MONS 025775

Isopropyl Alcohol Manufacturing (Strong Acid Process)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
The particular hazard cited is associated with the workplace. It is indicated that the process in which isopropyl oils are produced as by-products is decreasing. In addition, there is no indication that isopropyl oils are found in the effluents, emissions, or wastes of isopropyl alcohol manufacturers. (EPA)		

MONS 025776

KEPONE® (CHLORDECONE)

There is sufficient evidence that chlordecone is carcinogenic in experimental animals.[1,2] After administration of chlordecone in the feed, a significant increase was found in the incidence of hepatocellular carcinomas in Osborne-Mendel rats and B6C3F1 mice. In addition, the time to detection of the first hepatocellular carcinoma observed at death was shorter for treated than control mice, and in both sexes and both species, it appeared inversely related to the dose.[2] In an earlier experiment in which rats, of unspecified strain, were exposed to chlordecone in the diet, hepatocellular carcinomas were seen in both sexes.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 67-81.
[3]National Cancer Institute. Bioassay of Chlordecone (Kepone) for Possible Carcinogenicity. DHHS Publication No. (NIH) 76-1278. Bethesda, Maryland, 1976.

Chlordecone is the common name for a synthetic chlorinated organic compound, which was commercially available under the trade name of Kepone®.

Kepone®, first introduced in 1958, has been used as an insecticide for leaf-eating insects, ants, and cockroaches, and as a larvicide for flies.

Kepone® is not manufactured or used in the United States. In July 1975, the Virginia State Health Department ordered termination of production by the sole manufacturer of Kepone® when a number of workers were found to have serious neurological disorders. Before the shutdown, the average annual production was estimated as 882,000 lb. More than 99 percent of the production was exported, and only 0.8 percent was available for domestic use, mainly as bait in ant traps.

Chlordecone is a degradation product of the insecticide mirex. This compound has been detected in soil at a level of 0.02 ug/g of soil 12 years after application of 1 ug/g mirex. In the United States, detectable levels of Kepone® have been found in 400 samples of air, drinking water, plant and aquatic life, and municipal waste where Kepone® was manufactured.

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Human exposure to chlordecone can occur by inhalation, ingestion, and skin absorption. There are many reports of its occurrence in human body fluids. In 1976, NIOSH had identified 50 establishments processing or formulating pesticides using Kepone[R] (chlordecone), and had estimated that about 600 workers were potentially exposed.

In 1977, formulators of Kepone[R] voluntarily canceled production. EPA canceled the registration of Kepone[R] under its Federal Insecticide, Fungicide, and Rodenticide mandate. All registered products containing Kepone[R] were effectively canceled by May 1, 1978. Distribution, sale, and use of Kepone[R] products formulated prior to May 1, 1978, were permitted until such stocks were exhausted. EPA has also regulated this compound under the Clean Water Act and the Resource Conservation and Recovery Act. On January 27, 1976, NIOSH recommended that the workplace level for Kepone[R] be limited to 1 $\mu g/m^3$ as a time-weighted average concentration for up to 10 hours/workday, 40 hours/workweek.

Kepone[R] (Chlordecone)

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, 0.454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity, although the quantity triggering reporting requirements is most stringent under this rule.	40 CFR 117.3, 117.13
FIFRA, 6: Voluntary cancellations of registrators (7/27/77) effectively removing product from market. Notice of intent to cancel published 4/11/77; not challenged as foregoing entry indicates.	Registrants were permitted to sell 500 lb of active ingredients after a determination that any additional risk of cancer would be very low. (EPA)	42 FR, p. 38,[illegible] 42 FR 69, p. 18[illegible]
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates Kepone[R] as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR [illegible] (EPA)
Recommended workplace standard for Kepone[R], 1 $\mu g/m^3$ TWA for 10 hr/day, 40 hr/workweek. (NIOSH)		

MONS 025778

LEAD ACETATE AND LEAD PHOSPHATE

There is sufficient evidence for the carcinogenicity of lead acetate and lead phosphate in experimental animals.[1] Lead acetate and lead phosphate are carcinogenic to rats, producing benign and malignant tumors of the kidney when administered in the diet or parenterally. Gliomas occurred in rats given lead acetate in the diet.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 23. Lyon, France: IARC, 1980, pp. 325-415.

Lead acetate is water soluble. Lead phosphate is a white powder insoluble in water. Lead acetate is usually available commercially as hydrate (lead acetate trihydrate).

Lead acetate is used as a mordant in cotton dyes; in lead coating of metals; as a drier in paints, varnishes, and pigment inks; and in medicinals such as astringents. Concentrations up to 0.6 percent (weight to volume) are limited for use as color additives in hair dyes. For 1978, sales of lead acetate hair dyes exceeded 1 million bottles. Lead phosphate is used as a stabilizer in styrene and casein plastics.

In 1980, seven producers in three EPA regions reported domestic production levels of lead acetate to be approximately 407,000 lb. U.S. imports of lead acetate in 1978 were estimated at 250 lb. Imports in 1975 were approximately 6000 lb. No production figures were reported for lead phosphate, but the Toxic Substances Control Act, Chemical Substance Inventory, 1979 (public record), lists two producers.

Human exposure to lead acetate and lead phosphate occurs through ingestion, inhalation, and skin absorption. Lead acetate is absorbed at about 1.5 times the rate of other lead compounds. The National Occupational Hazard Survey (NOHS) in 1974 has estimated that 132,000 and 18,000 workers may have been exposed to lead acetate and lead phosphate, respectively. OSHA has estimated that 223,000 workers may be exposed to lead acetate, with 28,000 and 27,000 workers exposed to lead phosphate dibasic and lead phosphate tribasic, respectively. NOHS and OSHA numbers vary due to the difference in methodology used for estimating exposure.

NOHS 025779

The Consumer Product Safety Commission (CPSC) has banned paint and similar surface-coating materials for use in consumer products that contain lead or lead compounds in which the lead content is in excess of 0.06 percent of the weight of the product. This ban excludes artists' paints and related materials. CPSC staff evaluated consumer exposure to lead inks in printed consumer products. No lead was found in printed matter intended for children. Although lead was found in some inks used in printed products, the levels in the final products did not warrant further action. The CPSC staff indicated that there was little lead found in other printed consumer products. FDA regulates the use of lead acetate in hair dyes under the Food, Drug, and Cosmetic Act.

EPA regulates lead and certain lead compounds under the Resource Conservation and Recovery Act (RCRA), the Clean Water Act (CWA), and the Safe Drinking Water Act (SDWA). The dissociated lead addressed in these regulations would provide a degree of control over many lead compounds, including lead acetate and lead phosphate. CWA has published a water quality criteria document for the protection of human health. Under RCRA, the EPA established a maximum concentration of 50 ug/l in wastes for the protection of health. Under SDWA, a primary drinking water standard of 0.05 mg/l was published December 24, 1975. This standard was not based on carcinogenicity. OSHA has established permissible exposure levels of 50 $\mu g/m^3$ as an 8-hour time-weighted average and 60 ug/100 g as the maximum permissible blood lead level. In addition, the standard requires personal protective equipment, engineering and work practice controls, and medical surveillance with provisions for medical removal. OSHA regulates lead on the basis of acute and chronic toxicity for several organ systems, but not on the basis of carcinogenicity.

MONS 025780

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
In 1972 the Lead Based Poison Prevention Act set a 0.5 percent limit for lead in paints. In 1976, the Act was amended to set the standard at 0.06 percent; this limit became effective in February 1978. 1982: No current action. (CPSC)	Exposure has been reduced, based on the lower limits allowed in paints. The use of lead acetate in inks is scheduled for screening. (CPSC)	16 CFR 1303 (CPSC)
SDWA: Dissociated Lead: Primary standard of 0.05 mg/l, promulgated 12/24/75.	Not based on carcinogenicity. Major sources of lead in drinking water appears to be pipes, solder, and fixtures in the distribution system.	40 CFR 141.11
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1kg to handling and report/record-keeping requirements. Also designates both as hazardous constituents of wastes. Promulgated 5/19/80.		40 CFR 261.11, 261.33
Designated as a toxic waste. Requires testing to determine if total lead exceeds that concentration. Promulgated 5/19/80.	Establishes a maximum concentration of 50 mg/l in wastes as criterion for health (based on general toxicity).	40 CFR 261.24
CWA, 304(a): Water quality criteria published in final form, 11/28/80.	Because lead dissociates in water, any any standard would afford some control over the named chemical.	45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity for lead acetate (5000 lb) and imposing reporting requirements. Promulgated 8/29/79.	Fosters greater care in handling and shipping of chemicals. Based on aquatic toxicity. (EPA)	40 CFR 117.3, 117.13
FIFRA, 6: Lead acetate was reviewed for possible regulation under FIFRA. In April 1978, jurisdiction was passed to FDA under an agreement that the questioned use was as a veterinary drug. (EPA)		OPP, Status Reports (EPA)
FDA Bureau of Drugs, FD&CA: Limits lead acetate in hair dyes to 0.6 percent (weight to volume), 10/31.80. FDA listed lead acetate permanently for use in hair dyes, 3.8/81. (FDA)		45 FR, p. 72112 21 CFR 731.2396 (FDA)
PEL: 50 $\mu g/m^3$ 8-hr TWA, 60 $\mu g/100$ g maximum blood lead level. Protective clothing, hygiene, training, and medical surveillance requirements for workers; respirator requirements where engineering and work practice controls not sufficient or feasible; sign requirements for regulated areas; medical removal; income protection (for lead). (OSHA)	Regulatory History: 8/27/71: OSHA Takeover Standard--200 $\mu g/m^3$ 8-hr TWA. 2/1/79: Final Standard--current regulations effective (for lead). (OSHA)	29 CFR 1910 1025 (OSHA)

MONS 025781

LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS

The evidence for the carcinogenicity of lindane and other hexachlorocyclohexane isomers in experimental animals was judged as limited by a recent IARC working group.[1] Another working group considered that there was sufficient evidence that α-HCH, lindane, and technical HCH are carcinogenic in mice, but the evidence for the carcinogenicity of β-HCH was evaluated as limited.[2] Technical α- and β-hexachlorocyclohexane and lindane, the γ-isomer, were carcinogenic in mice when administered in the diet, producing liver tumors. The technical-grade hexachlorocyclohexane also produced neoplasms. Studies in rats and dogs were considered to be inadequate, and so were tests by skin application of technical hexachlorocyclohexane and lindane. Hexachlorocyclohexane increased the incidence of liver neoplasms in rats previously treated with N-nitrosodiethylamine.[1,2]

The evidence for the carcinogenicity of lindane and other hexachlorocyclohexane isomers in humans was judged as inadequate.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 195-239.

Lindane is the common name for the gamma isomer of hexachlorocyclohexane (HCH). Technical-grade HCH is a mixture of different isomers. Lindane is a colorless crystalline solid with a solubility of 10 mg/l in water.

Approximately 95 percent of the lindane and its isomers used in 1974 was in agriculture with the remainder used by industry. The major uses of lindane are for insecticidal treatment of hardwood logs and lumber, seed grains, and livestock; the minor uses are as an insecticide on several dozen fruit and vegetable crops and for personal hygiene (as a scabicide and pediculocide) in the form of lotion, cream, or shampoo.

Commercial production of lindane began in the United States in 1945 and ceased in 1976. Since 1976 lindane has been imported in an undisclosed amount. Production of lindane peaked in the 1950s when 15 million lb were manufactured. The chemical is not reported to the Toxic Substances Control Act, Chemical Substance Inventory, 1979 (public record); however, EPA in 1980 estimated that 1 million lb of lindane were used annually.

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Approximately 480,000 workers were occupationally exposed to these substances prior to Agency regulations (1977), which imposed limitations on uses. Workplace and residence use sites were primarily of concern as sources of exposure. Pesticide applicators were at highest risk of exposure to lindane.

The general population is at risk of exposure through the consumption of contaminated foodstuff. Major dietary sources include milk, eggs, dairy products, and, to a lesser extent, seafood. The dietary intake of lindane and its isomers by the U.S. population has been estimated to be in trace quantities with a significant, steady decline.

EPA has regulatory authority over the use of lindane and its isomers. EPA has proposed to limit exposure to lindane by canceling registration for all uses except on ornamentals, pineapples, livestock, and logs. The proposed action is scheduled to result in approximately an 80 percent reduction of the total estimated annual usage of 1 million lb. Continued use for the few permissible registrations would be restricted to certified personnel wearing appropriate protective clothing. EPA designated hexachlorocyclohexane as a toxic waste constituent. The Agency established a maximum concentration of 0.4 mg/l in wastes. During 1975, EPA promulgated drinking water standards limiting maximum contaminant levels to 0.004 mg/l. OSHA adopted a permissible exposure limit for lindane of 0.5 mg/m^3 as an 8-hour time-weighted average. This standard was adopted by OSHA for toxic effects other than cancer and noted lindane's potential for skin absorption.

MONS 025783

Lindane and Other Hexachlorocyclohexane Isomers

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
FIFRA, 6: NPAR issued 2/18/77.	Agreement by producers to discontinue use of nonganma isomers (mostly α and β). Based in part on recognition of inefficacy of nonganma isomers.	42 FR, p. 9816
Proposed determination published 7/3/80.	Proposed immediate cancellation of registrations for most uses. Proposed 2-year phase-out of use on logs and hardwood.	45 FR 130, p. 45362
RCRA, 3001-3004: Requires testing to determine if lindane exceeds stated concentration. Promulgated 5/19/80.	Designates lindane as a toxic waste. Established a maximum concentration of 0.4 mg/l of lindane in wastes as a criterion for toxicity.	40 CFR 261.24
Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg of hexachlorocyclohexane (unspecified isomers) to handling and report/recordkeeping requirements. Also designates hexachlorocyclohexane as a hazardous constituent of wastes. Promulgated 5/19/80.		40 CFR 261.11, 261.33
FIFRA, 6: Voluntary cancellation of registrations for all products using nonlindane isomers of HCH, 7/21/78. 319-84-6 α - HCH 319-85-7 β - HCH (Action applies to both).	Unreasonable risk and general ineffectiveness of ingredients.	42 FR, p. 31432
CWA, 304(a): Water quality criteria published in final, 11/28/80. Addresses α, β, and γ isomers, and technical grade products.		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishes reportable quantity (1 lb, 0.454 kg) and increases reporting requirement, 3/29/79.	Aquatic toxicity. Most stringent level, however. Fosters greater care in handling and shipping of chemicals.	40 CFR 117.3, 117.13
CWA, 311: Hazardous spill regulation designating reportable quantity, proposed, 7/9/80 (hexachlorocyclohexane other than lindane).	Based on carcinogenicity.	45 FR 133, p. 46094
SDWA, 1412: Primary drinking water standard. Promulgated 12/24/75.	Maximum contaminant level of 0.002 mg/l established.	40 CFR 141.12
SDWA, 1412: Revision of drinking water standard in development. (EPA)	Chronic toxicity is being considered. Target for proposal, 6/83. (EPA)	SDW, memorandum, 9/81 (EPA)
PEL: 0.5 mg/m³ 4-hr TWA; potential for skin absorption noted (lindane). [Standard adopted for toxic effects other than cancer.] (OSHA)	8/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025784

MELPHALAN

There is sufficient evidence for the carcinogenicity of melphalan in humans and in experimental animals.[1] Melphalan is carcinogenic in mice and rats following intraperitoneal injection, producing lymphosarcomas, a dose-related increase in lung tumors in mice, and peritoneal sarcomas in rats.[2]

Case reports of second primary malignancies (mainly acute leukemia) in patients treated with melphalan have been published. Epidemiological studies showed substantially increased rates of leukemia in patients treated with melphalan for multiple myeloma and ovarian cancer. Some of these patients were also treated with other alkylating agents and ionizing radiation; however, sufficient numbers of patients were treated with melphalan alone to implicate it as the causal factor. Additionally, the incidence of acute leukemia in patients with multiple myeloma has increased since the introduction of melphalan therapy.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 9. Lyon, France: IARC, 1975, pp. 167-80.

Melphalan is a nitrogen mustard that is practically insoluble in water.

This drug is used in the treatment of multiple myeloma and cancer of the ovary. It is also used in investigation on other types of cancer and as an antineoplastic in animals.

Melphalan is not produced in the United States, although one marketer in the United States has been reported. In 1979, 3000 lb were imported.

Human exposure to melphalan occurs principally during its use in cancer treatment. FDA estimates that 30,000 to 50,000 patients may be treated each year. Melphalan is administered orally or intravenously. Adult dose rate is 6 mg per day, 5 days per month.

Melphalan has been approved by the FDA for treatment of myeloma and epithelial ovarian cancer. For certain other cancers, it has been approved for investigational use only. As with other potent antineoplastic agents, the likelihood of these drugs being carcinogenic is not surprising, and its clinical use recognizes that risk by its restrictive approved clinical indications. EPA regulates melphalan under the Resource Conservation and Recovery Act.

MONS 025785

Melphalan

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/r..ordkeeping requirements. Also designates melphalan as a hazardous constituent of waste, and subjects wastes found to contain it to the same requirements. Promulgated 8/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Drugs, FDACA: Approved drug for treatment of myeloma and epithelial ovarian cancer. Investigational use only for certain other cancers. (FDA)	Use restricted to Bureau of Drugs-approved treatments. As with other potent antineoplastic agents, the restricted use limits potential risk to the patient. (FDA)	CFR 2*, Subchapter D (FDA)

MONS 025786

4,4'-METHYLENEBIS(2-CHLOROANILINE) (MOCA)

There is sufficient evidence for the carcinogenicity of 4,4'-methylenebis(2-chloroaniline) in experimental animals.[1] 4,4'-Methylenebis(2-chloroaniline) was carcinogenic in mice and rats (several strains) after dietary administration, producing vascular, liver and lung tumors. It also produced distant tumors (liver cell carcinomas and primary lung carcinomas) in Wistar rats after subcutaneous injection.[2]

There are no conclusive epidemiological studies on which the evaluation of human carcinogenic risk could be based. In a study of 31 men, whose exposure to MOCA ranged from 6 months to 16 years, no cytological evidence was found of bladder cancer. In addition, 178 other MOCA workers with unstated duration of exposure were also examined cytologically more than 10 years after exposure had ceased, and no cases of bladder cancer were found.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 65-71.

4,4'-Methylenebis(2-chloroaniline), an aromatic amine, is commonly referred to as MOCA. It is only slightly soluble in water, but soluble in most organic solvents and lipids. MOCA is commercially available in pellet, liquid, and granular form, and as a premixed compound with polyhydric alcohols.

MOCA has been used as a curing agent in urethane and epoxy resin systems containing isocyanates, which are utilized in the manufacture of certain products, particularly integral-skin polyurethane semirigid foam for crash padding, and solid urethane rubber moldings, such as gear blanks and industrial tires. It is also consumed in the manufacture of gun mounts, jet engine turbine blades, radar systems, and home appliances. In the laboratory, MOCA has been regarded as a model compound in the study of carcinogens.

Production of MOCA was first reported to the U.S. Tariff Commission in 1950. EPA estimated five producers and importers of MOCA in two regions, with a domestic production of 369,000 lb; no imports were reported (Toxic Substances Control Act (TSCA) Inventory, 1977, public record). MOCA was not reported to the U.S. International Trade Commission in 1980; however,

MONS 025787

production of MOCA was indicated in 1979 by two producers, which implied an annual production of more than 10,000 lb. The 1982 Directory of Chemical Producers indicates that one U.S. company now produces MOCA. CPSC indicated only one U.S. manufacturer of MOCA as of 1981.

The CPSC staff stated that residual levels of MOCA may be present in the final product. However, data describing the actual levels of impurities and the potential for consumer exposure are currently lacking. The National Occupational Hazard Survey in 1974 estimated that 33,000 workers were potentially exposed to MOCA.

When used as a curing agent, MOCA is melted before mixing into elastomer formulations and could possibly be volatilized and emitted into waste gases and wastewater from plants where it is being used. In 1971, MOCA was detected in all samples of soil that were obtained within a three-quarters mile radius of a chemical plant in Adrian, Michigan. Some samples taken from soil on public roads in the area contained more than 500 ppm MOCA. Sludge from the Adrian wastewater treatment plant contained as much as 86 ppm MOCA, whereas samples of sludge obtained from the industrial lagoon contained 2000 ppm. Urine from workers at the plant contained levels as high as 49 ppm of MOCA per liter of urine.

Currently MOCA is regulated by EPA under the Resource Conservation and Recovery Act, and regulation is proposed under TSCA, 8(a), that would provide detailed production and marketing data. NIOSH issued a Special Hazard Review on MOCA in 1978, recommending a standard of 3 ug/m^3 time-weighted average. The OSHA standard for MOCA was suspended by court action in 1974.

MONS 025788

4,4'-Methylenebis(2-chloroaniline) (MOCA)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3001-3004: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and reports/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity of chemical. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13645 (EPA)
Substance prohibited from use in human food. (FDA)		21 CFR 189 (FDA)
	Regulatory History: 5/3/73: Emergency Temporary Standard--protective clothing and hygiene requirements for workers, restrictions on open-vessel operations, engineering requirements. 1/29/74: Revised standard promulgated. 12/7/74: U.S. Court of Appeals remanded standard. (OSHA)	
NIOSH recommended a standard of 3 ug/m³ TWA. (NIOSH)		Special Hazard Review, 1978 (NIOSH)

MONS 025789

4,4'-METHYLENEBIS(N,N-DIMETHYL)BENZENAMINE

4,4'-Methylenebis(N,N-dimethyl)benzenamine, administered in the feed, was carcinogenic in male and female Fischer 344 rats, inducing thyroid follicular-cell carcinomas, and in female B6C3F1 mice, causing a combination of hepatocellular carcinomas and hepatocellular adenomas. There was no conclusive evidence that 4,4'-methylenebis(N,N-dimethyl)benzenamine was carcinogenic in male B6C3F1 mice.[1] An IARC working group considered that there was limited evidence for the carcinogenicity of this substance in experimental animals.[2] In view of another evaluation the evidence can be regarded as sufficient.[3]

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[1]National Cancer Institute. Bioassay of 4,4'-Methylenebis(N,N-dimethyl)benzenamine for Possible Carcinogenicity. Technical Report Series No. 186. DHEW Publication No. (NIH) 78-1742. Bethesda, Maryland, 1979.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 119-24.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

4,4'-Methylenebis(N,N-dimethyl)benzenamine, commonly referred to as Michler's base, is an aromatic amine. It is insoluble in water and soluble in benzene, acids, diethyl ether, and carbon disulfide.

Michler's base is used as an intermediate in dye manufacture and as an analytical reagent in the determination of lead.

The Society of Dyers and Colourists reported that six dyes and one pigment can be prepared from the chemical. In 1979, only one of the dyes, Basic Yellow 2, was being produced commercially by two companies.

Michler's base has been commercially produced in the United States since at least 1921. EPA estimated five producers and importers in two regions, with domestic production reported as 370,000 lb, and no imports (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). U.S. production of Michler's base was reported to the U.S. International Trade Commission as greater than 10,000 lb in 1980.

MONS 025790

According to the CPSC staff, it is possible that residual levels of Michler's base may be present in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on experience with other dyes derived from aromatic amines. However, data describing the actual levels of impurities in the final product are currently not available. The potential for exposure is greatest among workers in the dye and chemical manufacturing industries. In 1974, the National Occupational Hazard Survey estimated that 1600 workers were potentially exposed to Michler's base.

EPA is proposing a reporting rule for Michler's base under TSCA, 8(a).

4,4'-Methylenebis(N,N-dimethylbenzenamine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 1/31/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 025791

MICHLER'S KETONE

Michler's Ketone, administered in the feed, was carcinogenic in male and female Fischer 344 rats and female B6C3F1 mice, causing hepatocellular carcinomas; in male B6C3F1 mice it produced hemangiosarcomas.[1] These results can be considered as providing sufficient evidence for the carcinogenicity of Michler's Ketone in experimental animals.[2]

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[1]National Cancer Institute. Bioassay of Michler's Ketone for Possible Carcinogenicity. Technical Report Series No. 181. DHEW Publication No. (NIH) 78-1737. Bethesda, Maryland, 1979.

[2]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: U. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Michler's ketone, a derivative of dimethylaniline, is an aromatic amine, which is practically insoluble in water.

Michler's ketone is used as a chemical intermediate in the synthesis of at least 13 dyes and pigments, especially auramine derivatives.

EPA reported 10 producers and importers in three regions, with a domestic production of 37,000 lb and imports of 37,000 lb (Toxic Substances Control Act (TSCA), Chemical Substances Inventory, 1979, public record). One domestic producer manufactured a quantity insufficient for reporting to the U.S. International Trade Commission in 1979-1980, but imports of Michler's ketone amounted to 40,000 lb in 1980.

Human exposure to Michler's ketone may occur through inhalation and skin absorption. Occupational exposure is greatest for workers in facilities that manufacture the compound, or any of the dyestuffs for which Michler's ketone is an intermediate. In 1974, the National Occupational Hazard Survey made no estimate on potential worker exposure to Michler's ketone (NIOSH). Residual levels or trace impurities of Michler's ketone may possibly be present in some dyes based on this chemical and in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on the experience with other dyes derived from aromatic amines. Data are inadequate to describe the actual levels of impurities in the final product, the potential for consumer exposure, and the uptake.

EPA now regulates Michler's ketone under the Resource Conservation and Recovery Act and has proposed regulation under the Toxic Substances Control Act, 8(a).

MONS 025792

Michler's Ketone

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/ recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13606 (EPA)

MONS 025793

MIREX

There is sufficient evidence that mirex is carcinogenic in experimental animals.[1] Mirex has been tested in two strains of mice by gavage and by administration in the diet and in rats by administration in the diet. It has also been tested in two strains of mice by subcutaneous injection of single doses. In the studies using oral administration, it produced benign and malignant liver tumors in mice and rats of both sexes. An excess of liver tumors was also found in males of one of the two strains of mice following a single subcutaneous injection; this experiment also suggested that it produced reticulum-cell sarcomas in males of both strains.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 283-301.

Mirex, a chlorinated cyclic hydrocarbon, is practically insoluble in water. Mirex was used extensively in the southeastern United States for control of the fire ant. From 1962 to 1978, about 132 million acres in 10 states were treated with mirex bait (consisting of 497,000 lb of mirex). The bait was aerially applied in most cases. Mirex was also used to treat other species of ants and yellow jackets, but it was most effective as a species-specific pesticide. One company has marketed mirex as a fire-retardant additive.

Mirex first became commercially available in the United States in 1958. There is no current production of mirex because its registrations for technical products were canceled as of December 1977. Prior to this action, it was manufactured by two U.S. producers in significant amounts and some quantities were imported; no specific data were available.

According to the 1974 National Occupational Hazard Survey, an estimated 1000 workers were potentially exposed to mirex. Because insecticidal use of mirex has been discontinued, direct human exposure is small. However, residues have been detected in water, soil, food and beverages, and human tissues for as long as 12 years after exposure. These residues may result in general population exposure. Mirex is known to degrade in soil to yield Kepone®.

In December 1976, EPA, under the Federal Insecticide, Fungicide, and Rodenticide Act, canceled the registrations of pesticides containing mirex, effective December 1, 1977, with specified termination of uses of existing stock. The State of Mississippi received an emergency exemption from EPA for specific uses effective through June 1979.

MONS 025794

Mirex

REGULATIONS		
Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
FIFRA, 6: Registrations for technical products canceled, 12/76; effective 12/77. All products and uses were included. (EPA)	Remaining stocks could be used before 12/31/77. Emergency use permits were granted in 1977-78, but have been denied since that time. (EPA)	41 FR, p. 16703 (EPA)

MONS 025795

MUSTARD GAS

The evidence of carcinogenicity of mustard gas in humans is sufficient; the evidence in experimental animals is limited.[1] Mustard gas is carcinogenic in mice, the only species tested, after inhalation or intravenous injection producing lung tumors, and after subcutaneous injection producing local sarcomas.[2]

Several studies have shown an increased mortality from respiratory tract cancer among individuals exposed to mustard gas. This mortality was greater in those with chronic occupational exposure than in those with sporadic exposure.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 9. Lyon, France: IARC, 1975, pp. 181-92.

Mustard gas is a colorless, oily liquid that is sparingly soluble in water.

Mustard gas was used in chemical warfare primarily during World War I. Mustard gas has been tested as an antineoplastic agent, but its clinical use as a tumor inhibitor has been minimal. It is used as a model compound in biological studies of alkylating agents.

Mustard gas is not in the Toxic Substances Control Act, Chemical Substance Inventory (1979) of commercial chemicals nor is there any indication that there is any manufacture or use in the United States at the present time. Production and stockpiling of this chemical took place during World War II, and stocks may have existed in the United States as recently as 1974.

If production of mustard gas as a chemical warfare agent were to be resumed, it would probably be excluded from regulation under the National Security Clause. However, the Resource Conservation and Recovery Act designates mustard gas as a hazardous constituent of waste, should it be produced again.

MONS 025796

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Designates mustard gas as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. If production of mustard gas as a chemical warfare agent were to be resumed, it would probably be excluded from regulation under the National Security Clause contained in each authority. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)

MONS 025797

2-NAPHTHYLAMINE

There is sufficient evidence for the carcinogenicity of 2-naphthylamine both in humans and in experimental animals.[1] 2-Naphthylamine was carcinogenic, producing urinary bladder carcinomas in hamsters, dogs, and non-human primates, and hepatomas in mice, after oral administration (by stomach tube or in the diet).[1,2]

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or when present as an impurity in other compounds, is causally associated with bladder cancer.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1979, p. 38.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 97-111.

2-Naphthylamine, an industrial chemical, is soluble in hot water, alcohol, and many organic solvents.

2-Naphthylamine has been used principally as an intermediate in the manufacture of dyes and as an antioxidant in the rubber industry. In recent years, other chemicals have been substituted for 2-naphthylamine, and it is now used for research purposes only.

2-Naphthylamine has not been produced or imported in the United States since January 1, 1975. However, it had been produced commercially in substantial amounts for nearly 50 years. United States imports amounted to 38,000 lb in 1967. The company that had reported 2-naphthylamine for the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, withdrew their report in 1980 (CPSC). The Federal Register notice of this amendment was published in 1981 (CPSC, EPA).

Human exposure to 2-naphthylamine is primarily through inhalation. Prior to the discontinuation of domestic production and use in the dye and rubber industries, an estimated 1000 workers were potentially exposed. 2-Naphthylamine has been reported in coal tar, cigarette smoke (0.02 ug/cigarette), and as an impurity in commercial 1-naphthylamine (0.5 percent or less).

The EPA regulates 2-naphthylamine under the Resource Conservation and Recovery Act and under the TSCA. The OSHA standard for 2-naphthylamine, promulgated in 1974, includes protective clothing, engineering controls, and medical surveillance requirements.

MONS 025798

2-Naphthylamine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designated 2-naphthylamine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
EPA has removed 2-naphthylamine from the TSCA inventory and reported in June 1981, that there was no current manufacture, importation, or processing of 2-naphthylamine. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		46 FR 30663 (EPA)
Protective clothing, respiratory, hygiene training, and medical surveillance requirements for workers; exposure limit requirements; work-vessel operations prohibited; contamination control requirements; signs requirements for area; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standard--protective clothing and hygiene requirements for workers, work-vessel operations restricted, engineering requirements. 2/11/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1009 (OSHA)

MONS 025799

NICKEL REFINING, NICKEL, AND CERTAIN NICKEL COMPOUNDS

There is sufficient evidence that nickel refining is carcinogenic to humans.[1] Epidemiological studies have demonstrated increased incidences of cancer of the nasal cavity, lung, and possibly larynx in workers in nickel refineries. It is not possible, however, to specify which specific nickel compounds are carcinogenic for humans.[2]

The evidence of carcinogenicity of nickel and certain nickel compounds in experimental animals is sufficient.[1] Nickel subsulfide is carcinogenic in rats by inhalation, producing lung cancer. Nickel compounds (nickel powder, subsulfide, oxide, carbonate, and nickelocene) produced local sarcomas in mice, rats and hamsters when given intramuscularly. Inhalation of nickel carbonyl produced a low incidence of lung tumors in rats.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. Lyon, France: IARC, 1976, pp. 75-112.

Nickel is a metallic element used in steel and other alloy manufacturing and in electroplating. Nickel is also used to make coins, as a chemical catalyst, in ceramics, in storage batteries, electric circuits, coloring glass, petroleum refining, and in the hardening of edible oils.

The combined annual domestic production of nickel and 14 nickel compounds is 121 million lb, and imports total approximately 330 million lb.

Human exposure to nickel and nickel compounds is through ingestion, inhalation, and skin absorption. These exposures can occur from the presence of nickel in air, water, soil, food, and consumer products. OSHA estimates that 709,000 workers are potentially exposed to nickel and its compounds. EPA estimates that nearly 720,000 people living within 12.5 miles (20 km) of primary sources may be exposed to nickel at concentrations up to 15.8 ug/m^3 (median, 0.2 ug/m^3). As many as 160 million people live within 12.5 miles of all sources of nickel and nickel compounds, and they may be exposed to median concentrations of 0.05 ug/m^3. The entire population may be exposed to low levels of nickel (300-600 ug/day) in food and water. Nickel levels in U.S. drinking water are estimated as less than 10 ug/l. Food processing methods can increase dietary nickel levels by means of leaching from nickel-containing alloys.

MONS 025800

Environmental sources of nickel include emissions from coal- and oil-fired boilers, coke ovens, diesel-fuel burning, and gray iron foundries. Total annual emissions from these types of sources were estimated at 22.4 million lb. Soils normally contain nickel in the range of 5-500 ppm, and soils from serpentine rock may contain as much as 5000 ppm.

The EPA regulates nickel and nickel compounds under the Clean Water Act and the Resource Conservation and Recovery Act. Certain nickel compounds have been proposed for regulation under the Toxic Substances Control Act. FDA does not regulate nickel as a food additive. OSHA has adopted permissible exposure levels of 0.007 mg/m^3 as an 8-hour time-weighted average for nickel carbonyl and 1 mg/m^3 as an 8-hour time-weighted average for metal and soluble compounds. This standard was adopted by OSHA for toxic effects other than cancer.

The Consumer Product Safety Commission (CPSC) staff preliminarily determined in 1980 that nickel carbonyl was not present in consumer products under CPSC jurisdiction. The Commission subsequently requested (45 FR 16344) public comment to verify the accuracy of its information. No comments were received on this chemical. Pending the receipt of new information, the Commission plans no action on nickel carbonyl.

MONS 025801

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nickel: No current action. No known presence in consumer products. (CPSC)		45 FR, p. 16344 (CPSC)
CWA, 301: Effluent guidelines for certain industrial categories address nickel. Promulgated 3/12/74, 6/24/75 with subsequent revisions.	Control established through NPDES permits. Carcinogenicity was not considered in developing these guidelines. Repromulgation for some will occur in mid-1981.	40 CFR 413, 415 (portions)
CWA, 304(a): Water quality criteria published in final form, 11/28/80.	Protection of human health (general toxicity) 13.4 ug/l.	45 FR 231, p. 79318
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are listed as hazardous constituents of waste. Wastes known to contain nickel are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11
RCRA, 4004: Land application of sludges containing nickel under assessment, pending formulation of an EPA policy on sludge.		OSW, personal communication, 4/82
CWA, 405: Limitation on concentration of nickel and other toxics in sludge; intended for use as soil conditioners under study.	Development or hold pending formulation of an EPA policy on sludge. (EPA)	OSW, personal communication, 4/82
CAA: Assessment of sources and exposures completed 6/80. Under continuing assessment to determine if risks warrant regulation. Determination anticipated late 1981 or early 1982. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		OAQPS, personal communication, 10/80 (EPA)
FDA Bureau of Foods; Bureau of Medical Devices; FD&CA. Not regulated as a food additive. No regulations on nickel present in implants. No action has been taken on nickel as a carcinogen because the data available are not adequate to assess its carcinogenicity through dietary exposure. (FDA)		
PEL: 15 mg/m³ 10-hr TWA. Recommended standard for inorganic nickel (1977) containing recommendations for medical surveillance, labeling and posting, personal protective clothing and equipment, work practices, monitoring of workplace air, employee education. (NIOSH)		
PEL: 0.001 ppm (0.007 mg/m³) 8-hr TWA (except carbonyl), 1 mg/m³ 8-hr TWA (as Ni metal) and soluble Ni compounds). [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1952: Walsh-Healy, 1 ppm (nickel carbonyl) maximum allowable concentration. 6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

(Continued)

MONS 025802

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nickel Acetate: (Basic Nickel Acetate)		
TSCA, Sec): Reporting rule requiring process and use data proposed, 2/29/80.		45 FR 42, p. 13648
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of waste, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Nickel Ammonium Sulfate:		
CWA, 311: Hazardous spill regulation establishing reportable quantity (5000 lb, 2270 kg) and targeting reporting requirements. Promulgated 5/30/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.13
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of waste, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11
TSCA, Sec): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 42, p. 13648 (EPA)
See nickel. (NIOSH)		
See regulation for nickel. (OSHA)		29 CFR 1910.1000 (OSHA)
Nickel Carbonate:		
TSCA, Sec): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13648
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of waste, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA,
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 025803

Nickel Refining, Nickel, and Certain Nickel Compounds (Continued)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nickel Carbonyl:		
No current action. No known presence in consumer products. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1 kg to handling and report/recordkeeping requirements. Also designates nickel carbonyl as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 7/29/80. (EPA)		45 FR 42, p. 13646 (EPA)
PEL: 7 $\mu g/m^3$ (1 ppb) 8-hr TWA. Special Hazard Review containing recommendations for medical surveillance, ventilation engineering, signs for regulated areas, personal protective clothing and equipment, recordkeeping requirements. (NIOSH)		
PEL: 7 $\mu g/m^3$ (1 ppb) 8-hr TWA. (OSHA		29 CFR 1910.1000 (OSHA)
Nickel Chloride:		
CWA, 311: Hazardous spill regulation, establishing reportable quantity (RQ) 10000 lb, 2270 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.13
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of waste, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11
TSCA, 8(a): Reporting rule requiring process and use data, proposed 7/29/80. (EPA)		45 FR 42, p. 13646 (EPA)
See nickel. (NIOSH)		
See nickel regulation. (OSHA)		29 CFR 1910.1000 (OSHA)
Nickel Hydroxide:		
CWA, 311: Hazardous spill regulation establishing reportable quantity (10000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.13
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of wastes. Wastes known to contain any of them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. (EPA)		40 CFR 261.11 (EPA)

(Continued)

MONS 025804

Nickel Refining, Nickel, and Certain Nickel Compounds (Concluded)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nickel Oxide:		
RCRA, 3001-3004: Designates nickel compounds not otherwise specified as hazardous constituents of waste, and subjects wastes known to contain them to handling and report/recordkeeping requirements. Promulgated 5/19/81.		40 CFR 261.17
TSCA, 8(a): Reporting rule requiring process and use data, proposed 1/29/80. (EPA)		45 FR 41, p. 13646 (EPA)
Nickel Subsulfide:		
RCRA, 3001-3004: Designates nickel compounds not otherwise specified as hazardous constituents of waste, and subjects wastes known to contain them to handling and report/recordkeeping requirements. Promulgated 5/19/81.		40 CFR 261.17
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 41, p. 13646 (EPA)
Nickel Sulfate:		
CWA, 311: Hazardous spill regulation, establishing reportable quantity (5000 lb, 2270 kg) and imposing reporting requirements. Promulgated 6.29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of occupational exposures. (EPA)	40 CFR 117.3, 117.13
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of wastes, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. (EPA)		40 CFR 261.11 (EPA)
See nickel. (NIOSH)		
See regulation for nickel. (OSHA)		29 CFR 1910.1000 (OSHA)
Nickelocene		
RCRA, 3001-3004. Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of wastes, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. (EPA)		40 CFR 261.11 (EPA)

MONS 025805

NITRILOTRIACETIC ACID

Long-term feeding studies to test the monohydrate of the trisodium salt of nitrilotriacetic acid ($Na_3NTA \cdot H_2O$) for carcinogenicity were conducted using Fischer 344 rats; and both Fischer 344 rats and B6C3F1 mice. Similar bioassays, using rats and mice, were conducted with the free nitrilotriacetic acid (NTA). NTA and $Na_3NTA \cdot H_2O$ were shown to be carcinogenic to the urinary tract and kidneys of both rats and mice.[1] Trisodium nitrilotriacetic acid was found to be carcinogenic in the kidney when administered in drinking water to male albino rats (Crl/COBS CD (SD) BR).[2]

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[1]National Cancer Institute. Bioassay of Nitrilotriacetic Acid (NTA) and Nitrilotriacetic Acid, Trisodium Salt, Monohydrate ($Na_3NTA \cdot H_2O$) for Possible Carcinogenicity. Technical Report Series No. 6. DHEW Publication No. (NIH) 77-806. Bethesda, Maryland, 1977.

[2]Goyer, R.A., H.L. Falk, M. Hogan, D.D. Feldman, and W. Richter. Renal Tumors in Rats Given Trisodium Nitrilotriacetic Acid in Drinking Water for Two Years. J. Nat. Cancer Inst. Vol. 66, 1981, pp. 869-80.

Nitrilotriacetic acid (NTA) is a chelating agent that is insoluble in water and most organic solvents; however, it can form mono-, di-, and tri-basic salts that are soluble in water.

EPA reported that NTA replaced phosphates as a detergent builder in the late 1960s. In 1971, the use of NTA was discontinued. The possibility of resumed use arose in 1980. The Consumer Product Safety Commission (CPSC) stated that NTA is now used in laundry detergents in two states where phosphates are banned. FDA reported that NTA is also used as a boiler feedwater additive at a maximum use level of 5 ppm of trisodium salt. Currently, the remaining nondetergent uses of NTA are for water treatment, textile treatment, metal plating and cleaning, and pulp and paper processing.

EPA reported that the domestic production for 1979 was 70-75 million lb, with 50-65 million lb exported. Estimates indicate that reintroduction would increase production to 250 million lb immediately and to 1 billion lb in the near future, with most of this amount used domestically. The EPA (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record) estimated three producers and importers in three regions. Domestic production data were not available, but imports were 37,500 lb. Production reported to the U.S. International Trade Commission for 1980 was more than 5000 lb of NTA and more than 15,000 lb of its trisodium salt.

MONS 025806

The route of human exposure is ingestion of trace residues that possibly remain in processed foods. In 1974, the National Occupational Hazard Survey estimated that 14,600 workers were potentially exposed to NTA, and 46,000 workers were exposed to NTA trisodium salt. NTA levels in the U.S. drinking water prior to NTA's discontinued use in detergents was estimated by EPA to have ranged from 0.2D-24.5 ug/l. NTA is rapidly degraded under aerobic conditions at temperatures above 5° C, and biodegradation does not lead to the formation of persistent intermediates.

Until the spring of 1980, industry voluntarily abstained from using NTA in detergents in the United States. At that time, EPA released a risk assessment on the use of NTA in laundry detergents. In response to a request by one manufacturer to resume use of NTA, it was stated that "...projected levels of exposure from the use of this substance in laundry detergents are generally low, and therefore the associated risks would also be low." EPA decided not to take regulatory action against the use of this substance for laundry detergent, but cautioned against its use in shampoos, foods, hand dishwashing detergents, and other products designed to give direct oral or dermal exposure.

EPA has determined that the exposure to NTA is low (1 ug/kg/day/adult), but has included some caveats as recommendations to manufacturers and processors (March 1980). The recommendations were given under TSCA. FDA regulates NTA as a secondary direct food additive, i.e., as a substance added to food during preparation or handling, and subsequently removed before the food is ready for consumption. FDA limits the nitrilotriacetate added to boiler feedwater to 5 ppm. FDA is currently reviewing the carcinogenicity data on NTA for possible future regulatory actions.

MONS 025807

REGULATIONS

Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, 8, 6--Recommendations: • Manufacturers and processors should employ strict controls to limit occupational exposure. • Should not be used in consumer products designed to have direct oral or dermal exposures. • Manufacturers should conduct monitoring and environmental studies to confirm projections of low environmental levels; EPA to participate in design. • Manufacturers and processors should maintain record of reports of ingestion of NTA-containing detergents. (EPA)	Animal carcinogenicity is established, but the compound does not appear to be a mutagen or teratogen. Exposure projected to be low (1 ug/kg/day/adult). (EPA)	Letter from S.D. Jellinek, to Procter & Gamble and Monsanto, 5/27/80. Testimony to Investigations and Oversight Subcommittee, Interstate and Foreign Commerce Committee, House of Representatives, 6/2/80. Five other companies notified prior to 7/20/80. (EPA)
Nitrilotriacetate added to boiler feedwater is limited to 5 ppm. (FDA)		21 CFR 173.310(d) (FDA)

MONS 025808

5-NITRO-o-ANISIDINE

5-Nitro-o-anisidine, administered in the feed, was carcinogenic in Fischer 344 rats, causing tumors of the integumentary system in males and females, and tumors of the clitoral gland in females. The compound was also carcinogenic in female B6C3F1 mice, causing hepatocellular carcinomas.[1] This evidence of carcinogenicity in experimental animals was considered as limited by an IARC working group.[2] In view of another evaluation it can be regarded as sufficient.[3]

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[1]National Cancer Institute. Bioassay of 5-Nitro-o-anisidine for Possible Carcinogenicity. Technical Report Series No. 127. DHEW Publication No. (NIH) 78-1382. Bethesda, Maryland, 1978.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 133-39.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

5-Nitro-o-anisidine is a trisubstituted benzene derivative used primarily as an intermediate in the synthesis of dyes. 5-Nitro-o-anisidine is an orange-reddish crystalline solid, highly soluble in alcohol, acetone, acetic acid, and benzene, but only slightly soluble in water.

5-Nitro-o-anisidine is used in the production of C.I. Pigment Red 23; this pigment is used in printing inks, interior latex paints, lacquers, rubber, plastics, floor coverings, paper coatings, and textiles. 5-Nitro-o-anisidine can also be used with various coupling components to produce certain red, brown, yellow, and violet dyes for cotton, silk, acetate, and nylon. The chemical has been used in a formulation tested for pesticidal properties and in a formulation used to color keratin fibers, especially human hair.

5-Nitro-o-anisidine has been produced in this country since 1937. Two companies--both listed in Synthetic Organic Chemicals, U.S. Production and Sales, 1980--reported production or sales of this compound's stabilized diazonium salt, Azoic Diazo Component 13. According to Imports of Benzenoid Chemicals and Products, 63,720 lb of Azoic Diazo Component 13 base were imported into the United States in 1980. In addition, 23,000 lb of 5-nitro-o-anisidine were imported into the United States in 1980. According to the

MONS 025809

Consumer Product Safety Commission (CPSC) imports have significantly and steadily decreased since 1974. EPA estimated six producers and importers in four regions. Domestic production was reported as 37,000 lb, and no import data were available (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). In 1979, 332,000 lb of Pigment Red, produced from the diazonium salt of 5-nitro-o-anisidine, were produced by 11 companies in the United States. U.S. production of 5-nitro-o-anisidine was reported to the U.S. International Trade Commission for 1980 as greater than 15,000 lb.

Human exposure to 5-nitro-o-anisidine is principally through inhalation and skin absorption. The potential for exposure to this compound is greatest for workers who manufacture, handle, or use the dyes and pigments derived from 5-nitro-o-anisidine. The CPSC staff indicated that residual levels or trace impurities of 5-nitro-o-anisidine may possibly be present in some dyes based on this chemical and in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on the experience with other dyes derived from aromatic amines. However, data describing the actual levels of impurities in the final product, the potential for consumer exposure, and the uptake are currently lacking. The 1974 National Occupational Hazard Survey made no estimate of the number of workers potentially at risk of exposure to the chemical.

5-Nitro-o-anisidine is currently proposed for regulation by EPA under the TSCA, 8(a), reporting rule.

5-Nitro-o-Anisidine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 025810

NITROFEN

Nitrofen (technical grade)--a substituted diphenyl ether--administered in the feed, was carcinogenic to B6C3F1 mice, causing hepatocellular carcinomas in both sexes. There was no evidence of carcinogenicity in Fischer 344 rats.[1] In another bioassay, nitrofen (technical grade) administered in the feed was found to induce hepatocellular carcinomas in B6C3F1 mice of both sexes, and hemangiosarcomas of the liver in male B6C3F1 mice. In addition, adenocarcinomas of the pancreas were induced in female Osborne-Mendel rats.[2] These results can be considered as providing sufficient evidence for the carcinogenicity of nitrofen in experimental animals.[3]

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[1]National Cancer Institute. Bioassay of Nitrofen for Possible Carcinogenicity. Technical Report Series No. 184. DHEW Publication No. (NIH) 79-1740. Bethesda, Maryland, 1979.

[2]National Cancer Institute. Bioassay of Nitrofen for Possible Carcinogenicity. Technical Report Series No. 26. DHEW Publication No. (NIH) 78-826. Bethesda, Maryland, 1978.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Nitrofen, the trade name for 2,4-dichlorophenyl-p-nitrophenyl ether, is commonly referred to as TOK. Nitrofen is practically insoluble in acetone, methanol, and xylene.

Nitrofen is a contact herbicide used for pre- and postemergence control of annual grasses and broadleaf weeds on a variety of food and ornamental crops. Nitrofen has been applied in approximately 25 states by growers of rice, broccoli, cauliflower, cabbage, brussel sprouts, onions, garlic, and celery. Nitrofen has also been used in nurseries growing roses and chrysanthemums and on rights-of-way. The direct crop use of nitrofen for 1980 was estimated as 682,000 pounds. Nitrofen has not been used around homes and gardens.

According to EPA, nitrofen is produced by one company in one region (Toxic Substances Control Act (TSCA), Chemical Substances Inventory, 1979, public record). More than 5,000 lb were produced in 1980, according to NCI.

MONS 025811

In August 1980, the sole manufacturer of nitrofen (TOK-E-25 and TOK-WP-50) began recalling all existing stocks of the herbicide from dealers, distributors, and users.

Human exposure to nitrofen occurs through inhalation, skin absorption, and ingestion. Occupational exposure to nitrofen, primarily through inhalation and dermal contact, may occur among workers at production facilities. Field handlers of the herbicide are subject to inhalation exposure during application procedures. The 1974 National Occupational Hazard Survey made no estimate of the number of workers potentially exposed to nitrofen.

EPA has established tolerances for nitrofen residues on a variety of raw agricultural commodities, dairy products, and meat products.

Nitrofen

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Tolerances have been established for nitrofen residues on a variety of raw agricultural commodities and on a variety of dairy and meat products (11/25/71; 2/19/74; 8/6/74). (EPA)	Based on adverse effects of the chemical use patterns and detection limits. Enforcement vested in FDA and USDA. (EPA)	40 CFR 180.223 (EPA)

MONS 025812

N-NITROSODI-n-BUTYLAMINE

There is sufficient evidence that N-nitrosodi-n-butylamine (DBN) is carcinogenic in experimental animals.[1] DBN was carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, rabbits and guinea pigs, after oral (diet, drinking water and/or gastric intubation), subcutaneous, intraperitoneal or intravenous administration. It produces benign and malignant tumors in the urinary bladder, esophagus, liver, respiratory tract, stomach and intestine, and also leukemia; it is particularly effective as a bladder carcinogen. It was carcinogenic if administered prenatally (subcutaneous injection to mothers) and in single doses.[2]

The two metabolites, N-nitroso-n-butyl-N-(4-hydroxybutyl)amine and N-nitroso-n-butyl-N-(3-carboxypropyl)amine, were also carcinogenic, the first in mice, rats, hamsters and dogs and the second in rats. When given in drinking water to mice, N-nitroso-n-butyl-N-(4-hydroxybutyl)amine produced carcinomas of the urinary bladder; when given in drinking water or intravesicularly to rats, it produced papillomas and carcinomas of the urinary bladder; when given subcutaneously to hamsters, it produced tumors of the urinary bladder and respiratory tract and cholangiocellular tumors; and when given subcutaneously to dogs, it produced urinary bladder tumors. N-Nitroso-n-butyl-N-(3-carboxypropyl)amine produced tumors of the urinary bladder in rats after administration in drinking water or intravesicular instillation.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 51-75.

DBN, a yellow oil that is soluble in water, is used primarily as a research chemical and may have limited use as an intermediate in the organic synthesis of di-n-butylhydrazine. DBN has also been tested for fungistatic activity.

Annual production of DBN is approximately 725 lb; no imports or exports have been reported. DBN is prepared in a closed, pressurized process system.

MONS 025813

The extent of human exposure to DBN during commercial production and use is unknown. Persons at risk are researchers engaged in the study of DBN's biological effects and workers exposed to DBN as a contaminant. DBN may be formed from ingested secondary or tertiary n-butyl amines and quarternary ammonium salts by reaction with nitrites. The degree of this exposure in the general population is not known, but it is assumed to be sporadic and at low levels.

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

The most probable source of environmental nitrosamines is nitrosation of amines, which are ubiquitous in the environment. It has been estimated that air, diet, and smoking contribute to human exposure at levels of a few micrograms per day. Microgram quantities of DBN have been detected in tobacco smoke, the effluents from a coke plant, a variety of cooked meat products, animal feeds, and soybean oil.

EPA regulates DBN under the Resource Conservation and Recovery Act as a constituent of hazardous waste. The water quality criteria document for nitrosamines (Clean Water Act) published November 28, 1980, also includes this compound. DBN is regulated under the Clean Water Act hazardous spill regulation, and is proposed for regulation under the Toxic Substances Control Act reporting rule.

MONS 025814

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are assessing the amounts of nitrosamine released from pacifiers. (CPSC)		
CWA, 304(a): Water quality criteria for nitrosamines published in Final Rule, 1/28/80 (addresses N-nitrosodi-n-butylamine).		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to hazardous waste report/recordkeeping requirements. Also designates N-nitrosodi-n-butylamine as a hazardous constituent of waste, and subjects wastes known to contain it to the land requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring use data, published 2/29/80.		45 FR 42, p. 13646
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, 0.454 kg), proposed 7/30/80.	Based on carcinogenicity. (EPA)	45 FR 133, p. 48094 (EPA)
Ad Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025815

N-NITROSODIETHANOLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosodiethanolamine (NDELA) in experimental animals.[1] NDELA was carcinogenic in rats after administration in drinking water and in hamsters after subcutaneous injection. It produced hepatocellular carcinomas and renal adenomas in rats, and adenocarcinomas of the nasal cavity, papillary tumors of the trachea, hepatocellular adenomas and local fibrosarcomas in hamsters.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 77-82.

NDELA is a yellow, viscous liquid miscible with water in all proportions. NDELA belongs to the group of N-nitroso compounds, which are widely distributed in the environment.

No evidence of commercial production or use has been found; however, the EPA has reported production of 350 lb annually by one producer.

Human exposure to NDELA is possible by ingestion, skin absorption, and to a lesser extent by inhalation. It is a known contaminant of various cosmetics, cutting fluids, certain pesticides, and tobacco. The concentrations of NDELA range from 1 ppb to 49,000 ppb. As of June 1980, FDA has analyzed 335 cosmetic products for NDELA, and 42 percent were found to be contaminated with this compound. Cutting fluids have been reported to contain up to 3 percent NDELA. Atrazine, a pesticide, contained 0.5 mg/kg of NDELA. Maleic hydrazide, a pesticide commonly applied to tobacco, has been reported to contribute to the formation of NDELA in tobacco at concentrations up to 173 ug/kg. The number of persons exposed to NDELA is not known.

The Consumer Product Safety Commission (CPSC) staff preliminarily determined in 1980 that NDELA was not present in consumer products under CPSC jurisdiction. The Commission subsequently requested (45 FR 61344) public comment to verify the accuracy of this information. No comments were received. Pending the receipt of new information, the Commission plans no action on NDELA. Currently, this compound is regulated by EPA under the Resource Conservation and Recovery Act as a constituent of hazardous waste. FDA has alerted the cosmetic industry to the presence of this compound in a number of products; FDA is also conducting a survey for product contamination.

MONS 025816

N-Nitrosodiphenylamine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1300 kg to handling and report/recordkeeping requirements. Also designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FD&CA, 601(a). (FDA)	Survey for product contaminants and contract research under way. Industry alerted to problem by 44 FR 21388 notice. (FDA)	

MONS 025817

N-NITROSODIETHYLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosodiethylamine (NDEA) in experimental animals.[1] NDEA was carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, guinea pigs, rabbits, dogs, gerbils, pigs, monkeys, hedgehogs, various fish, frogs and birds. It induced benign and malignant tumors after administration by various routes, including ingestion, parenteral injection, inhalation and rectal instillation. The major target organs were the liver, respiratory and upper digestive tracts and the kidney. It was carcinogenic when administered prenatally (subcutaneous injection to mothers) and in single doses. In several studies, dose-response relationships were established.[2]

N-Nitroso-N-ethyl-N-(2-hydroxyethyl)amine, a metabolite of N-nitroso-diethylamine, produced mainly liver tumors when given orally to BD rats.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 77-82.

NDEA is a yellow, volatile liquid that decomposes in the presence of sunlight and is soluble in water and organic solvents.

NDEA is predominantly used as a research chemical; minor applications include the use in plastics, as a lubricant additive, and as an antioxidant.

Two producers are listed in the EPA public records, which show a domestic production of 725 lb annually. Human exposure is possible in laboratory, copolymer, lubricant, and pesticide workers. There is no estimate of the number of people exposed.

The general public may be potentially exposed to unknown quantities of NDEA because it occurs in the environment and is present in food and beverages. The concentration of NDEA in the air of a major U.S. city was estimated as 200 $\mu g/m^3$. Wastewater from chemical plants contained up to 0.24 $\mu g/l$, and high nitrate well water used for drinking contained 0.01 $\mu g/l$; however, it does not persist in environments exposed to sunlight. Various kinds of fish, treated or untreated meats, cheeses, and vegetable products such as soybean oil contain NDEA in the microgram per kilogram range. Similar concentrations have been found in alcoholic beverages and in tobacco smoke condensates. For example, up to 0.008 μg/cigarette was found in mainstream smoke and about 10 times more in sidestream smoke.

MONS 025818

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

EPA issued a notice in September 1977 requiring all registrants of pesticides potentially contaminated with nitroso compounds to analyze and document the levels by specified analytical procedures. The compound is regulated under the Clean Water Act and the Resource Conservation and Recovery Act as a hazardous waste constituent. A water quality criteria document for the protection of human health has been issued.

N-Nitrosodiethylamine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine released from pacifiers. (CPSC)		
CWA, 304(a): Water quality criteria for nitrosamines published in final form, 11/28/80. Addresses N-nitrosodiethylamine.		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, 0.454 kg), proposed 7/9/80.		45 FR 133, p. 46094
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates N-nitrosodiethylamine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring use data, published 2/19/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025819

N-NITROSODIMETHYLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosodimethylamine (DMNA) in experimental animals.[1] DMNA was carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, guinea-pigs, rabbits, ducks, mastomys, various fish, newts and frogs. It induced benign and malignant tumors when administered by various routes, including ingestion and inhalation, in various organs and in various species. It produced tumors, mainly of the liver, kidney and respiratory tract. It was carcinogenic when administered prenatally (injection to mothers) and in single doses. In several studies dose-response relationships were established.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 125-75.

DMNA is a yellowish oily liquid that is very soluble in water.

Prior to April 1, 1976, DMNA was used in the United States as an intermediate in the production of 1,1-dimethylhydrazine, a storable liquid rocket fuel that contained approximately 0.1 percent DMNA as an impurity. In addition, DMNA was used as a solvent in the fiber and plastics industry, as an antioxidant, as a softener of copolymers, and as an additive to lubricants. No evidence has been found that DMNA is used at present except as a test chemical for research purposes.

DMNA came into industrial use in the United States in the manufacture of 1,1-dimethylhydrazine in the mid-1950s. DMNA is currently not produced in commercial quantities. The EPA public records indicate previous annual domestic production at 750 lb. In 1976, the last commercial plant making DMNA was closed.

Human exposure to DMNA can be by inhalation and ingestion. The exposure potential to N-nitroso compounds is believed to be widespread. Precursors of N-nitroso compounds, such as nitrates, nitrites, and amines, are naturally occurring substances, and N-nitroso compounds, including DMNA, may be found in soil, water, air, food, and the gastrointestinal tract of humans and animals.

MONS 025820

Workers in dimethylamine and dimethylhydrazine manufacturing plants, leather workers, oil and gas extraction workers, pesticide workers, and research workers may have been occupationally exposed to DMNA. Formulations of the pesticide 2,3,6-trichlorobenzoic acid with dimethylamine contain DMNA as a contaminant in concentrations up to 640 ug/l.

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

In September 1977, EPA issued a notice requiring all registrants of pesticide products potentially contaminated with N-nitroso compounds to analyze for the compounds by specified analytical methods to document the levels from potential sources. The compound has been regulated under the Resource Conservation and Recovery Act and the Clean Water Act. A water quality criteria document for the protection of human health is available. FDA has established action levels of 5 ppb DMNA in malt beverages and 10 ppb in barley malt. This is expected to reduce or eliminate exposure to DMNA from these sources. In February 1974, OSHA promulgated a standard for DMNA, which included protective clothing, respirators, medical surveillance requirements, and engineering controls.

MONS 025821

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are ascertaining the amounts of nitrosamine released from pacifiers. (CPSC)		
CWA, 304(a): Water quality criteria for nitrosamines published in final form, 2/28/80 (encompasses N-nitrosodiethylamine).		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, 0.454 kg), proposed 7/5/80.	Based on carcinogenicity. (EPA)	45 FR 133, p. 46904
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residue in excess of 1 kg to handling and report/recordkeeping requirements. Also designates N-nitrosodiethylamine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring use data, published 2/15/80.		45 FR 42, p. 13444 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, respiratory, hygiene training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standard--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Final Standard--current regulations effecting. (OSHA)	29 CFR 191.1016 (OSHA)
FDA Bureau of Foods, FDACP. (FDA)	The FDA has established action levels of 5 ppb DMNA in malt beverages and 10 ppb in barley malt. (FDA)	

MONS 025822

p-NITROSODIPHENYLAMINE

p-Nitrosodiphenylamine, administered in the feed, was carcinogenic in male B6C3F1 mice, causing hepatocellular carcinomas. The chemical was also carcinogenic in male Fischer 344 rats, causing liver neoplasms. There was no evidence for the carcinogenicity of p-nitrosodiphenylamine in female B6C3F1 mice or in female Fischer 344 rats.[1] These results were considered as providing limited evidence of carcinogenicity in experimental animals,[2] but in view of another evaluation, they can be regarded to provide sufficient evidence.[3]

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[1]National Cancer Institute. Bioassay of p-Nitrosodiphenylamine for Possible Carcinogenicity. Technical Report Series No. 190. DHEW Publication No. (NIH) 79-1746. Bethesda, Maryland, 1979.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 213-25.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

p-Nitrosodiphenylamine (4-nitroso-N-phenylbenzenamine) is an industrial chemical that is slightly soluble in water and petroleum ether and soluble in alcohol and benzene.

p-Nitrosodiphenylamine is used as a chemical intermediate for dyes and pharmaceuticals and as a polymerization inhibitor during the manufacture of vinyl monomers. Use of p-nitrosodiphenylamine as a chemical intermediate is believed to be limited primarily to the production of N-phenyl-p-phenylenediamine and its derivatives. p-Nitrosodiphenylamine has also been used as an accelerator in the vulcanization of rubber.

Commercial production of p-nitrosodiphenylamine in the United States was first reported to the U.S. International Trade Commission (USITC) by one company in 1975, although it is believed to have been produced since 1970. EPA estimated one producer in one region. Domestic production was reported as 369,000 lb; imports were not reported (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The U.S. production of p-nitrosodiphenylamine was reported to the USITC as greater than 5000 lb for 1980.

MONS 025823

The potential for exposure to p-nitrosodiphenylamine is greatest for workers in elastomer, dye, pharmaceutical, and vinyl monomer manufacturing facilities. The 1974 National Occupational Hazard Survey made no estimate of the number of workers potentially exposed to p-nitrosodiphenylamine.

p-Nitrosodiphenylamine is proposed for regulation by EPA under the TSCA, 8(a), reporting rule.

p-Nitrosodiphenylamine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 025824

N-NITROSODI-n-PROPYLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosodi-n-propylamine (NDPA) in experimental animals.[1] NDPA was carcinogenic in rats after administration in drinking water and in rats and hamsters after subcutaneous injection. It produced benign and malignant tumors of the liver, kidney, esophagus and respiratory tract. The metabolite N-nitroso-N-(2-hydroxy-n-propyl)-n-propylamine was also carcinogenic in rats and hamsters: it produced benign and malignant tumors of the respiratory tract and liver after subcutaneous injection.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 177-89.

NDPA is a yellow liquid that has been found as a contaminant in microgram quantities in wastewater from chemical factories, in cheese, in brandy and liquors, and in pesticides such as Treflan and Isopropalin.

Under the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979 (public record), EPA reported two U.S. producers with an estimated domestic NDPA production of 350 lb.

The general population may be exposed sporadically to low levels of NDPA. However, no exposed group suitable for an epidemiological investigation has been identified. The potential population at risk includes pesticide workers and research personnel. There are no data available on the number of people exposed.

EPA regulates NDPA under the Resource Conservation and Recovery Act. The proposed reporting rule under TSCA would require the reporting of process and use information. In 1980, EPA published water quality criteria for the protection of human health. However, the document addressed nitrosamines as a class, rather than NDPA as a specific chemical.

MONS 025825

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates NDPA as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data, published 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025826

N-NITROSO-N-ETHYLUREA

There is sufficient evidence for the carcinogenicity of N-nitroso-N-ethylurea (ENU) in experimental animals.[1] ENU was carcinogenic in all animal species tested: mice, rats, Syrian golden hamsters, rabbits, opossums, pigs and monkeys. It produced benign and malignant tumors following administration by different routes, including single oral doses; the main target organ appeared to vary with the route of administration. Prenatal exposure to the substance was shown to be particularly effective in producing tumors of the nervous system. In several studies, dose-response relationships were established.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 191-7.5.

ENU is a water-soluble crystalline solid. ENU belongs to a group of chemicals that are widely distributed in the environment as contaminants. This compound has been used for the laboratory synthesis of diazoethane.

ENU is produced in small quantities for research purposes. However, the Toxic Substances Control Act, Chemical Substance Inventory, 1979 (public record), reports approximately 360 lb of ENU were produced domestically by one producer.

Data on human exposure to ENU are not available, although laboratory personnel may be exposed to this compound.

The EPA proposes to regulate ENU under the Safe Drinking Water Act and has regulated it under the Resource Conservation and Recovery Act as a hazardous waste constituent.

MONS 025827

N-Nitrosa-N-ethylurea

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
SDWA: Primary drinking water standard in progress, 6/82.		SDW memorandum, 8/80
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1300 kg to handling and report/recordkeeping requirements. Also designates EMU as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring use data, published 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025828

N-NITROSO-N-METHYLUREA

There is sufficient evidence for the carcinogenicity of N-nitroso-N-methylurea (NMU) in experimental animals.[1] NMU was carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, guinea-pigs, rabbits, gerbils, pigs, dogs and monkeys. It induced benign and malignant tumors following administration by different routes, including ingestion. It produced tumors at different sites, including the nervous tissue, stomach, esophagus, pancreas, respiratory tract, intestine, lymphoreticular tissues, skin and the kidney. It is carcinogenic following its administration prenatally by injection to mothers and in single doses.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 227-55.

NMU is soluble in water and polar organic solvents. NMU is used for laboratory synthesis of diazomethane, but it has been largely replaced by other reagents. It has also been studied as a cancer chemotherapeutic agent, either alone, or in combination with cyclophosphamide.

There is no evidence of any commercial production or use of NMU; any production would be for research purposes. The EPA listed one producer, and the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, reported production of 350 lb (public record).

Few workers are exposed during the production of this compound, and only a limited number of research laboratory workers are potentially exposed. The only direct exposure would be to cancer patients through the administration of NMU as a chemotherapeutic agent, but there are no reliable data for the frequency or extent of this use.

Under the TSCA, 8(a), EPA has proposed a reporting rule requiring NMU use data. The EPA regulates this compound under the Resource Conservation and Recovery Act.

MONS 025829

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/record-keeping requirements. Also designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, Otal: Proposed reporting rule requiring process and use data, published 2/29/88. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		45 FR 42, 0, 13645 (EPA)

MONS 025830

N-NITROSOMETHYLVINYLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosomethylvinylamine (NMVA) in experimental animals.[1] NMVA was carcinogenic in rats, the only species tested. It produced carcinomas of the esophagus, tongue and pharynx after continuous administration in drinking water and carcinomas of the nasal cavities after inhalation exposure.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 257-61.

NMVA is a pale yellow liquid that is very volatile and photolabile. NMVA is soluble in water, organic solvents, and lipids. It is relatively unstable in aqueous solutions.

The only known use for NMVA is limited to laboratory research. NMVA has reportedly been found as a contaminant in apple brandy.

There is no evidence that this chemical has ever been produced commercially. The small number of researchers using NMVA could be exposed to it, and consumers of contaminated apple brandy might be directly exposed.

The EPA has included NMVA on its list of carcinogens and regulates it under the Resource Conservation and Recovery Act.

N-Nitrosomethylvinylamine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3[illegible]: Subjects waste products, off-specification batches, and spill residues in excess of 1 kg to handling and reporting recordkeeping requirements. Also designates this compound as a hazardous constituent of waste and subjects wastes known to contain it to the same requirements. Promulgated 6/13/80.		40 CFR 261.11, 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025831

N-NITROSOMORPHOLINE

There is sufficient evidence for the carcinogenicity of N-nitrosomorpholine (NMOR) in experimental animals.[1] NMOR was carcinogenic in various fish, mice, rats, and hamsters (Syrian golden, Chinese and European). When administered in drinking water, it produced benign and malignant tumors of the liver and lung in mice, and of the liver, kidney and blood vessels in rats. After subcutaneous injection it produced tumors of the upper digestive and respiratory tracts in hamsters; it was carcinogenic after administration in single doses. It produced liver tumors in rats following intravenous injection. When dissolved in tank water, it produced liver tumors in various fish. A study in hamsters has been reported in which a dose-response relationship was established.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 263-80.

NMOR is a yellow crystalline solid that is water soluble. NMOR belongs to the chemical group of N-nitroso compounds, which are widely distributed in the environment and can also be formed in the human body.

NMOR is neither commercially produced nor used in the United States, although patents have been issued for its use as a solvent for polyacrylonitrile, an intermediate in the production of N-aminomorpholine, and for application as an antimicrobial agent. NMOR has been detected as a contaminant in analytical grade dichloromethane and chloroform, in morpholine (0.8 ug/g), and in a rubber cross-linked accelerator (0.4-0.7 ug/g).

Human exposure to NMOR may occur by inhalation and less frequently through ingestion and skin absorption. Workers in chemical research laboratories and in the rubber and tire manufacturing industry may be exposed to the chemical. An average worker in a rubber or tire factory may be exposed to amounts in the range of 9-130 ug NMOR/day. Wastewater from these factories contained NMOR at levels of 0.003 ug/g. Dirt scrapings from a staircase in one of the factories revealed an NMOR level of 730 ug/g. A soil sample taken outside the same chemical plant contained NMOR at 4.4 ug/g.

MONS 025832

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

The EPA regulates NMOR under the Resource Conservation and Recovery Act.

N-Nitrosomorpholine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine released from pacifiers. (CPSC)		
RCRA, 3001-3004; Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 8/30/80. See Carcinogen Assessment Group statement under N-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)

MONS 025833

N-NITROSONORNICOTINE

There is sufficient evidence that N-nitrosonornicotine (NNN) is carcinogenic in experimental animals.[1] NNN was carcinogenic in rats, mice and Syrian golden hamsters. Following oral administration to rats, it produced carcinomas of the upper digestive tract, mainly the esophagus, and of the nasal cavities. In hamsters, subcutaneous injections produced mainly tracheal tumors. In mice, intraperitoneal injections produced lung tumors.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 281-86.

NNN is a yellow oil that is insoluble in water. NNN reportedly does not have a commercial use, but it may be synthesized for research purposes. No evidence was found that NNN has been manufactured commercially in the United States.

Cigarette smokers, tobacco chewers, cancer researchers, and organic chemists are at greatest risk of exposure to NNN. Cigarette workers and tobacco farmers have low exposure to NNN because the compound is released during curing. Smokers and persons breathing tobacco smoke may inhale a significant amount of NNN. The amount of the substance in commercial U.S. tobacco products varies from 1.9 to 88.6 ppm; this is one of the highest values of an environmental nitroso compound reported in the literature. Approximately half of the NNN originates in the unburnt tobacco, whereas the remainder is formed during burning. The Office on Smoking and Health has estimated that there are currently 54 million smokers in the United States.

The EPA has placed NNN on its Carcinogen Assessment Group list of carcinogens and has regulated it under the Resource Conservation and Recovery Act.

N-Nitrosonornicotine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
OCRA, 3006-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)

MONS 025834

N-NITROSOPIPERIDINE

There is sufficient evidence for the carcinogenicity of N-nitrosopiperidine (NPIP) in experimental animals.[1] NPIP was carcinogenic in mice, rats, hamsters (Syrian golden, European and Chinese), and monkeys when administered by several routes. It produced benign and malignant tumors of the liver, lung, forestomach and esophagus in mice, of the liver, esophagus and respiratory system in rats, and of the upper digestive tract, respiratory system and liver in hamsters; it also produced hepatocellular carcinomas in monkeys. It was carcinogenic in mice and hamsters when administered in single doses.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 287-301.

NPIP belongs to the group of compounds known as nitrosamines. NPIP has been used in the production of epoxy resin for electrical leads and for cardiovascular implants.

NPIP is not manufactured on an industrial scale but is produced by one company specializing in laboratory chemicals and sold in 25 g quantities. Because of the small quantities produced, exposure during production is limited. Nitrosamines are rapidly decomposed by sunlight and therefore do not persist in ambient air or water.

The general population may be sporadically exposed to low concentrations of NPIP from cigarette smoke and certain foods. Several scientists have reported trace amounts of NPIP in cigarettes; however, these observations have not been confirmed in all brands of cigarettes tested. There is evidence that NPIP is present in processed and preserved meats. Concentrations ranging up to 60 ug/kg have been detected in meat and fish products such as bacon, bologna, wieners, and smoked cod. FDA published a regulation on November 16, 1972, which requires separate packaging of spices from sodium nitrite in dry, premixed cures; this dramatically lowered NPIP in dry mixes. The presence of NPIP in meat, cheese, and spices results from the use of the nitrite as a preservative. FDA has estimated that between 10,000 and 100,000 patients may be exposed to NPIP by medical implants. The FDA Bureau of Medical Devices has not taken regulatory action at this time. Occupations with the highest probability of exposure to NPIP are cancer researchers, organic chemists, and workers engaged in the manufacture of pacemakers.

MONS 025835

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

NPIP has been included in the list of chemicals assessed as carcinogens by the EPA Carcinogen Assessment Group and is regulated under the Resource Conservation and Recovery Act. The FDA regulates NPIP under the Food, Drug, and Cosmetic Act.

N-Nitrosopiperidine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamines released from pacifiers. (CPSC)		
RCRA, 3001-3008: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and record/recordkeeping requirements. Also designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data, published 2/29/80.		45 FR 42, p. 13646 (EPA)
·See Carcinogen Assessment Group statement presented under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Foods, FDCCA. (FDA)	Enforcement of regulations precludes the formation of nitrosamines in meat-curing preparations. (FDA)	FR Notice, 11/16/73, p. 31879-80 CFR 21, 170.40 (FDA)

MONS 025836

N-NITROSOPYRROLIDINE

There is sufficient evidence for the carcinogenicity of N-nitrosopyrrolidine (NPYR) in experimental animals.[1] NPYR was carcinogenic in rats after administration in drinking water. It produced hepatocellular carcinomas. It also increased the incidence of lung adenomas in mice when given in drinking water. A study in rats was reported in which a dose-response relationship was established.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 313-26.

N-Nitrosopyrrolidine (NPYR) is a water-soluble liquid. NPYR belongs to the group of chemicals called N-nitroso compounds, which are widely distributed in the environment and can also be formed in the human body.

There is currently no evidence of commercial use of NPYR, although it was reported by one producer for the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979 (public record). Exposure to NPYR can occur by inhalation and by ingestion of nitrite-treated meats (e.g., bacon, sausage, and ham), condiments, tobacco, curing spices, and animal feed. Heating nitrite-treated foodstuffs may result in formation of NPYR. The recent trend to decrease the concentration of sodium nitrite in food and use ascorbic acid as a substitute preservative has decreased exposure to NPYR. For example, bacon contained an average of 67 ug/kg of NPYR in 1971-74; but by 1975-76, it contained only 17 ug/kg. When bacon is fried, an average of 50 percent of the NPYR normally present in bacon is found in the vapor. NPYR has also been found in tobacco smoke in amounts up to 0.113 ug/cigarette. The residue in pipe bowls has been found to contain 1.6 mg of NPYR/kg of residue.

In 1978, NPYR production and manufacturing facilities were reported as having 0.09-0.20 ug/l NPYR in their effluents. Dry premixed cures containing spices and sodium nitrite have been found to contain 40 ug/kg NPYR. In spices, NPYR increased to 520 ug/kg during 6 months of storage. NPYR has been found in 50 percent of certain animal feeds at levels of 1-26 ug/kg.

There are no available estimates of the extent of human exposure to NPYR; but it should be assumed that exposure is probable when nitrite-preserved foods, especially fatty foods, are heat-prepared and ingested.

MONS 025837

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

Currently, the EPA regulates NPYR under the Clean Water Act (CWA), the Resource Conservation and Recovery Act (RCRA), and the TSCA. Under the CWA, the EPA has published a water quality criteria document for nitrosamines; the document addresses NPYR. The RCRA subjects spill residues in excess of 2200 lb to handling and report/recordkeeping requirements. The TSCA reporting rule requires use and process data to be published.

N-nitrosopyrrolidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine released from pacifiers. (CPSC)		
CWA, 304(a): Water quality criteria for nitrosamines published in final form, 11/28/80. Addresses N-nitrosopyrrolidine.		45 Fm 231, p. 79338
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reports/record-keeping requirements. Also designates N-nitrosopyrrolidine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data, published 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025838

N-NITROSOSARCOSINE

There is sufficient evidence for the carcinogenicity of N-nitrososarcosine (NSAR) in experimental animals.[1] NSAR was carcinogenic in mice and rats. It produced carcinomas of the nasal cavities in mice and esophageal carcinomas in rats after administration in feed or drinking water, and liver-cell carcinomas in newborn mice after intraperitoneal injection.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 327-35.

NSAR is a pale yellow crystalline solid that is soluble in water and in polar organic solvents.

NSAR is neither produced nor used commercially in the United States. It is, however, produced by various chemical reactions in air, water, soil, food, and animal systems. This compound has been detected in foodstuffs, particularly meat, in concentrations of 2-56 µg/kg of sample. The general population may be exposed to NSAR by dietary intake or through its presence in the environment.

NSAR has been included in the list of carcinogens prepared by the EPA Carcinogen Assessment Group. EPA regulates NSAR under the Resource Conservation and Recovery Act.

N-Nitrososarcosine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025839

OXYMETHOLONE

Ten cases of liver-cell tumors have been reported in patients with blood disorders treated for long periods with oxymetholone alone or in combination with other androgenic drugs; however, a causal relationship cannot be established. The increased risk of liver-cell tumors could be related to hepatic damage known to be caused by oxymetholone. Alternatively, patients with congenital anemias may be at higher risk of developing these tumors, and this risk may become manifest during the extended survival resulting from oxymetholone treatment.[1] This is considered to provide limited evidence of carcinogenicity of oxymetholone in humans. No data are available concerning the carcinogenicity of oxymetholone in experimental animals.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 13. Lyon, France: IARC, 1977, pp. 131-39.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

Oxymetholone is a synthetic steroid hormone having actions similar to those of the male hormone, testosterone. As a pure substance, oxymetholone is a crystalline solid that is practically insoluble in water.

Oxymetholone is used for adjuvant therapy for senile and postmenopausal osteoporosis. At one time, a major use was for treatment of anemias. In 1972, the FDA dropped its approval of this use pending further investigation. Oxymetholone is also used as an anabolic steroid for small animals.

No evidence has been found that oxymetholone has ever been commercially produced in the United States. One U.S. distributor has been reported. The U.S. International Trade Commission reported in 1981 that oxymetholone was imported; however, no specific import data are available.

Human exposure to oxymetholone can occur principally during its use as a pharmaceutical. FDA's Bureau of Drugs estimates that 50,000 to 100,000 patients are treated each year with oxymetholone for postmenopausal osteoporosis. The usual adult dose of 5-10 mg/day is administered orally for about 3 weeks, but not exceeding 13 weeks, for a single course of therapy.

FDA reduced the list of approved uses of oxymetholone in 1972. Since 1977, warning labels of possible adverse effects have been required.

MONS 025840

Oxymetholone

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
Because oxymetholone is a pharmaceutical, EPA has minimal regulatory interest in it. Because there is no evidence of domestic manufacture, it is unlikely that EPA will investigate sources for possible regulation. (EPA)		
Oxymetholone was indicated only for treatment of anemia caused by deficient red blood cell production and was approved in 1970 for safety and effectiveness. Since 1978, all other indications except "probably" effective as adjuvant therapy in senile and postmenopausal osteoporosis have been deleted from the labeling pending further investigation of uses less than effective indication. (FDA)	In 1972, FDA required a labeling revision in the adverse reaction section that would include a statement on the occurrence of hepatocellular neoplasms and peliosis hepatitis in association with anabolic androgenic therapy. Use restricted to indicated therapy only. (FDA)	CFR 21, Subchapter D (FDA)

MONS 025841

PHENACETIN

There is sufficient evidence that phenacetin is carcinogenic in experimental animals.[1] Rats fed a diet containing phenacetin had an excess of nasal and urinary tract tumors. Phenacetin given in the diet to rats enhanced the urinary bladder carcinogenesis after they had received N-nitrosobutyl-N-(4-hydroxybutyl)-amine in drinking water.[1,2] The evidence for the carcinogenicity of phenacetin in humans is limited.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 24. Lyon, France: IARC, 1980, pp. 135-61.

Phenacetin is a crystalline powder that is soluble in water.

Phenacetin is used as an analgesic and antipyretic drug. It is used alone or in combination with aspirin and caffeine for the relief of mild to moderate muscle pain. Phenacetin has also been used as a stabilizer for hydrogen peroxide in hair bleaching preparations. In veterinary medicine, it is used as an analgesic and antipyretic.

Phenacetin has been produced commercially in the United States for over 50 years. In 1979, the EPA indicated an annual domestic production of approximately 550,000 lb and imports of 240,000 lb.

Human exposure to phenacetin is primarily through ingestion. The chemical is generally formulated with other pharmaceutical agents and used in over-the-counter (OTC) remedies for pain and fever. A high proportion of the population may be exposed to doses ranging up to 1 g per day. The usual dose is 300 mg taken 4-6 times per day.

The EPA regulates phenacetin under the Resource Conservation and Recovery Act. After an advisory panel determined that phenacetin could not be considered "safe" for OTC use, the FDA held hearings to remove it from OTC products. This action has been challenged by objections concerning the validity of the carcinogenicity data.

MONS 025842

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004. Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also identifies phenacetin as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Drugs, FD&CA: Phenacetin has been reviewed by the Advisory Review Panel on OTC internal analgesic, antipyretic, and antirheumatic products and categories as an effective OTC analgesic and antipyretic but not safe for OTC use. The FDA has initiated administrative proceedings to accomplish this, but objections have been raised concerning the validity of the carcinogenesis data. The FDA is thus not in a position at this time to call phenacetin a known human carcinogen. It can class it as an animal carcinogen with some human data available but inadequate to permit human carcinogenicity evaluation. (FDA)	The proposed action would remove phenacetin from over-the-counter preparations. (FDA)	Recommendation of OTC Internal Advisory Review Panel for analgesics and antirheumatic products. (FDA)

MONS 025843

PHENAZOPYRIDINE HYDROCHLORIDE

There is sufficient evidence for the carcinogenicity of phenazopyridine hydrochloride in experimental animals.[1] Phenazopyridine hydrochloride was tested in BC3F1 mice and Fischer 344 rats by dietary administration.[2] In female mice, it significantly increased the incidence of hepatocellular adenomas and carcinomas. In male and female rats, it induced tumors of the colon and rectum.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]National Cancer Institute. Bioassay of Phenazopyridine Hydrochloride for Possible Carcinogenicity. Technical Report Series No. 99, DHEW Publication No. (NIH) 78-1349. Bethesda, Maryland, 1978.

[3]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 24. Lyon, France: IARC, 1980, pp. 163-73.

Phenazopyridine is a heterocyclic organic compound that is slightly soluble in water.

Phenazopyridine hydrochloride has been used for 40 years as an analgesic drug either alone or in combination with other drugs to reduce pain associated with urinary tract infections.

Large-scale production of phenazopyridine hydrochloride began in the United States in 1944. In 1972, two companies reported production, but no data were published. The National Disease and Therapeutic Index reported in 1980 that 21 percent of this chemical was used in hospitals. Data from the National Prescription Audit reported that retail pharmacies dispensed 4.4 million prescriptions in 1980. The average adult dose rate is 200 mg three times daily.

Exposure to phenazopyridine hydrochloride occurs during manufacture and formulation. The 1974 National Occupational Hazard Survey estimated a potential occupational exposure for 2800 persons.

The FDA has approved the use of phenazopyridine hydrochloride for symptomatic relief of pain and other discomforts arising from irritation of the lower urinary tract.

MONS 025844

Phenazopyridine Hydrochloride

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
As a pharmaceutical, EPA has minal regulatory authority over phenazopyridine Hydrochloride. (EPA)		
FDA Bureau of Drugs, FD&CA: Approved for prescription use only. FDA is considering the inclusion of statements about carcinogenicity and dose duration limitations on the labels of this urinary analgesic. (FDA)	Use limited to short-term symptomatic relief of pain, burning, urgency, frequency, and other discomforts associated with lower urinary tract infection. Future labeling will reflect current toxicological data. (FDA)	21 CFR, Subchapter B (FDA)

MONS 025845

PHENYTOIN

The evidence of carcinogenicity of phenytoin in human subjects and in experimental animals is considered as limited.[1] Phenytoin was shown to be carcinogenic in mice after administration in a liquid diet or by intraperitoneal injection, producing lymphomas and leukemias. Studies performed with rats were considered inadequate.[2,3]

There are case reports and epidemiological studies of lymphomas occurring in patients that received phenytoin; however, no excess of lymphomas was reported in a followup study of epilepsy patients, many of whom received phenytoin along with other antiepileptic drugs. Three recent papers report one case of malignant mesenchymoma and two cases of neuroblastoma in children with phenytoin-induced malformations. An epidemiological study looked at the frequency of use of phenytoin and of phenobarbitone in mothers of children with childhood cancers compared with mothers of normal children. While more mothers of cancer cases reported a history of epilepsy, no differences were seen in the proportion of epileptic mothers who took either phenytoin or phenobarbitone. An excess of lymphomas was seen in children of epileptic mothers, but the occurrence of brain tumors was not reported.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1979.

[3]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 13. Lyon, France: IARC, 1977, pp. 201-25.

Phenytoin is a heterocyclic organic compound used in the treatment of grand mal epilepsy and Parkinson's syndrome and in veterinary medicine.

Commercial production of phenytoin was first reported in the United States in 1946. The EPA indicated that phenytoin was not reported to the Toxic Substances Chemical Inventory (1975-1977). In 1977, IARC reported that U.S. sales of phenytoin for use in human medicine were 171,000 lb annually. Imports for 1974 were approximately 15,000 lb.

MONS 025846

Human exposure to phenytoin occurs principally during its use as a drug. Figures on the number of patients using phenytoin are not available, but phenytoin is given to a major segment of individuals suffering from epilepsy. The oral dose rate, initially 100 mg three times per day, can gradually increase by 100 mg every 2-4 weeks until the desired therapeutic response is obtained. The intravenous dose is 200-350 mg/day. The EPA has not reported any data indicating the presence of phenytoin in effluents, emissions, or wastes from pharmaceutical manufacturers.

The FDA regulates phenytoin as a prescription drug. The Bureau of Drugs is examining the information on potential human hazards from phenytoin; an advisory committee will recommend further regulatory action if required.

Phenytoin

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
Because phenytoin and its monosodium salt are pharmaceuticals, EPA has minimal regulatory interest in them. The Agency has no indication of their presence in effluents, emissions, or wastes from pharmaceutical manufacturers. The fact that the monosodium salt of phenytoin was reported for the TSCA inventory indicated that there may be other uses that should be investigated for possible control. The small production volume, compared with other chemicals (including carcinogens) of concern, may limit interest for the foreseeable future. (EPA)		
FDA Bureau of Drugs, FD&CA: Regulated as a prescription drug. The Bureau of Drugs points out that the scientific data are not conclusive to call phenytoin a "known human carcinogen." The problem has been sent to an advisory committee and their recommendation will be considered before any statement is issued from FDA. (FDA)	No specific regulatory action will be taken until an advisory opinion has been submitted. (FDA)	CFR 21, Subchapter D (FDA)

MONS 025847

POLYBROMINATED BIPHENYLS (Firemaster FF-1)

Firemaster FF-1 (Firemaster BP-6 containing 2 percent of calcium trisilicate)--a mixture of pentabromobiphenyl, hexabromobiphenyl and heptabromobiphenyl with hexabromobiphenyl being the major component--administered by gavage produced neoplastic nodules and hepatocellular carcinomas in female Sherman strain rats.[1] In another bioassay, Firemaster FF-1--also administered by gavage--was carcinogenic to Fischer 344 rats and B6C3F1 mice of each sex, inducing neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas in rats and hepatocellular carcinomas in mice.[2]

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[1]Kimbrough, R.D., D.F. Groce, M.P. Korver, and V.W. Burse. Induction of Liver Tumors in Female Sherman Strain Rats by Polybrominated Biphenyls. J. Nat. Cancer Inst. Vol. 66, No. 3, 1981, pp. 535-42.

[2]National Toxicology Program. NTP Technical Report on the Toxicology and Carcinogenesis Bioassay of Polybrominated Biphenyl Mixture (Firemaster FF-1). Technical Report Series No. 244. NIH Publication No. 82-1800. Research Triangle Park, North Carolina, 1982.

Polybrominated biphenyls (PBBs) were widely used as flame retardant additives in synthetic fibers and in molded plastics. PCBs are solid at room temperature and practically insoluble in water. They are mixtures of compounds containing, on the average, six bromine atoms per molecule.

PBBs have been incorporated into the plastic housing of many commercial products. PBBs have been sold to manufacturers of polycarbonates, polyesters, polyolefins, and polystyrenes. The Consumer Product Safety Commission (CPSC) reported that hexabromobiphenyl (HBB) was the major component in the most widely used PBB mixture, and that PBBs are not presently being used in consumer products.

The commercial production of PBB began in 1970. Approximately 11 million lb of HBB were manufactured by a single U.S. company from 1970 to 1974 and marketed under the trade names Firemaster BP-6 and Firemaster FF-1. CPSC reported that the sole U.S. manufacturer of HBB ceased production in 1974. The remaining stock of this product held by the sole producer was reportedly exhausted in April 1975.

Other PBB production ceased in the late 1970s. EPA reported one U.S. producer (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The U.S. production of other PBBs (decabromobiphenyl), as reported to the U.S. International Trade Commission, was greater than 10,000 lb for 1980, according to YCI.

MONS 025848

Workers of a chemical company that manufactured PBB were directly exposed to PBB by skin contact, inhalation, and unintentional ingestion. HBB was detected in workers sera at a range of 1.1 to 1729 ppb, and in their adipose tissue at a range of 0.51-581 ppm. Approximately 2000 lb of PBBs were inadvertently mixed into livestock feed in Michigan in 1973. Thousands of animals died or were destroyed. Initially, 8000 to 12,500 Michigan residents were exposed in 1973 and 1974 to meat, milk, and eggs contaminated with PBBs. A general population survey conducted in Michigan revealed that only 10 percent of the population did not have detectable levels of PBB in their blood. Because the PBBs are biologically stable and slowly eliminated, significant body burdens could persist throughout their lifetimes.

In 1974, the National Occupational Hazard Survey estimated that 4900 workers were potentially exposed to PBBs. The sources of PBBs currently appear to be residues remaining in and around plants that at one time manufactured, processed, or produced products using PBBs. FDA stated that a potential for human exposure exists from the ingestion of foods containing residues of these compounds.

EPA is currently proposing a reporting rule for PBBs under the TSCA, 8(a). Under section 406 of the Food, Drug, and Cosmetic (FD&C) Act, FDA regulates PBB compounds as unavoidable environmental contaminants. In cooperation with CDC and the Public Health Department of the State of Michigan, FDA monitors the long-term human health effects from acute exposure to PBBs.

Polybromated Biphenyls

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
No regulations are directed specifically at this chemical. The PBB's category, containing potentially some 200-300 chemicals, is subject to a special TSCA, 8(a), reporting rule.		
TSCA, 8(a): Requires manufacturers to report intent to resume or initiate manufacture of any PBBs. Manufacture includes import. Promulgated 6/30/81. (EPA)	Regulation based on known hazards including possible carcinogenicity and on indications that these chemicals were not being produced. (EPA)	40 CFR 704.95 (EPA)
Regulated as unavoidable environmental contaminant under Section 406 of the FD&C Act. (FDA)	Action levels for PBB content: Milk, dairy products* 0.3G mg/kg Meat* 0.30 mg/kg Eggs 0.06 mg/kg Animal feeds 0.06 mg/kg * Fat basis. (FDA)	

MONS 025849

POLYCHLORINATED BIPHENYLS

The evidence for carcinogenicity of polychlorinated biphenyls (PCBs) in experimental animals is sufficient, and the evidence in humans is inadequate.[1]

Certain mixtures of PCBs (e.g., Kanechlor 500, Aroclor 1254 and 1260) were carcinogenic in mice and rats after administration in the diet, producing liver tumors.[2]

A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men exposed occupationally to Aroclor 1254, a mixture of PCBs.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 18. Lyon, France: IARC, 1978, pp. 43-103.

PCBs vary in appearance from mobile, oily liquids to white crystalline solids to hard noncrystalline resins, with all forms insoluble in water.

Before 1972, PCBs were used in transformer cooling liquids, heat transfer and hydraulic fluids, vacuum pump fluids, lubricants, plasticizers, fillers in investment casting waxes, surface coatings and sealants, pesticide extenders, and for copy paper. By 1974, all domestic uses of PCBs were confined to closed systems.

PCBs have been produced in the United States since 1929. Domestic production reached a peak volume of 86 million lb in 1970 and decreased to approximately 41 million lb by 1974. Annual domestic production prior to 1977 was approximately 35 million lb. Except for limited research and development applications, the PCBs are no longer produced in the United States, and no import or export of the compounds has been permitted since July 1979.

The release of PCBs from prior industrial uses and the persistence of the compounds in the environment have resulted in widespread contamination of water and soil, with subsequent exposure of the general public. Routes of exposure include skin absorption and ingestion; a major source of exposure is through the diet. A 1976 report indicated that fish, cheese, eggs, and contaminated animal feed were the major U.S. commodities in which PCBs were found. The percentage of food samples contaminated with PCBs decreased between 1973 and 1975. Residues of PCBs have been detected in human milk and fat samples collected from the general U.S. population. EPA reports that approximately 12 million persons within 12 miles of three existing and nine projected commercial incinerators could be exposed to releases of PCBs.

MONS 025850

In 1970, EPA banned PCBs as a pesticide ingredient and canceled registration of products containing the PCBs. EPA promulgated toxic pollutant effluent standards in 1977 and modified the marking and disposal rule in 1979. This latter regulation has been effective in identifying and eliminating some sources. In 1979, EPA issued a ban on manufacturing, processing, and distributing of PCBs in commerce; most manufacturing had ceased voluntarily before these rules were issued. EPA proposed a water quality criteria document that will protect freshwater, saltwater, and aquatic organisms, as well as human health. Air pollution sources of PCBs were recently assessed by EPA, and the need for regulation of emissions from incinerators, the only source for which controls may be essential, is under consideration. Under the Safe Drinking Water Act, EPA is preparing a report to the Congress concerning the nature and extent of PCB contamination, as well as recommendations for further regulatory action if necessary.

In 1973, FDA established tolerances for PCBs in several foods and in feeds for food-producing animals. In 1979, four of those tolerances were reduced. The current tolerances are 1.5 ppm (fat basis) in milk and manufactured dairy products; 3 ppm (fat basis) in poultry; 0.3 ppm in eggs; 0.2 ppm in finished animal feed; 2 ppm in animal feed components of animal origin; 5 ppm in fish and shellfish (edible portion); and 0.2 ppm in infant and junior foods. FDA is currently considering the lowering of PCB standards in fish and shellfish from 5 ppm to 2 ppm and has established action levels of 3 ppm (fat basis) in red meat and 10 ppm in paper food-packaging material. OSHA has adopted an 8-hour time-weighted average standard of 1 mg/m^3 for PCBs containing 42 percent chlorine, and 0.5 mg/m^3 for PCBs containing 54 percent chlorine. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 025851

Polychlorinated Biphenyls

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
FIFRA, 6: Banned as active or inert ingredient of pesticides (with polychlorinated terphenyls). Registration of products not reformulated, canceled 10/20/78.	Effectively removed pesticides as source of exposure.	FR notice 70-75 sent to all registrants affected.
TSCA, 6: Marking and disposal rule. Promulgated 2/17/78.	Sources have been identified. Wastes are being isolated and/or destroyed. Some sources have been eliminated.	40 CFR 761.10, 761.20
TSCA, 6: ANPR addressing issues raised by the court order (EDF versus EPA, 79-1960). Published 5/20/81.	Rulemaking slated for proposal by 4/23/82. (Actually published 4/22/82.)	46 FR, p. 27614
Ban on manufacturing, processing, and distribution in commerce (including some modifications to marking and disposal rule). Promulgated 5/31/79.	Most manufacturing has been voluntarily discontinued prior to these rules (except for certain R&D applications).	40 CFR 761
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CWA, 307(a): Toxic pollutant effluent standard. Promulgated 8/28/79.		40 CFR 129.105
CWA, 311. Hazardous spill regulation establishing reportable quantity (10 lb, 4.54 kg) and imposing reporting requirements. Promulgated 8/30/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping of chemicals, and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13
RCRA, 3001-3004: Proposed rule included six Arochlor compounds in list of toxic wastes, 12/18/78.	Final rule did not include these, as the TSCA disposal rule addressed PCBs in a more stringent fashion than had been conjectured.	43 FR 243, p. 58946
Designates PCBs as hazardous constituents of wastes, and subjects them to special handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11
RCRA, 4004: Prohibition on open burning, use on food, croplands, or open dumping of municipal sludges designated hazardous. Promulgated 9/13/79.	Prohibition on food crop and specifically addresses PCBs.	40 CFR 257
CAA: Assessment of sources completed, 5/80. Under review to determine if regulation is warranted.	Incinerators deemed only source that may require control in view of TSCA bans. (EPA)	OAQPS, draft source assessment, 5/80
SDWA: Report to Congress, now in preparation, will document nature and extent of PCB contamination, treatment, and other implications, and establish what, if any, controls may be needed.		ODW, personal communication, 6/80 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 025852

Polychlorinated Biphenyls (Concluded)

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
FDACA, 406: Tolerances for PCBs as unavoidable contaminants in certain raw agricultural and animal foods established 7/6/73. Four tolerances revoked 9/29/78.	Holds human exposure to lowest practicable level.	21 CFR 109.30, 509.30
Action level of 3 ppm (fat basis) for red meat established 6/30/80.	Holds human exposure to lowest practicable level. (FDA)	CFR 7111.02
FDA announced the availability of documents on the administrative law judge's ruling on whether to consider the economic impact of lowering PCB standards in fish and shellfish from 5 ppm to 2 ppm. (FDA)		46 FR, p. 24651 and 47 FR, p. 10879 (FDA)
PEL: 1 mg/m³ 8-hr TWA (42 percent chlorine), 0.5 mg/m³ 8-hr TWA (54 percent chlorine).	Regulatory History: 1962: Ceiling, 5 mg/m³ maximum allowable concentration.	29 CFR 1910.1000 (OSHA)
Potential for skin absorption noted. (Standard adopted for toxic effects other than cancer.) (OSHA)	6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	

MONS 025853

PROCARBAZINE AND PROCARBAZINE HYDROCHLORIDE

There is sufficient evidence for carcinogenicity in humans of intensive chemotherapeutic regimens that include alkylating agents, vinca alkaloids, procarbazine hydrochloride, and prednisone. There is inadequate evidence for carcinogenicity of procarbazine hydrochloride alone in humans. There is sufficient evidence for the carcinogenicity of procarbazine in experimental animals.[1,2]

Laboratory exposure of animals to procarbazine was studied by intraperitoneal injection. In rats, malignant lymphoma, adenocarcinoma of the mammary gland, and olfactory neuroblastomas were induced in statistically significant numbers. In mice, malignant lymphoma or leukemia, olfactory neuroblastoma, alveolar/bronchiolar adenoma, and adenocarcinoma of the uterus were induced in statistically significant numbers.[2]

Evidence of carcinogenicity was also found in mice and rats following administration by gavage; in rats following intravenous administration, and in one instance following transplacental exposure. Two studies in two species of nonhuman primates suggest that procarbazine hydrochloride may also produce myelogenous leukemia when administered by multiple routes to the same aniral.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 26. Lyon, France: IARC, 1981, pp. 311-39.

[2]National Cancer Institute. Bioassay of Procarbazine for Possible Carcinogenicity. Technical Report Series No. 19, DHHS Publication No. (NIH) 79-819. Bethesda, Maryland, 1979.

Procarbazine, an organic compound is soluble but unstable in water or aqueous solutions.

Procarbazine hydrochloride is primarily used as an antineoplastic agent in the treatment of advanced Hodgkin's disease and oat-cell carcinoma of the lung. The FDA approved the use of procarbazine hydrochloride in 1969 and indicated that the drug should be used as an adjunct to standard therapy.

Possible exposure occurs during manufacture of the drug, and direct exposure occurs during administration to patients. The National Prescription Audit reported 1.5 million prescriptions dispensed in 1980. Some of the metabolites of procarbazine are both carcinostatic and carcinogenic.

MONS 025854

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
EPA has minimal interest in regulating procarbazine or its hydrochloride as pharmaceuticals. (EPA)		
FDA, FD&CA: Approved for prescription use in 1969. (FJA)	Use restricted to palliative management of Hodgkin's disease and for use by patients who are nonresponsive to other forms of cancer treatment. Clear physician warning of secondary onset of leukemia after treatment with procarbazine is present in package insert. (FDA)	CFR 21, Subchapter D (FDA)

MONS 025855

β-PROPIOLACTONE

There is sufficient evidence for the carcinogenicity of β-propiolactone in experimental animals.[1] β-Propiolactone was carcinogenic in the mouse by skin application or subcutaneous injection, and in the rat by subcutaneous injection. Administration by gavage to a small group of female Sprague-Dawley rats gave squamous cell carcinoma of the forestomach.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 259-69.

β-Propiolactone is a water-soluble industrial chemical. More than 85 percent of the β-propiolactone produced in the United States was used in captive consumption for the manufacture of acrylic acid and esters. Less than 15 percent was used as a sterilant of blood plasma; for vaccines, tissue grafts, surgical instruments, and enzymes; and as a vapor-phase disinfectant in enclosed spaces.

β-Propiolactone was first produced commercially in the United States in 1958. The sole U.S. manufacturer reportedly halted production at the end of 1973. However, for the period 1975-1977, EPA reported one producer in one region (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record).

Exposure to β-propiolactone occurred primarily in the occupational setting, notably through skin absorption and by inhalation of vapors. OSHA estimated that 450 persons were occupationally exposed to β-propiolactone. Occupations at greatest risk of exposure included disinfectant workers and makers of viricidal agents, acrylic plastics, and resins. Potential exposure to waste effluents from production and manufacturing plants was minimal because of β-propiolactone's short half-life in water.

OSHA regulates β-propiolactone on the basis of its carcinogenicity in animals. The regulation requires protective clothing, use of respirators, training in hygiene, medical surveillance, engineering controls to limit contamination, sign requirements for posting regulated areas, and labeling requirements for containers.

MONS 025856

β-Propiolactone

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, respirators, hygiene training, and medical surveillance requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 6/16/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 8/11/76: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1013 (OSHA)

MONS 025857

RESERPINE

Reserpine was tested in B6C3F1 mice by administration in the diet; it induced malignant mammary tumors in females and carcinomas of the seminal vesicles in males. When given in the diet to F344 rats it increased the incidence of pheochromocytomas in males.[1] This available evidence is considered as limited by an IARC working group,[2] but in view of another evaluation of NCI results, it can be considered as sufficient.[3]

The 14 epidemiological case-control and 2 cohort studies are not consistent in showing an increase in breast cancer associated with the use of reserpine. The available evidence of carcinogenicity in humans is considered inadequate.[2]

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[1]National Cancer Institute. Bioassay of Reserpine for Possible Carcinogenicity. Technical Report Series No. 193. DHEW Publication No. (NIH) 80-1749. Bethesda, Maryland, 1980.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Reserpine, a pharmaceutical, is a naturally occurring substance that is isolated from the roots of the plant Rauwolfia serpentina. It is marketed under at least 150 trade names.

In humans, medicinal preparations are used for treating hypertension and as a tranquilizer and sedative. Reserpine is also used in veterinary practice as a tranquilizer or sedative. Reserpine preparations are also added to various animal feeds, such as turkey feed, to lessen the incidence of aortic rupture.

Reserpine was produced by at least six manufacturers. EPA reports one producer in one region (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). The annual U.S. sales of reserpine for use in human medicine were reported to be about 440,000 lb in 1976. Approximately 16.7 million prescriptions were dispensed by retail pharmacies during 1979, and an additional 2.3 million prescriptions were ordered in hospitals. Sales figures dropped 50 percent from 1976-79, indicating a reduction in reserpine use.

MONS 025858

An estimated 1300 to 2700 persons are occupationally exposed to reserpine. Exposure of the general population is unknown but sizable, based on the number of prescriptions. The average therapeutic dose ranges from 0.1 to 1.0 mg/day.

Federal regulations affecting exposure include EPA's hazardous waste rule, which restricts environmental release, and regulations under the Safe Drinking Water Act and the Resource Conservation and Recovery Act. FDA regulates reserpine as a prescription drug. FDA also regulates its use in animal diets, and on February 25, 1980, FDA revoked the use of reserpine as a component of premixed turkey feed.

Reserpine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
PCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/.3/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Veterinary Medicine, FDACA: Regulated for use in turkeys to lessen the incidence of aortic rupture. Approval withdrawn at the request of sponsor; 45 FR 33, p. 10.34, 1/15/80.	Reduces to zero the exposure of the public to residues of reserpine in food animals.	21 CFR 558.506, 558.570 (1979) Sec. 558.570 (revoked) 1. Part 558 is amended by revoking Sec. 558.570 reserpine
Zero residue for reserpine and its metabolites. FDA Bureau of Drugs: Approved for prescription use in treatment of hypertension and for treatment of behavioral diseases. (FDA)	Restricted to approved uses. It has been assessed for risk of human mammary cancer without definitive outcome by a NIH ad hoc advisory committee. An NCI recent study showed increased incidence of mammary and adrenal tumors. As with neuroleptic drugs, there has been a correlation suggested between reserpine's prolactin-releasing activity and increased incidence of mammary tumors in rodents, but it is not to be included among the group of neuroleptic drugs which will be required to be relabeled with an appropriate precautionary statement (see 45 FR, 8/8/80, p. 52931-J). A Federal Register statement has been prepared by FDA proposing a labeling change for all reserpine-containing products to include a description of the animal carcinogenicity study results and the ambiguous results from human epidemiology studies. (FDA)	Sec. 558.506 (revoked) 2. Part 558 is amended by revoking Sec. 558.506 reserpine (FDA)

MONS 025859

SACCHARIN

In April 1977, the Commissioner of the Food and Drug Administration proposed to revoke an interim food additive regulation which permitted the use of saccharin and its salts in prepackaged food (e.g., soft drinks) and as a tabletop nonnutritive sweetener.[1] This proposal was based on several U.S. studies[2,4] and one Canadian study[3] showing that saccharin caused bladder cancer in male rats. An analysis published by the Office of Technology Assessment confirmed this conclusion.[4] According to an IARC working group, there was sufficient evidence that saccharin alone, given in high doses, was carcinogenic in male rats and can promote the action of known carcinogens in the bladder of rats of both sexes; and that the evidence of carcinogenicity is limited in mice.[5] Another IARC working group considered the same evidence as being limited both in rats and mice.[6]

The available epidemiological data provide no clear evidence that saccharin alone, or in combination with cyclamates, causes urinary bladder cancer, but a small increase in the risk of urinary bladder cancer in the general population or a larger increase in some individuals consuming very high doses of saccharin and cyclamates cannot be excluded.[4] The existing human evidence has been classified as inadequate.[5]

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[1]Food and Drug Administration. Saccharin and Its Salts. Proposed Rule Making. Federal Register, Vol. 42, No. 73, 1977, pp. 19996-20010.

[2]Food and Drug Administration. Histopathologic Evaluation of Tissues from Rats Following Continuous Dietary Intake of Sodium Saccharin and Calcium Cyclamate for a Maximum Period of Two Years. Final Report. Project P-169-70. Typescript, December 21, 1973

[3]Health Protection Branch, National Health and Welfare Department, Canada. Toxicity and Carcinogenicity Study of Orthotoluensulfonamide and Saccharin. Project 2405/405E General Protocol. Typescript, 1977.

[4]Office of Technology Assessment, Congress of the United States. Cancer Testing Technology and Saccharin. Washington, D.C.: U.S. Government Printing Office, 1977.

[5]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 22. Lyon, France: IARC, 1980, pp. 111-85.

[6]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

MONS 025860

Saccharin is a white crystalline powder that is soluble in water. Saccharin and sodium saccharin have been produced commercially in the United States for over 80 years. Production levels of saccharin in 1977 were estimated at 4.8 million lb. Imports of saccharin were estimated in 1977 at 3 million lb, and 1.3 million lb in 1980. Saccharin and its ammonium and sodium salts were reported for the TSCA Inventory. EPA reported domestic production of 746,000 lb and imports of 4.2 million lb (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). There is only one reported manufacturing plant in the United States, and no current production figures are available. Approximately 6-8 million lb of saccharin were used among FDA-regulated products in 1976.

Saccharin has been used as a nonnutritive sweetening agent; however, its use substantially increased after cyclamates were banned in food in 1970. The 1976 U.S. consumption pattern for all forms of saccharin has been estimated as 45 percent in soft drinks; 18 percent in tabletop sweeteners; 14 percent in fruits, juices, sweets, chewing gum, and jellies; 10 percent in cosmetics and oral hygiene products; 7 percent in drugs such as coating on pills; 2 percent in tobacco; 2 percent in electroplating; and 2 percent for miscellaneous uses.

Human exposure to saccharin occurs primarily through ingestion from its use in many dietetic foods and drinks and in some personal hygiene products, including toothpastes and mouthwashes. The general public is exposed, especially those persons who have to reduce sugar intake. The National Occupational Hazard Survey and OSHA estimated that approximately 28,000 workers are occupationally exposed.

In compliance with the Delaney clause, FDA proposed to ban saccharin as a food additive in 1977 on the available evidence of carcinogenicity in animals. However, final regulations are pending because of Congressional action in 1977 requiring further study and labeling of saccharin. A joint FDA/NCI group, the Saccharin Working Group, was formed in 1977. A preliminary report of the epidemiological findings has been published, but an analysis of all the information gathered is yet to be completed. EPA regulates saccharin under the Resource Conservation and Recovery Act.

MONS 025861

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
be current action. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste, and subject waste known to contain saccharin to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Based on chronic toxicity. (EPA)	40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Foods, Bureau of Drugs; FD&CA: After receiving data indicating that saccharin caused cancer in experimental animals, the FDA proposed to ban the use of the compound. The Congress overruled the Agency's action, and the compound is now listed on an interim basis awaiting results from studies being presently conducted. (FDA)	No effect because Congress has overruled FDA. (FDA)	21 CFR 180.37 (FDA)

MONS 025862

SAFROLE

There is sufficient evidence for the carcinogenicity of safrole in experimental animals.[1] When given in the diet, safrole produced various liver tumors in several strains of male mice and male and female rats.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 10. Lyon, France: IARC, 1976, pp. 231-44.

Safrole is a colorless liquid that is insoluble in water and very soluble in alcohol.

This compound has been used to flavor beverages and foods and as a pesticide ingredient. It is reported to be used in soap manufacture, perfumery, sleep aids, and sedatives.

EPA indicated that nine companies produced and imported a total of over 2 million lb of the compound in 1977. No production data are available in the trade literature after 1977. However, according to the United States International Trade Commission (1981), approximately 36,000 lb of safrole were imported from Brazil during 1980.

OSHA estimated that 30 workers were potentially exposed. The FDA indicated that exposure to safrole of the general public through food consumption was extremely low since the Agency prohibited its use in food. Minimal exposure may occur through the use of edible spices, including nutmeg and mace, which contain low levels of naturally occurring safrole. The compound does not pose a hazard to the general population through consumption of drinking water because of its insolubility in water.

The EPA and the FDA regulate the use of safrole. During 1977, EPA promulgated standards for voluntary cancellation of safrole in pesticide products. The Agency did, however, permit one registrant to distribute and sell one safrole-containing product until March 11, 1978. Thereafter, no stocks were available for pesticide use. The FDA banned the use of oil of safrole and sassafras bark in food. However, edible spices (nutmeg and mace), which contain very small quantities of naturally occurring safrole, were permitted for use in foods. The Agency has been reviewing the use of safrole in sleeping aids and sedatives.

MONS 025863

Safrole

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
FIFRA, 6: Voluntary cancellation of all registrations, 6/77.	Removal of pesticides as source of exposure. (EPA)	42 FR, p. 29957 (last notice)
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 100% kg to handling and report/recordkeeping requirements. Also designates the compound as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data, published 2/29/80.		45 FR 42, p. 13946 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Foods, FDACA: Banned for use in foods, oil of sassafras; sassafras bark as source of safrole also banned.	Prohibited use of safrole and oil of sassafras and sassafras bark as sources of safrole in foods. Risk from safrole and these sources of safrole completely eliminated. Safrole-free extract of sassafras permitted under 172.580. Safrole-free extract permitted by both 172.510 and 172.580 (added 1/30/68--30 FR 592). Amended to 189.161 on 5/11/76 (41 FR 19207).	25 FR, p. 13412 (12/3/60) 42 FR, p. 14689 (3/15/77, amended) 42 FR, p. 56729 (10/20/77) (FDA)
FDA Bureau of Foods, FDACA: Spices (nutmeg and mace) GRAS (182.10). (FDA)	Use of spices in foods permitted. (FDA)	

MONS 025864

SELENIUM SULFIDE

Dermal application of selenium sulfide to ICR Swiss mice was not carcinogenic, but the study was limited to 88 weeks because of test animal deaths from amyloidosis.[1] An NCI skin painting study with ICR Swiss mice using Selsun®, a commercial selenium sulfide formulation, also gave negative results, and was terminated after 88 weeks because of the same amyloidosis problem.[2] In another chronic skin painting study of mice and rabbits, Selsun® was also reported negative.[3] However, selenium sulfide administered by gavage to F344 rats and B6C3F1 mice induced hepatocellular carcinomas in male and female rats and female mice, and alveolar/bronchiolar carcinomas and adenomas in female mice, but it was not carcinogenic to male mice.[4] These results can be regarded as providing sufficient evidence of carcinogenicity in experimental animals.[5]

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[1]National Cancer Institute. Bioassay of Selenium Sulfide for Possible Carcinogenicity (Dermal Study). Technical Report Series No. 197. DHHS Publication No. (NIH) 80-1753. Bethesda, Maryland, 1980.

[2]National Cancer Institute. Bioassay of Selsun® for Possible Carcinogenicity (Skin Painting Study). DHHS Publication No. (NIH) 80-1753. Bethesda, Maryland, 1980.

[3]Stenback, F. Local and Systemic Effects of Commonly Used Cutaneous Agents: Lifetime Studies of 16 Compounds in Mice and Rabbits. Acta Pharmacol. Toxicol. Vol. 41, 1977, pp. 417-31.

[4]National Cancer Institute. Bioassay of Selenium Sulfide for Possible Carcinogenicity (Gavage Study). Technical Report Series No. 199. DHHS Publication No. (NIH) 80-1750. Bethesda, Maryland, 1980.

[5]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Selenium sulfide, an inorganic compound, is insoluble in water and soluble in alcohol.

EPA reports that selenium sulfide is used for the treatment of seborrhea, especially in shampoos. The chemical is available over the counter as Selsun®, a stabilized buffered suspension. FDA reports that selenium sulfide is an active ingredient in some drug products used for the treatment of dandruff

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and certain types of dermatitis. A dandruff shampoo containing 1 percent selenium sulfide is available without a prescription and is recommended for use once or twice a week. By prescription, selenium sulfide is available in a 2.5 percent shampoo or lotion, with the recommended application limited to 10 minutes for 7 days to avoid the possibility of acute toxic effects. Selenium sulfide is also used topically in veterinary medicine for eczemas and dermatomycoses.

Selenium sulfide was not reported for the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, public record. In 1979, approximately 1800 lb of selenium sulfide were imported. NCI reports that no separate current data on production or imports of selenium sulfide are available. No current U.S. producers were listed in the 1982 Directory of Chemical Producers.

NCI estimates that substantial exposure of the population to selenium sulfide is questionable. Skin absorption has been reported only in patients with open scalp lesions. In 1974, the National Occupational Hazard Survey estimated that 8500 workers were potentially exposed to selenium sulfide.

Selenium is widely distributed throughout the environment, occurring in groundwater, surface water, rocks, and soil. No data on the environmental occurrence of selenium sulfide are available; however, the EPA in 1976 estimated that about 700 lb of selenium sulfide wastes are generated annually by the medicinal industry.

Selenium sulfide is currently regulated by EPA under the Resource Conservation and Recovery Act. OSHA has adopted a permissible exposure level of 0.2 mg/m^3 time-weighted average for selenium compounds.

Selenium Sulfide

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
PEL: 0.2 mg/m^3 TWA (Selenium compounds as Se). (OSHA)	Regulatory history: 1972: Walsh-Healy, 0.1 mg/m^3 maximum allowable concentration. 6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025866

SOOTS, TARS, AND MINERAL OILS

There is sufficient evidence that soots, tars, and some mineral oils are carcinogenic both in humans and in experimental animals.[1] Soots, coal tars, creosote oils, shale oils and cutting oils are carcinogenic in experimental animals after skin painting or subcutaneous injection.[1]

Occupational exposure to coal soot, coal tar and pitch, coal tar fumes and some impure mineral oils causes cancer of several sites, including skin, lung, bladder, and gastrointestinal tract. Recent epidemiological data support these conclusions. This effect may be due to the presence of polycyclic aromatic hydrocarbons in these materials.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

Soots, tars, and mineral oils (including creosote, shale, and cutting oils) are largely byproducts, contaminants, or wastes. These substances result from fossil fuel processing technology such as coal carbonization and from incomplete combustion of other carbonaceous materials. Each of these materials is composed of many ingredients.

Although these substances are largely byproducts, contaminants, or wastes, there are commercial uses of these substances. Coal tars have been used to treat skin disorders; however, their commercial importance is based on their use as chemical intermediates for a number of products such as creosote, pitch, timber preservatives, pesticide formulations, benzene, toluene, xylene, and naphthalene. Petrolatum and mineral oils are commercially important because of their use in pharmaceuticals, in protective coatings on fruits and vegetables, and in bakery products.

In 1975, approximately 35 million lb of coal tar and 2 million lb of coal tar neutral oil were manufactured or processed for use. In 1976, about 948 million lb of creosote were produced in the United States.

Human exposure to soots, tars, and oils occurs through inhalation, ingestion, and skin absorption. NIOSH has estimated that 10,000 coal handlers, coke oven workers, and byproduct plant workers are occupationally exposed to coal tar. OSHA has estimated that 121,000 workers are exposed to tars. The environmental contamination by these substances is widespread, and it can be assumed that the entire population is exposed to these substances at some level.

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EPA regulates these substances under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which restricts use, and under the Resource Conservation and Recovery Act (RCRA), which fosters greater care in handling of chemical wastes. The EPA Carcinogen Assessment Group included soots, coal tars, and creosote in its list of carcinogens; and as a result of this listing, these substances are included in the hazardous waste disposal rule of the RCRA. FDA regulates the use of petrolatum and mineral oil in food and the use of coal tar in drugs. The FDA Advisory Panel on Over the Counter Drug Products has recently determined that coal tar is not safe when used as a topical antifungal agent. Only petrolatum and mineral oil that contain no PAH may be used in coatings for fruits and vegetables and in release agents for bakery products. OSHA adopted a permissible exposure limit for coal tar pitch volatiles of 0.2 mg/m^3 as an 8-hour time-weighted average.

Soots, Tars, and Mineral Oils

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Creosote		
RCRA, 3001-3020: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting recordkeeping requirements. Also designates creosote as a hazardous constituent of waste. 1/19/80. (EPA)	Based on chronic toxicity. Fosters greater care in handling chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
Coal Tar, Coal Tar Neutral Oil, and Creosote		
FIFRA, 6: Cancellation of registration of products not conforming to provision below. Proposed, 2/19/81.	Possible reduction in use and consequent reduction in exposure.	46 FR, p. 13020
FIFRA, 3: Restricted use for specified wood preservative products. Proposed 2/19/81. (EPA)	By imposing conditions of use, exposure potential is reduced. (EPA)	46 FR, p. 13020 (EPA)
Coal Tar, Soot, and Creosote		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Coal Tar		
The FDA Advisory Panel on Over the Counter Drug Products has determined that coal tar is not safe to be used as a topical antifungal agent. (FDA)		47 FR, p. 12914-6 (FDA)
Criteria Document: Coal tar products, NIOSH recommendations; engineering controls, medical surveillance, labeling and posting, respirators, training. Recommended standard for coal tar products (1977): 0.1 mg/m^3 in cyclohexane extractable fractions. (NIOSH)	Work practices to minimize exposure to emissions. (NIOSH)	
PEL: 0.2 mg/m^3 8-hr TWA (coal tar pitch 29 CFR 1910.1000 volatiles). (OSHA)	6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	

MONS 025868

STREPTOZOTOCIN

There is sufficient evidence that streptozotocin (STR) is carcinogenic in experimental animals.[1] Streptozotocin is carcinogenic in mice, rats and Chinese hamsters following intravenous or intraperitoneal administration. It produced benign and malignant tumors of the liver and kidney and islet-cell tumors of the pancreas. It is carcinogenic after administration in single doses.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 337-49.

STR, a water-soluble N-nitroso compound, was of interest as a potential antibacterial agent, but the chemical has not been used commercially. STR has been used in studies on diabetes because it has specific toxic action on pancreatic β-cells, including hyperglycemia. It has been shown to have cytotoxic effects, and it could be used as an antineoplastic drug.

STR is produced by the soil microorganism Streptomyces achromogenes. STR production was reported by two manufacturers of research biochemicals (U.S. International Trade Commission Publication 804, 1977), but the amounts were not indicated.

Human exposure to STR could occur primarily through ingestion and less likely through skin absorption and inhalation. Occupational exposure to STR is limited to pharmaceutical workers and researchers.

EPA regulates STR under the Resource Conservation and Recovery Act. The FDA in 1980 reported that STR was submitted for approval as a new drug application, but the application was withdrawn before evaluation was completed.

MONS 025869

Streptozotocin

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designate streptozotocin as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement for 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
Bureau of Drugs, FDDCA: Request for approval was withdrawn. (FDA)	No approved uses allowed. (FDA)	

MONS 025870

SULFALLATE

Sulfallate, a chlorinated dithiocarbamate, administered in the feed, was carcinogenic to Osborne-Mendel rats and to B6C3F1 mice, inducing mammary gland tumors in females of both species, tumors of the forestomach in male rats, and lung tumors in male mice.[1]

[1]National Cancer Institute. Bioassay of Sulfallate for Possible Carcinogenicity. Technical Report Series No. 115. DHEW Publication No. (NIH) 78-1370. Bethesda, Maryland, 1978.

Sulfallate is a trade name for diethyldithiocarbamic acid 2-chloroallyl-ester; it is soluble in water. The chemical is formulated into emulsifiable concentrates, liquids, and granules.

The major use for sulfallate in the United States is as a preemergent selective herbicide to control certain annual grasses and broadleaf weeds around vegetable and fruit crops. Sulfallate has also been used for weed control among shrubbery and ornamental plants.

Sulfallate was introduced as a herbicide in 1954. According to NCI, during 1980, the production was greater than 5000 lb. Sulfallate was not reported for the Toxic Substances Control Act (TSCA), Chemical Substance Inventory (public record).

The 1974 National Occupational Hazard Survey provided no estimate of the number of workers potentially exposed to sulfallate. A potential for exposure exists during the manufacture and application of the herbicide. Agricultural workers have the greatest risk of sulfallate exposure, and rural residents of agricultural communities may be exposed to airborne residues of sulfallate after spraying operations. At commercially recommended rates of 4 lb/gal, the average persistence of sulfallate in soil is 3-6 weeks. The general population may be exposed through ingestion of residues in food crops.

The EPA has established tolerances for sulfallate residues on a variety of raw agricultural commodities. Enforcement is vested in FDA.

Sulfallate

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Tolerances established for pesticide chemicals in or on raw agricultural commodities (11/25/71, 2/7/73). (EPA)	Based on adverse effects of the chemical, use patterns, and detection limits. Enforcement vested in FDA. (EPA)	40 CFR 180.247 (EPA)

MONS 025871

2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN (TCDD)

The evidence for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in experimental animals is considered as sufficient.[1] An increased incidence of hepatocellular carcinomas and squamous-cell carcinomas of the lung, hard palate/nasal turbinates or tongue was observed in rats maintained on diets containing TCDD. In another study, increased incidence of tumors in a variety of organs was observed at all dietary levels of TCDD greater than 0.001 µg/kg.[1] TCDD administered by gavage to rats and mice induced follicular-cell thyroid adenomas in males and neoplastic nodules of the liver in females. TCDD also induced hepatocellular carcinomas in mice of both sexes and follicular-cell thyroid adenomas in females.[2] TCDD applied to the skin was not carcinogenic to male mice but in females it produced fibrosarcomas in the integumentary system.[3]

There is no report of human exposure to TCDD alone without the other chemicals such as 2,4,5-trichlorophenol or 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) being present. The available evidence from human studies is considered as inadequate.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]National Toxicology Program. Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Osborne-Mendel Rats and B6C3F1 Mice (Gavage Study). Technical Report Series No. 209. NIH Publication No. 82-1765. Research Triangle Park, N.C., and Bethesda, Maryland: NTP, 1982.

[3]National Toxicology Program. Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Swiss-Webster Mice (Dermal Study). Technical Report Series No. 201. NIH Publication No. 82-1757. Research Triangle Park, N.C., and Bethesda, Maryland: NTP, 1982.

2,3,7,8-Tetrachlorodibenzo-p-dioxin, commonly referred to as TCDD, is a very toxic chemical. TCDD has no reported use other than as a test chemical in basic research.

The total estimated release of TCDD is about 80 lb per year. Sources of potential exposure to TCDD are pesticidal spraying; cigarette smoke; and combustion of gasoline, diesel fuel, and wood. Trace concentrations (3-6 ppb) of TCDD have been reported in 3 of 23 samples of beef adipose tissues.

MONS 025872

EPA, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), banned detectable TCDD in 2,4,5-T and silvex. An emergency suspension order issued under FIFRA is still under litigation. Under the Resource Conservation and Recovery Act, TCDD has been designated as a hazardous constituent of waste, which subjects the chemical to special handling and record requirements. A health-related water quality criteria document was published under the Clean Water Act.

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
FIFRA: Ruling forbidding detectable TCDD and related chlorodioxins in 2,4,5-T and silvex, 9/20/79.	Limited effectiveness. Probably did result in some reduction in contamination.	PR Notice 79-22, sent to all affected registrants
FIFRA, 6: RPAR issued for 2,4,5-trichlorophenol, 9/13/78.	Based on oncogenicity/fetotoxicity. Final decision on proposed action will come after completion of cancellation hearings on 2,4,5-T and silvex.	43 FR, p. 41260
Emergency suspension order; cancellation suspension notices for 2,4,5-T, 2,4,5-T esters, and silvex, 3/15/79.	Litigation seeking temporary injunction against emergency suspension order dismissed. Issues in abeyance pending cancellation hearings, begun 3/14/80, and still in progress.	44 FR, p. 15874
RCRA, 3001-3004: Designates TCDD as a hazardous constituent of waste, and subjects any waste containing this chemical substance to handling and reporting/recordkeeping requirements; does not require testing. Promulgated 5/19/80.		40 CFR 261.11
CWA, 304(a): Water quality criteria proposed, 10/79.	Final criteria on hold for technical reasons.	OWRS, personal communication, 4/81
CAA: Assessment of sources and exposures completed, 5/80.		OAQPS, personal communication, 8/80
TSCA, 6: Conditions for disposal of TCDD contaminated wastes, including notification to EPA.	Restricts removal of wastes except with EPA approval in compliance with RCRA requirements. (EPA)	44 CFR 775 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025873

THIOACETAMIDE

There is sufficient evidence for the carcinogenicity of thioacetamide in experimental animals.[1] Thioacetamide was carcinogenic in mice and rats following administration in the diet, the only exposure route tested. It induced liver-cell tumors in Swiss mice and liver-cell and bile duct tumors in Wistar rats. No carcinogenicity was observed in hamsters given thioacetamide dissolved in distilled water by stomach tube.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France: IARC, 1974, pp. 77-83.

Thioacetamide (TAA) is a synthetic organic chemical, which is soluble in water and in ethanol. TAA is available in the United States as a laboratory chemical containing 99 percent of the active ingredient.

TAA is used as a replacement for hydrogen sulfide in qualitative analyses. TAA has been used as an organic solvent in the leather, textile, and paper industries; as an accelerator in the vulcanization of buna rubber; and as a stabilizer of motor fuel.

Commercial production of TAA in the United States was first reported in 1921. EPA estimated six producers and importers in three regions, with a domestic production of 4000 lb and imports of 4000 lb (Toxic Substances Control Act (TSCA), Chemical Substances Inventory, 1979, public record). TAA production was not reported to the U.S. International Trade Commission for 1979-1980. No evidence was found that this chemical is now commercially produced or imported in the United States, according to NCI.

Human exposure to TAA is principally through inhalation and skin absorption. Chemists and laboratory technicians are at greatest risk of exposure. In 1974, the National Occupational Hazard Survey estimated that 4600 workers were potentially exposed to TAA.

TAA is regulated by EPA under the Resource Conservation and Recovery Act, and regulation is proposed under the TSCA, 8(a), reporting rule that would provide detailed production and marketing data.

MONS 025874

Thioacetamide

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 100lb kg to handling and record/keeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.33, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 025875

THIOUREA

There is sufficient evidence for the carcinogenicity of thiourea in experimental animals.[1] Thiourea produced thyroid, liver and Zymbal's gland tumors in several strains of rats after administration in drinking water or diet. Intraperitoneal injection followed by administration in drinking water also produced Zymbal's gland tumors in rats. Administration of thiourea in the diet or by subcutaneous injection to mice did not produce thyroid tumors; however, this experiment was considered inadequate. An increased incidence of liver-cell tumors in a feed experiment with trout was reported, but this result cannot be considered as conclusive.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France: IARC, 1974, pp. 95-109.

Thiourea is an almost colorless crystalline solid that is soluble in water and in alcohol.

Thiourea was used in a variety of consumer applications including fire retardants, photographic chemicals, rust removers, animal glue liquefiers, and silver tarnish removers. But a recent evaluation has indicated that it is now used only in animal glue liquefiers and silver tarnish removers. Liquid animal glues may contain 10-20 percent thiourea as a liquefying agent. Ever these uses are diminishing.

Thiourea is reported to be used commercially in the production of flame retardant resins and as a vulcanization accelerator.

Two companies began commercial production of thiourea in the United States in 1938. One company transferred the production to Canada in 1952, and the other discontinued production in 1954. In their initial inventory of chemical manufacturers and importers, EPA reported that in 1977 there were 21 producers and importers in six regions, with a domestic production of 4.4 million lb and imports of 2 million lb (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). Production of thiourea was not reported to the U.S. International Trade Commission in 1979-1980. There are now no manufacturers in the U.S. that produce either thiourea or its

MONS 025876

major derivative, thiourea dioxide. The U.S. consumption depends at present on imports. About 70 companies have been reported by EPA as distributors of thiourea. The chemical is imported mainly from Japan, with small quantities coming from the Federal Republic of Germany. According to CPSC, there has been a recent upsurge in the market for thiourea.

Because liquid animal glues containing thiourea have been largely replaced by better woodworking glues, the chemical is probably a minor source of consumer exposure. In silver tarnish-remover dips, thiourea is used to dissolve silver sulfide tarnish. Thus, substantial skin contact is possible, and small amounts of thiourea may be ingested if newly cleaned utensils are not washed thoroughly before use. Two tarnish-remover dips have been identified, and one is widely distributed (CPSC). In 1974, the National Occupational Hazard Survey estimated that 213,000 workers were potentially exposed to thiourea.

EPA regulates thiourea under the Resource Conservation and Recovery Act. The FDA prohibits the use of thiourea in human food.

Thiourea

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action; under evaluation; project to begin in FY83. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
Substance prohibited from use in human food. (FDA)		21 CFR 189 (FDA)

MONS 025877

THORIUM DIOXIDE

Thorotrast (thorium dioxide) has received much attention since 1947 when MacMahon et al.[1] reported the first death due to its use. Their patient developed an endothelial cell carcinoma of the liver 12 years after the intravascular use of Thorotrast. Since that time, there have been over 60 cases of neoplasms attributed to its use.[2] Additional evidence for the carcinogenicity of thorium dioxide (administered diagnostically as "Thorotrast") is given by a study in Portugal.[3] One-thousand one-hundred and seven (46.6 percent of the exposed Thorotrast population) had been traced up to December 31, 1963; of these 699 had died and 408 were still living. Twenty-two cases of a special sarcoma of the liver, hemangioendothelioma, have occurred. This tumor is virtually Thorotrast-specific in the liver. The latent period between Thorotrast administration and onset of the fatal illness was 20 years or more with only one exception.

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[1]MacMahon, H.E., A.S. Murphy, and M.I. Bates. Endothelial-Cell Sarcoma of Liver Following Thorotrast Injection. American Journal of Pathology. Vol. 23, 1947, pp. 585-613.

[2]Barry, W.J., and C.J. Rominger. Thorotrast Granulomas. American Journal of Roentgenology. Vol. 92(3), 1954, pp. 584-90.

[3]Das Horta, J., J.D. Abbatt, L.C. Da Motta, and M.L. Roriz. Malignancy and Other Late Effects Following Administration of Thorotrast. Lancet: 1965, pp. 201-05.

The chemical thorium dioxide is a crystalline powder that is insoluble in water, acids, and alkalies.

This chemical was used in the development of nuclear reactors. Because of its long-life incandescent properties, however, thorium dioxide was primarily used in gas mantles. The chemical was also used in electrodes for arc welding and in Thorotrast, a radiopaque medium for X-ray imaging in medical diagnostic procedures.

EPA reported for 1977 five producers and importers in four regions, with domestic production as 373,000 lb and imports of 4200 lb (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record).

Exposure to the compound may occur through inhalation of dust or gas, intravenous injection, ingestion of liquid thorium dioxide, and skin absorption. Occupations at greatest risk of exposure were ceramic makers, incandescent lamp makers, magnesium alloy makers, metal refiners, nuclear reactor workers, chemists, and vacuum tube makers. OSHA estimated that 128,500 workers were potentially exposed to the compound during production and use. A number of patients were exposed to Thorotrast when it was administered for X-ray procedures.

MONS 025878

Because of the reported carcinogenic effects of Thorotrast in humans, several Government Agencies have restricted the use of this material. The FDA has approved thorium dioxide for use as a radiopaque medium for X-ray imaging where there is limited life expectancy. In March 1980, the Nuclear Regulatory Commission (NRC) withdrew authorizations for use and transfer of the material for internal or external medicinal use in humans. Authorizations were issued, however, for research, development, educational, commercial, or operational purposes under conditions specified by the NRC. The Agency further stated that use and transfer of the material for these purposes may not exceed 15 lb at any one time and no more than a total of 150 lb in any one calendar year.

Thorium dioxide

REGULATIONS		
Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
Although reported for the TSCA inventory, thorium dioxide appears primarily to be used in medicine. Its production is sufficiently low as to place regulatory interest at a low priority. (EPA)		
FDA Bureau of Drugs, FD&CA: Must meet New Drug Application and labeling requirements. Approved for use as a radiopaque medium for X-ray imaging. (FDA)	Label limits use to cases where there is limited life expectancy (disease, age). Prohibits use in food-producing animals. (FDA)	21 CFR, Subchapter D, 21 CFR 250.183 (FDA)

MONS 025879

o-TOLUIDINE AND o-TOLUIDINE HYDROCHLORIDE

There is sufficient evidence for the carcinogenicity of ortho-toluidine hydrochloride in experimental animals.[1] Ortho-toluidine hydrochloride was tested in several experiments, but only two experiments in mice and two experiments in rats in which the compound was administered in the diet were adequate. It was carcinogenic in mice, producing hepatocellular carcinomas or adenomas in females and hemangiosarcomas at all sites in males of one strain and hemangiosarcomas and hemangiomas of the abdominal viscera in animals of both sexes of another strain. It was carcinogenic in rats: In animals of one strain it produced sarcomas of multiple organs in animals of both sexes, fibromas of the subcutaneous tissue and mesotheliomas in males, and sarcomas of the spleen, transitional-cell papillomas, and carcinomas of the urinary bladder, and mammary gland fibro-adenomas and adenomas in females. In male rats of another strain, it produced subcutaneous fibromas and fibrosarcomas as well as a slight increase in the incidence of multiple tumors, including transitional-cell carcinomas of the urinary bladder.[2,3]

In epidemiological studies, an increased incidence of bladder cancer has been observed in workers exposed to ortho-toluidine, but as all were exposed to other possibly carcinogenic chemicals, ortho-toluidine cannot be identified specifically as the responsible agent.[1] The evidence is considered inadequate in humans.

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 155-75.

[3]National Cancer Institute. Bioassay of o-Toluidine Hydrochloride for Possible Carcinogenicity. Technical Report Series No. 153. DHHS Publication No. (NIH) 79-1709. Bethesda, Maryland, 1979.

o-Toluidine hydrochloride is a salt of an aromatic amine, and it is used primarily in the manufacture of a large number of commercial dyes including azo pigment dyes, triarylmethane dyes, sulfur dyes, and indigo compounds.

o-Toluidine hydrochloride has been used commercially in the United States for over 50 years. Commercial production was first reported in 1956. In 1977, 1000 lb of o-toluidine hydrochloride were manufactured. In 1976, 25,000 lb of o-toluidine hydrochloride were imported.

MONS 025880

The principal route of human exposure to o-toluidine hydrochloride is the respiratory system, although the compound may also be adsorbed through the skin. OSHA has reported that an estimated 13,900 workers were exposed to o-toluidine. Occupations with the greatest potential for exposure include dyemakers and pigment makers. Consumer exposure to o-toluidine hydrochloride may occur from residues present in commercial dyes used on textiles. The presence of o-toluidine hydrochloride even as a trace contaminant would be a cause for concern. However, in September 1980, the Consumer Product Safety Commission (CPSC) staff preliminarily determined that o-toluidine hydrochloride was not present in consumer products under CPSC jurisdiction. The Commission subsequently requested (45 FR 61344) public comment to verify the accuracy of its information, but no comments were received. Pending the receipt of new information, the Commission plans no action on o-toluidine hydrochloride.

EPA regulates o-toluidine hydrochloride under the Resource Conservation and Recovery Act and is proposing regulation under the TSCA, 6(a), reporting rule. FDA reports that exposure is limited to trace amounts in any products under its jurisdiction. OSHA adopted a permissible exposure limit of 5 ppm (22 mg/m^3) as an 8-hour time-weighted average for occupational exposure to o-toluidine. OSHA adopted this standard for toxic effects other than cancer.

o-Toluidine and o-Toluidine Hydrochloride

REGULATIONS

Regulations and Other Actions	Effects of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3004-3004: Subjects waste products, off-specification botches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 1/80.		40 CFR 261.33
Also designates o-toluidine hydrochloride as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11
TSCA, 8(a): Reporting rule requiring process and use data; proposed 2/29/80 (o-Toluidine only).		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Regulatory Authority: FDCA, 201(s). (FDA)	Action pending completion of contaminants policy. (FDA)	
PEL: 5 ppm (22 mg/m^3) 8-hr Time-Weighted Ave.	6/27/71: OSHA Takeover Standard--current limits effective. (OSHA)	29 CFR 1910.1000 (OSHA)
Potential for skin absorption noted. [Standard adopted for toxic effects other than cancer.] (OSHA)		

MONS 025881

TOXAPHENE

There is sufficient evidence for the carcinogenicity of toxaphene in experimental animals.[1,2] Technical grade toxaphene administered in feed increased the incidence of hepatocellular carcinomas in male and female B6C3F1 mice. An increased incidence of thyroid tumors was observed in Osborne-Mendel rats.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 327-438.
[3]National Cancer Institute. Bioassay of Toxaphene for Possible Carcinogenicity. CAS No. 8001-35-2-NCI-CG. Technical Report Series No. 37. DHHS Publication No. (NIH) 79-837. Bethesda, Maryland, 1979.

Toxaphene is a mixture of chlorinated camphenes that appears as a waxy amber solid. The exact composition of the mixture is not known.

During the last 10 years, toxaphene has been used in larger quantities in the United States than in previous years. Its use increased, due in part to the phasing out of DDT.

Toxaphene was first commercially produced in the United States in 1947. It is available as wettable powder, emulsifiable concentrate, dust, granule, bait, oil, and emulsion. During 1976-78, a reported 39-42 million lb of the compound were produced. Eighty-five percent of the toxaphene used in this country was for the control of cotton insect pests, and the remaining 15 percent was used for the control of insect pests on livestock, poultry, and for a few field crops other than cotton. In 1976, farmers used 30 million lb of toxaphene on cotton crops, 2.2 million lb on soybeans, 1 million lb on sorghum, and 400,000 lb on peanuts. The Southeast and Delta States consumed most of the toxaphene produced.

Manufacturers of toxaphene, cotton farmers, and pesticide applicators were among the persons at highest risk of exposure. OSHA estimated that only 100 industrial workers were potentially exposed. This figure very likely included only workers involved in the manufacture of the insecticide. No estimates are available on the number of people potentially exposed through agricultural use and handling. This number may be significant because toxaphene represented 41 percent of the total insecticide used on cotton crops in 1976.

MONS 025882

In the National Soils Monitoring Program, few toxaphene residues were found (4.2 percent of 1729 sites sampled). The range of toxaphene residues detected was 0.1 to 11.72 ppm in positive samples. However, the material can be extremely persistent in soil receiving direct application (i.e., cropland). In one study, 45 percent of the toxaphene applied to a sandy loam soil in 1951 was detectable 20 years later. In some instances, agricultural runoff has polluted local lakes and streams.

In 1980, EPA published a water quality criteria document for the protection of human health. In 1977, under the Clean Water Act, EPA promulgated a toxic pollutant effluent standard and a hazardous spill regulation requiring stringent reporting of spills involving quantities of 1 lb or more. A Rebuttable Presumption Against Registration had been issued under the Federal Insecticide, Fungicide, and Rodenticide Act. In October 1982, the EPA published a notice of intent to cancel or restrict registrations for products containing toxaphene. Under the Safe Drinking Water Act, a maximum contaminant level of 0.005 mg/l was established. The OSHA standard for toxaphene is 0.05 mg/m^3 as an 8-hour time-weighted average. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 025883

Toxaphene

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CWA, 307(a): Toxic pollutant effluent standard. Promulgated 1/12/77.	Based on general toxicity.	40 CFR 129.4, 129.109
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, 0.454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity; most stringent limitation.	40 CFR 117.3, 117.13
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates toxaphene as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
SDWA, 141.2: Revised drinking water maximum contaminant level scheduled for proposal, 8/83.	Existing maximum contaminant level of 0.005 mg/l (5 µg/l) remains in force. Chronic toxicity, including carcinogenicity, is being considered. (EPA)	40 CFR 141.12 SDW, memorandum, 9/[illegible]
FIFRA, 6: RPAR issued, 5/27/77.		45 FR, p. 26860
FIFRA, 6: Notice of intent to cancel or restrict registrations for products containing toxaphene, 11/29/82. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		47 FR 229, p. 53704 (EPA)
PEL: 0.5 mg/m^3 8-hr TWA. Potential for skin absorption noted. [illegible] for toxic effects other than cancer.] (OSHA)	Regulatory History: 8/27/71: OSHA Takeover standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 025884

2,4,6-TRICHLOROPHENOL

2,4,6-Trichlorophenol was tested in one experiment in two strains of mice treated initially by gavage and then given the substance in the diet, but this experiment was not considered as adequate.[1] The National Cancer Institute also tested this compound, and under the conditions of this bioassay 2,4,6-trichlorophenol administered in the diet was carcinogenic in male F344 rats, inducing mononuclear cell leukemias or lymphomas. The test chemical was also carcinogenic in both sexes of B6C3F1 mice, inducing hepatocellular carcinomas and adenomas.[2] The available data are regarded as providing sufficient evidence for the carcinogenicity of this substance in experimental animals.[3]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 349-67.

[2] National Cancer Institute. Bioassay of 2,4,6-Trichlorophenol for Possible Carcinogenicity. Technical Report Series No. 155. DHEW Publication No. (NIH) 79-1711. Bethesda, Maryland, 1979.

[3] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

2,4,6-Trichlorophenol, an organic aromatic compound, is soluble in water, acetone, alcohol, and ether.

2,4,6-Trichlorophenol has been used as a wood preservative, a glue preservative, and an antimildew treatment for textiles. The chemical has also been used as a bactericide, a herbicide, and a defoliant.

Commercial production of 2,4,6-trichlorophenol in the United States was first reported in 1950. Production of this compound was limited in 1975, due to the high cost of removing toxic chlorinated dibenzo-p-dioxins, which have been found in samples of 2,4,6-trichlorophenol as impurities.

The U.S. International Trade Commission (USITC) reported in 1976 that 2200 lb were imported. In their initial inventory of commercial chemicals, the EPA estimated four producers and importers, with a domestic production of 37,000 lb and imports of 37,500 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The production of 2,4,6-trichlorophenol was not reported to the USITC in 1979-1980, but 1980 imports through principal U.S. customs districts were 550 lb. The 1982 Directory of Chemical Producers lists two U.S. companies currently producing this chemical.

MONS 025885

2,4,6-Trichlorophenol is a strong dermal irritant. Human exposure to 2,4,6-trichlorophenol can occur through skin absorption or ingestion. In the 1974 National Occupational Hazard Survey, NIOSH estimated that 110 workers were exposed to 2,4,6-trichlorophenol. Substantial exposure of the population is questionable, according to NCI.

2,4,6-Trichlorophenol can be produced when industrial waste water containing phenol or certain aromatic acids is treated with hypochlorite. Trichlorophenol (unspecified isomers) has been detected in river water samples, landfill leachate samples (40 ng/l), and tapwater samples (2-4 ng/l). Production emissions have been estimated at 1.0 lb/ton.

2,4,6-Trichlorophenol is currently under evaluation by CPSC. EPA regulates 2,4,6-trichlorophenol under the Clean Water Act (CWA, 304 and 311) and under the Resource Conservation and Recovery Act (RCRA, 3001-3006). EPA has published a water quality criteria document (11/28/80) on 2,4,6-trichlorophenol for the protection of human health.

2,4,6-Trichlorophenol

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Under evaluation. (CPSC)		
CWA, 304: Water quality criteria published in final form on 11/28/80.		45 FR, p. 79318
CWA, 311: Hazardous spill regulation established reportable quantity (10 lb, 4.54 kg) and imposed reporting requirement. Promulgated 6/29/79.	Regulation based on aquatic toxicity. Fosters greater care in handling and shipping of chemicals.	40 CFR 117.3, 117.13
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 100 kg to handling and reporting/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. (EPA)	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)

MONS 025886

TRIS(1-AZIRIDINYL)PHOSPHINE SULFIDE (THIOTEPA)

There is sufficient evidence for the carcinogenicity of tris-(1-aziridinyl)phosphine sulfide (thiotepa) in experimental animals.[1] Thiotepa was carcinogenic in mice and rats after administration by various routes, producing a variety of malignant tumors.[2,3]

There are several reports and epidemiological studies suggesting the development of acute non-lymphocytic leukemia in patients treated with thiotepa for ovarian and other malignant tumors,[2] but the evidence is considered as inadequate in humans.[1]

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[1]International Anency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 9. Lyon, France: IARC, 1975, pp. 85-94.
[3]National Cancer Institute. Bioassay of Thiotepa for Possible Carcinogenicity. Technical Report Series No. 58. DHEW Publication No. (NIH) 78-1308. Bethesda, Maryland, 1978.

Thiotepa, a white crystalline solid, is a polyfunctional alkylating agent used in the chemotherapy of some neoplastic diseases.

Thiotepa has been prescribed for a wide variety of neoplastic diseases (adenocarcinomas of the breast and the ovary, superficial carcinoma of the urinary bladder, controlling intracavitary or localized neoplastic disease, lymphomas such as lymphosarcoma and Hodgkin's disease, as well as bronchogenic carcinoma). It is now largely superseded by other treatments.

There is only one known producer of thiotepa in the United States, and production data are not reported. The National Prescription Audit reported that 30,000 prescriptions were dispensed by retail pharmacies in 1980. An unknown quantity was ordered by hospitals.

The EPA designates thiotepa as a hazardous constituent of wastes and regulates it under the Resource Conservation and Recovery Act. The FDA approved thiotepa on February 19, 1959, with the warning that dosing must be carefully individualized.

MONS 025887

Tris[1-aziridinyl]phosphine Sulfide
(Thiotepa)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Designates thiotepa as a hazardous constituent of wastes, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)
FD&CA: Approved for prescription use in 1950. (FDA)	Limited to approved uses in treatment of cancer. Like all alkylating agents, thiotepa is clearly labeled as a carcinogen with both human and animal data. Thiotepa has now been largely superseded by other treatments. (FDA)	

MONS 025888

TRIS(2,3-DIBROMOPROPYL)PHOSPHATE

There is sufficient evidence for the carcinogenicity of this substance in experimental animals.[1,3] Tris(2,3-dibromopropyl)-phosphate (TRIS) administered in the diet was carcinogenic to B6C3F1 mice, causing increased incidence of tumors in livers, lungs, and stomachs of male mice and in kidneys, lungs, and stomachs of male mice. TRIS was also carcinogenic in Fischer 344 rats, causing an increased incidence of kidney tumors in both sexes.[2] After skin application to ICR/Ha Swiss female mice, it produced tumors of the skin, lung, forestomach and oral cavity.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]National Cancer Institute. Bioassay of Tris(2,3-dibromopropyl)-phosphate for Possible Carcinogenicity. Technical Report Series No. 76. DHHS Publication No. (NIH) 78-1326. Bethesda, Maryland, 1978.

[3]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 575-88.

Tris(2,3-dibromopropyl)phosphate, commonly known as TRIS, is no longer used in the United States.

Major uses of tris(2,3-dibromopropyl)phosphate were in plastics, and as a flame-retardant additive for synthetic textiles used in children's nightwear. Other applications were for the treatment of polyurethane foams used in cushions for aircraft and automotive interiors, home insulating foam, upholstered furniture, packaging, draperies, institutional bedding, toys, doll clothing, and wigs.

All domestic production of TRIS was banned in 1978. Commercial production in the United States was first reported in 1959. In 1975 production was estimated to range between 9 and 11 million lb.

During 1972-76, a significant number of infants and children were exposed to TRIS, primarily through skin absorption and occasionally through ingestion from oral contact with TRIS-treated garments. The Consumer Product Safety Commission (CPSC) stated that over a 6-year period a child wearing TRIS-treated clothing could absorb a total of 2-77 mg/kg TRIS. More recent data indicated this estimate may be even higher. The National Occupational Hazard Survey in 1974 estimated that 29,000 workers were exposed to TRIS through skin absorption.

MONS 025889

In 1977, CPSC acted under the Federal Hazard Substance Act to remove all TRIS-treated children's clothing and other consumer products containing TRIS from the market, and in 1978, it prohibited the export of such products. As a result, in 1977, approximately 20 million garments were recalled and some destroyed; however, some may still be in warehouses. Some TRIS-treated children's sleepwear, manufactured prior to 1978 and stored in warehouses, may reappear illegally in the marketplace. Consumers who suspect they may be purchasing pre-1978 TRIS-treated sleepwear are advised to contact the manufacturer or call the CPSC Hotline at 800/638-8326. EPA regulates TRIS under the Resource Conservation and Recovery Act and under the Toxic Substances Control Act, 8(a), which requires that EPA be notified of intent to resume manufacture or importation.

Tris(2,3-dibromopropyl)phosphate

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Federal Hazardous Substances Act: On 4/6/77, CPSC acted under FHSA to remove all TRIS-treated children's clothing from the market--a recall of all articles in the channels of distribution and if any treated garments in the hands of consumers was ordered. On 3/5/78, CPSC issued a rule under FHSA to prohibit the export of the same products. (CPSC)	In the spring of 1977, approximately 16-20 million garments were recalled. Some of the garments were destroyed; some may still be in warehouses. TRIS is no longer manufactured or used domestically. (CPSC)	42 FR, p. 18858 (CPSC)
RCRA, 3004-3006: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and record/recordkeeping requirements. Also designates TRIS as a hazardous constituent of waste, and subjects wastes known to contain it, to the same requirements. Promulgated 5/19/80.		30 CFR 261.11, 261.33
TSCA, 8(a): Because manufacture of this chemical has been discontinued, no regulatory action under TSCA was deemed necessary; because this chemical was toxic, it would not be subjected to premanufacturing notification requirements. Accordingly, a rule requiring that EPA be notified of intent to resume manufacture or importation was promulgated, 10/29/'82. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Would severely limit the potential for further introduction of TRIS into the environment. (EPA)	45 FR 7C, p. 7C720 (EPA)

MONS 025890

URETHANE

There is sufficient evidence of the carcinogenicity of urethane in experimental animals.[1] Urethane was carcinogenic in mice, rats and hamsters following oral administration (in drinking water or by stomach tube), inhalation, and subcutaneous or intraperitoneal injection producing lymphomas, hepatomas, melanomas, and vascular, lung and other tumors. It was an initiator of skin carcinogenesis in mice when given either orally or topically. Urethane also enhanced the leukemogenic effect of X-irradiation in mice. It was carcinogenic in single dose experiments and following prenatal exposure. Neonatal and infant mice were more susceptible to cancer induction by urethane than were adult mice.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France: IARC, 1974, pp. 111-40.

Urethane (ethyl carbamate) is a colorless, odorless organic compound that is soluble in water. Urethane is available in the United States in crystal form or as a fused solid.

The primary use of urethane is as a chemical intermediate in the preparation of amino resins. Urethane is also used as an intermediate in the production of pharmaceuticals, insecticides, and fungicides; in biochemical research; and in human and veterinary medicine. In the past, urethane was used as an active ingredient in drugs prescribed for the treatment of neoplastic diseases, as a hypnotic, as a component of a sclerosing solution for varicose veins, and as a topical bactericide. In 1970, approval of new drug applications for products containing urethane as an active ingredient was withdrawn after it had been found that urethane was ineffective. Urethane has also been used as an inactive component or solubilizer in liquid preparations for injections. FDA withdrew the new drug application approval for all drug products containing urethane as an inactive ingredient (Federal Register, 41 FR 8523, 4, 2/27/76). Two anticonvulsant drugs, trimethadione and paramethadione, can be contaminated by urethane. The allowable limit has been set at 1 ppm. These anticonvulsant drugs may be used only to treat epilepsy that is refractory to other available drugs.

MONS 025891

Urethane has been commercially produced in the United States since 1945. Between 1975 and 1977, there were five producers in four EPA regions manufacturing about 4 million lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). Several companies now produce urethane solely for research. No estimate was available to NCI on the volume of urethane currently used in the United States, but the use is believed to be small.

Reports of human exposure are not available. In 1974, the National Occupational Hazard Survey made no estimate on the potential worker exposure to urethane. Urethane is volatile at room temperature, and exposure can occur through inhalation and skin absorption during manufacture and processing. Urethane may also be ingested by humans. Urethane has been found in diethylpyrocarbonate-treated beverages. Urethane was also found in wine, beer, orange juice, and some soft drinks.

Currently, urethane is regulated by EPA under the Resource Conservation and Recovery Act (RCRA), and regulation proposed under TSCA, 8(a), would provide detailed production and marketing data. EPA has also designated urethane as a hazardous constituent of waste and will determine the appropriateness of additional regulatory or other control actions. The use of urethane in drugs is prohibited, and approval has been withdrawn of all drugs containing urethane as an inactive ingredient (2/27/76) (FDA).

Urethane

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. (EPA)	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR Pt. 11, 261.33
TSCA, 8(a): reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
Prohibits the use of urethane as an active or inactive ingredient in drugs.		41 FR, pp. 8623-4
Withdrew approval of all drugs containing urethane as an inactive ingredient. (FDA)		41 FR, pp. 8623-4, 2/27/76 (FDA)

MONS 025892

VINYL CHLORIDE

There is sufficient evidence that vinyl chloride (VC) is a human carcinogen.[1] Its target organs are the liver (angiosarcomas), brain, lung and hemo- and lymphopoietic systems. Although evidence of a carcinogenic effect of VC in humans has come from groups occupationally exposed to high doses of VC, there is no evidence that there is an exposure level below which no increased risk of cancer would occur in humans.[2]

VC was tested in rats by oral, subcutaneous and intraperitoneal administration, and in mice, rats and hamsters by inhalation exposure. Following gastric intubation of a solution in olive oil, VC was carcinogenic in rats; inhalation exposure produced tumors at different sites in all three species, including angiosarcomas of the liver. VC was carcinogenic in rats following prenatal exposure. A dose response has been demonstrated.[2] There is sufficient evidence of the carcinogenicity of this compound in experimental animals.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 19. Lyon, France: IARC, 1979, pp. 377-437.

VC is a colorless gas that is slightly soluble in water.

The principal use of VC is in the production of plastics. VC is also used in the synthesis of other chemicals, and it was formerly a component of aerosol propellants. The vinyl chloride-vinyl acetate copolymers are used extensively in the production of vinyl asbestos floor tiles.

Annual production of VC in the United States is approximately 7 billion lb. Domestic production of the VC homopolymer is reported as 5 billion lb, and imports amount to 55 million lb. The estimated domestic production of the VC acetate copolymer is 279 million lb.

Human exposure to VC occurs primarily through inhalation and less frequently through skin absorption. More than 3.5 million workers are potentially exposed to this chemical. In addition, there is a potential exposure for 4.6 million people who live within 5 miles of industrial sites at which environmental emissions occur. Air emissions measured near several production facilities contained 3.1-12.5 ppb of VC. Very low exposure may occur if unreacted VC remaining in polyvinyl chloride packaging materials leaches into food and beverages (0.05-25 ng/kg), or medical products.

MONS 025893

The Consumer Product Safety Commission, the EPA, and the FDA each banned the use of VC as an aerosol propellant, eliminating exposure of 1-5 million people annually. Under the Clean Water Act, EPA has published a water quality criteria document for the protection of human health. The document addresses VC. The Clean Air Act, National Emission Standards for Hazardous Air Pollutants, addresses VC emissions from production and manufacturing facilities. The Resource Conservation and Recovery Act (RCRA) subjects VC waste products, off-specification batches, and spill residues in excess of 2270 lb to handling and report/recordkeeping requirements. RCRA also designates VC as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. FDA has eliminated the use of VC in drug products and has alerted food manufacturers to the need for monitoring packaging materials for VC. The Bureau of Foods is presently reevaluating its position on the September 3, 1975, proposal and may withdraw it. The OSHA standard of 1 ppm as an 8-hour time-weighted average, and a 5 ppm ceiling for any 15-minute period, was adopted in October 1974. Medical surveillance, training for workers, use of protective clothing and respirators, warning signs, product labeling, and periodic monitoring are required by OSHA.

MONS 025894

Vinyl Chloride

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Ban of self-pressurized household products that contain vinyl chloride monomer as an ingredient or in the propellant. (CPSC)	As a result of bans by CPSC, FDA, EPA, 1-5 million persons no longer exposed. (CPSC)	1600 CFR 1500.17(a)(10) (CPSC)
CAA, 112: NESHAP addressed vinyl chloride emissions from vinyl chloride monomer production and polymerization, and certain ethylene dichloride manufacturing facilities. Promulgated 10/21/76, 12/3/76, 6/7/77.	Imposes engineering controls that have been shown to reduce emissions by 95 percent over precontrol levels. 4.6 million people live within 5 miles of facilities subject to these standards.	40 CFR 61.60, 61.71
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
FIFRA, 3: Cancellation/suspension of all vinyl chloride monomer-containing pesticides registered for use in homes, food-handling establishments, hospitals, and enclosed areas, 3/75.	Most vinyl chloride in pesticides was used as an aerosol in propellants. (EPA)	40 FR, p. 3934
RCRA, 300.-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates vinyl chloride as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Drugs, Bureau of Medical Devices.	Has eliminated the use of vinyl chloride in drug products and as a propellant vehicle in aerosol products.	39 FR, p. 30830 (1974)
Any drug products containing vinyl chloride must pass through the new drugs Application Process.	This has alerted manufacturers to the need to monitor their packaging materials for vinyl chloride monomer. Bureau of Alcohol, Tobacco, and Firearms has banned polyvinyl chloride containers for alcoholic beverages, based on FDA work.	40 FR, p. 40529 (FDA)
FDA Bureau of Foods published notice to regulate vinyl chloride monomer in packaging material, 40 FR 40528 (1975), but rules were not finalized. (FDA)	The Bureau of Foods is presently reevaluating its position on the 9/3/75 proposal and may withdraw it. (FDA)	
PEL: 1 ppm 8-hr TWA, 5 ppm/15-min TWA ceiling; no direct contact with liquid. Protective clothing, respiratory, training, and medical surveillance requirements for workers; monitoring requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 1952: Walsh-Healy, 500 ppm maximum allowable concentration. 8/27/71: OSHA Takeover Standard--500 ppm (1300 mg/m³) ceiling. 4/5/74: Emergency Temporary Standard--50 ppm ceiling. 4/5/75: Final Standard--current limit effective. (OSHA)	29 CFR 1910.1017 (OSHA)

MONS 025895

IV. REQUESTS TO DHHS FOR RESEARCH AND TESTING, AND TO PROVIDE INFORMATION

Table 1 lists chemicals nominated to the NTP for carcinogenicity testing in calendar year 1981.

Table 2 contains status changes of compounds previously listed in Table 2, Section IV of the Second Annual Reports on Carcinogens.

Table 3 lists the chemicals acted upon by the NCI Chemical Selection Working Group (CSWG) but not submitted to NTP for Chemical Evaluation Committee (CEC) review.

Table 4 contains information related to the National Center for Toxicological Research's (NCTR) research and testing relevant to the carcinogenicity of substances.

Table 5 contains information requests received by NIOSH pertaining to the chemicals in the Annual Reports.

Table 6 lists the requests for chemical information received by the National Library of Medicine during 1980-1982.

MONS 025896

TABLE 1. CHEMICALS NOMINATED TO THE NTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY NTPS
108-24-7	Acetic anhydride	Acetic oxide	NCI	High consumption; representative anhydride	Recommended for pharmacokinetics, acrylating ability and strain A mouse lung adenoma assay by CEC
6206-57-0	2-Amino-6-nitrobenzothiazole	6-Nitro-2-amino-benzothiazole	NCI	Possible carcinogen; potential for human exposure	Nominated for carcinogenicity testing
20304-74-5	Antimony potassium tartrate	Tartaramatic; tartrated antimony	NCI	Possible carcinogen	Nominated for carcinogenicity testing
1912-24-9	Atrazine	6-Chloro-N-ethyl-N'-(1-methylethyl)-1,3,5-triazine-2,4-diamine	California Regional Water Quality Control Board	Widespread water pollutant and plant mutagen	Nominated for mutagenicity, carcinogenicity and reproductive effects testing
106-24-0	Butyric anhydride	Butyryl oxide	NCI	Anhydride Class Study; acrylic subclass; unknown suspicion of carcinogenicity	No testing recommended by CEC - await results from anhydride studies
127-00-4	1-Chloro-2-propanol	Propylene chlorohydrin	NCI	Considerable exposure; suspected carcinogen	Nominated for carcinogenicity testing
07-07-9	2-Chloro-1-propanol	Propylene chlorohydrin	NCI	Considerable exposure; suspected carcinogen	Nominated for carcinogenicity testing
98-56-5	p-Chloro-α,α,α-trifluorotoluene	p-Chlorobenzotrifluoride	NCI	Structurally related to known carcinogen	Nominated for carcinogenicity testing
15826-37-0	Cromolyn sodium	Disodium cromoglycate; FPL 670; Fenasma	NCI	Possible carcinogen	Nominated for carcinogenicity testing
118-52-5	1,3-Dichloro-5,5-dimethylhydantoin	Halane, DCSHH	NCI	Increased usage and exposure; previous invalid results	Recommended for mutagenicity, skin absorption & distribution reproductive effects; carcinogenicity (gavage) by CEC
78-88-6	2,3-Dichloropropylene		NCI	High potential for human exposure; structural relationship to known carcinogen	Nominated for carcinogenicity testing

MONS 025897

TABLE 1. CHEMICALS NOMINATED TO THE PTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981 (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
75381-20-9	1,5-Dinitropyrene		AFL/CIO	High potential for human exposure	Nominated for general toxicity, human reproductive effects & carcinogenicity testing
42397-64-8	1,6-Dinitropyrene		AFL/CIO	High potential for human exposure	Nominated for general toxicity, human reproductive effects & carcinogenicity testing
42397-05-9	1,8-Dinitropyrene		AFL/CIO	High potential for human exposure	Nominated for general toxicity, human reproductive effects & carcinogenicity testing
64-18-6	Formic acid		NCI	Structurally related to known carcinogen; high potential for human exposure	Nominated for carcinogenicity testing
206-21-8	Linoleiaidic acid	trans,trans,linoleic acid	NCI	Human exposure; suspected carcinogen	Nominated for carcinogenicity testing
6317-18-8	Methylene bis(thiocyanate)	Methylenedirhodamide	NCI	High potential for human exposure; unique chemical structure	Nominated for carcinogenicity testing
74-83-9	Methyl bromide	Bromomethane	Calif. Dept. Health Svs.	Lack of info. on toxicology; high production volume	Recommended for carcinogenicity (inhalation) tests by CEC
421-20-5	Methyl fluorosulfonate	Magic methyl	NCI/Cummins	Potential carcinogen; use as methylating agent	Recommended for mouse strain A lung adenoma assay by CEC
108-10-1	Methyl isobutyl ketone	Mesone	NCI	High potential for human exposure	Nominated for carcinogenicity testing
333-27-7	Methyltrifluoromethane sulfonate	Methyl triflate	NCI	Use as methylating agent	Recommended for Salmonella assay mammalian cell mutagenesis and strain A mouse lung adenoma assay by CEC

MONS 025898

TABLE 1. CHEMICALS NOMINATED TO THE NTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981 (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
1313-99-1	Nickel oxide	Nickel monoxide	NCI	Mat.l Class Study; relatively large exposure; possible cancer inducing compound	Recommended for carcinogenicity testing (inhalation) by CEC
79-98-8	Nitroethane	Nitrocarbol	NCI	High potential for human exposure; structural relationship to known carcinogen	Nominated for carcinogenicity testing
9520-43-0	1-Nitropyrene		AFL/CIO	High potential for human exposure	Nominated for general toxicology, reproductive effects & carcinogenicity testing
2212-87-1	Ordram (molinate)	S-ethyl N,N-hexamethylene-thiocarbamate	California Regional Water Quality Control Board	Found in drinking water associated with fish kills; linked to reproductive effects in workers	Nominated for general toxicology, reproductive effects & carcinogenicity testing
127-91-3	beta-Pinene	Pepinen	NCI	Structural relationship to known carcinogen; high potential for human exposure	Nominated for tumor promoter studies
110-86-4	Piperidine	Hexahydropyridine	NCI	Wide use as solvent, hardening agent catalyst, rubber additive & constituent of human urine	Rejected due to lack of suspicion of carcinogenicity
38641-94-0	Poundup (glyphosphate isopropylamine salt)	HOE 2139	Calif. Regional Water Quality Control Board	Widespread use & exposure	Nominated for mutagenicity, carcinogenicity and reproductive effects testing
990-79-1	Salicylazosulfapyridine	Azopyrin	NCI	Aryl sulfonamide class study; low suspicion as a possible carcinogen; high human use	Recommended for Salmonella microsomal assay, Drosophila studies and carcinogenicity by CEC
7778-11-3	Sodium chromate	Chromic acid	NCI	High suspicion of carcinogenicity; great potential for exposure; representative soluble chromium VI compound	Recommended for carcinogenicity by CEC (inhalation)
144-82-1	Sulfamethizole	Methazol	NCI	Aryl sulfonamide class study; suspected carcinogen; used as a major sulfa drug	Recommended for Salmonella microsomal assay, Drosophila studies by CEC

MONS 025899

TABLE 1. CHEMICALS NOMINATED TO THE NTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981 (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY NTP
63-74-1	Sulfanilamide	p-Sulfamidoaniline	NCI	Model for acyl sulfonamides; potential for human exposure	Recommended for Salmonella assay, [redacted] studies by CIC
72-14-0	Sulfathiazole	N'-2-Thiazolylsulfanilamide	NCI	Aryl sulfonamide class study; considerable human exposure; low suspicion as possible carcinogen	Recommended for Salmonella assay, [redacted] studies by CIC
95-94-3	1,2,4,5-Tetrachlorobenzene	1,4-Tetrachlorobenzene	NCI	Structurally related to known carcinogen	Nominated for carcinogenicity testing
25167-83-3	2,3,4,6-Tetrachlorophenol	Dowicide 6; TCP	Calif. Regional Water Quality Control Board	Found in drinking water, wide exposure	Nominated for mutagenicity, carcinogenicity & reproductive effects testing
117-08-8	Tetrachlorophthalate anhydride	Tetrathal	NCI	Anhydride class study; suspicion of potential carcinogenicity	Recommended for in vitro cytogenetics; [redacted] studies & carcinogenicity by CIC
88767-61-5	1,3,5,8-Tetranitropyrene		AFL/CIH	High potential for human exposure	Nominated for general toxicology, reproductive effects & carcinogenicity testing
198-55-1	Thiophene	Thiofuran; thiole; divinylene sulfide	NCI	Potential carcinogen	Nominated for carcinogenicity testing
4460-86-0	2,4,5-Trimethoxybenzaldehyde	Asaronaldehyde	NCI	Structural interest; potential exposure	Recommended for bat try of short term mutagenicity tests, reproductive effects & carcinogenicity by CIC
94094-20-8	Trimethylanonium Isochloro-potassate		NCI/Cumulus	Potential carcinogenicity; use as methylating agent	Recommended for mutagenicity and strain A mouse lung adenoma assay by CIC

CIC

MONS 025900

TABLE 1. CHEMICALS NOMINATED TO THE NTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981 (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
129-79-3	8,4,7-Trinitrofluorenone	TNF	ACL/CIG	Widespread exposure; structurally related to known carcinogen	Nominated for general toxicology, reproductive effects, carcinogenicity & epidemiology testing
79301-19-6	1,3,6-Trinitropyrene		AFL/CIG	High potential for human exposure	Nominated for general toxicology, reproductive effects, & carcinogenicity testing
69-60-1	2,6-Xylidine	2,6-Dimethylbenzamine	NCI/Meisburger	Decomposition product of xylocaine; structure activity relationship	Recommended for no additional testing at this time by CEC

CEC = NTP Chemical Evaluation Committee

Nominated = Executive Summaries written but no action by CEC.

Recommended = Rationale for request accepted by CEC. Executive Summary reviewed by CEC and recommendation for testing given.

MONS 025901

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
75-07-0	Acetaldehyde	Ethanal	NCI	Class Study; potential for high exposure; suspicion of carcinogenic activity	Nominated but not selected (deferred 6/81)
75-05-8	Acetonitrile	Cyanomethane; methyl nitrile; methane carbonitrile; methyl cyanide	NCI	Potential for high exposure (found in water supplies)	Prechronic test in progress
10361-37-2	Barium chloride		NCI	Class Study; potential for considerable human exposure	Assigned for carcinogenicity testing
17804-36-2	Benomyl	Benlate® Methyl 1-(butyl-carbamyl)-2-benzimidazole carbonate	NCI	Class Study; potential for significant exposure; ability to cause point mutations in microbial systems and chromosomal abnormalities in both microbial and mammalian systems	Nominated for mutagenicity testing
100-52-7	Benzaldehyde		NCI	Potential for high human exposure	Chronic test in progress
121-04-0	Benzethonium chloride	Hyamine® 1622	NCI	Class Study; nominated by CSMB because suspicion of carcinogenicity was judged to be high	Nominated for battery of short term mutagenicity tests, reproductive effects & carcinogenicity (4/81)
100-47-0	Benzonitrile	Cyanobenzene Phenyl cyanide	NCI	Present in water supplies; unknown suspicion of carcinogenicity; mod-high production	Nominated for carcinogenicity testing
85-02-9	Benzo(f)quinoline	β-naphthoquinoline Naphthopyridine	NCI	Class Study; potential for exposure; evidence of activity in Ames Salmonella; representative nitrogen-containing aromatic heterocycle	Nominated for carcinogenicity testing
98-07-7	Benzotrichloride		Air Pollution Board, Chattanooga, TN	Potential for lung cancer in production workers involved with the many production facilities in the U.S.	Nominated for carcinogenicity testing (4/81)
98-88-4	Benzoyl chloride	Benzenecarbonyl chloride Alpha-Chlorobenzaldehyde	NCI	Class Study; potential for significant human exposure; use as an acylating agent, therefore suspicion of carcinogenicity	Nominated for in vitro cytogenetics, Drosophila studies, sister chromatid exchange & carcinogenicity (4/81)

MONS 025902

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
100-44-7	Benzyl chloride		Air Pollution Board, Chattanooga, TN	Potential for lung cancer in production workers involved with the many production facilities in the U.S.	Chronic test in progress
120-32-1	o-Benzyl-p-chlorophenol	Chlorophene; Santophen 1	NCI	Class Study; high potential for human exposure	Selected for testing by NTP, assigned to contractor
91939-50-6	[4,4'-Bithiazole]2,2'-diamine		NCI	Class Study; model test compound structurally analogous to the primarily hydrocarbon solar carcinogen benzidine	Nominated for strain A lung adenoma assay and other short term tests
307-57-3	Bruc ine	2,3-Dimethoxystrychnidin-10-one	NCI	Class Study; potential for considerable human exposure; unknown proportion of carcinogenicity	Nominated for mutagen.city, dermal absorption study (1/81)
112-56-1	2-[2-Butoxyethoxy]ethyl thiocyanate	Butyl carbitol rhodanate tetheme 204	NCI	Class Study; potential for significant human exposure	Nominated for carcinogenicity testing
614-45-9	t-Butyl perbenzoate	Benzoyl t-butyl peroxide Esperox 10 Trigonox C	NCI	Structure a; potential for human exposure	Nominated for battery of short term mutagenicity tests, reproductive effects & carcinogenicity (4/81)
123-72-8	Butyraldehyde	n-butyl aldehyde	NCI.	Class Study; suspicion of carcinogenicity; significant potential for human exposure; occurrence in water	Nominated to NTP for testing
1306-19-0	Cadmium oxide	Cadmium monoxide	NCI	Class Study; reported carcinogenicity of other cadmium-containing inorganics; significant potential for human exposure	Nominated but not selected (deferred 6/81)
1306-23-6	Cadmium sulfide		NCI	Class Study; reported carcinogenicity of other cadmium-containing inorganics; significant potential for human exposure	Nominated but not selected (deferred 6/81)

MONS 025903

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION OR STATUS
58-08-2	Caffeine		FDA	High human exposure	Prechronic test in progress
1260-17-9	Carminic acid	C.I. 75470 C.I. Natural Red 4	NCI	Class Study; high exposure estimates for carmine and cochineal (both of which use carminic acid as the chief coloring principle)	Nominated for carcinogenicity testing
2244-16-8	d-Carvone		NCI	Potential for high human exposure	Prechronic test in progress
120-80-9	Catechol		NCI	Known cocarcinogen	Prechronic test in progress
9004-34-6	Chlorazine		EPA	Very large potential for exposure	Prechronic test in progress
608-61-8	m-Chloroaniline	C.I. Azoic Diazo Components 2	NCI	Occurs in water; potential for human exposure; high annual production	Nominated for battery of short-term mutagenicity tests, reproductive effects & carcinogenicity (4/81)
106-47-8	p-Chloroaniline		NCI	High production and exposure; potential carcinogen	Report available
99-63-8	4-Chloro-2-nitroaniline	2-Nitro-4-chloroaniline; C.I. Azoic Diazo Component 9, Base	NCI	Class Study; high suspicion of possible carcinogenicity; potential for considerable human exposure	Selected & assigned for carcinogenicity by NTP
57-88-5	Cholesterol	Cholest-5-en-3-ol Cholesterin	FDA/NCI	Class Study; representative nonhormonal steroid; widespread uses	No testing recommended (12/81)
1250-96-9	Cholesterol 5 ,6 -epoxide	---	FDA/NCI	Potential for human exposure; suspicion of potential carcinogenicity	No testing recommended (12/81)
62373-04-5	C.I. Basic Red 29	C.I. 11460 Cartacryl Red GL	NCI	Class Study; potential for human exposure; structurally analogous to orthoanisidine which reportedly is carcinogenic and mutagenic, and to o-tolidine-o-toluene, which reportedly is a weak carcinogen in rats	Nominated for strain A mouse lung adenoma assay and other short term tests

MONS 025904

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY OHMS
6420-31-5	C.I. Direct Black 19	C.I. 35255	NCI	Class Study; potential use in a direct laser printing technique	Deferred (1/81)
2610-05-1	C.I. Direct Blue 1	C.I. 24410; Calcomine Sky Blue 6BX; Fenamin Sky Blue 3F; Atlantic Sky Blue 6B	NIOSH	Derived from known carcinogen; no test data; potential high human exposure	Nominated but not selected
2429-73-4	C.I. Direct Blue 2	C.I. 22590; Diazo Black 8H; Fenamin Navy Blue H; Phenazo Black 9H	NIOSH	Derived from known carcinogen; potential for considerable human exposure; no adequate test data	Nominated but not selected
2429-74-5	C.I. Direct Blue 15	C.I. 24400 Pontacyl Sky Blue 4BX	NIOSH/CPSC	High potential for human exposure; suspicion of potential carcinogenicity as an o-dianisidine-based dye	Recommended for no additional tests (1/81)
20400-37-5	C.I. Direct Blue 210		NCI	Class Study; potential for considerable human exposure; high suspicion of potential carcinogenicity	Selected for testing by NTP, assigned to contractor
992-00-8	C.I. Direct Red 2	C.I. 23500 Benzopurpurin 4B	NIOSH/CPSC	Significant potential for human exposure; suspicion of potential carcinogenicity as an o-tolidine-based dye	Recommended for no additional tests (1/81)
6300-29-0	C.I. Direct Red 39	C.I. 23630 Atlantic Scarlet 3B	NIOSH/CPSC	Significant potential for human exposure; suspicion of potential carcinogenicity as an o-tolidine-based dye	Recommended for no additional tests (1/81)
6471-80-4	C.I. Pigment Red 23	3-(hydroxy-4-[2-methoxy-5-nitrophenyl]-azo)-N-[3-nitrophenyl]-2-naphthalenecarbonamide	NCI	Class Study; high suspicion of possible carcinogenic activity; reductive cleavage of azo linkage would yield compound related to proven carcinogens; potential for considerable human exposure	Prochronic test in progress
6300-31-2	C.I. Pigment Yellow 74	2-(2-Methoxy-4-nitrophenyl)azo)-N-(2-methoxyphenyl)-2-oxo butanamide	NCI	Class Study; potential for considerable human exposure; high suspicion of possible carcinogenic activity because reductive cleavage of azo linkage would yield compound related to proven carcinogen	Selected for testing, assigned for carcinogenicity testing

MONS 025905

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION TO BE DONE
482-89-3	C.I. Vat Blue 1	C.I. 73000 C.I. Pigment Blue 66 D & C Blue No. 6 Indigo (synthetic)	NIOSH/CPSC	High exposure; common use as a dye for denim jeans	Nominated for muta-genicity, reproduc-tive effects, skin absorption, & distri-bution & carcino-genicity (s.p.) tests (1/81)
470-82-6	1,8-Cineole	Eucalyptol	FDA	High human exposure	Prechronic test in progress
104-55-2	Cinnamaldehyde	3-Phenyl-2-propenal	FDA	High human exposure	Prechronic test in progress
76-57-3	Codeine	Methylmorphine	DCI	Class Study; potential for considerable human exposure; unknown suspicion of carcino-genic activity	Nominated for repro-ductive effects & carcinogenicity tests (5/81)
64-86-8	Colchicine		DCI	Class Study; potential for considerable human exposure; representative of the tropolone group of the phenylalanine-and tyrosine-derived alkaloids	Nominated for muta-genicity tests & carcinogenicity tests
91-64-5	Coumarin		FDA	Structure relationship; species specificity	Prechronic test in progress
458-37-7 8024-37-1	Curcumin (see tumeric)				
52-90-4	L-Cysteine	β-Mercaptoalanine	FDA/DCI	Class Study; potential for signifi.ant exogenous exposure; unique structure containing a mercapto moiety	Under considera-tion by DCI
65-46-3	Cytidine	Cytosine riboside 1-β-Riboforanosyl-cytosine	FDA/DCI	Class Study; representative pyrimidine which, after admi-istration to animals in large doses, might lead to the ac.umulation of cytotoxic and/or oncogenic products	No testing recommended (12/81)
6004-30-1	Dehydroemetine hydro-chloride		FDA	Potential exposure as a drug	Under considera-tion by DTP

MONS 025906

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY OMNS
81-11-0	4,4'-Diamino-2,2'-stilbenedisulfonic acid		EPA	Large production; wide exposure; lack of data	Prechronic test in progress
84072-75-1	4,5-Dichloro-2-benzothiazolamine	2-Amino-5,6-dichlorobenzothiazole	NCI	Class Study; potential for significant human exposure suspicion of potential carcinogenicity because of its structural analogy to 2-naphthylamine	Nominated for carcinogenicity testing
54200-46-2	N,N-Diethyl-4-[(5-nitro-2-thiazolyl)azo]benzenamine		NCI	Class Study; suspicion of potential carcinogenicity	Nominated for strain A mouse adenoma assay and other short term tests
84-66-2	Diethyl phthalate		EPA	Chemical identified in drinking water	Withdrawn after carcinogenesis testing begun
119-84-6	3,4-Dihydrocoumarin		NCI	Potential for high human exposure	Prechronic test in progress
800-80-2	Dimethoxane ("dioxin")		NCI	Potential carcinogen	Prechronic test in progress
68-12-2	N,N-Dimethylformamide	Dimethylformamide; DMF; DMFA; N-formyldimethylamine	NCI	Present in water; potential for human exposure	Selected for testing by NTP, assigned to contractor
1064-28-0	Dimethyloldihydroxyethylenurea	4,5-dihydroxy-1,3-bis(hydroxy-methyl)-2-imidazolidinone; dimethylolglyoxaluron; DMDHEU	NCI	Class Study; low/moderate suspicion of carcinogenicity based on potential of N-nitrosation; potential for human exposure	Prechronic test in progress
97-77-8	Disulfiram		Dr. Sheppard (FDA)	High exposure and potential as a human teratogen	Under consideration by NTP
469-23-0	Dosylamine		FDA	No carcinogenicity testing	Prechronic test in progress
366-42-7	Enetine hydrochloride		FDA/NCI	Potential high exposure; old drug never studied by present standards	Under consideration by NTP
55-31-2	Epinephrine hydrochloride		FDA/NCI	Lack of toxicological data; devise meaningful tests	Prechronic test in progress

MONS 025907

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SCCC:D ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION OR STATUS
00-00-9	Epoxol		Drs. Huff & Schumacher (NTP)	Potential for neurologic damage by inhalation of exothermal products	Under consideration by NTP
000-00-7	1,2-Epoxybutane		EPA/OSHA/ CPSC/NCI		Prechronic test in progress
00-79-7	Ergonovine	Ergotrate®	NCI	Class Study; potential for considerable human exposure	Nominated for Ames test (1/81)
113-15-5	Ergotamine		NCI	Class Study; potential for considerable human exposure; low level of carcinogenic suspicion based on its potential to undergo N-nitrosation	Nominated for battery of short term tests including Ames (1/81)
74-96-4	Ethyl bromide		OSHA/NCI	Structurally related to known carcinogens	Chronic test in progress
75-00-3	Ethyl chloride		OSHA/NCI	High production & exposure	Chronic test in progress
107-15-3	Ethylenediamine		EPA	Chemical related to hydrazines, a group containing known carcinogens	Withdrawn after carcinogenesis testing began
107-21-1	Ethylene glycol		FDA/NCI	High production & potential exposure	Prechronic test in progress
75-21-8	Ethylene oxide		OSHA/EPA/NCI	High production & exposure, potential carcinogen	Chronic test in progress
100-76-7	2-Ethylhexanol	2-(Ethyl-1-hexanol 2-Ethylhexyl alcohol	Dr. Gould (EPA)	Metabolite of di(2-ethylhexyl)-phthalate (DEHP) which has been found to be carcinogenic in rats and mice	Nominated for carcinogenicity testing
7720-78-7	Ferrous sulfate	Copperas Green vitriol Iron (II) sulfate	FDA/NCI	Class Study; potential for human exposure; moderately high production; used in the treatment of iron-deficient anemia and as a nutritional supplement	No testing recommended (12/81)
2164-17-2	Fluometuron		Drs. Huff & Schumacher (NTP)	Suspicion of carcinogenicity; positive in rats	Report available

MONS 025908

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 1 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	BASIS FOR REQUEST	ACTION BY DHHS
59-30-3	Folic acid	Folacin Pteroylglutamic acid Vitamin B_c	FDA/NCI	Class Study; interest in the 2-aminopteridine moiety; potential for accumulation after administration to animals in large doses	No testing recommended (12/81)
50-00-0	Formaldehyde		OSHA/CPSC/NIEHS/NCI	High production & exposure	Withdrawn after carcinogenesis testing began
57-48-7	D-Fructose	Fructose Fruit sugar Levulose	FDA/NCI	Class Study; representative member with potential for accumulation of its anabolic and/or catabolic intermediates after administration to animals in large doses	Under consideration by NTP
110-17-8	Fumaric acid	trans-1,3-Ethylene-dicarboxylic acid	Dr. A. Gregory (USDSM)	Class Study; role as a intermediate in the tricarboxylic acid cycle and potential for bioaccumulation of its anabolic and/or catabolic intermediates after administration to animals in large doses	Recommended Salmonella assay (12/81)
98-00-0	Furfuryl alcohol		NCI	Potential carcinogen	Withdrawn after carcinogenesis testing began
1303-00-0	Gallium arsenide		Dr. J. Mann (NCI)	Projected use in the semiconductor industry for photovoltaic cells; structural interest	Unwanted for metabolism studies
9005-65-6	Glycol (Polysorbate 80)		CPSC/NIOSH	Wide industrial exposure; oxalic acid formation	Prechronic test in progress
73-40-5	Guanine	C.I. Natural White 1 2-Aminohypoxanthine Natural Pearl Essence	FDA/NCI	Class Study; representative purine; endogenous exposure	No testing recommended (12/81)
67-72-1	Hexachloroethane		EPA/NIOSH	Potential carcinogen; industrial exposure	Report available at NTIS
548-62-9	Gentian violet	N-methyl-4-rosaniline chloride	FDA/NCI	Potential large exposure through tissue residues; for regulatory purposes	Chronic test in progress

MONS 025909

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
124-09-4	1,6-Hexanediamine		EPA	Occupational and nonoccupational exposure	Scheduled for mutagenicity tests
56-69-9	5-Hydroxytryptophan		FDA	Wide exposure; need to develop protocols	Withdrawn after carcinogenesis testing begun
73-32-5	L-Isoleucine	2-Amino-3-methylpentanoic acid	FDA/NCI	Class Study; representative neutral amino acid	Under consideration by NTP
60-33-3	Linoleic acid	Isolinoleic acid (2,2)-9,12-Octadecadienoic acid	FDA/NCI	Class Study; representative unsaturated fatty acid; significant exogenous exposure	No testing recommended (12/81)
463-40-1	Linolenic acid	-Linolenic acid (2,2,2)-9,12,15-Octadecatrienoic acid	Dr. Gould (EPA)/NCI	Class Study; potential for bioaccumulation of its anabolic and/or catabolic intermediates after administration to animals in large doses	No testing recommended (12/81)
56-87-1	L-Lysine	2,6-Diaminohexanoic acid; Lysine	FDA/NCI	Class Study; representative basic amino acid; potential for exogenous exposure	Under consideration by NTP
7700-87-7 10424-56-7	Manganese sulfate		NCI	Class Study; significant potential for human exposure; high suspicion of carcinogenicity of manganese chloride	Selected for testing by NTP, assigned to contractor
149-30-4	2-Mercaptobenzothiazole		NCI	Potential wide exposure; (medicinal solution capped with rubber stopper containing compound)	Chronic test in progress
7725-93-1	2-Mercapto-4-methyl-5-thiazolyl methyl ketone	5-(2,3-Dihydro-4-methyl-2-thiazo-5-thiazolyl) ethanone	NCI	Class Study; suspicion of potential carcinogenicity because of the relationship to ethylenethiourea and thioacetamide which are carcinogenic in rats	Nominated for strain A mouse lung adenoma assay and other short term tests
7487-94-7	Mercuric chloride		NCI/FDA	Metal class study	Prechronic test in progress
1344-48-2	Mercuric oxide	C.I. 77760 Yellow mercuric oxide	NCI	Class Study; potential for significant human exposure; representative mercury (II) salt	No testing recommended (5/81)

MONS 025910

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION OF DHHS
5002-37-2	Methodilazine		FDA	No carcinogenicity testing	Selected for testing by NTP, assigned to contractor
91-80-5	Methapyrilene		FDA	Use as positive control	Prochronic test in progress
126-31-0	Methiodol sodium	Sodium iodomethane-sulfonate; Skiodan® sodium	NCI	Probably significant human exposure; previously tested with inadequate test results	Selected for mutagenicity testing (S/NI)
1747-06-0	6-Methoxy-2-benzothiazolamine	2-Amino-6-methoxybenzothiazole 6-Methoxy-2-amino-benzothiazole	NCI	Class Study; suspicion of potential carcinogenicity because of its activity, as a mutagen in the Ames procedure; structurally analogous to 2-naphthylamine, a carbocyclic aromatic amine carcinogen	Nominated for carcinogenicity testing
92-36-4	4-(6-Methyl-2-benzothiazolyl)-benzenamine	Dehydrothio-p-toluidine	NCI	Class Study; estimated significant potential for human exposure; structurally analogous to the carcinogenic biphenylamines	Nominated for carcinogenicity testing
74-83-9	Methyl bromide		Dept. of Health, State of California	Two recent in vitro tests showed mutagenic activity	Under consideration by NTP
75-09-2	Methylene chloride		EPA/NCI	High production & exposure	Chronic test in progress
624-83-9	Methyl isocyanate	Isocyanatomethane MIC	NCI	Potential for exposure; review of chemicals produced in the largest quantities in the United States in 1975	Nominated for mutagenicity testing (S/NI)
24340-76-9	3-Methyl-5-isothiazolamine	5-Amino-3-methylisothiazole	NCI	Class Study; potential for human exposure; suspicion of potential carcinogenicity because of its relationship to single-ring carbocyclic aromatic amines and 5-N-substituted thiazoles found to be carcinogenic in the laboratory	Nominated for strain A lung adenoma assay & other short term tests

MONS 025911

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
80-62-6	Methyl methacrylate		NCI	Considerable potential for human exposure and carcinogenic activity	Chronic test in progress
80-11-5	N-Methyl-N-nitroso-p-toluenesulfonamide	Diazald® N-Nitroso-N-methyl-4-tolylsulfonamide p-tolylsulfonylmethylnitrosamide	Dr. E. Weisburger (NCI)	Nominated as a research chemical because it is considered to be structurally interesting; suggestive evidence of carcinogenicity from previous study	Nominated for strain A mouse lung adenoma assay (5/81)
924-42-5	N-Methylolacrylamide	N-(hydroxymethyl)-2-propenamide; N-methanol-acrylamide; N-(hydroxymethyl)acrylamide	NCI	Class Study; moderate suspicion based on structural relationship to known carcinogen; potential for nitrosation; considerable potential for exposure	Prechronic test in progress
113-45-1 [illegible]	Methylphenidate	Ritalin® alpha-phenyl-2-piperidine-acetic acid methyl ester	NCI/FDA	Class Study; significant levels of estimated exposure; chronic use in children; lack of data	Selected for testing by NTP assigned to contractor
79-11-8	Monochloroacetic acid		EPA	High toxicity in animals indicated potential hazard to humans	Prechronic test in progress
4376-20-9	Mono(2-ethylhexyl) phthalate	2-Ethylhexyl hydrogen phthalate	Dr. Gould (EPA)	One of the two major primary metabolites of di(2-ethyl hexyl)phthalate which was reported to be hepatocarcinogenic	Nominated for carcinogenicity testing
13463-30-1	Nickel carbonyl		PIENS	Potential human carcinogen	Under consideration by NTP
486-42-2	Ninhydrin		Maryland State Police Dept.	Used in forensic medicine by Maryland State Police Department	Nominated for Salmonella assay (4/81)
100-01-6	p-Nitroaniline	1-Amino-4-nitrobenzene; Azoic Diazo Component 37	NCI	Class Study; high suspicion of possible carcinogenicity; potential for considerable human exposure	Selected for testing by NTP, assigned to contractor
91-23-6	o-Nitroanisole	2-Methoxynitrobenzene	NCI	Class Study; high suspicion of carcinogenic activity because it is a nitro analog of known carcinogen; potential for considerable human exposure	Selected for testing by NTP, assigned to contractor

MONS 025912

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY OHMS
[illegible]-90-3	Nitrobenzene	Nitrobenzol; oil of mirbane	NIOSH/NCI	Class Study; moderate suspicion of carcinogenicity; potential for considerable human exposure	Prechronic test in progress
121-90-4	o-Nitrobenzoyl chloride	3-Nitrobenzoyl chloride	NCI	Class Study; high production; possible carcinogen because of its structure as an aryl nitro compound and acyl chloride	Nominated for cell transformation studies
122-04-1	p-Nitrobenzoyl chloride	4-Nitrobenzoyl chloride	NCI	Class Study; high U.S. imports; possible carcinogen because of its structure as an aryl nitro compound and acyl chloride	Nominated for cell transformation studies
100-02-7	p-Nitrophenol		OSHA/NCI	Large production/exposure; potential carcinogen	Histopathology in progress
1136-54-7	N-Nitrosodiethanolamine		FDA		Report available
1321-12-6	Nitrotoluene		NIOSH	Wide occurrence/exposure; potential carcinogen	Report available
120-82-1	Noscapine	1- -narcotine (noscapine)	NCI	Class Study; potential for considerable human exposure; of interest as an antitussive which is not controlled	Nominated for mutagenicity tests (1/80)
303-47-9	Ochralamin A		FDA	Potential wide exposure; potential carcinogen	Prechronic test in progress
30530-[illegible]-1	2-Octyl-2-isothiazolone	Kathon LP Kathon 893 SP Shane M-8 2-Octyl-4-isothiazolin-3-one	NCI	Class Study; high potential for human exposure; single representative of the saturated thiazoles	Nominated for carcinogenicity testing
7647-30-1	Palladium (2+) chloride		OSHA	Potential environmental pollutant; lack of toxicology data	Prechronic test in progress
1025-21-4	Pentachloroanisole		FDA/NCI	Potential high exposure to low levels from fish and finished water	Prechronic test in progress
78-11-5	Pentaerithritol tetranitrate		NCI	Potential exposure as drug	Prechronic test in progress

MONS 025913

TABLE 2. STATUS (RANGE) OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
22224-92-6	Fenamiphos	Bay 68138 Fenamiphos Nemacur	NCI	Class Study; significant potential for human exposure; unique structure as a phosphoramide	Nominated for carcinogenicity testing
66-71-7	o-Phenanthroline	4,5-Diazaphenanthrene 1,10-Phenanthroline	Dr. Harry Klauda (Stoffel Research Institute)	Structurally interesting because it contains two nitrogens in the phenanthrene nucleus	Nominated for battery of mutagenicity tests (4/81)
490-91-1	5-Phenyl-2,4-thiazole-diamine	Aniphenazole 2,4-Diamino-5-phenylthiazole	NCI	Class Study; model compound on the basis of its structural analogy to carbocyclic aromatic amine carcinogens	Nominated for in vitro A lung adenoma assay & other short term tests
57-41-0	Phenytoin		NIEHS/NCI	Large production/exposure; inadequate carcinogenicity data; used as an anti-convulsant	Prechronic test in progress
75-44-5	Phosgene		EPA	Occurs in environment; data on extremely low level inhalation	Withdrawn
9003-39-8	Polyvinylpyrrolidone polymers		CPSC/FDA/OSHA	Potential wide exposure	Withdrawn
7681-11-0	Potassium iodide	Potassium monoiodide	FDA/NCI	Class Study; most widely used form of iodine as a nutritional supplement; representative iodine-containing inorganic	On testing recommended (12/81)
57-66-9	Probenecid		NCI	High exposure as drug	Prechronic test in progress
60-87-7	Promethazine		FDA	No carcinogenicity testing	Prechronic test in progress
50-34-0	Propantheline bromide	beta-Diisopropylaminoethyl xanthene-9-carboxylate methobromide; Pro-Banthine	FDA/NCI	Class Study; chronic use and large estimated level of exposure; lack of carcinogenicity data	Selected for testing by NTP, assigned to contractor
107-89-1 78-87-5	Propylene chlorohydrins	1-Chloro-2-propanol/ 2-chloro-1-propanol mixture	NCI	Class Study; potential for significant human exposure; suspicion of possible carcinogenicity, associated with short chain chlorinated alcohols	Under consideration by NTP

MONS 025914

TABLE 8. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 8 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY NTP
91-84-9	Pyridamine		FDA	No carcinogenicity testing	Prechronic test in progress
127-17-3	Pyruvic acid	2-Oxopropanoic acid	FDA/NCI	Class study; potential for accumulation of its anabolic and/or catabolic intermediates after administration to animals in large doses	Under consideration by NTP
117-39-5	Quercetin		FDA	Wide exposure/potential mutagen	Assigned to contractor
106-51-4	p-Quinone		NCI	Potential carcinogen	Prechronic test in progress
108-46-3	Resorcinol		CPSC	Occurs in environment and ground waters; potential large exposure	Prechronic test in progress
83-88-5	Riboflavin	Lactoflavin Vitamin B_2 Vitamin G	FDA/NCI	Class Study; significant potential for exogenous exposure	No testing recommended (12/81)
51-34-3	Scopolamine	Hyoscine	NCI	Class Study; potential for considerable human exposure; suspicion of potential carcinogenicity	Nominated for reproductive effects and carcinogenicity tests (5/81)
480-81-0	Senecionphylline		FDA	Potential wide exposure; potential carcinogen	Withdrawn
127-85-5	Sodium arsanilate		FDA	Potential large exposure due to presence in feed and environment; chemical form of arsenic in tissues unknown; may present health effects	Nominated but not selected
26628-22-8	Sodium azide		EPA	Potential wide exposure/ nucleophilic agent; needs retesting	Prechronic test in progress.
57-68-1	Sulfamethazine	4,6-Dimethyl-2-sulfanilamidopyrimidine; sulfadimidine	NCI	Class Study; low suspicion of carcinogenicity; potential for considerable human exposure; potential tissue residue in swine	Chronic test in progress

MONS 025915

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
129-17-9	Sulfan Blue		FDA	Nonprofit drug with no current replacement; suspicion of carcinogenicity	Under consideration by NTP
1746-01-6	2,3,7,8-Tetrachlorodibenzo-dioxin		FDA	Occurs in environment; IARC could not evaluate carcinogenicity from available data	Report in press
116-14-3	Tetrafluoroethylene	Tetrafluoroethene Perfluoroethylene TFE	NCI	Significant potential for human exposure; no adequate carcinogenicity tests have been conducted	Nominated for mutagenicity & carcinogenicity tests by IIC
30968-32-3	Tetraglycidol methylene dianiline		Drs. Huff & Schumacher (NTP)	Potential for neurological damage by inhalation of exothermal products	Under consideration by NTP
109-99-9	Tetrahydrofuran	Diethylene oxide; THF; tetramethylene oxide	NCI/NIOSH	Medium exposure; Class Study	Prochronic test in progress
509-14-8	Tetranitromethane		NCI	Potential for wide exposure	Prochronic test in progress
91-79-2	Thenyldiamine		FDA	No carcinogenicity testing	Prochronic test in progress
58-55-9	Theophylline		NCI	Class Study; potential for considerable human exposure; some suspicion of potential carcinogenicity	Nominated for strain A mouse lung adenoma assay (5/81)
148-79-8	Thiabendazole	Mertect® Metasol TK-100® Mintezol® Thiabenzole	NCI	Class Study; potential for human exposure; unknown suspicion of carcinogenicity	Nominated for carcinogenicity testing
67-03-8	Thiamin hydrochloride	Aneurine hydrochloride Thiamine hydrochloride Vitamin B_1 hydrochloride	FDA/NCI	Class Study; potential for accumulation of the catabolic products of thiamine after administration to animals in large doses	No testing recommended (12/81)
96-50-1	2-Thiazolamine	Abadol Basedol 2-Aminothiazole	NCI	Class Study; potential for human exposure; some suspicion of its potential carcinogenicity	Under consideration by NTP

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MONS 025916

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY OHMS
300-47-1	Thiazole		NCI	Class Study; unknown suspicion of carcinogenicity; model compound for thiazoles class	Nominated for carcinogenicity testing
96-69-5	4,4'-Thiobis(6-tert-butyl-m-cresol)	Santowhite crystal	NCI	Class Study; potential for human exposure; unknown suspicion of carcinogenicity	Nominated for mutagenicity, reproductive effects, uptake & distribution, carcinogenicity tests (1/83)
108-88-3	Toluene		EPA/NCI	Large production/exposure	Nominated but not selected
206-01-0	Triamterene	2,4,7-Triamino-6-phenyl-pteridine; Dyrenium	FDA/NCI	Class Study; high estimated level of exposure; chronic use; lack of carcinogenicity data; suspicious structure; interest of FDA	Selected for testing by NTP, assigned to contractor
95-95-4	2,4,5-Trichlorophenol	Dowicide 2	NCI	Class Study; significant potential for human exposure; moderate suspicion of carcinogenicity	Nominated but not selected
96-18-4	1,2,3-Trichloropropane		NIOSH	Potential carcinogen; potential substitute for chlorinated solvents	Selected for testing by NTP, assigned to contractor
98-07-7	α,α,α-Trichlorotoluene	Benzotrichloride (Trichloromethyl)-benzene	NCI	Class Study; potential for significant human exposure; interest in possible carcinogenic activity which may be associated with the benzyl trichloride structure	Nominated for carcinogenicity testing
1330-78-5	Tricresyl phosphate	Tritolyl phosphate; phosphoric acid tris (methylphenyl)ester	EPA/NCI	Class Study; representative aromatic phosphate plasticizer	Selected for testing by NTP, assigned to contractor
102-71-6	Triethanolamine	TEA	Dr. E. Weisburger (NCI)	Potential for exposure; high incidence of malignant lymphomas reported in a preliminary study using female mice	Nominated for battery of short term mutagenicity assays, oncogenism, reproductive effects and carcinogenicity (4/81)

MONS 025917

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Concluded)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DOHS
885-30-7	Trimellitic anhydride		EPA	Potential carcinogen	Assigned to contractor
91-01-6	Tripelennamine		FDA	No carcinogenicity testing	Prechronic test in progress
12070-12-1	Tungsten carbide	Tungsten monocarbide	NCI	Class Study; considerable potential for human exposure representative tungsten with +4 valence	Nominated for testing by NTP
458-37-7 8024-37-1	Turmeric	Curcumin (Diferesin)	NCI	High potential for exposure	Nominated for S.typhimurium assay (11/81) Assigned to contractor
60-18-4	L-Tyrosine	Tyrosine	FDA/NCI	Class Study; highest potential for exogenous exposure of the candidate aromatic amino acids	No testing recommended (11/81)
106-89-8	Vinyl cyclohexene dioxide		NIOSH	Potential carcinogen; occupational exposure	Prechronic test in progress
75-38-7	Vinylidene fluoride		OSHA	Wide exposure; potential carcinogen	Selected for testing by NTP
1330-20-7	Vinyl toluene		NCI	High production & exposure; potential carcinogen	Chronic test in progress
59-02-9	Vitamin E	α-tocopherol	FDA/NCI	Class Study; highest U.S. production of the fat-soluble vitamins considered; effect of very large doses is of interest	Recommended for no further testing except Salmonella testing (12/81)
57-62-7	β,δ-Xylidine		NCI	Potential exposure & carcinogen	Withdrawn after carcinogenesis testing began
13463-41-7	Zinc pyrithione	Zinc omadine	NCI	Class Study; potential for human exposure	Under consideration by NTP

MONS 025918

Table 3. Chemicals Acted Upon by NCI (CSWG*) but not Submitted to NTP for CEC Review

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
84-65-1	Anthraquinone	9,10-Anteracenedione Anthradione	NCI	Air Pollutants Class Study; one of two representatives of the polycyclic aromatic hydrocarbon subclass; interest in testing parent compound of class of carcinogenic amino- nitro- substituted anthraquinones	CSWG-Rejected-no reason given
225-11-6	Benz(a)acridine	1-Azabenz[a]anthracene 1,2-Benzacridine	NCI	Air Pollutants Class Study; single nomination from N-heterocycles subclass; suspicion of carcinogenic risk, environmental occurrence and environmental fate	CSWG-Short Term Tests
2634-33-5	1,2-Benzisothiazolin-3-one	1,2-Benzisothiazolone Proxel	NCI	Biocides Class Study; single representative of nitrogen heterocyclic compounds; significant potential for human exposure from its use as a slimicide and fungicide	CSWG-Rejected. Negative mutagenicity tests; limited carcinogenicity studies
104-88-1	p-Chlorobenzaldehyde	4-Chlorobenzaldehyde p-Chlorobenzenecarboxaldehyde	NCI	Chemicals found in dumps; high potential for human exposure; unknown suspicion of carcinogenicity	CSWG-Short term tests only
2373-98-0	3,3-Dihydroxybenzidine	4,4'-Diamino-(1,1'-biphenyl)-3,3'-diol	CPSC/NCI	No previous adequate carcinogenicity tests; confirm suggestive evidence that it is carcinogenic in rodents	CSWG-Rejected. Awaiting results of benzo-dyes short term tests

*NCI Chemical Selection Working Group

MONS 025919

Table 3. Chemicals Acted Upon by NCI (CSMG) but not Submitted to NTP for CEC Review

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	REQUESTING	RATIONALE FOR REQUEST	ACTION BY NOMS
124-40-3	Dimethylamine	N-Methylmethanamine	NCI	Air Pollutants Class Study; mutagenic in Ames test; high potential for human exposure	CSMG-Rejected. CIIT testing.
193-43-1	Indeno(1,2,3-cd)-fluoranthene	1,2,;5,6-Dibenzo-pyracylene o-Phenylenefluoranthene 4,5-(1,2-Phenylene)-fluoranthene	NCI	Air Pollutants Class Study; one of two representatives of the PAG subclass; structural interest in PAH	CSMG-Mutagenicity tests only
74-93-1	Methanethiol	Mercaptomethane Methyl mercaptan	NCI	Air Pollutants Class Study; sole nomination from the alkane sulfur compounds subclass whose potential carcinogenicity is unknown; environmental occurrence	CSMG-Short term tests only
107-25-5	Methyl vinyl ether	Methoxyethylene Vinyl methyl ether	NCI	Ethers Class Study; representative of simple aliphatic ethers; moderate suspicion of carcinogenicity; commercial importance as a monomer and comonomer	CSMG-Rejected. Readily hydrolyzed; limited exposure
21564-17-0	2-(Thiocyanomethylthio)-benzothiazole	Busan 30[R] Busan 72[R] TCMTB	NCI	Thiazoles Class Study; potential carcinogenicity and significant potential for human exposure	CSMG-Rejected. Low exposure.
75-69-4	Trichlorofluoromethane	Freon[R] 11	NCI	Air Pollutants Class Study; sole nomination from alkyl halides subclass; widespread presence in atmosphere; structural relationship to chloroform and carbon tetrachloride	CSMG-Rejected. Already regulated; low exposure

NOMS 025920

TABLE 0. INFORMATION RELATED TO NCTR'S RESEARCH & TESTING RELEVANT TO CARCINOGENICITY OF SUBSTANCES

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION OR DATE
53-96-3	2-Acetylaminofluorene	2-AAF; N-2-fluorenyl acetamide; Fluoren-2 acetamide; N-acetyl-2 aminofluorene	NCI/OHCP/ FDA	Methodology development	Chronic study phase
1336-53-9	3,3'-Dimethoxybenzidine		EPA	Regulatory, potential carcinogenicity	Review of final report; chronic study phase; analytical method development
119-90-7	3,3'-Dimethylbenzidine		EPA	Regulatory, potential carcinogenicity	Review of final report; chronic study phase; analytical method development
1937-37-7	Direct Black 38	C.I. 30235	EPA	Environmental contamination	Review of final report (metabolism)
64700-56-7	Direct Black 154	Cuprophenyl Black; DBL	CPSC/EPA	Consumer exposure	Review of final report (metabolism)
72-57-1	Direct Blue 53	C.I. 23860	CPSC/EPA	Consumer exposure	Review of final report (metabolism)
2610-11-0	Direct Blue 60 (Substituted with Blue 10)	Pergasol Blue CLAL	CPSC/EPA CPSC/EPA	Consumer exposure Consumer exposure	Dropped Review of final report
16071-86-6	Direct Blue 218	C.I. 24401	NIOSH/OSHA	Occupational exposure	Dropped
992-59-6 2610-05-1	Direct Red 2	C.I. 23500	NIOSH/OSHA	Occupational exposure	Review of final report (metabolism)
6360-29-6	Direct Red 28	C.I. 22120	CPSC/EPA	Consumer exposure	Review of final report (metabolism)
61725-09-2 2429-74-5	Direct Yellow 58 (Substituted with Violet 28)	Cuprophenyl yellow RL	CPSC/EPA CPSC/EPA	Occupational exposure Occupational exposure	Dropped Review of final report
548-62-9	Gentian Violet	Hexamethyl-p-rosaniline chloride	FDA/EV/ETM	Regulatory; residues in edible meats	Chronic study phase
58-89-9	Lindane	a-Hexachlorobenzene	EPA	Evaluation of liver tumors	Chronic study phase

MONS 025921

TABLE 4. INFORMATION RELATED TO N.I.H.'S RESEARCH & TESTING RELEVANT TO CARCINOGENICITY OF SUBSTANCES (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
134-32-7	1-Naphthylamine	alpha-Naphthylamine	FDA/EPA	Possible carcinogenicity	On test
91-59-8	2-Naphthylamine	beta-Naphthylamine	FDA/EPA	Possible carcinogenicity	On test
83-79-4	Rotenone		EPA	Regulatory, potential carcinogenicity	Review of final report
81-07-2	Saccharin	o-Benzosulfimide;	FDA	Regulatory, potential carcinogenicity	Chronic study phase
587-98-1	Sulfamethazine	4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)-benzene sulfonamide	FDA/DF/BVM	Regulatory, residues in edible meats	Chronic study phase

MONS 025922

TABLE 5. 1981 REQUESTS TO NIOSH TO EVALUATE INFORMATION REGARDING THE RISK OF CARCINOGENICITY DUE TO EXPOSURE TO CHEMICALS LISTED IN THE ANNUAL REPORTS ON CARCINOGENS - Compiled 1/1/82

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	REQUESTING AGENCY	APPLICABLE STANDARD	CDC/NIOSH RESPONSE
71-43-2	Benzene	benzin benzine benzol	DOE		Field study in progress to assess health effects of coal gasification system.
do	do	do	OSHA		NIOSH developing tests for skin absorption.
92-87-5	Benzidine		NTP		Research in progress to study the pharmacokinetics of carbon-14 labelled amines and dyes in the rat including metabolism and tissue distribution.
101-14-4*	4,4'-methylene bis (2-chloro)	Benzenamine MOCA	OSHA		Skin study in draft form where rates of skin absorption and excretion of carbon 14-MOCA were determined in experimental animals.
119-90-4*	3,3'-dimethoxybenzidine		NTP		Research in progress to study the pharmacokinetics of carbon-14 labelled amines and dyes in the rat including metabolism and tissue distribution.
119-93-7*	3,3'-dimethylbenzidine		NTP		do
2002-46-2*	Direc. Blue 6 (C,1,22610)		NTP		do
05896-93-2	Coal tar pitch volatiles	CTPV	OSHA (4 requests)	(coke oven emissions)	Provide technical input and literature.
8062-42-4	Asphalt fumes	bitumen	OSHA (4 requests)	(coke oven emissions)	Provide results of ongoing contract study.
59-89-2	N-nitrosomorpholine	NMPL 4-nitrosomorpholine	Library of Congress	29CFR 1910	Provided technical information.
50-00-0	Formaldehyde	methylene oxide formalin	CPSC	29CFR 1910	Provided technical information.
1333-82-0	Chromium VI		OSHA		Mortality study of chrome plating in progress.

(Continued)

* New chemical for the Third Annual Report.

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TABLE 5. 1981 REQUESTS TO NIOSH TO EVALUATE INFORMATION REGARDING THE RISK OF CARCINOGENICITY DUE TO EXPOSURE TO CHEMICALS LISTED IN THE ANNUAL REPORTS ON CARCINOGENS - Compiled 1/1/82 (Concluded)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	REQUESTING AGENCY	APPLICABLE STANDARD	CDC/NIOSH RESPONSE
7738-94-5	Chromic Acid				
1333-82-0	Chromium VI		MSHA		Field study in progress of exposure to welding fumes.
1332-21-4	Asbestos		Postal Service U.S. Customs		Health hazard Evaluation report and recommendation provided.
	Nickel		MSHA		Field study in progress of exposure to welding fumes.
	Benzo[a]pyrene		DOE		Field study in progress to assess health effects of coal gasification system.
117-81-7*	Di-(2-ethylhexyl)phthalate	DEHP	EPA		NIOSH determining feasibility of conducting mortality study of workers exposed to DEHP.

* New chemical for the Third Annual Report.

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TABLE 6. REQUESTS FOR INFORMATION (INCLUDING CARCINOGENESIS) ABOUT 118 CHEMICALS: 1980-1982

Search Requested by (date):	Chemical	Sources searched*	No. of References Located
A. NCI (1980)	Cadmium Sulfide	TOX/MED DIALOG LIT LIB TIRC LIB	158
" "	Di-(2-ethylhexyl) phthalate	as above	893
" "	Cadmium Oxide	as above	301
" "	Nickel Sulfate	as above	484
" "	Thiourea	TOX/MED DIALOG TIRC LIB	696
" "	Thioacetamide	as above	609
" "	Diethylstibestrol	as above	895
" "	Cyclophosphamide	as above	1857
" "	Benz(a)anthracene	as above	2832
" "	Lead Acetate	as above	466
" "	Benzo(a)pyrene	as above	1618
" "	Formaldehyde	TOX/MED DIALOG	293

(Continued)

TABLE 6. REQUESTS FOR INFORMATION (INCLUDING CARCINOGENESIS) ABOUT 118 CHEMICALS: 1980-1992

Search Requested by (date):	Chemical	Sources Searched*	No. of References Located
A. NCI (1981)	Cadmium Sulfide	TOX/MED DIALOG	0
" "	Cadmium Oxide	as above	16
" (1982)	Cadmium Nitrate	MEDLARS DIALOG	578
B. NIEHS (1980)	Reserpine	TOX/MED	253
C. Naval Ordnance Station (1980)	Chromium Octoate	TOX/MED	0
" "	Urethane	TOX/MED	649
D. Dept. of Energy (1981)	Arsenic in coal	RECON	294
E. Industry (1980)	Nickel Nitrate	TOX/MED DIALOG	18
" "	Formaldehyde	TOX	1505
" "	Cadmium	TOX/MED	430
" "	Nickel formate	TOX	1
F. Attorneys (1980)	Diethylstilbestrol (review articles only)	MED	35
" (1980)	Benzene	TOX/MED	337

(Continued)

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TABLE 6. REQUESTS FOR INFORMATION (INCLUDING CARCINOGENESIS) ABOUT 118 CHEMICALS; 1980-1982

Search Requested by (date):	Chemical	Sources Searched[a]	No. of References Located
F. Attorneys (1981)	Formaldehyde (gas)	MED	221
" "	" in Mobile Homes	TOX/MED	3
" (1982)	Formaldehyde in Mobile Homes	DIALOG RECON	15
" (1982)	Benzene	MEDLARS	540
G. Libraries (1980)	Polychlorinated Biphenyls (teratogenicity of)	TOX/MED	700
" "	Cadmium (teratogenicity of)	TOX/MED	272
" "	Chloroform (teratogenicity of)	TOX/MED	104
" "	Carbon tetrachloride (teratogenicity of)	TOX/MED	93
" "	Benzene (teratogenicity of)	TOX/MED	229
H. Government Contractor (1981)	2-Naphthylamine, N-Phenyl; N-Nitrosodibutylamine; N-Nitroso-di-N-Propylamine; Benzo(b)fluoranthene	MED	4
" "	Dodecane;benzene; Benzo(a)pyrene;formaldehyde (reviews only desired)	TOX/MED	390
" "	Benzo(b)fluoranthene and Cycloheximide	TOX	2

(Continued)

MONS 025927

TABLE 6. REQUESTS FOR INFORMATION (INCLUDING CARCINOGENESIS) ABOUT 118 CHEMICALS; 1980-1982 (Concluded)

Search Requested by (date):	Chemical	Sources Searched*	No. of References Located
H. Government Contractor (1981)	Beryllium	MEDLARS	423
" (1982)	Thioacetamide, acetamide, & sulfanilamide	TOX/TOB	52
" (1982)	Lead Acetate	TOX/MED DIALOG	197
" (1982)	Benzidine	MED/DIAL CANCERLIT	74
" (1982)	Chromium	MED/DIAL CANCERLIT	663
" "	Nickel Subsulfide	as above	63
" "	Formaldehyde	as above	473
" "	Benzo(a)Pyrene	as above	482
I. Private Individual (1980)	Chloroform update	TOX/MED	69
J. Private Individual (1981)	Tetraethyl Lead and Cadmium	TOX/MED TIRC LIB	370
K. Foreign Requestor	Carbon Tetrachloride	TOX/MED	480
L. U.S. Government	Asbestos	MEDLARS	707

* TOX = TOXLINE and back files
MED = MEDLINE and back files
MEDLARS = All NLM databases
DIALOG = CAS and BIOSIS files, plus others as appropriate
LIT LIB = Standard Library References
TIRC LIB = Library resources available in Toxicology Information Response Center

MONS 025928

V. APPENDIXES

MONS 025929

A. Alphabetized Synonym and Trade Name Index to the Substances Listed*

* The index also includes the trade names of preparations or formulations only because they contain the listed substance as a part of a mixture of several chemicals.

MONS 025930

ALPHABETIZED SYNONYM AND TRADE NAME INDEX
TO THE SUBSTANCES LISTED

A 100 (PHENYLMERCURIC) See 100% DEITROL
A 100 (PAINT) See 100% DEITROL
3,4-T See WHITEOUT
ABIDOR See 3,3-DICHLOROBENZIDINE
ACP See 2-ACETYLAMINOFLUORENE
2-AAF See 2-ACETYLAMINOFLUORENE
ACETAMIDE, N-(4-(2-CHLOROETHYLSULFONYL)PHENYL)- See 2-ACETYLAMINOFLUORENE
AAM See 2-ACETYLAMINOFLUORENE
ABRASIVE See DESICRYSTAL
ABRIDOL See DESICRYSTAL
ACETAMIDE See ACRYLFE
ACET-P-PHENETIDIDE See PHENACETIN
ACET-P-PHENETIDIDE See PHENACETIN
ACETAMIDE, N-(4-ETHOXYPHENYL)- (8CI) See PHENACETIN
ACETAMIDE, N-FLUORENYL-2-YL- (8CI) See 2-ACETYLAMINOFLUORENE
ACETAMIDE, N-9H-FLUOREN-2-YL- (8CI) See 2-ACETYLAMINOFLUORENE
ACETAMIDE, THIO- (8CI) See THIOACETAMIDE
ACETAMIDOTE ACID, THIO- See THIOACETAMIDE
1-ACETAMIDO-4-(2-HYDROXYETHYL)BENZENE See PHENACETIN
2-ACETAMIDOFLUORENE See 2-ACETYLAMINOFLUORENE
ACETAMINE DIACID BLACK 38 See 2,2'-DIMETHOXY-4,4'-BIPHENYLENEDIAMINE
ACETAMINE DIACID BLACK 48 See 3,3'-DIMETHOXY-4,4'-BIPHENYLENEDIAMINE
2-ACETAMINOFLUORENE See 2-ACETYLAMINOFLUORENE
ACETANILIDE, 4'-ETHOXY- See PHENACETIN
ACETANT FAST ORANGE G See 1-AMINO-2-METHYLANTHRAQUINONE
ACETIC ACID, MERCURY(2+) (2CI) See MERCURIC ACETATE
ACETOPHENONAZOL See THIOACETAZONE
ACETO-PARA-PHENETIDIDE See PHENACETIN
ACETO-PARA-PHENETIDINE See PHENACETIN
ACETO-P-PHENETIDINE See PHENACETIN
P-ACETOPHENETIDIDE See PHENACETIN
P-ACETOPHENETIDINE (8CI) See PHENACETIN
ACETOPHENETIDIN See PHENACETIN
ACETOPHENETIDINE See PHENACETIN
P-ACETOPHENETIDINE See PHENACETIN
ACETOPHENETIN See PHENACETIN
ACETOPHENONE LIGHT ORANGE JL See 1-AMINO-2-METHYLANTHRAQUINONE
'PHENACETIDIN See PHENACETIN
'P-PHENETIDIN See PHENACETIN
B,N-ALKANOYLAMINE Page 61
ACETYLAMINOFLUORENE See 2-ACETYLAMINOFLUORENE
N-ACETYL-2-AMINOFLUORENE See 2-ACETYLAMINOFLUORENE
N-ACETYL-P-(PHENYLAZO)ANILINE See PHENACETIN
N-ACETYL-P-PHENETIDINE See PHENACETIN
ACETYLPHENETIDIN See PHENACETIN
ACHROMIDIN See PHENACETIN
ACID LEAD ARSENATE See ARSENIC AND CERTAIN ARSENIC COMPOUNDS
ACID LEAD ORTH ARSENATE See ARSENIC AND CERTAIN ARSENIC COMPOUNDS
ACNESTROL See DIETHYLSTILBESTROL
ACRYLAM See ACRYLONITRILE
ACRYLONITRILE Page 69
ACRYLONITRILE (8CI) See ACRYLONITRILE
ACRYLONITRILE (8CI) See ACRYLONITRILE
ACRYLPHOTRILE MONOMER See ACRYLONITRILE
ACTINOLITE See ASBESTOS
ACTINOLITE (CA(OH)2(FE2SI8O22)) See ASBESTOS
ADELFAN See DESICRYSTAL
ADELPHANE See DESICRYSTAL
ADELPHIN See DESICRYSTAL
ADELPHIN-GRUBBER-E See DESICRYSTAL
ADRENIDIN See DIETHYLSTILBOL
ADRIA'S See DIETHYLSTILBOL
AFLAT See AFLATOXINS
AFLICIDE See AFLATOXINS
AFLATOXIN B See AFLATOXINS
AFLATOXIN G1 See AFLATOXINS
AFLATOXIN G2 See AFLATOXINS
AFLATOXIN B1 See AFLATOXINS
AFLATOXIN G2 See AFLATOXINS
AFLATOXINS Page 87
AGENSTILBEN See DIETHYLSTILBESTROL
AGRICIDE MAGGOT KILLER #7 See TOKAPHENE
AGRISOL G-20 See LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS
AGROCIDE See LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS
AGROCIDE III See LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS
AGROCIDE WP See LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS
AGROCIDE 7 See LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS
AGROCIDE 6B See LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS
AGROCIDE 7 See LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS
AGROMERSOL See LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS
AHLO DIRECT BLACK BB See DIRECT BLACK 38
AI 3-FLUOXYL See TRIETHYLAZIRIDINYLPHOSPHINE OXIDE
AIDEQUALE BLACK EB See DIRECT BLACK 38
AIDEQUALE BLUE 2RD See DIRECT BLUE 6
AIDEN DIRECT BLUE 2RW See DIRECT BLUE 6
AIDEN DIRECT DEEP BLACK EW See DIRECT BLACK 38
AIDEN DIRECT DEEP BLACK RW See DIRECT BLACK 38
AIDEN DIRECT DEEP BLACK EW See DIRECT BLACK 38
ALANIMAL, 3-(P-(2(SULFOXYETHYL)SULFONYL)PHENYL)-, 1- (8CI) See POLYMOLAM
ALCOZ, See ISOPROPYL ALCOHOL
ALCOHOL 99 2 See ISOPROPYL ALCOHOL
ALCRYSIN See PHENYTOIN
ALGUSEN See N,N-DIMETHYL-2-(4-METHYLBENZHYDRYLOXY)
ALGYCETIN See PHENYTOIN
ALGYCETIN SODIUM See PHENYTOIN
ALKARAN See MELPHALAN
ALKASOM See DESICRYSTAL
ALKESAN See MELPHALAN
ALKETER See TOKAPHENE
ALLYDE See TOKAPHENE
5-ALLYL-1,3-BENZODIOXOLE See SAFROLE
ALLYLBENZENE, METHYLENE ETHER See SAFROLE
ALLYLBENZODIOXOLENE METHYLENE ETHER See SAFROLE
5-ALLYL-1,3-METHYLENEDIOXYBENZENE See SAFROLE
4-ALLYL-1,2-METHYLENEDIOXYBENZENE See SAFROLE
5-ALLYLPYRROLAFFETIN ALDEHYDE ETHER See SAFROLE
4-ALLYLPYRROCATECHOL FORMALDEHYDE METHYL See SAFROLE
ALLYLPYROCATECHOL METHYLENE ETHER See SAFROLE
2-ALPHA-AMINOBUTAN-1-OL, 1?-DITO-BY-BOOT-2-(1H-IMIDAZOL-4-YLMETHYL)-4?-METHYL-
(8CI) See DETHYLTHALONE
See DETHYLTHALONE

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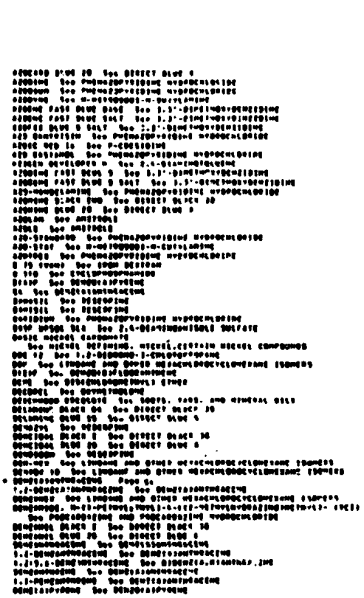

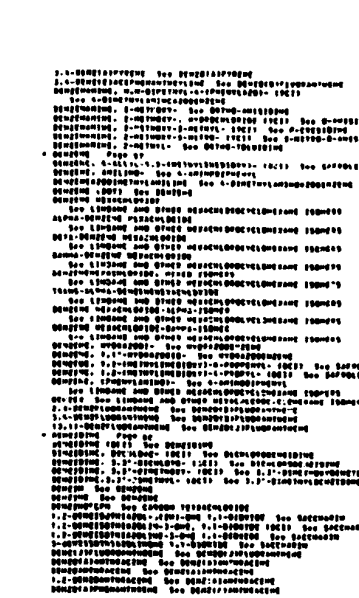

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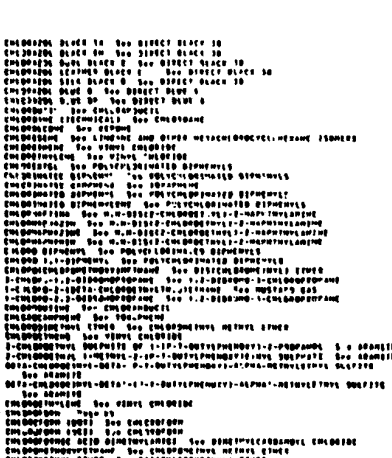

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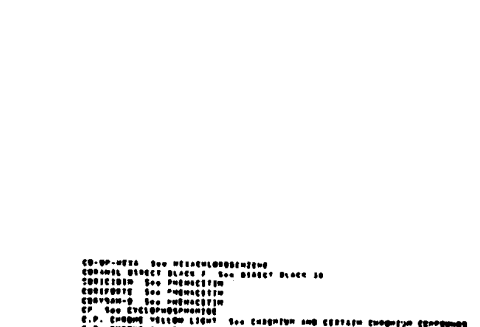

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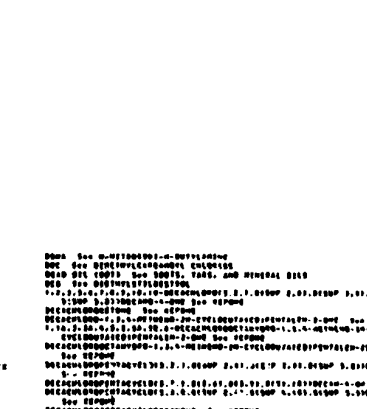

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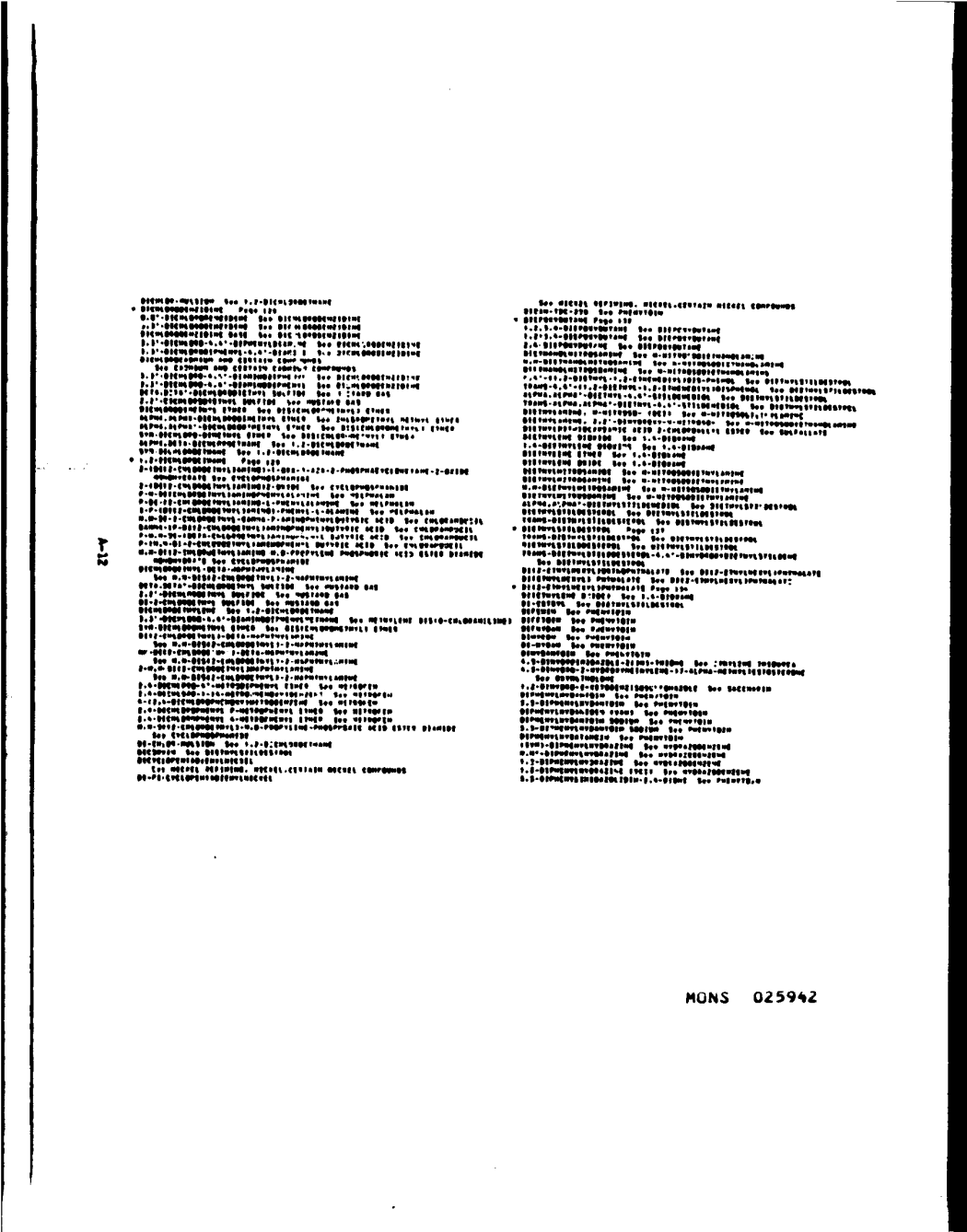

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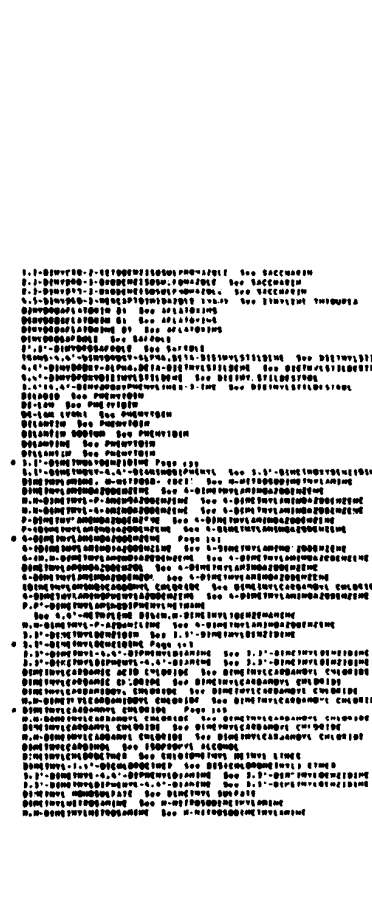

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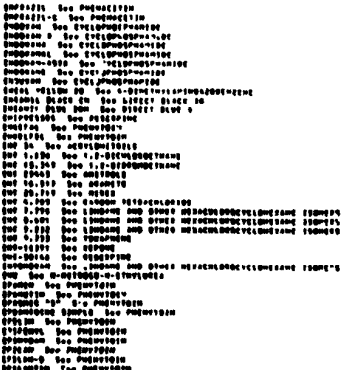

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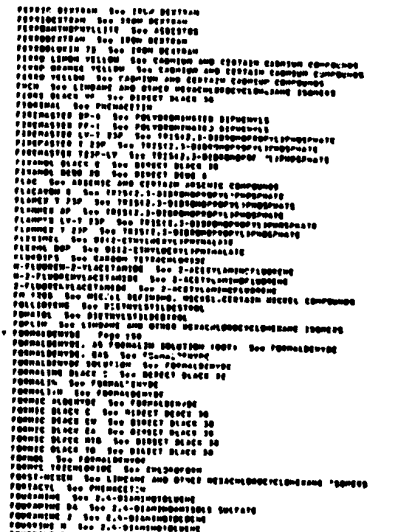

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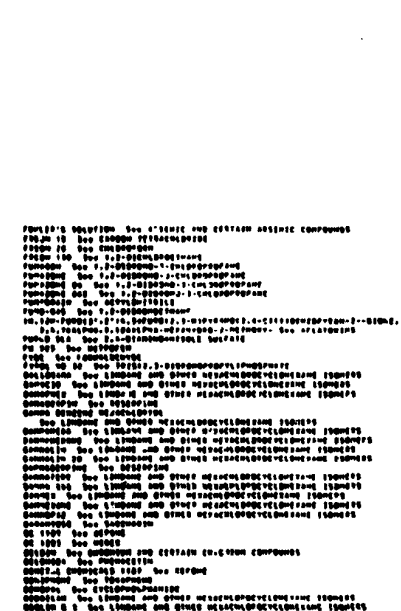

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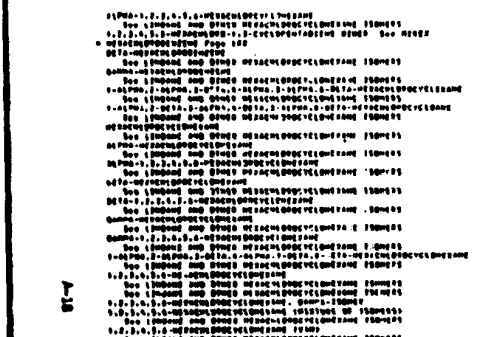

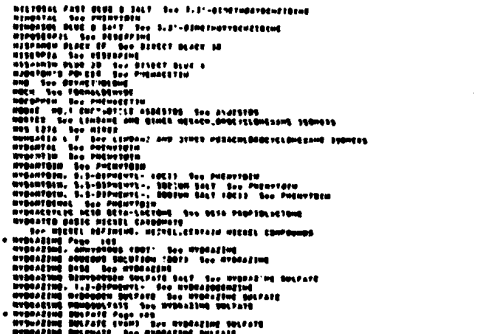

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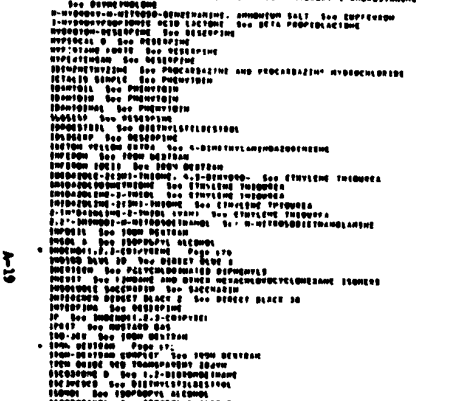

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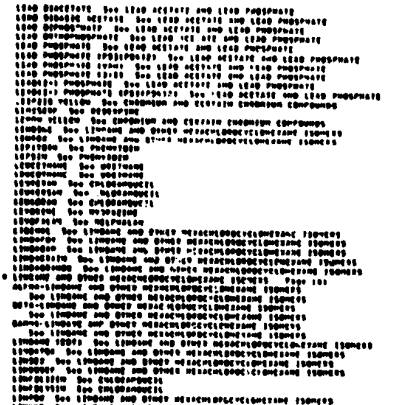

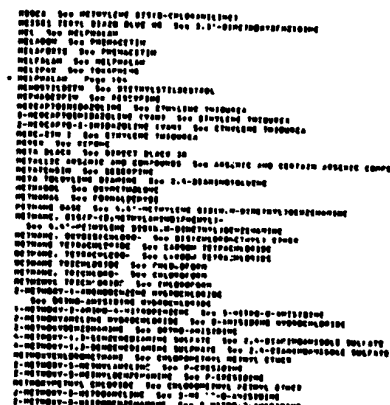

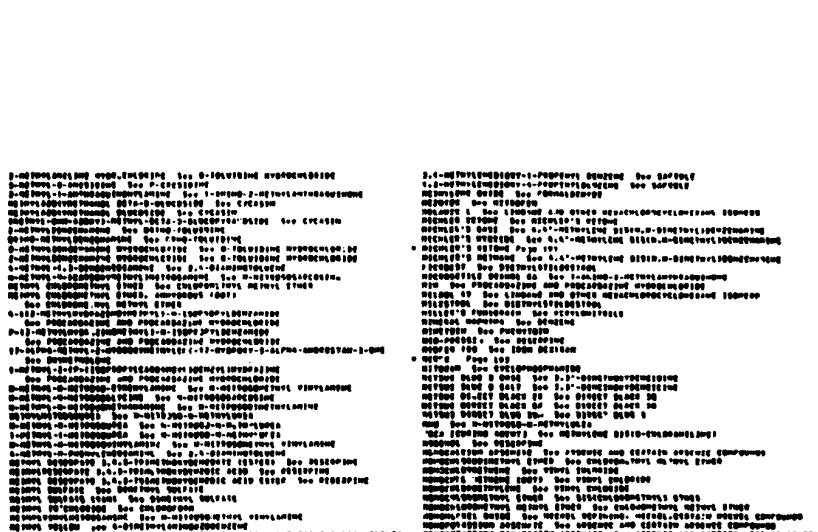

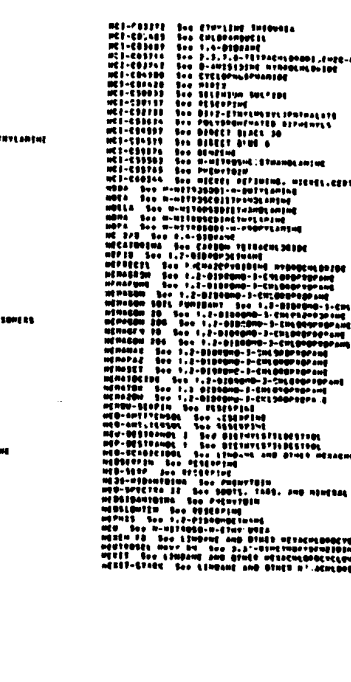

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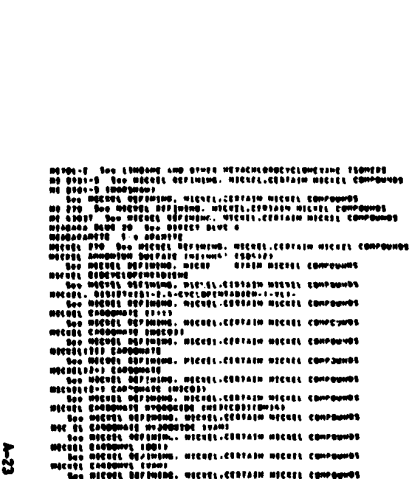

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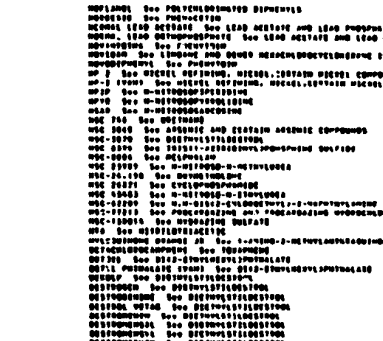

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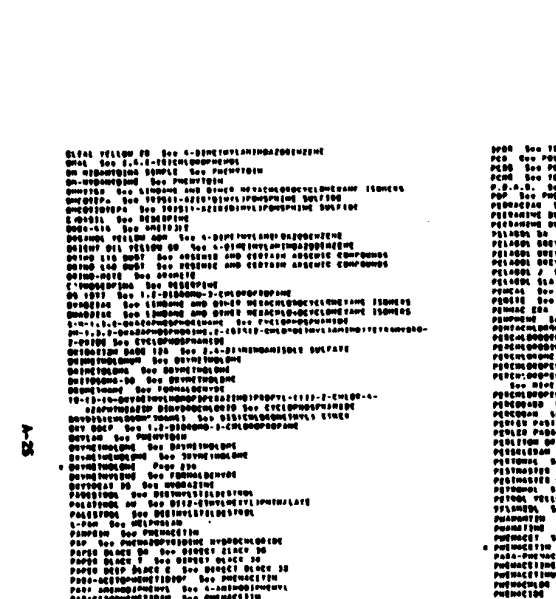

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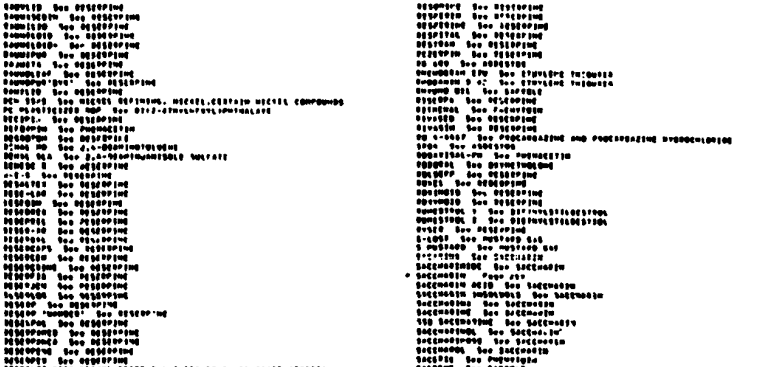

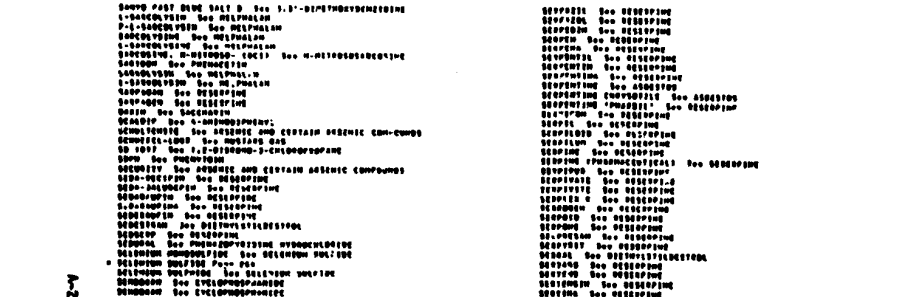

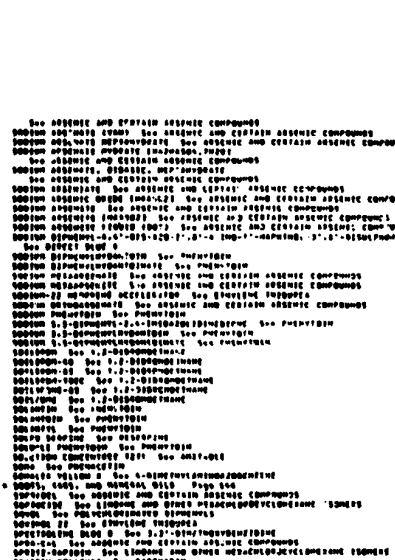

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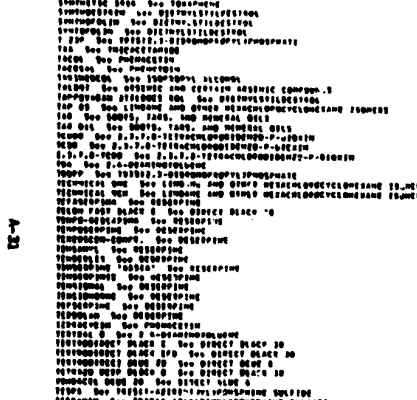

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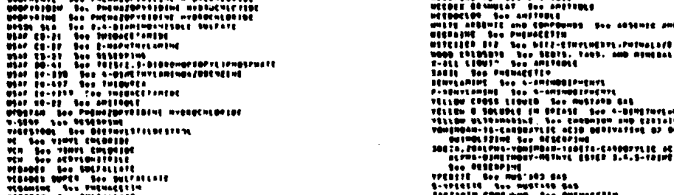

MONS 025963

B. Glossary, Acronyms, and Units of Measurement

MONS 025964

GLOSSARY

adenocarcinoma--a malignant epithelial tumor arising from the glandular epithelial tissue

adenoma--a benign neoplasm of glandular epithelial tissue

adrenal gland--a hormone-secreting organ located near each kidney

albino--an organism exhibiting deficient pigmentation in skin, eyes, and/or hair

alkylating agent--a substance that produces a reaction product containing an alkyl group

alveolar--small saclike pouches that may be located in the jaws where the teeth arise, the air cells of the lungs, or in glands

amines--any member of a group of chemical compounds formed from ammonia by replacement of one or more hydrogen atoms by organic radicals

amyloidosis--the accumulation of amyloid (an abnormal complex material most probably a protein compound with a carbohydrate) in various body tissues

analgesic--pain relieving

analytical grade--the highest available purity of a chemical

anemia--a condition in which the number of red blood cells or the amount of hemoglobin in a given volume of blood is less than normal

antibiotic--a chemical substance produced by a microorganism that has the capacity to inhibit the growth of or kill other microorganisms

anticonvulsant--relieving convulsions

antiepileptic--preventing epileptic seizures

anti-inflammatory--counteracting or suppressing inflammation

antimicrobial--destroying microorganisms or arresting their growth

antineoplastic--inhibiting the survival and proliferation of malignant cells

MONS 025965

antioxidant--synthetic or natural substance added to a product to prevent or delay its deterioration by the action of oxygen

antipyretic--relieving or reducing fever

aorta--the main trunk of the arterial system, conveying blood from the left ventricle of the heart to all of the body except the lungs

aplastic anemia--a form of anemia characterized by greatly decreased formation of red blood cells and hemoglobin

aromatic amine--an organic base characterized by a benzene-type ring system containing one or more amino groups

aromatic hydrocarbon--an organic base characterized by the presence of at least one benzene ring and containing only carbon and hydrogen atoms

arsenical--a compound containing arsenic

auditory sebaceous gland--gland of the skin, secreting an oily substance, sebum, and situated in the cerumen

basal diet--the ordinary adequate diet fed to animals during experiments and to which special ingredients to be tested may be added

benign tumor--a tumorous growth that is not malignant and usually is not life threatening

bile duct--a tube for the passage of bile from the liver into the intestine

bioaccumulation--the process by which the amount of an environmental contaminant present in a living organism increases with time

breakdown product--a chemical derived from a parent compound that has been altered, usually by heat, light, or enzymes

bronchogenic--originating in one of the larger air passages in the lung

cancer--a general term used to indicate any of various types of malignant neoplasms

carbonization--the process of converting carbon or a carbonic residue

carcinogen--a cancer-producing agent

carcinogenesis--formation of cancer

carcinogenic--producing carcinoma, a malignant neoplasm of epithelial tissue

MONS 025966

carcinogenicity--the power, ability, or tendency to produce carcinoma, a malignant neoplasm of epithelial tissue

carcinoma--a malignant neoplasm of epithelial tissue

carcinostatic--tending to check the growth of carcinoma

cardiovascular--of, relating to, or involving the heart and blood vessels

central nervous system (CNS)--the division of the nervous system comprising the brain and spinal cord

cervix--the neck of the uterus

chemosterilant--a chemical compound that causes sterility of an organism when ingested

chemotherapeutic--pertaining to the treatment of disease by chemical agents

cholangiocarcinoma--adenocarcinoma of the bile ducts

cholangiocellular--of or pertaining to the gallbladder or bile ducts

chronic--continuing for a long time

clitoral--pertaining to a small, elongated, erectile body situated at the anterior or ventral part of the vulva

colon--the part of the large intestine extending from the cecum (blind gut) to the rectum (terminal portion of the digestive tube)

conjunctiva--the membrane that lines the eyelid and covers part of the eyeball

connective tissue--a tissue that connects, supports, or surrounds other tissues or organs

contaminant--an impurity; in the environment, a chemical that is not usually present and that may have deleterious effects

copolymer--a polymer containing more than one kind of monomer

corpus uteri--the main part of the uterus

cystitis--inflammation of the urinary bladder

cytology--study of cells, their origin, structure, function, and pathology

cytotoxic--having a toxic action to cells

dermal--pertaining to skin

MONS 025967

desiccator--a heavy glass container from which moisture is removed by vacuum or chemicals

diabetes--a disease in which the ability of the body to use sugar is impaired and sugar appears abnormally in the urine and is characterized by excessive urination

diamine--a compound that contains two amino groups

distant tumor--a tumor that is located far from the point of attachment or origin

distillation--a process that consists of driving gas or vapor from liquids or solids by heating and condensing to liquid products

D,L--refers to mirror images of compounds that rotate polarized light to the right (D) or left (L)

dose-response relationship--a relationship between dose (amount) of a chemical administered, or taken into the body, and the effects

dyscrasias--a pathological condition resulting from the presence of abnormal material in the blood

effluent--waste material discharged into the environment

endometrium--the mucous membrane that lines the uterus

enzyme--a complex organic compound (protein) produced in the organism that can accelerate a particular biochemical reaction; a biological catalyst

epidemiology--a science concerned with the occurrence and distribution of disease in human populations

epilepsy--a nervous disease usually characterized by seizures with convulsions and loss of consciousness

epithelium--tissue covering internal and external surfaces of the body

esophagus--the passage that carries food from the throat to the stomach

estrogen--any of a group of female sex hormones

estrus--the female sexual cycle

fibroadenoma--a benign neoplasm that contains fibrous tissue

fibrocarcinoma--carcinoma with a hard structure owing to the formation of dense connective tissue

MONS 025968

fibrosarcoma--a malignant neoplasm derived from fibrous connective tissue

follicular cell--modified epithelial cells that surround the ovum in various follicles and secrete follicular fluid

forestomach--a nonglandular section of the stomach that is lacking in the human organism

fungi--a major group of saprophytic and parasitic lower plants, that lack chlorophyll and the tissue differentiation of higher plants

fungicide--an agent that destroys fungi

gallbladder--a reservoir for the bile located near the liver

gastric (stomach) intubation--insertion of a tube into the stomach

gastric tube--a tube passed through the mouth and into the stomach

gastrointestinal--pertaining to or communicating with the stomach and intestine

gavage--feeding through a tube passed through the mouth into the stomach

genitourinary--pertaining to the genital and urinary organs

geothermal--of or relating to the heat of the earth's interior

gestation--pregnancy; in mammals, the period of the development of the young from the time of fertilization of the ovum (egg)

gland--an aggregation of cells specialized to secrete certain substances of biological importance

glomerulonephritis--a renal disease characterized by inflammation of the capillary loops in the glomeruli of the kidney

gonad--the sex gland of the male or female

gonadal dysgenesis--impaired development of the gonads

grand mal seizure--major epileptic convulsion

hemangioendothelioma--a neoplasm derived from blood vessels in which the endothelial cells are the most prominent component

half-life--the time in which a substance will be reduced to one-half of its present value through degradation or elimination from the organism

harderian gland--accessory lacrimal glands at the inner corner of the eye in animals referred to as the "third eyelid" or the semilunar conjunctival fold

hard palate--the anterior, rigid portion of the partition separating the nasal and oral cavities

hemangiosarcoma--a rare malignant neoplasm of endothelial cells derived from blood vessels

hematopoietic--pertaining to or affecting the formation of blood cells

hepatic--pertaining to the liver

hepatitis--inflammation of the liver

hepatocellular--pertaining to liver cells

hepatoma--a tumor of the liver

herbicide--an agent that is destructive to weeds

histological--pertaining to the study of the microscopic structure and composition of tissues

histology--the study of anatomy that deals with the minute structure, composition, and function of tissues

Hodgkins disease--a malignant condition characterized by painless, progressive enlargement of the lymph nodes, spleen, and general lymphoid tissues

hormone--chemical substances produced by the endocrine glands that have specific regulatory effects on the activity of certain organs

hyperglycemia--an abnormally increased content of sugar in the blood

hyperplasia--an increase in the size of a tissue or organ due to an increase in the number of cells

hypnotic--sleep-inducing; a sleep-inducing drug

hypotensive--causing diminished blood pressure

impurity--a contaminant; an unnecessary part of a mixture or compound

inhalation--the drawing of air or other substances into the lungs

MONS 025970

initiator--a chemical that permanently alters a cell or group of cells and in the case of carcinogens is tumor producing

integumentary system--an enveloping layer (as a skin, membrane) of an organism or one of its parts

intrabronchial--situated or occurring within a bronchus, a division of the trachea that leads into the lung

intragastric--within the stomach

intramuscular (im) injection--injection into muscle tissue

intraperitoneal (ip) injection--injection into the abdominal cavity that is lined by a serous sac (peritoneum)

intrapleural--within the pleura, a serous membrane enveloping the lungs and lining the walls of the pleural cavity

intratracheal--within the trachea (windpipe)

intravenous (iv) injection--injection into a vein

in utero--within the uterus

invasive--spreading beyond specific body tissues

labile--unstable; tending to dissociate into component parts

lactation--the secretion of milk

larynx--the upper end of the trachea (windpipe)

latency period--a seemingly inactive period, as that between the exposure of tissue to an injurious agent and the manifestation of response, or that between the instant of stimulation and the beginning of a response

leaching--a process by which a substance or contaminant in the soil is displaced, usually by water, to another location

lesion--a wound or injury

leukemia--a cancer of the blood-forming tissues characterized by a marked increase in the number of abnormal white blood cells

leukemogenic--causing leukemia, an acute or chronic disease characterized by an abnormal increase in the number of leukocytes

lymph--a clear liquid that is collected from the tissues throughout the body and flows in lymphatic vessels

MONS 025971

lymphatic--pertaining to vascular channels that transport lymph or to a lymph node

lymphoid--resembling lymph or lymphatic tissue

lymphoma--a neoplasm of the lymphatic tissue

lymphoreticular--proliferation of the reticuloendothelial cells of the lymph glands

lymphosarcoma--malignant neoplastic disorders of lymphoid tissue, but not including Hodgkin's disease

malignant--tending to become progressively worse; life-threatening

mammary--pertaining to the breast

marmoset--a soft furred, clawed monkey found in South and Central America

melanoma--a neoplasm derived from cells that are capable of forming melanin

menopause--the cessation of menstruation

mesentery--a fold of peritoneum that attaches the small intestine to the posterior abdominal wall by which the viscera are supported

meso--a compound whose molecules are superimposable on their mirror images

mesothelioma--a neoplasm derived from cells lining the pleural and peritoneal cavities

metabolism--the transformation of chemicals by which energy is made available for the uses of the organism and by which contaminants may be converted to different compounds for easier elimination

metabolite--any substance produced by metabolism or by a metabolic process

metastasis--in cancer, the appearance of a neoplasm in parts of the body remote from the site of its origin

miscible--capable of being mixed without separation into phases

mononuclear--a cell having a single nucleus, especially a monocyte of the blood or tissues

multiple myeloma--a malignant neoplasm derived from plasma cells and found at several foci in the body

MONS 025972

mutagenicity--the property of being able to induce an inheritable change

myasthenia gravis--a disease of the muscular system characterized by progressive weakness of muscles

myeloma--a malignant neoplasm derived from plasma cells

myeloproliferative disorder--a disorder characterized by proliferation of one or more bone marrow elements

nasal turbinates--the convoluting supportive structure of the nose

necropsy--the examination of a dead body by dissection for detailing the effects of disease

neonatal--relating to or effecting the first four weeks after birth

neoplasia--the process that results in the formation and growth of a tumor

neoplasm--any new and abnormal growth; neoplasms may be either benign or malignant

neoplastic--pertaining to or like any new or abnormal growth

neural--pertaining to the nerves

neuroblastoma--a malignant tumor of the nervous system

neurogenic--originating in the nervous tissue; forming nervous tissue

nodule--a swelling or protuberance

oat cell carcinoma--a type of lung cancer

olfactory--pertaining to the sense of smell

oropharynx--a division within the tube connecting the mouth and nasal passages to the esophagus

osteoporosis--an abnormal thinning of the bone

ovarian--pertaining to an ovary or ovaries, the female reproductive organ in which eggs develop

ovary--the female reproductive organ in which eggs develop

palate--the partition separating the nasal and oral cavities

pancreas--a large gland behind the stomach that secretes both hormones and enzymes involved in digestion and metabolism

MONS 025973

papilloma--a benign tumor derived from epithelial tissue

parathyroid--any one of four small glands situated beside the thyroid gland

parenteral--not through the alimentary (food) canal, but by subcutaneous, intramuscular, or intravenous injection

Parkinson's syndrome--a disease characterized by muscular rigidity, tremor, and salivation

particulates--composed of separate particles having characteristic properties and structures

pathologist--an expert in the study of the nature of diseases

pelvis--the lower (caudal) portion of the trunk of the body, bounded anteriorly and laterally by the two hip bones and posteriorly by the sacrum and coccyx

percutaneous absorption--absorption through the skin

peritoneum--the lining surrounding the abdominal cavity and containing the viscera

pesticide--a poison used to destroy pests of any kind

pH--the negative logarithm of the hydrogen ion concentration used in expressing both acidity and alkalinity. On a scale of 0-14, 7 represents neutrality

pituitary--a small gland at the base of the brain that secretes several important hormones

pleural--pertaining to the membrane surrounding the lungs and lining the thoracic cavity

polycyclic--containing more than one benzene ring

polycythemia vera--a disease characterized by an absolute increase in red cell mass and total blood volume, associated frequently with splenomegaly, leukocytosis, and thrombocythemia

postpartum--occurring after childbirth

prenatal--existing or occurring before birth with reference to the fetus

primary cancer--the original cancer developed in an organism

MONS 025974

promoter--a chemical that, though not itself carcinogenic, serves to potentiate, sometimes quite dramatically, the effect of a carcinogen

prostate--a gland in males that surrounds the neck of the urinary bladder and the urethra, and secretes a milky fluid that is discharged at the time of emission of semen

prostatitis--inflammation of the prostate gland

pulmonary--pertaining to the lungs

pyelonephritis--inflammation of the kidney and its pelvis

pyrolysis--decomposition of a substance by heat

quarternary--containing four chemical elements or groups

racemate--the rotation of an isomer that is exactly cancelled by an equal and opposite rotation

radioactive--having the property of emitting radiation (such as alpha, beta, or gamma rays) from an atomic nucleus

remission--a diminuation or abatement of the signs or symptoms of a disease

renal--pertaining to the kidney

respiratory--pertaining to the act of breathing

reticulum cell--a network, especially a protoplasmic network in cells, such as the flattened double membrane sheets of the endoplasmic reticulum

retrospective study--a study (epidemiological) that collects information about past events that may be related to the present distribution of disease

rheumatoid arthritis--a chronic disease of the joints, marked by inflammatory changes of joint structures

rodenticide--any agent used for destroying rodents

salivary--pertaining to the saliva, or the glands that secrete saliva

sarcoma--a malignant neoplasm derived from connective tissue

scrotum--the pouch that contains the testes and their accessory organs

secondary cancer--a cancer arising through metastases of primary cancer

MONS 025975

sedative--an agent that relieves excitement or anxiety and induces sleep

small intestine--the small tube of the intestine, about 20 feet long, extending from the opening of the stomach to the large intestine

smelter--an establishment used to separate or refine a metal often with accompanying chemical change

spleen--a large vascular lymphatic organ that lies in the upper abdominal cavity; it stores blood cells and produces lymphocytes

squamous cells--thin, flat cells

stomach tube--a tube passed through the mouth down into the stomach, used sometimes as a means of dosing animals

subcutaneous (sc)--beneath the skin

systemic--pertaining to or affecting the body as a whole

target organ--the organ affected by a specific chemical in a specific species

technical grade chemical--a chemical that has not been purified after production and may contain multiple impurities

testes--the male gonads situated in the scrotum that produce sperm

thorax--the part of the body between the neck and the respiratory diaphragm encased by ribs; the chest

topically--pertaining to a particular surface area and affecting only that area

toxic--poisonous

tracheal--pertaining to the trachea, the main trunk of the system of tubes by which air passes into the lungs

transitional cell--a cell that is changing, such as in movement, development, or evolution from one form, stage, or style to another

transplacental--through the placenta (the organ uniting mother and fetus)

thrombophlebitis--inflammation of a vein with secondary clot (thrombus) formation

thymus--a gland that is located in the lower neck

thyroid gland--a gland that produces, stores, and secretes hormones that regulate the rate of metabolism

MONS 025976

tubular cell--pertaining to a cell, with a tubule or small tube-like structure

tumor--a neoplasm; a mass of new tissue that persists and grows independently of its surrounding structures and that has no physiological use; it may be benign or malignant

tumorigenic--causing or producing tumors

urinary tract--pertaining to the organs and passageways concerned with the formation and discharge of the urine

uterus--the hollow muscular organ in female animals that is the abode and place of nourishment of the fetus

vagina--the passage leading from the uterus to the outside of the female body

valency--the electrical charge of a chemical atom

vascular--pertaining to blood vessels or indicative of a copious blood supply

vector control--control of insects and other organisms transmitting infectious agents of disease

vehicle--the substance in which a compound is dissolved or mixed prior to dosing an animal with that compound

vesicant--causing blisters; a small round hollow outgrowth of the skin

volatile--readily changes to a vapor

X-irradiation--X-ray exposure

Zymbal's glands--sebaceous glands surrounding the external ear canal in rodents

MONS 025977

ACRONYMS AND ABBREVIATIONS

AFL/CIO	American Federation of Labor/Congress of Industrial Organizations
ANPR	Advance Notice of Proposed Rulemaking
BATF	Bureau of Alcohol, Tobacco, and Firearms
BC	Bureau of Census
BD	Bureau of Drugs, FDA
BF	Bureau of Foods, FDA
BMD	Bureau of Medical Devices, FDA
BVM	Bureau of Veterinary Medicine, FDA
CAA	Clean Air Act
CAG	Carcinogen Assessment Group, EPA
CAS	Chemical Abstract Service
CDC	Centers for Disease Control
CEC	Chemical Evaluation Committee, NTP
CFR	Code of Federal Regulations
CI	Colour Index
CIIT	Chemical Industry Institute of Toxicology
CMR	Chemical Marketing Register
CPSA	Consumer Product Safety Act
CPSC	Consumer Product Safety Commission
CSWG	Chemical Selection Working Group, NTP
CWA	Clean Water Act
DHEW	U.S. Department of Health, Education, and Welfare
DHHS	U.S. Department of Health and Human Services
DHCP	Diet, Nutrition, and Cancer Programs, NCI
DOC	U.S. Department of Commerce
DOE	U.S. Department of Energy
EDF	Environmental Defense Fund
EEC	European Economic Community
EPA	U.S. Environmental Protection Agency
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FD&CA	Food, Drug, and Cosmetic Act
FHSA	Federal Hazard Substances Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FY	Fiscal Year
GRAS	Generally Recognized As Safe
HCN	Hydrogen Cyanide
H_2O_2	Hydrogen Peroxide
hr	hour

MONS 025978

IARC	International Agency for Research on Cancer
insol	insoluble
ip	Intraperitoneal
IRLG	Interagency Regulatory Liaison Group
iv	Intravenous
max	maximum
MCL	Maximum Contaminant Level
min	minute
MSHA	Mine Safety and Health Administration
NCI	National Cancer Institute
NESHAP	National Emissions Standards for Hazardous Air Pollutants
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NOHS	National Occupational Hazard Survey
NORS	National Organic Reconnaissance Survey
NOS	Not Otherwise Specified
NPDES	National Pollutant Discharge Elimination System
NRC	Nuclear Regulatory Commission
NTP	National Toxicology Program
OAQPS	Office of Air Quality Planning and Standards, EPA
ODW	Office of Drinking Water, EPA
OPP	Office of Pesticide Programs, EPA
OPTS	Office of Pesticides and Toxic Substances, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTC	Over The Counter
OTS	Office of Toxic Substances, EPA
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PEL	Permissible Exposure Limit
PHS	Public Health Service
PL	Public Law
PPPA	Poison Prevention Packaging Act
PR	Pesticide Registration
RCRA	Resource Conservation and Recovery Act
R&D	Research and Development
RPAR	Rebuttable Presumption Against Registration
RTECS	Registry of Toxic Effects of Chemical Substances
SDWA	Safe Drinking Water Act
sec	section
sol	soluble
SPRD	Special Pesticide Review Division
SUS	Saybolt Universal Seconds

TB	Tuberculosis
TDB	Toxicology Data Bank
TLV	Threshold Limit Value
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
USDA	United States Department of Agriculture
USITC	United States International Trade Commission
USP	United States Pharmacopeia
Vol.	volume
WHO	World Health Organization

MONS 025980

UNITS OF MEASUREMENT

Weights

g	gram	1 g	=	0.035 oz
kg	kilogram	1 kg	=	2.2 lb
lb	pound(s)	1 lb	=	0.45 kg
mg	milligram	1 mg	=	10^{-3} g
mg/kg	when referring to dosing, it means mg of chemical administered per kg body weight of the dosed animal			
ng	nanogram	1 ng	=	10^{-9} g
oz	ounce	1 oz	=	28.3 g
ppb	parts per billion	1 ppb	=	ug/kg
ppm	parts per million	1 ppm	=	mg/kg
ppt	parts per trillion	1 ppt	=	ng/kg
ug	microgram	1 ug	=	1 x 1^{-6} g

Volumes

cc	cubic centimeter	1 cc	=	1 ml
gal	gallon (U.S.)	1 gal	=	3.8 l
l	liter	1 l	=	0.95 liquid quart
m^3	cubic meter	m^3	=	35 cubic feet
ml	milliliter	1 ml	=	10^{-3} l

Lengths

cm	centimeter	100 cm	=	1 m
km	kilometer	1 km	=	0.6 mile
m	meter	meter	=	3.3 feet
mm	millimeters	1 mm	=	1/1000 m
mppcf	million parts per cubic foot			

Temperature

° C	degree Centigrade	1° C	=	(° F-32)
° F	degree Fahrenheit	1° F	=	(° C x 9/4) + 32

Exponentials

10^2, 10^3, 10^6, etc.: superscripts refer to the number of times "10" is multiplied by itself, e.g., 10^2 = 10 x 10 = 100; 10^3 = 10 x 10 x 10 = 1000.

MONS 025981

C. List of Substances and Their Synonyms and Trade Names*

* The index also includes the trade names of preparations or formulations only because they contain the listed substance as a part of a mixture of several chemicals.

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2-ACETYLAMINOFLUORENE
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4-ACETYL-2-ACETAMIDOFLUORENE
5-(N-ACETYL-2-FLUORENYL)-HYDROXYLAMINE
6-(N-ACETOXY-N-2-FLUORENYL)-ACETAMIDE
7-FLUORENE-2-YLACETAMIDE
8-(N-2-FLUORENYL)-ACETAMIDE
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ACRYLON
ACRYLONITRILE (DOT)
ACRYLONITRILE (OCI)
ACRYLONITRILE MONOMER
CARBACRYL
CYANOETHYLENE
DOT 84
FUMIGRAIN
NITRILE VINYLCYANIDE
PROPENENITRILE
2-PROPENENITRILE
UN 1093
VCN
VINYLON
VINYL CYANIDE

APLASTOMYCIN CAS# 1402-88-2 27
APPI
APLASTOMIN A
APLASTOMIN B1
APLASTOMIN B2
APLASTOMIN B3
APLASTOMIN B4
APLASTOMYCIN A1
APLASTOMYCIN B1
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2-AMINONAPHTHALENESULFONIC CAS# 117-79-3 29
AAS
AMINONAPHTHALENESULFONIC
2-AMINO-8,1G-NAPHTHALENESULFONIC

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AMINONAPHTHALENESULFONIC, 2-AMINO- (OCI)
BETA-NAPHTHALENESULFONIC
NCI-C01870

4-AMINOBIPHENYL CAS# 92-67-1 31
P-AMINOBIPHENYL
P-AMINODIPHENYL
4-AMINODIPHENYL
AMILINE, N-PHENYL-
ANILINOBENZENE
BENZENE, ANILINO-
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BIG DIPPER
DIPHENYLAMINE
P-DIPHENYLAMINE
(1,1'-DIPHENYL)-4-AMINE
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4-DIPHENYLYLAMINE
C.I. 10315
DPA
DSP 4DPA
DIPHENYLAMINE (OCI)
N,N-DIPHENYLAMINE
DPA
DPA (TAM)
NP 10ILD
PAPA AMINOBIPHENYL
N-PHENYLANILINE
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ACETATE PASE ORANGE 0
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ARTIFIL ORANGE 3RP
CELLITON ORANGE O
C.I.DISPERSE ORANGE 11
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C.I. 60700
DISPERSE ORANGE (TAM)
DYANAL ORANGE 3
2-METHYL-1-AMINOANTHRAQUINONE
NCI-C01701
PHLOXINE " ORANGE 2G
PONCITO ORANGE 3G

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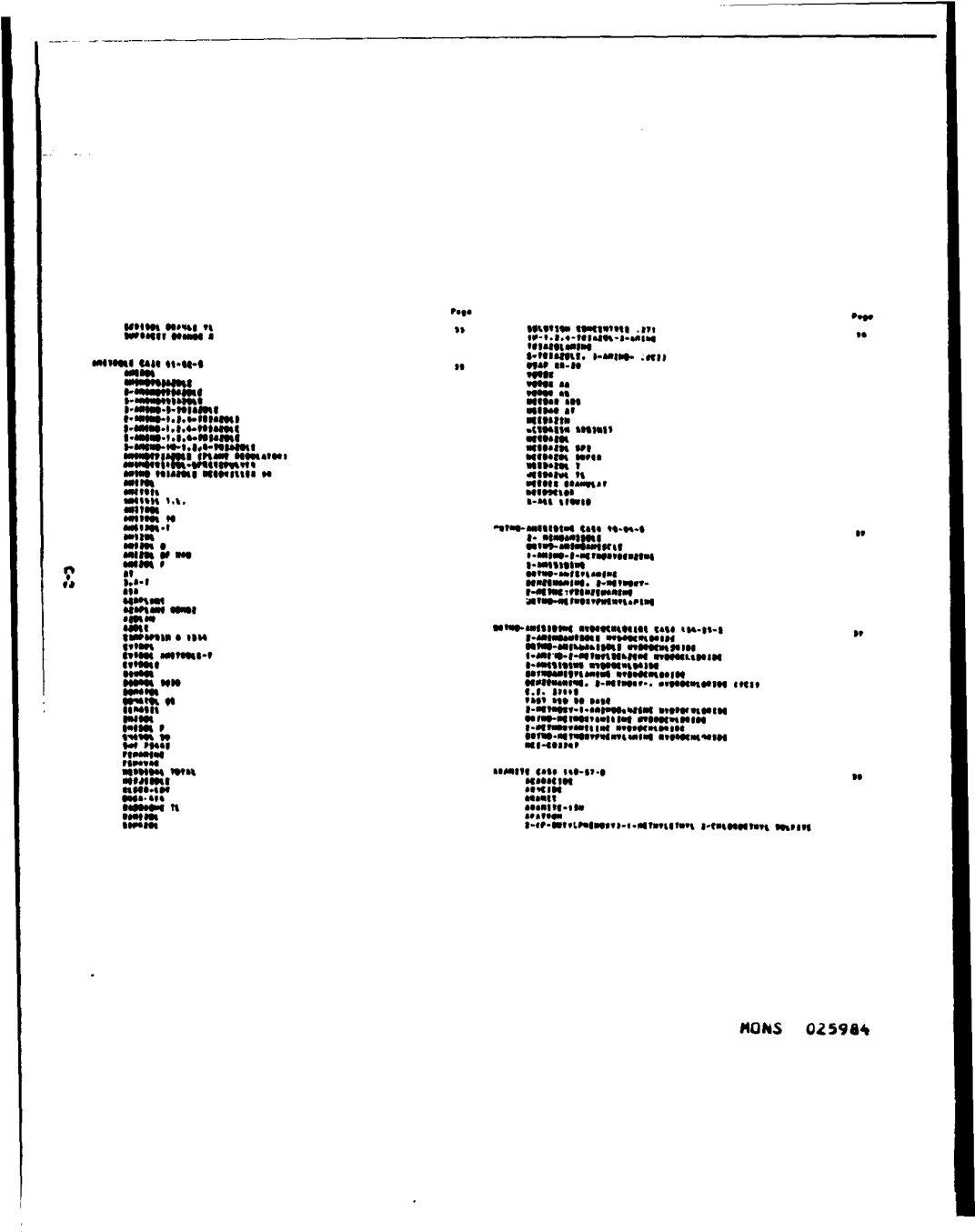

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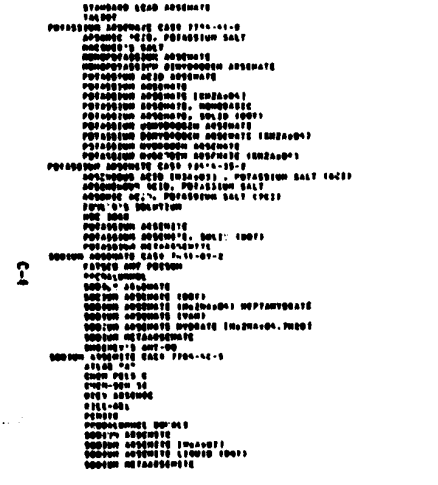

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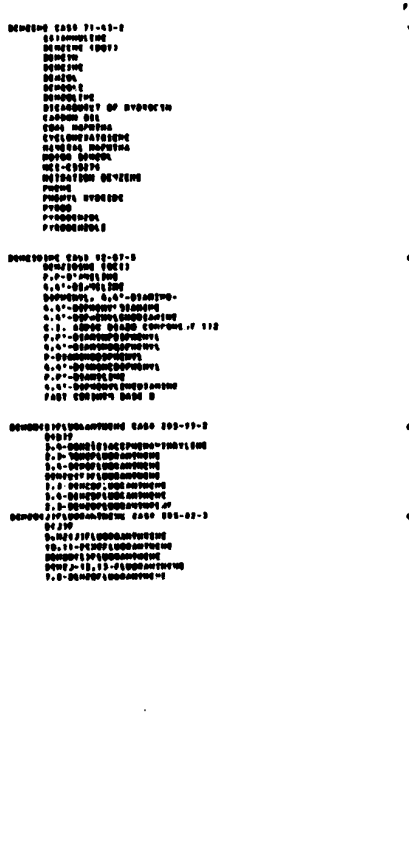

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[illegible]
BENZENE (DOT)
BENZEN
BENZENE
BENZOL
BENZOLE
BENZOLINE
DICARBONIST OF HYDROGEN
CARBON OIL
COAL NAPHTHA
CYCLOHEXATRIENE
MINERAL NAPHTHA
MOTOR BENZOL
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C.I. ACIDS DIAZO COMPONENT 112
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BERYLLIUM ZINC SILICATE CASE 39413-47-8
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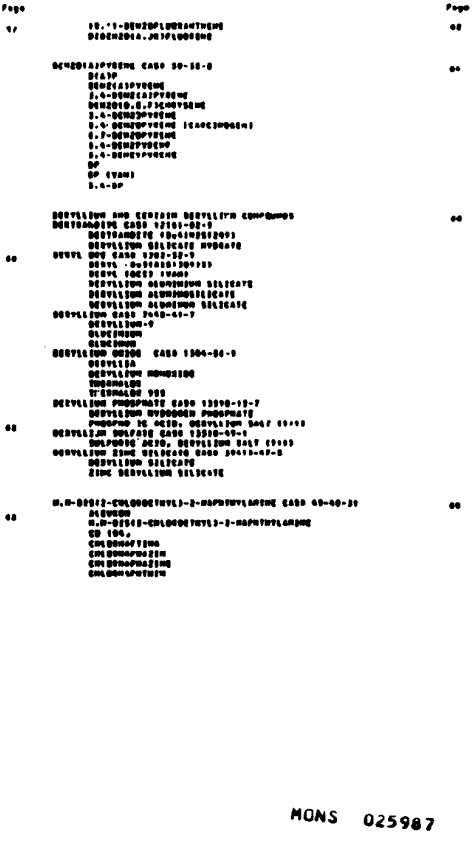
CHLORNAFMAZIN
CHLORNAFMAZINE
CHLORNAPHTHIN



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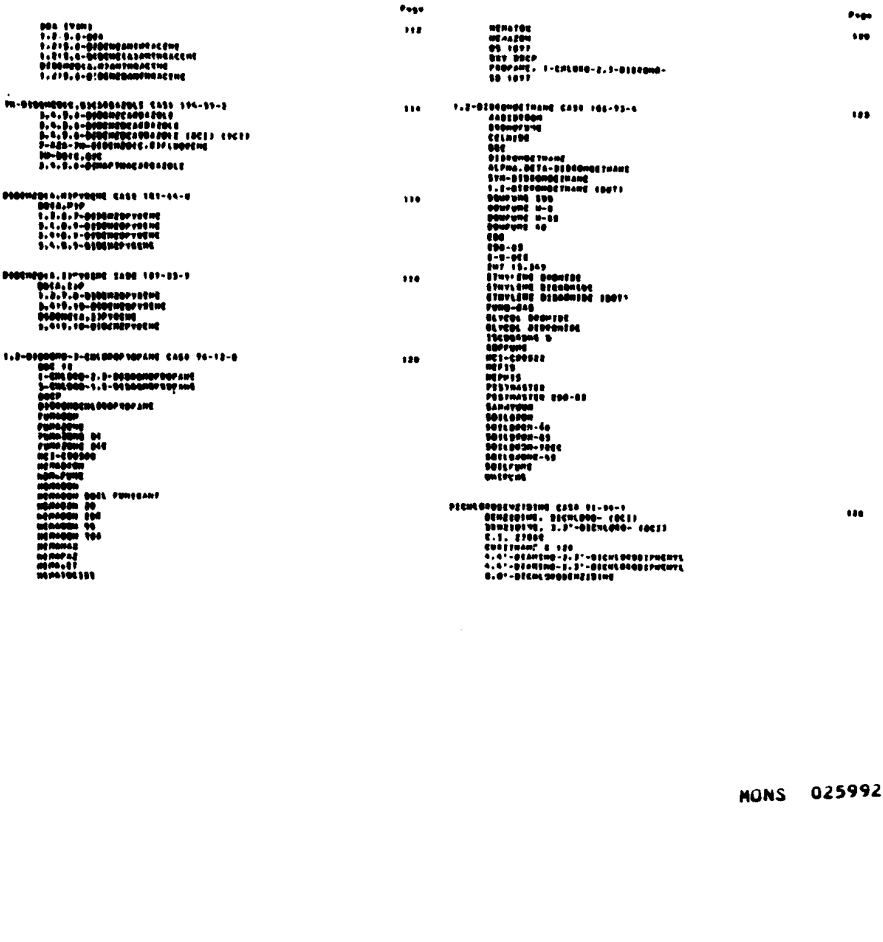

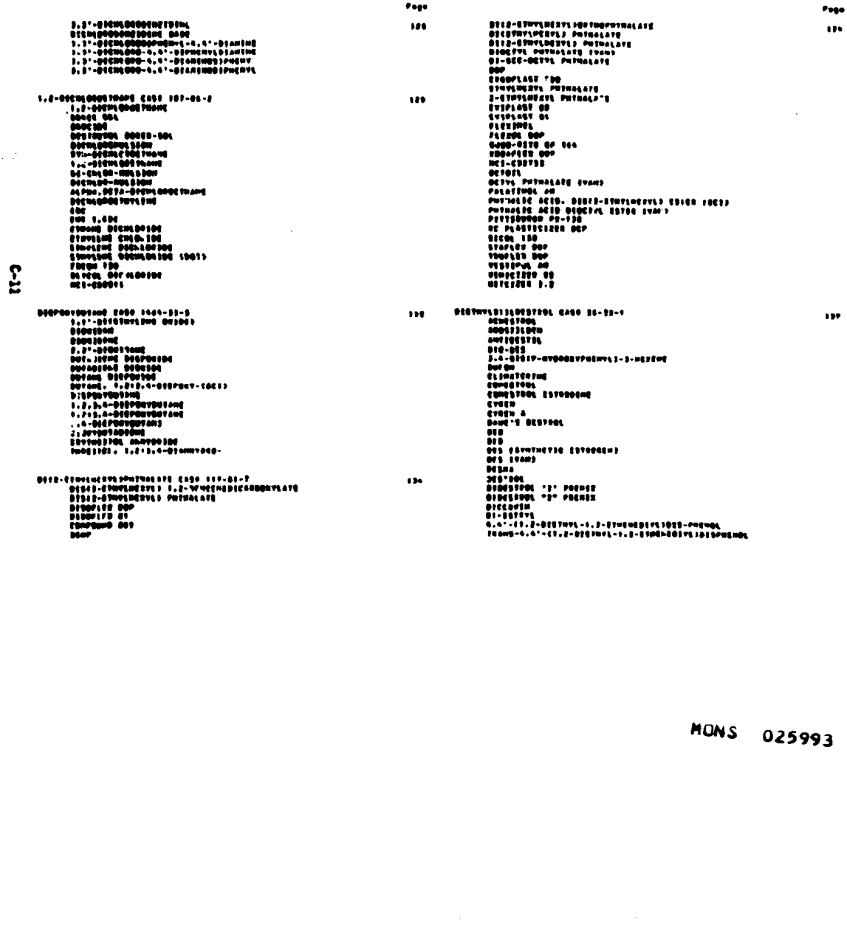

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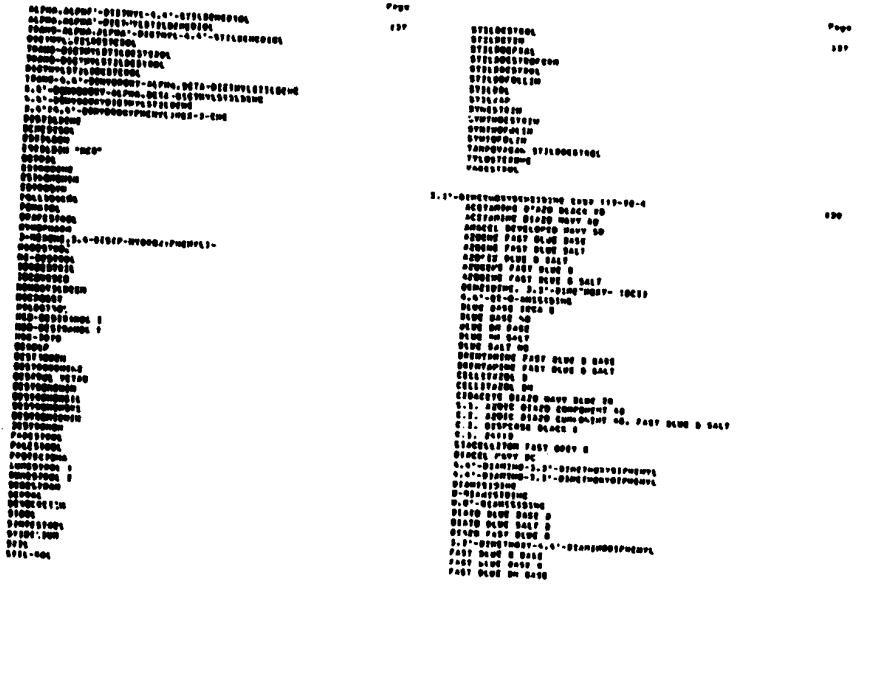

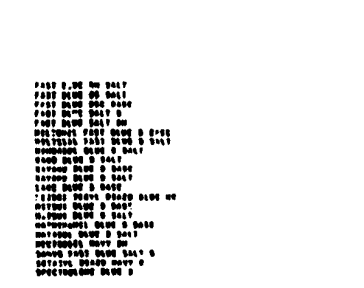

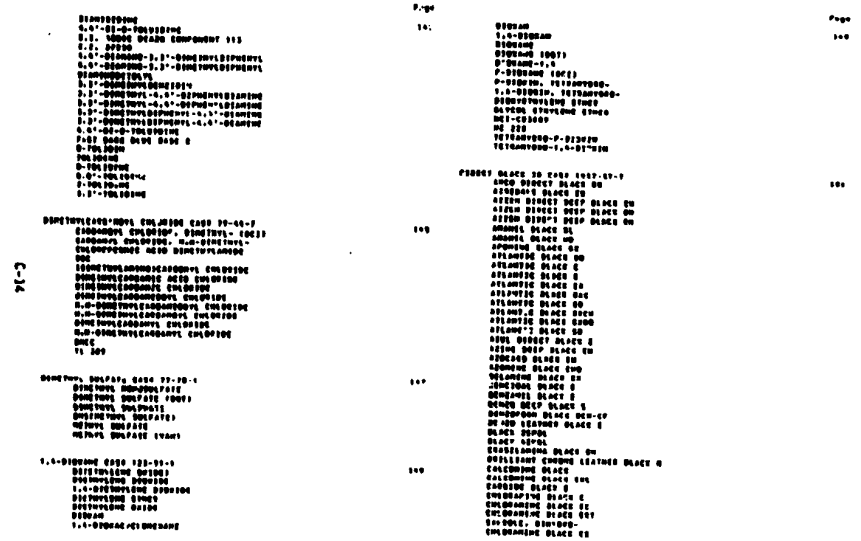

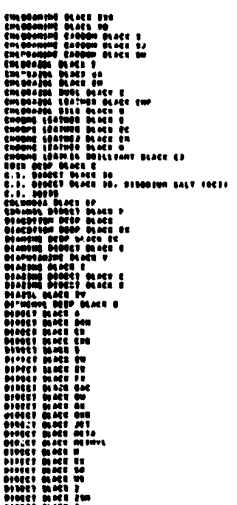

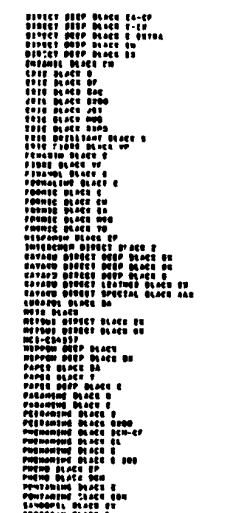

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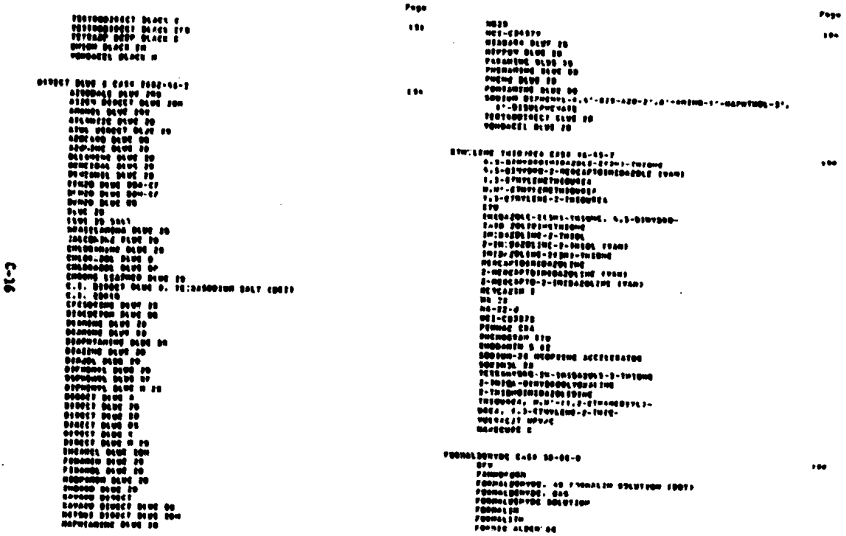

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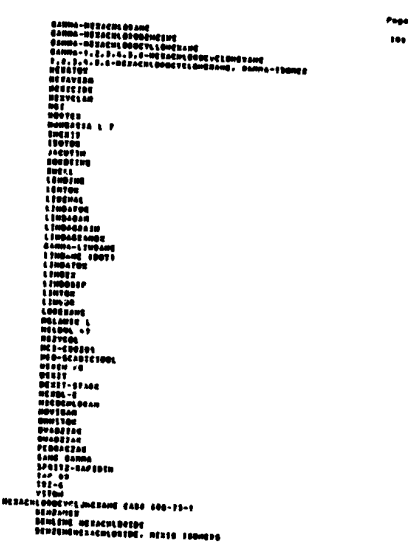

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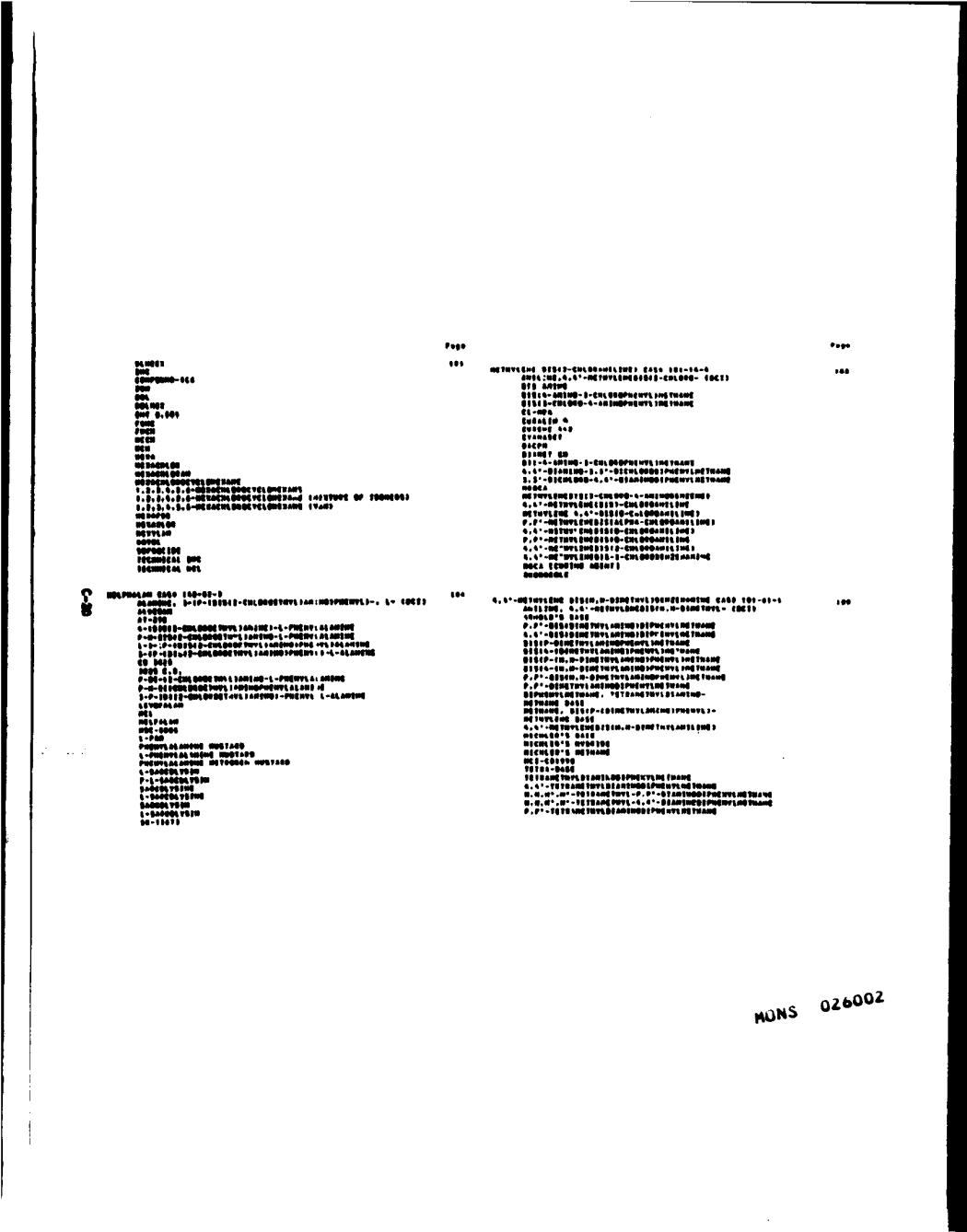

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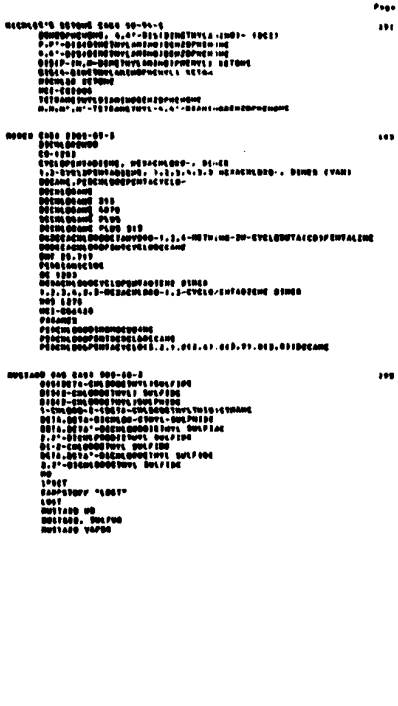

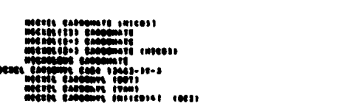

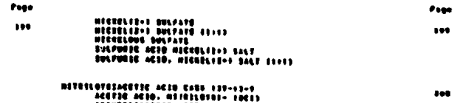

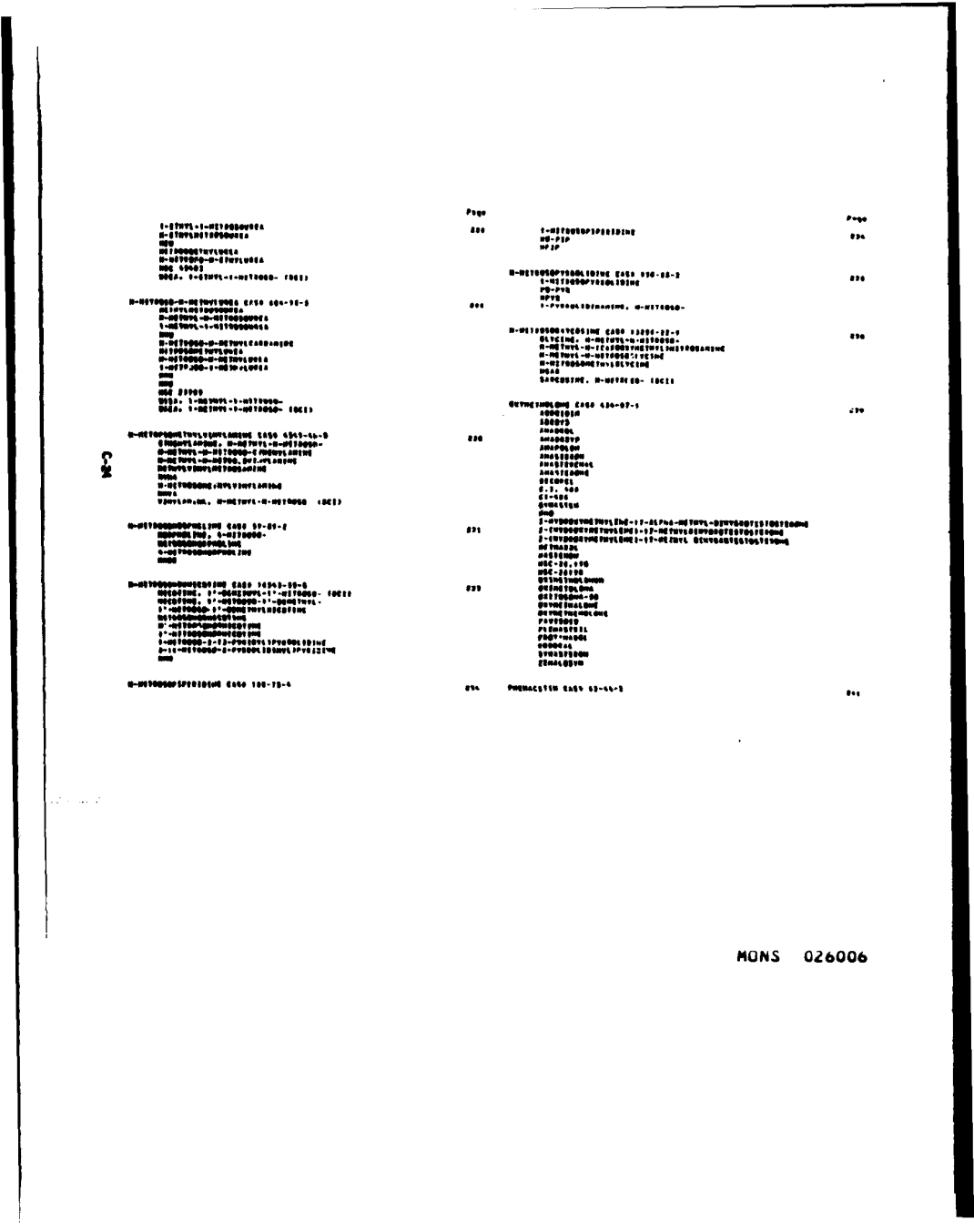

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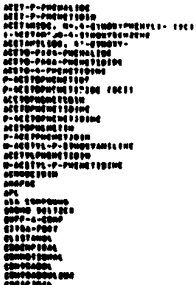

ACET-P-PHENETIDINE
ACET-P-PHENETIDIN
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DILLANTIN
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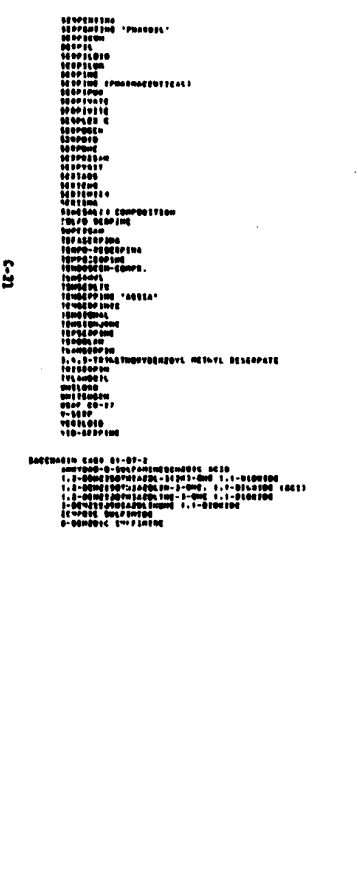

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N-ANILINO-4-METHYLBENZENE
2-ANILINOTOLUENE
DIPHENYLAMINE
DIPHENYLAMINE, 2-METHYL-
C.I. 37077
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ALLYSI
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CAMPHORENOL
CAMPHORIC NOTLOVE
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MCI-CO1449
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OMCOTEPA
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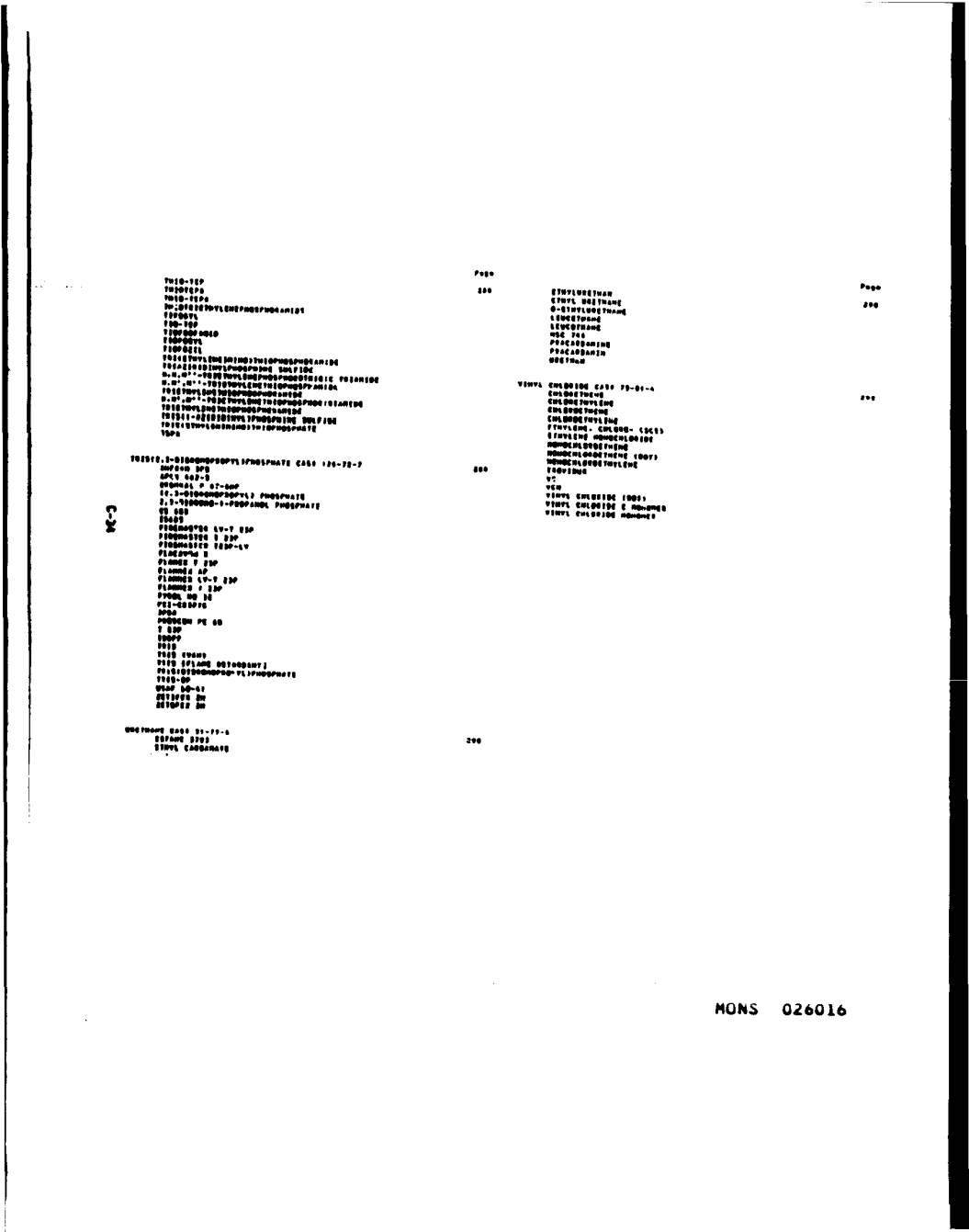
THIOPHOSPHORAMIDE, N,N',N''-TRI-1,2-ETHANEDIYL-
THIOPHOSPHORAMIDE, N,N',N''-TRIETHYLENE-
THIOTEF



D. List of Participants

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LIST OF PARTICIPANTS

Centers for Disease Control/National Institute for Occupational Safety and Health

Mr. Richard Lemen*
Mr. Roger Nelson

Consumer Product Safety Commission

Dr. Marilyn Wind*

U.S. Environmental Protection Agency

Ms. Eleanor Merrick*
Office of Toxics Integration

Food and Drug Administration

Dr. Allen Heim*
Office of Science Coordination

Dr. Herbert Schumacher
National Center for Toxicological Research

National Institutes of Health/National Cancer Institute

Dr. Richard Adamson*
Director, Division of Cancer Cause and Prevention

Dr. Elizabeth Weisburger
Assistant Director for Chemical Carcinogenesis

National Institutes of Health/National Institute of Environmental Health Sciences

Dr. Raymond E. Shapiro*
Assistant Director for Toxicology Coordination
(Executive Secretary NTP/WG ARC)

---

* Member, NTP Working Group for the Annual Reports on Carcinogens (NTP/WG ARC)

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National Institutes of Health/National Institute of Environmental Health Sciences (continued)

Office of Health Hazard Assessment

National Institutes of Health/National Library of Medicine

Dr. Paul Craig
Dr. Henry Kissman*

U.S. Department of Labor/Occupational Safety and Health Administration

Dr. Patricia Breslin*

National Toxicology Program

Dr. David P. Rall*
Director, National Toxicology Program
(Chairperson, NTP/WG ARC)

Dr. Dorothy Canter*
Dr. James Huff
Mr. Steve d'Arazien

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* Member, NTP Working Group for the Annual Reports on Carcinogens (NTP/WG ARC)

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