SUMMARY OF THE HEALTH EFFECTS OF PCBs

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CHEMICAL MANUFACTURERS ASSOCIATION

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PREFACE

The technical review concerned with the effects of PCBs, as provided on the following pages, summarizes the findings reported in the following documents:

- "The Epidemiology of PCBs" by William Gaffey, a Monsanto publication, (1981).
- "A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies with Polychlorinated Biphenyls" by George Levinskas, a Monsanto publication, (1981).
- "The Toxicity of Aroclor Products 1242, 1254, and 1260 to the Liver of Albino Rats" by George Levinskas, a Monsanto publication, (1981).
- "Human Health Effects of Electrical-Grade PCBs" by J.F. Brown, Jr., J.T. Coe, and H.D. Pocock, Jr., a General Electric publication, (1981).
- "Technical Review of the Health Effects of PCBs" by Robert James, Morris Cranmer, and Raymond Harbison, a New England Gas Association publication, (1981).
- "Assessment of Carcinogenic Risks From PCBs in Food" by Kenny S. Grump and Marjory Masterman, prepared for the United States Congress Office of Technology, contract # 933.1350.0, (1979).

EXECUTIVE SUMMARY

In this paper we examined the human health risks associated with exposure to PCBs. To accomplish this purpose, we reviewed all significant published or readily available studies of the effects of PCBs as well as the pertinent current theories of carcinogenesis, the scientific body of knowledge which supports these theories; and have provided an analysis of the chemical carcinogenesis testing performed with commercial PCBs. As a result of this review and evaluation, it is our independent professional opinion that "any exposure to PCBs" does not pose a significant health risk to humans. These conclusions are based on data of the primary exposure to commercial grade PCBs.

After reviewing the carcinogenesis test data, we have concluded that commercial PCBs do not represent a carcinogenic (genotoxic/initiator) risk and that, even if they possess oncogenic (epigenetic/promoting) activity, the risk at low exposures is insignificant. This mechanistic distinction is a very important basis from which to address the cancer risk. To paraphrase a succinct summary of this distinction by Weisburger and Williams, promoters (oncogens) share the characteristic of being active only at high, sustained doses, and up to a certain point, the lesion may be reversible. Thus, these types of carcinogens represent only quantitative hazards to humans, and safe levels of exposure may be established by carrying out proper dose-response studies.

Attempts to estimate the potential risk of cancer to man caused by PCB exposure using data developed in rodents represents a controversial but crucial dilemma. Numerous studies involving both mice and

dysfunction or other physical disorders, no remarkable clinical findings have been uncovered. Furthermore, several investigators have commented to the effect that there is a "paucity of abnormal results" and that "there is no evidence of physical harm resulting from working with PCBs." In spite of over 50 years of use, no causal relationship has been established for any specific type of cancer, nor has it been proved that the incidence of cancer mortality has increased. The largest study, by the National Institute for Occupational Safety and Health (NIOSH), which involved over 2,500 persons, did not detect any statistically significant excess in the cancer mortality. Since this study failed to demonstrate an excess cancer rate in a high exposure population, it provides some reassurance that it is unlikely that future studies will show any increased risk of cancer from PCBs.

In summary, 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 serious or permanent nature. Chronic exposures have added little or no additional adverse effects of note to this picture. The preponderance of studies has not identified a clinical disease associated with exposure to PCBs, nor has it provided persuasive evidence of health impairment. There is no 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, and studies to date indicate it is highly unlikely future studies will establish such a link. Therefore, it appears that PCBs are not a remarkable toxicant, but a chemical which requires high doses to produce harmful effects.

The chemical analyses of PCBs have shown that they often contain polychlorinated dibenzofurans (PCDFs) at low levels. The concentrations of these toxic contaminants are generally in the parts-per-million range in pure PCB mixtures, but percent of contamination can be substantially increased as a result of industrial use. Since levels of PCBs generally found in the environment are in the parts-per-million range or lower, the concomitant concentrations of PCDFs would be expected to be unmeasurable. For this reason and because the toxicity data of all PCB exposures have probably included this

1. MAMMALIAN TOXICOLOGY OF PCBs

Any assessment of hazards posed by exposure to a chemical must consider the doses required to elicit each toxic response as well as the spectrum of toxicities the chemical is capable of inducing. All of these factors must be carefully incorporated into the final estimation of risk. Many toxicity tests depend upon clearly observable effects, such as organ injury or tissue damage. For these tests, detection of the effects in question is clear, and the results can directly be extrapolated to determine the potential for a similar adverse effect in man. However, a complete safety assessment and evaluation must also include tests designed to measure mutagenic or carcinogenic potential. While the biological manifestations for these tests may be easily measured and reproduced, what the experimental results represent with respect to the expected human response is less clear. Therefore, results from the latter tests should not necessarily overshadow findings in the former tests. Instead, the results from all tests must be evaluated for internal consistency. As new data emerges, this information should likewise be incorporated and, if necessary, the risk reassessed.

Polychlorinated biphenyls (PCBs) are not capable of causing immediate life-threatening responses in animals except at very high doses. When given as a single oral dose to rats, mice, or rabbits, the dose lethal to 50% of the test species lies in the 1,000 to 16,000 mg/kg of body weight dosage range. According to the scheme proposed by the American Industrial Hygiene Association, this dosage range for acute or immediate toxicity classifies PCBs as only a slightly toxic to

increase the cancer risk from other causative agents have produced inconsistent results. PCBs have been reported to inhibit the tumor growth of Walker 256 carcinosarcoma cells, to enhance the growth rate of MCB cells derived from the moloney sarcoma virus, and to be without any effect on the moloney leukemia virus.

Test procedures designed to indicate serious long-term or chronic effects have been somewhat variable, but these too have provided fairly unremarkable effects when compared to the potential harm caused by other useful industrial chemicals that have been similarly tested. Mammalian studies indicate that there is little reproductive risk associated with moderate to high doses of PCBs. Studies using up to 100 mg/kg/day did not affect reproduction in the rat, and similar results have been reported from tests in mice and monkeys. PCBs do, however, cross the "placental barrier." Primates born to exposed mothers have shown symptoms of intoxication. Also, those doses high enough to disrupt the estrus cycle have been shown to decrease the implantation rate. Yet PCBs did not produce any histopathological changes in the reproductive tracts of either sex of rats, caused no chromosomal damage or arrested spermatogenesis, and were negative in the dominant lethal test for inheritable damage to germ cells. More importantly, PCBs have not significantly altered embryo or fetal development in either rodents or nonhuman primates at doses that were not maternally toxic; thus, it can be concluded that there appears to be little or no teratogenic or reproductive risk associated with exposure to PCBs.

The overall mutagenic potential of PCBs is inconsequential. Direct mutagenic activity as measured by point mutations in bacterial tester strains has been recently reviewed by Levinskas (1981). According to the results of seven different studies, a group of chlorinated biphenyl compounds did not demonstrate any mutagenic activity. Although there is one report in the literature that 4-chlorobiphenyl might have mutagenic activity, other researchers have not been able to reproduce this observation. Additionally, Aroclor 1254 was found not to stimulate unscheduled DNA synthesis in the rat hepatocyte. In tests designed to observe chromosomal aberrations or alterations in number, the results were also overwhelmingly negative. PCBs were

approximately 1,000 times higher than expected for commercial Japanese PCB mixtures. Studies have revealed that the oxidation of PCBs to PCDFs is 2% to 3% for Aroclor 1254 at 550° to 600°C and that, during combustion, the rate of formation is time and temperature dependent. However, these conditions do not exist in the normal manufacture or use of PCBs nor in the normal use of PCBs in capacitors or transformers. These conditions might have occurred, however, in some heat exchange equipment. So, at present, the conditions for and the extent of PCDF contamination in PCB wastes is unknown.

While it should always be considered that PCDFs may increase the toxicity of commercial PCB mixtures, the variety of acute and chronic tests reviewed on the preceding pages are tests in which the contribution of PCDF toxicity was, no doubt, unconsciously measured. Therefore, concern for the greater toxicity of this contaminant, when it is in concentrations approximating those previously measured in commercial PCB mixtures (i.e., about 1 ppm), should be tempered by the possibility that its risk is that reflected by the animal test data gathered for what was previously considered to be a PCB mixture alone.

To reiterate the original premise, evaluating the hazard of any chemical on the basis of animal data requires careful consideration of (1) the spectrum and types of toxic responses induced; (2) the degree of species variation or consistency of the effects monitored; (3) the relevancy and validity of the test performed; (4) the dosage required to elicit the response; and (5) the level of relevance of the toxic effects observed, based upon the expected level of human exposure.

Thus, many of the PCB-induced adverse effects would be expected for 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 because of 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, teratogenic, mutagenic, and carcinogenic tests, chlorinated biphenyls were consistently negative with only a few exceptions. These exceptions

2. THE ROLE OF PCBs IN PRODUCING CANCER

Chemically induced carcinogenesis is a special aspect of toxicology, for the toxicants may or may not observe 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 event and any cellular or physiologic expression.

In recent years, the scientific community has concluded that even among chemical carcinogens there exist vast differences in the mechanisms by which they induce cancer. One can separate chemical carcinogens into two groups. One group obeys traditional toxicologic principles while the other does not. This classification of carcinogens has been described by Weisburger and Williams in Casarett and Doulls' "Toxicology: The Basic Science of Poisons." These authors separate carcinogens into genotoxic (initiator) and epigenetic (promoter) carcinogens, 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 is extremely important because genotoxic carcinogens are irreversible and may not have thresholds; therefore, some risk is present at any dose. Promoting

to tradition, detection of vascular invasion or metastases was not considered by NCI to be essential for the diagnosis of hepatocellular carcinoma. Instead, the utilization of inclusive cytological criteria describing changes which may or may not have the potential to become the disease process we call cancer, including many responses which will never progress to cancer, was accepted at the expense of the more definitive criteria of malignant or invasive neoplasms.

The first report of PCB-induced tumors was that of an increased incidence of hepatomas. A later publication of the first study, which appears to have included the animals from the original report, terms the previously described hepatomas as well-differentiated hepatocellular carcinomas. Similarly, another study describes the production of hepatomas by PCBs in mice, but later the hepatomas are described as neoplastic nodules. Changes in liver cellular morphology were observed in mice only when the PCB chlorine content was 52% to 54%, and then only at exposure levels of 300 to 500 ppm. Lower doses did not produce tumors, and those PCBs with a chlorine content below 52% to 54% did not induce tumors. Further, the reported study of PCB-induced cancer in mice included only 12 mice studied for 32 weeks. This is not an acceptable bioassay procedure because of the small number of experimental animals used and the short time of exposure. Also, there was an inconsistency in reporting terminology. The liver changes were reported as hepatocellular carcinoma and also as hepatomas or tumors or nodular hyperplasia. A better bioassay was performed later that included larger numbers of test animals exposed for longer periods of time, and no increased incidence of tumors was reported. Subsequent studies were consistent with this larger study, and the majority of scientific literature supports the claim that PCBs are not carcinogenic in mice.

Similarly, only PCBs with a chlorine content of 60% produced those cellular morphological changes in rat liver that were classified using NCI guidelines as hepatocellular carcinoma. However, this same PCB mixture was tested in another strain of rat and did not significantly increase the incidence of tumor formation. Moreover, four other studies also failed to show any PCB-induced tumors. With one exception, there is a consistent absence of reports finding PCB-induced hepatocellular carcinomas. Again, those PCBs with a chlorine

which are initiators (genotoxic) and on those which are promoters (epigenetic). The following discussion of cancer will make the importance of this point clear.

Initiation of cancer is the process of producing damage to DNA of a magnitude sufficient to be sustained, but of a nature which permits cell survival and thereby predisposes the capacity of uncontrolled growth. Those cells containing damaged DNA then produce clones containing an inheritable mutation. Mutagenicity is defined as production of an inheritable alteration in the genome of a cell. An altered genome will increase the probability of cellular dysfunction. Therefore, inheritable mutations or initiation of genes responsible for cellular regulation increase the probability of producing cancer, a condition of regulatory dysfunction expressed as uncontrolled growth. Since most mammalian genes exist in allelic pairs and the malignant phenotype is probably recessive for nonviral induced cancers, a recessive mutation would not normally express itself as cancer until a second mutation occurred in the other allele. While there is normally a low probability of this occurring spontaneously by chance, given enough mutations in enough cells and a prior inheritance of susceptible genes through the germ cell line, the chance of having a successful mutation within both alleles of a critical gene, thereby producing a dysfunction in cellular regulation like cancer, becomes probable.

Thus, we can easily see how genotoxic agents (initiators) can apply selective pressure upon the cell toward the cancerous state. However, in our most often used test species, the mouse and the rat, there is a normal background incidence of the initiation process leading to cancer in the liver. Thus, where there is a history of spontaneous cancer incidence, there is little doubt that cancer will occur; only the rate and the time required to develop cancer (latency) is unknown. In this situation, the risk of cancer increases with time and the magnitude of the initiated response is a cumulative probability. In rodents, several factors have been shown to alter their background cancer incidence including total dietary calories, fat content, vitamin E, stress, crowding, and gender. Therefore, to define a chemical as a carcinogen (initiator) rather than another promoting factor in these species by using changes in liver cytoarchitecture requires proof that the chemical is an initiator and not a promoter of the

Comparison of the Characteristics of Promoting Agents and Effects of PCBs

1. Promoters produce increases of spontaneous tumors at selected sites. PCBs produce only liver tumors.

2. Tumors produced by promoters usually do not increase the metastatic characteristics of spontaneous tumors of the same site. PCB-increased liver tumors do not metastasize.

3. Promoters do not produce transplantable tumors unless the naturally occurring tumor is capable of transplantation. PCB tumors do not transplant.

4. Tumors influenced by promoters are often affected by factors such as nutrition, stress, chronic injury, and sex of the animal. Liver tumors are affected by these factors.

5. Promoters need not be mutagenic. PCBs are not mutagenic.

6. Neoplastic lesions increased by promoters may be reversible. PCB-increased liver tumors regress.

7. Progression of differentiation of neoplastic lesions increased by promoters often ceases when the stimulus is removed. Continued presence of PCBs is required to sustain liver neoplasia.

8. Neoplastic effects of promoters are usually associated with the chronic dysfunction of the affected site. PCBs produce chronic hepatotoxic responses.

9. Promoters do not necessarily increase the effect of carcinogens acting at the target site. PCBs reduce the response of several other liver carcinogens.

10. Promoters affecting the liver often increase microsomal enzyme activity and eventually produce evidence of metabolic dysfunction. PCBs stimulate LME and produce metabolic dysfunction.

It is apparent that the neoplastic effects of PCBs match the definitions of a promoting agent and do not match the definitions of an initiator.

It might also be mentioned that Butler and Jones (1978) have previously stated that certain compounds, especially persistent chlorinated compounds including PCBs, increase the incidence of only liver tumors in rodents and that these tumors may not be malignant. In fact, halogenated chemicals are the most numerous class of chemicals to induce rat or mouse liver tumors alone, and most are known not to be mutagenic. These chemicals produce liver cell damage and regeneration and/or induction of hypertrophic and hyperplastic changes. Thus, it is likely that these nonmutagenic chemicals are causing rodent tumors by an epigenetic mechanism.

This distinction concerning the halogenated hydrocarbons has been noted by other scientists as well. For example, Weisburger and Williams have stated:

> Validation of this concept of a promoting rather than a genotoxic action of chlorinated hydrocarbons is not only an important distinction from a theoretic point of view, but is even more relevant in terms of regulatory actions indicated to prevent chronic disease.

They further reiterated this idea by stating:

> If, on the other hand, no convincing evidence for genotoxicity is obtained, but the chemical is carcinogenic in animal bioassays, then the possibility exists that the chemical is an epigenetic carcinogen. The strength of this conclusion depends on the relevance of the in vitro tests. For example, the finding that certain stable organochlorine pesticides do not display genotoxic effects in liver cell systems, which are identical to the in vivo target cell for these carcinogens, strongly supports the interpretation that these carcinogens may act by epigenetic mechanisms. The nature of these mechanisms is poorly understood at present and is probably quite different for different classes of carcinogens. They may involve chronic tissue injury, immunosuppressive effects, hormonal imbalances, blocks in differentiation, promotion of pre-existing altered cells, or processes not yet known.

In conclusion, we have raised the question, Does one experiment utilizing prolonged exposures at high levels, in a single sex of a

Therefore, a rational policy for chemical utilization is to produce the highest standard of living consistent with a quantitatively acceptable hazard-to-benefit ratio.

A product containing chemicals should be approved for use if there is an acceptable margin of safety between the anticipated exposure and the level estimated as hazardous to humans or the environment. Yet, to accomplish this task, the toxicologist must face the dilemma of estimating the risk to an enormous and variable human population by extrapolating the hazards determined from studies conducted on small numbers of environmentally controlled and genetically homogeneous experimental animals. With the limitations of present experimental and theoretical techniques, there is considerable potential for error in assessing both sides of the hazard-to-benefit ratio. For these reasons, the limitations of toxicological evaluations should be clearly stated. It never has been, and is not now possible to guarantee absolute safety. Small populations of experimental subjects, either animal or human, may provide an imprecise estimate of hazard for comparison to a large human population of variable genetic disease states, cultural backgrounds, and ages. Ways of overcoming these limitations are slowly being recognized, and techniques for extrapolation must make maximum use of available data.

Thresholds

As a prologue to the discussion, it must be stated that we should resist falling into the intellectual and experimental quagmire called "threshold" and the mischief of "value judgement." There is no mathematical reason to distinguish cancer from many other toxicological effects. For cancer or any measurable response that may theoretically lack a threshold, the no-effect dose merely becomes a sample-size-dependent phenomena. To argue threshold is to obfuscate. We will later develop the thesis that time is the critical point of consideration.

The concept of a threshold dose is based on the premise that unless a specific set of conditions exists, some smaller dose will not produce the measured effect. For carcinogens (i.e., initiators), since there always exists the possibility of a response, the threshold limits of an effectively measured response only depend upon the sample

approaches capriciously eliminate from consideration the use of chemicals whose benefits might be documented to outweigh a worst-case calculation of the carcinogenic hazard.

Value Judgement and Emphasis

Ambiguities in the process of articulating an acceptable safety policy will automatically arise if proposed criteria require incorporation of the unobtainable goal of attempting to prove scientifically that no deleterious effect will take place, i.e., to prove the absence of the possibility of an occurrence in some future time. Examples have been described by Dr. Alvin Weinberg as "transcience." Such a policy postulates society's need to insure an absence of positive findings beyond the range of the methods available for data collection. Toxicologists' tools, however, are limited to experiments employing the scientific method. These experiments are usually designed to establish that phenomena resulting from repeated experimental manipulations are real, are not artifacts, and have not occurred simply by chance.

We are all aware that positive as well as negative findings may be artifacts and that in most scientific disciplines there is a positive reward for investing in adequate techniques and replication of experiments. Insistence on any desired degree of assurance against making a wrong conclusion is standard operating procedure. The quality of safety evaluations will suffer if we adopt ingrained unidirectional attitudes which demand that, once we find a positive carcinogenic effect, no number of negative studies provide an adequate counterbalance. Such attitudes inappropriately ignore false positives and discourage rigorous and repeated experimentation by even the most responsible sponsor. In addition, this emphasis places the sponsor and the conscientious regulator alike in the position of being bludgeoned with experiments carried out by third parties under conditions that often are not appropriate for safety evaluation or for which the results have not been validated. This dilemma ferments frustration, and inevitably intellectual problem-solving deteriorates into arguments of the wrong issue--for example, thresholds.

Table 3-1

DOSES REQUIRED TO PLACE UPPER LIMITS
ON ESTIMATED RISKS

Estimated Risk	Probit	Logistic	One-Hit
10^{-3}	1/67	1/323	1/714
10^{-6}	1/714	$1/9.8 \times 10^{5}$	$1/7.14 \times 10^{5}$
10^{-8}	1/2440	$1/6.3 \times 10^{6}$	$1/7.14 \times 10^{7}$

Table 3-2

FRACTION OF EXPERIMENTAL DOSE YIELDING ZERO TUMORS
USING PROBIT EXTRAPOLATION WITH DIFFERENT SLOPES
FOR AN ESTIMATED RISK NOT TO EXCEED
ONE IN 100 MILLION

	Fraction of Dose X Not Exceeding Risk		
Tumors Observed at Dose	Slope = 1	Slope = 1.5	Slope = 2.0
0/50	X/18,000	X/690	X/135
0/100	X/ 8,300	X/410	X/ 91
0/500	X/ 1,800	X/150	X/ 42
0/1000	X/ 1,000	X/100	X/ 32

When P(d) is small, the excess risk P(d)-(0) is approximately

$$P(d)-P(0) = a_1 d + a_2 d^2 + \ldots,$$

and the pseudo-question of nonthreshold low-dose linearity for purposes of modeling is determined by whether or not the coefficient a_1 is zero. There are plausible assumptions, such as detoxification mechanisms, DNA repair, or the necessity for multiple molecular interactions, that lead to $a_1 = 0$. There are also plausible assumptions for some agents that can lead to positive values for a_1. We will almost never have the knowledge to completely discriminate between these alternatives. Acceptable approaches to extrapolation must make efficient use of what experimental data we have or can get. Injection of value judgements, such as selected worst-case confidence limits in place of central expected values for the coefficients a_1, incorporates a bias value judgement into the extrapolation procedures that almost always outweighs the information inherent in the data. When one applies selected worst-case confidence limits rather than the central expected value (i.e., the most likely value) for a_1 it is equivalent to accepting that a_1 is positive. At low dose rates, this value judgement (such as an arbitrary worst-case confidence limits) dominates the remaining terms. The requirement to use upper confidence limits rather than central expected values in fact guarantees that models will yield nonthreshold linearity at low dose rates. Masquerades should not be necessary. If a policy calls for the selection of nonthreshold linear models, let us state so clearly and forthrightly. The arguments associated with masked conservatism have become redundant, predictable, and intellectually unappealing.

The lack of mathematical logic supporting certain value judgements becomes apparent when they are applied to the procedures of Crump et al. (1) and Guess et al. (4). Techniques become untenable when they are insensitive to responses at experimental dosages and fail to distinguish between low levels of potent carcinogens and noncarcinogenic substances. Guess et al. (4) have documented this by constructing two sets of dose response data for a noncarcinogenic agent. One simulation contained 150 responses at each of 10 dose rates, while the second was made up of 300 responses at each of 5 dose

Table 3-4

LOWER 97.5% CONFIDENCE LIMIT FOR DOSAGES PREDICTED
TO HAVE A RISK OF LESS THAN ONE MILLION IN RODENT POPULATIONS

Substance	Dose Unit	Sci. Com. FSC 1978	Linear	Armitage-Doll
Aflatoxin B_1	ppb	3.4×10^{-5}	7.9×10^{-6}	5.9×10^{-6}
Vinyl Chloride	ppm	1.6×10^{-3}	7.1×10^{-4}	5.2×10^{-4}
Ethylenethiourea	ppm	4.4×10^{-4}	1.0×10^{-4}	3.2×10^{-4}
Dieldrin	ppm	9.4×10^{-6}	5.7×10^{-6}	2.9×10^{-6}
DDT	ppm	2.0×10^{-2}	3.4×10^{-5}	2.6×10^{-5}

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Salmonella typhimurium to detect reverse-point mutation at the histidine locus. Only 4-chlorobiphenyls have demonstrated any activity in the Ames 1538 tester strain. In this same study, PCBs such as 2, 2', 5, 5' tetrachlorobiphenyl, 1254, and 1260 were negative. In subsequent studies, not even the positive for monochlorobiphenyl could be reproduced.

It has been demonstrated that PCBs do not cause significant clastogenic effects in rat bone marrow or sperm cells even at high doses. Aroclor 1242 was given at a single dose of 1,250 to 5,000 mg/kg and at 500 mg/kg for four days (a regimen causing the condition of the animals to deteriorate), while Aroclor 1254 was given at doses of 75 to 300 mg/kg for five days. These findings are consistent with the lack of chromosomal aberrations observed in human lymphocyte cultures with doses of 100 mg/kg Aroclor 1254.

The possible mutagenicity of PCBs has also been studied using the dominant lethal test. There was no statistically significant increase in the number of dead implants, again at high dosages of Aroclor 1242 and 1254. This test, the dominant lethal assay, has been repeated and again the results were negative. PCBs do not have significant mutagenic potential.

Crump continues to try to justify his models and approach taken for risk estimation for PCBs by stating:

> 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.

Crump also offers a possible explanation of why the dose response function should be linear at low dose when background is present (Crump, et al. 1976), as does Peto (1977), which will be briefly outlined here. Crump et al. and Peto argue that when background carcinogenesis is present, the cellular mechanisms 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

When tested without DMBA initiation, PCBs did not demonstrate any carcinogenic activity. PCBs did not produce any observable skin lesions.

Crump himself invalidates the model's use with the linear low dose assumption for PCB risk analysis when he states:

> 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.

The reader should be reminded that for the purposes of the discussion, promoter and indirect carcinogen can be used interchangeably. That PCBs are at worst an indirect carcinogen is supported by a large amount of data. PCBs induce microsomal mixed-function oxidases and cause hepatomegaly in rodents and other mammals. Heptomegaly has been interpreted by Kimbrough to be the result of the hypertrophy of individual hepatocytes. Hyperplasia also commonly occurs and increased mitotic activity can occasionally be noted. Hepatocytes enlarge and may accumulate lipid in their cytoplasm. At the ultrastructural level, enlarged hepatocytes show an increase in smooth endoplasmic reticulum and inclusions within the cytoplasm, which appear like concentric whorls, surrounding lipid vacuoles. Morphologic changes in the mitochondria have also been described (Kimbrough et al. 1972).

In addition to these alterations, PCBs induce experimental hepatic porphyria. In the rat, experimental hepatic porphyria only occurs in the Sherman strain female. This observation indicates a unique sensitivity for the Sherman female rat. On microscopic examination, an increase in macrophages and prominent Kupffer cells containing brown ceroid pigment and necrobiosis of liver cells is prominent. Lipid accumulates in the cytoplasma of hepatocytes, resulting at times in hepatocytes with foamy cytoplasm.

Acute as well as chronic toxicity of PCBs has been studied in rats, monkeys, mice, and cows. The organ consistently affected was

7. Progression of differentiation of neoplastic lesions increased by promoters often ceases when stimulus is removed. Continued presence of PCBs is required to sustain liver neoplasia.

8. Neoplastic effects of promoters are usually associated with the chronic dysfunction of the affected site. PCBs produce chronic hepatotoxic responses.

9. Promoters do not necessarily increase the effect of carcinogens acting at the target site. PCBs reduce the response of several other liver carcinogens.

10. Promoters affecting the liver often increase microsomal enzyme activity and eventually produce evidence of metabolic dysfunction. PCBs stimulate LME and produce metabolic dysfunction.

11. Promoters rarely if ever increase tumor incidence at exposure levels producing no toxic effects. PCBs are tumorogens only at toxic doses.

Characteristics of Initiators (Direct-Acting Carcinogens)

1. Initiators usually produce neoplastic lesions at multiple sites. PCBs only increase lesions of the liver.

2. Initiators often increase the malignancy of spontaneous tumors at the same site. PCB-increased liver tumors are of low malignancy.

3. Carcinomas irreversibly progress once a critical tissue mass is established. PCB-increased tumors can regress.

4. Initiators produce tumors which metastasize. PCB-increased liver tumors do not metastasize.

26 tumors/184 animals 1 ppb PCB/200 ppm PCB/70 years = 4.3 cancers/year.

Crump's analysis of risk to infants is markedly overstated. A rat consumes approximately 10% of its body weight per day. Feed with 100 ppm PCB equals a consumption of 100 mg/kg. Therefore, a rat consumes the equivalent of 10 mg PCB/kg/day. If the human milk sample was 2% fat, then the whole milk would contain 2% of the 4 ppm Crump considered, or .08 ppm. A liter of milk would contain .08 mg of PCB. A child weighing 6 kg would have to consume 750 liters of milk a day to equal the exposure of the rats. If the child truly only consumes 1.5 liters a day, then there is a 500-fold difference in exposure rate between rat and baby.

If the baby is exposed, as suggested by Crump, for only 1/140 of its lifespan, this has to be considered. The 500-fold difference times the 1/140 of the lifespan is equal to a 70,000 exposure differential. The linear risk as calculated by Crump's technique would be 2/1,000,000, not the 1/4,800 reported by Crump.

If we approach the problem another way, we obtain other interesting comparisons. The PCB dose to high exposure women averaged 1.7 µg/kg/day. A lactating female maintaining her weight would then have 1.7 µg x 50 kg, or 85 µg/day of PCB, available for transfer to the baby. If the baby weighs 6 kg, the dose is 14 µg/kg/day. This, when compared to the 10 mg/kg/day dose to the rats, yields an exposure ratio differential of 700 times. The exposure period of 1/140 times the exposure ratio yields a total exposure risk of 98,000 times less for the human than the rat. The linear risk as calculated by Crump's technique would be 1.4×10^{-4}, not the 1/4,800 reported by Crump. If we insist on <u>linear extrapolation</u>, what are the relative risks? Let us assign an average exposure resulting in 500 ppb blood level to capacitor workers, 70 ppb to the heavy fish eaters in Michigan, and 20 ppm to the general Michigan population. Let us assign an exposure of 12 µg/kg/day to the capacitor workers, 1.7 ug/kg/day to the fish eaters, and .5 µg/kg/day to the general population. These estimates were taken from the documents of Crump and the EPA water quality criteria for PCBs.

Capacitor worker	.005 + .0012 x 26 = .0362	(724% background)
Fish eater	.005 + .00017 x 26 = .0094	(188% background)
General population	.005 + .00005 x 26 = .00552	(110% background)

Again, this hypothesis cannot be rejected at the lower exposures because it is not possible to analyze it on the basis of information available. However, the capacitor workers aid in the evaluation of this hypothesis since the highly exposed individuals would demonstrate an incidence which is seven times the background incidence.

How Did EPA Analyze the Data?

The preceding discussion of human exposure makes clear the fact that a high percentage of the United States population has been and is exposed to low levels of PCBs in food, water, and air. Those groups at particular risk for PCB exposure include industrial workers exposed in the workplace and individuals consuming large amounts of contaminated fish, such as sport fishermen (42 FR 17487).

An assessment of carcinogenic risk was made by EPA performing extrapolation from animal data using a linearized multistage (non-threshold) model. The extrapolation used was reported to take into account the bioaccumulation of PCBs in fish and shellfish. It is assumed that an average of 2 l/day of water are consumed along with 6.5 g of fish taken from that water source. Exposures from other food sources, air, or occupational exposure are not included in the criterion level derived by this model.

Among the studies reviewed by EPA, only one was considered suitable for use in the cancer risk assessment. EPA made the remarkable statement that, "Of the rat studies, the only one involving long-term exposure and adequate numbers of animals is the study of Sherman rats by Kimbrough et al. (1975)." EPA goes on to state, "Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of PCBs in water for maximum protection of human health is zero." Since attaining a zero concentration level may be infeasible in some cases, and in order to assist the agency and states in the possible future development of water quality regulations, the concentration of PCBs corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides

Table 3-5

EPA INTERIM TARGET RISK LEVELS

Exposure Assumptions	Risk Levels and Corresponding Criteria[1] 10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish only[2]	0.0079 ng/l	0.079 ng/l	0.79 ng/l (80 ug/day)
Consumptions of fish and shellfish only	.0079 ng/l	0.079 ng/l	0.79 ng/l (80 ug/day)

1Calculated by applying a linearized multistage model as discussed in the Human Health Appendices to the October 1980 Federal Register notice which announced the availability of this document. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations shown in the table above vary by factors of 10, 100, 1,000, and so forth.

2Approximately 99 percent of the PCB exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 31,200-fold. The remaining 1 percent of PCB exposure results from drinking water.

these estimates. On the contrary, it is obvious that the EPA standard is from 10 to 100 times more severe than can be justified on the basis of human experience, and from 10- to 20-fold more severe than can be excluded on the basis of human experience. As our data base grows, it is likely that the standard will be found to be at least another order of magnitude too severe.

In summary, the rationale that was used by Crump and Masterman in establishing the PCB cancer risk was based on a genotoxic theory of carcinogenesis and was compiled from a series of ultra-conservative assumptions. These assumptions ignored the fact that PCBs are not genotoxic; utilized only the positive data and ignored the negative data; applied constraints to mathematical models which transformed them to the equivalent of linear extrapolation; ignored all other competing causes of death; equated cancer risk in the last moment of life with the risk of a newborn; and exaggerated exposures, for example: assumed that mother's milk was 100% fat, equated all PCBs' toxicities as the most toxic results observed for any PCB, and ignored the reversibility of PCBs' effects and the marked improvement in human exposure levels that has occurred in the last five years.

Furthermore, using a mathematical model to extrapolate the risk at lower doses does not increase the reliability of animal data. The most important question still remains: "Does the animal data reflect the human situation and response?" With the addition of the NIOSH study on capacitor workers to the PCB literature it can be demonstrated that the risks estimated using Crump's model are unrealistically conservative by serveral orders of magnitude. In a practical sense, a substantial number of people have been chronically exposed to higher levels of PCBs for a longer period of time than that which occurs for the general population. Since no adverse health effects were causally demonstrated in this population, no measurable adverse effects would be expected for the general population.

4. SUMMARY AND CONCLUSIONS

In past decades, a combination of "open" systems and sloppy or illegal disposal practices resulted in the release of large quantities of chemicals into the surrounding environment. In the 1960s, when it became apparent that persistent chemicals like DDT and PCBs were ubiquitous environmental contaminants which took years to biodegrade, attention became focused on their potential bioaccumulation and the possible negative effects of this on animals and humans. Even though the principal United States manufacturer, Monsanto Industrial Chemical Company, had voluntarily restricted PCB sales to manufacturers of "closed" electrical equipment in 1971, Congress enacted the Toxic Substances Control Act in 1976, mandating a phaseout of PCB manufacturing and use. During this time, PCBs were considered as highly toxic and dangerous chemicals capable of causing permanent adverse health effects such as cancer and birth defects. In recent years, however, a substantial increase in scientific data has resulted in a better understanding of the actual effects of human exposure to PCBs. It was the purpose of this document to review the data regarding the health effects of PCBs to provide an updated perspective to the PCB issue.

While it is the consensus of this report that PCBs do not pose the health hazards once feared, this conclusion may be complicated by a contaminant, polychlorinated dibenzofurans (PCDFs), often found in commercial PCB mixtures, which in some special circumstances may pose an increased risk. Yet PCDFs are only a minor component of PCBs produced in America, probably in the range of only 0.1 to 2 parts per million (ppm) of commercial PCBs. In addition, such commercial PCB

effects. The question then asked is, "What is considered safe and under what circumstances?" Critical to this determination is predicting the impact of the substance and the variations that are likely to occur within the exposed population. A critical evaluation of experimental evidence is necessary to define the probable hazard to man and the magnitude of the hazard. The accuracy of the prediction will depend on the types of experiments performed; the adequacy with which they have been performed; and, most importantly, the interpretation of the experimental results and the limits of the data.

The questions to be asked are, "Are PCBs poisons or are they safe? And if they are poisonous, when?" The problem is thus reduced to predicting an agent's safety based upon experimental evidence and a comparison of the results to the likely levels of human exposure. PCBs can be poisons. That is, like all other chemicals, PCBs are capable of altering normal function and can destroy life under specific circumstances and conditions. Alternatively, PCBs are safe under specific circumstances and conditions. The following summary of PCB properties and effects is meant to provide a perspective on their safety.

PCBs are chlorinated compounds of the biphenyl molecule. Theoretically, approximately 209 separate chlorinated biphenyls can be produced chemically. These compounds have unique physical and chemical properties that have made them useful and applicable to many commercial needs. The physical-chemical properties that make these compounds useful are their thermal stability; resistance to alteration by acids, bases, and other chemical agents; and their ability to provide excellent electrical insulation, fire resistance, and low volatility. PCBs are useful as lubricants, heat transfer liquids, and hydraulic fluids.

PCBs are ubiquitous to the human environment, as evidenced by their detection in the fat and blood of persons not occupationally exposed to them. These compounds have been identified in air, water, soils, wildlife, marine organisms, fish, and in our food supply. Thus, to minimize man's environmental exposure to PCBs, the United States Food and Drug Administration (FDA) has set tolerances of 0.5 to 5.0 ppm for the various components of our daily food supply. In the early 1970s, the daily consumption of PCBs was estimated by FDA to be

animal tests versus the expected human exposures; and, finally, to the extent that the data are available, 6) the outcomes of serious poisonings and long-term occupational exposures. Only when a consistent pattern of toxicity in animals is consistent with the human experiences can safe guidelines be promulgated.

When assessing the hazards associated with human PCB exposure based upon the mammalian test data, we must consider all of the animal data. While concern is given to positive findings, our decisions must also address the negative data and those doses required to induce the toxicities seen in animals versus our expected human exposures.

A review of the PCB literature reveals that PCBs are not very toxic if the exposure is of short duration. The organ dysfunctions caused by longer but nonchronic exposures also occur only at relatively high doses. This suggests that while organ dysfunction such as liver injury or chloracne might occur in man, it should occur only after high or sustained exposures. This suggestion has, in fact, been supported by the available human data. Therefore, there is little risk that these effects will occur in persons exposed to the generally low levels of PCBs in today's environment, if exposure occurs at all.

Similarly, the animal data indicate that there is little reproductive risk and that PCBs do not cause birth defects even at moderately high exposures. Again the animal data reflect the findings in humans. The Yusho incident, a high PCB exposure combined with exposure to other toxic chemicals, failed to demonstrate a substantive concern for teratogenic effects. Considering the balance of the reproduction studies and the breadth of the mutagenic tests performed, it has been concluded that PCBs do not pose a significant mutagenic or reproductive hazard.

While positive carcinogenic activity has been reported in one study using rats, this study must be placed in perspective against a far greater number of studies involving rats and mice that were negative. When a positive test result is our only available data, then that result should be considered as an obvious basis of concern for human exposure. However, a lack of comparable results in subsequent or other similar studies surely decreases the concern for and the validity of focusing on only the positive data. Such is the situation for PCBs. It would seem more reasonable to place greater emphasis on

there presently exist sufficient PCB test data to reevaluate those concerns for PCBs initiated by reported findings years ago. Further, the data now allow us to make the important distinction of whether or not PCBs are indeed initiating carcinogens.

Current theories of chemically-induced tumorogenesis differentiate tumorogens by mechanism. One class is the initiating carcinogens that alter DNA and produce permanent, inheritable, expressible changes in the initiated cell. These initiated cells may ultimately be transformed into the disease process we call cancer. The second class is the promoting agents, which do not directly alter DNA, do not produce inheritable changes, and are not effective with single or limited exposures. Chemicals producing tumors by a promoting mechanism have demonstrable threshold levels below which chemical exposure will not result in the expression of tumors. The risk caused by these chemicals therefore is insignificant in some for exposures that are below the threshold.

A review of animal testing data documents the case that PCBs, at worst, have some of the characteristics of a promoting agent and do not exhibit characteristics of an initiating carcinogen. A review of chronic cancer bioassay data further reveals that PCBs produced only a single species-, sex-, and mixture-specific positive response. The large number of negative tests indicate that they do not possess broad, potent, promoting activity. At the hepatotoxic doses tested, one reported PCB-induced increase in rodent liver tumor incidence after the many studies conducted should not be a totally unexpected finding. The animal testing data and biological characteristics of PCBs overwhelmingly indicate that if they produce an increase in tumors they do so by a promoting mechanism. Therefore, it can further be concluded that there are indeed safe levels of PCB exposure and that not all exposures carry a risk of producing cancer.

The occupational exposures are certainly the most extensive and longest-term human PCB exposures that we are currently aware of and are most representative of what adverse effects might be expected. A comparative review of these occupational-exposure studies reveals that, like other chemicals, PCBs can cause adverse health effects, but in many respects these have been minimal. While dermatitis and chloracne, which were reversible after discontinuing the exposure, have

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. Additionally, it is not uncommon to see measurable increases in one type of cancer over what is mathematically expected because we cannot choose a subpopulation to observe 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 attributed to any finding of excess cancer which is not statistically significant but 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: (1) a positive association must be seen in individuals with known exposures; (2) the positive association cannot be explained by bias in recording, detection, or experimental design; (3) the positive association must be statistically significant; (4) the positive association should show both dose and exposure period dependency; and (5) 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, they 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.

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. Chronic exposures have added little or no additional adverse effects of note to this picture. The preponderance of studies has not identified a clinical disease associated with exposure to PCBs nor has it provided persuasive evidence of health impairment. There is no evidence of an excess

Group	Blood Levels of PCBs	Estimated Exposure	EPA Calculated Risks
Highly Exposed Capacitor Workers	≥1,000 ppb	2.0 mg PCB/day	25.0
Average Capacitor Worker	500 ppb	.84 mg PCB/day	10.0
Michigan Fish-Eater	70 ppb	.12 mg PCB/day	1.4
Michigan Control Population	20 ppb	.035 mg PCB/day	.5
General Population	2 ppb	.0035 mg PCB/day	.05

The chances of dying from liver cancer can be expressed in several ways. But simply speaking, there will be about 2,000,000 deaths in 1981. Of these, it is estimated that 9,400 will be from liver cancer. Therefore, 9,400/2,000,000 equals a .47% chance that those dying this year will be dying from liver cancer. Rounding off these estimates to a .5% chance for the purposes of our discussion, and using these comparisons, thus leads to the conclusion that for the general population, about 10% of the liver cancer in the United States would be due to PCB exposures; that the Michigan control population would expect a 100% increase in liver cancer incidence, that the Michigan fish-eaters would have a three-fold increase, and that the average capacitor worker would have a 20-fold increase, while the highly exposed worker would have a 25% incidence or a 50-fold increase. There is no human evidence to support any of this. The EPA's proposed water criteria standard is from 10 to 100 times higher than can be justified on the basis of recently published human experience, and from 10 to 20 times higher than can be concluded on the basis of the negative findings from the human experience.

It is our conclusion that commercial PCBs do not represent a significant health hazard. However, the presence and extent of contaminants (e.g., PCDFs) may alter the health concerns. Therefore, it is essential to determine the level of contaminants present when dealing with PCB wastes before applying the conclusions of this report to waste mixtures.