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Project Summary

Development of Advisory Levels for Polychlorinated Biphenyls (PCBs) Cleanup

Polychlorinated biphenyls (PCBs), commercially known as Aroclors, consist of mixtures of chlorinated biphenyl compounds. Many sites contaminated by PCBs remain contaminated because of PCB persistence in the environment. Although commercial PCB production in the United States has been banned by the Toxic Substances Control Act, continued use in previously existing commercial equipment can result in spills which require cleanup. The Environmental Protection Agency (EPA) has become increasingly involved in the discovery, assessment, and cleanup of these sites.

The purpose of this study is to provide advisory levels for PCB cleanup, and to describe the technical and scientific rationale and methods used in developing these advisory levels for PCBs in contaminated soil. This required the development of exposure and risk assessment methodology related to hazardous waste and spill sites, and analyses of health effects data.

The currently available modeling techniques considered most appropriate are used to estimate exposures. PCBs advisory levels are presented as ranges of values to reflect the difference in soil-air partition coefficients depending on soil type, different types of commercial Aroclors, and variations in the soil ingestion rate.

This Project Summary was developed by EPA's Office of Health and Environmental Assessment, Washington, D.C., to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

The full report of this project summary was prepared in response to a request from the Office of Emergency and Remedial Response (OERR), that the Office of Health and Environmental Assessment (OHEA) develop advisory levels for polychlorinated biphenyls (PCBs) which can be used as guidelines for initiating removal action for sites contaminated with PCBs. Interested offices within EPA, including OERR, have advised OHEA that these advisory levels for PCBs cleanup should be developed based on considerations of public health protection from short-term and long-term exposures. The advisories presented include permissible levels of PCBs in soil corresponding to 10-day and lifetime acceptable intakes.

Exposure routes considered in developing these advisory levels include drinking water, ingestion of PCB-contaminated soil by children and adults, and inhalation of ambient air contaminated with PCBs. Other exposure routes, such as dermal exposure, food intake, and ingestion of fish which have bioaccumulated PCBs, are considered in relation to their importance and their relevance to this project. In view of the high bioaccumulation factor for PCBs, the consideration of bioaccumulation is important in setting PCB levels in surface water in which aquatic animals live. If one of these routes is a controlling factor in relation to the exposure route of human intake considered the advisories need to be reevaluated.

Chemical Composition

Commercial-grade PCBs, consisting of mixtures of different composition, are sold under the trade name Aroclors impurities such as chlorinated dioxins

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furans and chlorinated naphthalenes are known to exist in commercial PCBs. The sole producer of Aroclors in the United States for the period 1957 to 1972 was the Monsanto Chemical Company. Their products are characterized by four-digit numbers. The first numbers represent the type of molecule (12 = biphenyl-based; 54 = terphenyl-based; 25 or 44 = blends of PCBs and chlorinated terphenyls); and the last two digits refer to the percentage of chlorine by weight. PCB products are also manufactured in other countries, including Germany, France, Japan and the U.S.S.R.

Although one might expect some 140 to 150 separate congeners in an Aroclor, the actual analysis of Aroclor 1248, for example, identified less than 50 peaks using high-resolution gas chromatography. No compounds which can be formed by addition of chlorine rather than substitution were found in a detailed study of PCBs published in 1976. It is suspected that the conditions prevailing during industrial manufacturing of PCBs do not favor the formation of addition compounds, or that these latter compounds might have been destroyed in the step used to purify the Aroclor. The literature data show that even for the same type of Aroclor, the compositions of individual biphenyls vary slightly.

Major PCB components in foreign products bearing the names of Kanechlor and Phenoclor for Japanese and French products, respectively, have been identified. The number of the major components separated from Kanechlor 400 is five, and that from Phenoclor DP6 is seven.

Exposure Assessment

It is likely that not all of the PCBs ingested or inhaled by humans are absorbed. Proper calculations of absorption rate and hence exposure should be based on realistic pharmacokinetics-type models to determine intake. Lack of experimental data with which to estimate the parameters needed in the pharmacokinetics models has prevented their applications to the analysis for PCB absorptions through human exchange boundaries. Future work should consider these models. Although most animal studies (in rats and mice) on the extent of absorption in the gastrointestinal tract show absorption in excess of 90%, there are two experiments on monkeys reporting less than 68% absorption in one case and less than 13% and 40% absorption for a specific congener in another case, based on the analysis of feces and urine. Vehicles used in administering PCBs were not specified. It is likely that the high adsorption characteristics of PCBs on soil could retard the absorption rate in the human intestinal tract. In the risk analysis performed in the present study, the absorption rate for humans after ingestion of PCB-contaminated soil is considered to be 30%.

Absorption from dermal exposure has been reported to be as significant as from other routes of exposure, but little information is available for the quantitative evaluation of dermal absorption rates. Five percent dermal absorption is assumed for soil contaminants in contact with human skin.

Inhalation studies using PCB aerosols show that the absorption of PCBs from inhalation exposure readily occurs. In the present analysis, an absorption factor of 50% is assumed for absorption of PCB vapors after inhalation into human lungs.

The circumstances under which human exposure occurs are divided into three classes depending on population distribution: (1) Exposure occurs onsite. This can be further subdivided into: (a) sites that are readily accessible to children, and, hence, the soil from which will be subject to ingestion, dermal contact, and inhalation, and (b) sites for which there is no possibility of soil ingestion, and, hence, exposure is only through inhalation; (2) sites which no population is assumed to enter within a radius of 0.1 km from the site; and (3) sites which no population is assumed to enter within a radius of 1 km from the site.

The soil ingestion rates used for Class (1)(a) evaluations are 3 and 0.6 g/day. The former is a value based on data from a study of an adult person with pica, while the latter represents a long-term average value for soil ingestion. If sites are not accessible to populations at distances of 0.1 km or 1 km from the site, as in Classes (2) and (3) above, it is assumed that no ingestion of contaminated soil occurs and the exposure route is that of inhalation.

Emission Evaluation

The emission rate of volatilized PCBs can be considerably reduced by covering the contaminated soil by low-porosity uncontaminated soil or clay material. The reduction in the emission rate will result in a decrease in ambient air concentrations of PCBs by the action of blowing winds. When PCB-contaminated material is directly exposed to the atmosphere, the PCB levels in soil required to maintain the same level of exposure will be less than those expected when the PCB-contaminated material is covered with low-permeability material of appropriate thickness. The cover would also serve as a deterrent to soil ingestion and direct dermal contact.

The depletion of PCBs from soil caused by volatilization is accounted for in the exposure analysis by solving a partial differential equation simulating PCB vapor diffusion through the soil air-phase pores, and the distribution of PCBs between air and soil phases. Boundary conditions assume that the air-phase resistance is relatively small compared to the diffusional resistance in the soil air-phase pores. The available experimental data reasonably follow the time-emission rate relationship predicted from the models based on this assumption. Since the depletion rate varies over time, it is averaged over the exposure period. Depletion averaged over a period of time should lead to a lesser inhalation exposure than that based on the model, assuming that depletion does not occur.

The worst-case emissions would occur when the contaminated soil is initially exposed to the atmosphere and the soil is contaminated up to the conditions exhibiting saturation vapor pressure. A constant emission rate can be assumed if the vapor-phase concentration maintains a constant value at the surface of soil contamination for time-varying emission rates. Calculations corresponding to Classes (1), (2), and (3) for exposure possibilities with surface contamination are repeated at an assumed 25-cm thickness of a soil cover initially free from PCB contamination. Among many factors affecting the emission rate (including vapor pressure, soil-air partition coefficient, Henry's Law constant, etc.), the value of the soil-air partition coefficient shows the most wide-ranging variation, because of the variation of the experimental soil-water partition coefficient available in the literature for soil textures ranging from 40 to 1,000 cm^3 g.

PCB Levels in Soil

The method for determining the permissible PCB levels in soil, which combines the routes of soil ingestion, inhalation, and dermal exposure, has been computerized to avoid the necessity for hand calculations.

The results of these computer calculations are summarized in Tables 1 and 2, which have been prepared using different combinations of the following variables:

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Table 1. Permissible PCB Soil Contamination Levels (Uncovered Surface Contamination)

Location and Route of Human Exposure	Permissible Levels (ug PCB/g soil) Corresponding to: Noncancer Short-Term[a] Acceptable Intake (ug/day)[b] — 100 for Child	700 for Adult	Cancer Risk Specific Doses (ug/day) — 0.00175 (10^{-7} Risk)	0.0175 (10^{-6} Risk)	0.175 (10^{-5} Risk)	1.75 (10^{-4} Risk)
On the contaminated site						
-Soil ingestion[c], inhalation[d]	25-100[f]	510-730	0.008-0.01	08-0.1	0.8-2	8-17
-Soil ingestion[c], inhalation[e]	42-420	2100-3000	0.01-0.06	0.1-0.6	1-6	35-61
-Inhalation only[e]	47-vs[g]	vs	0.01-0.2	0.1-2.0	1-20	77-470
0.1 km from contaminated site -Inhalation only[e]	vs	vs	2.0-220	90-2.2x10[4]	$7.7x10^{3}$-vs	$8.7x10^{3}$-vs
1 km from contaminated site -Inhalation only[e]	vs[g]	vs	220-1.3x10[4]	$2.2x10^{4}$-1.3x10[5]	vs	vs

[a] Short-term = 10-day intake.
[b] Based on average weights of 10 and 70 kg for a child and an adult, respectively.
[c] Children ages 1-6, with pica (consuming 3 g soil/day).
[d] Children ages 1-6, without pica (consuming 0.6 g soil/day).
[e] Inhalation rates are assumed to be 20 m^3/day for the short-term and 1.3 for longer-term noncancer exposures; all other (more chronic) exposures assumed to be 10 m^3/day as a result of 182 days' exposure per year.
[f] Ranges result in each case because (1) four PCBs (1242, 1248, 1254, 1260) are considered, each with a different vapor pressure, and (2) high and low values for soil-air partition coefficient are used in the calculations.
[g] vs denotes no theoretical upper-bound limit. Practical reasons require no free-flowing PCB liquids for the limit.

(1) Surface contamination representing a situation where the contaminated soil surface has been left uncovered after removal action.
(2) 25-cm (10-inch) clean cover applied, representing a situation in which clean soil material is used on top of the contaminated soil surface.
(3) Two different soil ingestion rates (3 and 0.6 g/day) for Class (1) (a), corresponding to sites accessible to children.
(4) Different acceptable intake (AI) levels (short-term AI, and AIe at different cancer risk levels).
(5) Four Aroclors (Aroclor 1242, 1248, 1254, and 1260).
(6) Two selected values of the soil-air partition coefficient, representing the high and low values.
(7) Exposures for 10 days after cleanup or spill of contaminants for short-term advisories.

Table 1 shows the range of values for permissible PCB concentrations in soil when the soil is contaminated up to the surface in contact with the atmosphere and is left uncovered. Table 2 represents the case where the contaminated soil left at the site, or after remediation, is covered with a 25-cm (10-inch) clean soil layer. The ranges in both tables result from the use of four Aroclors and the use of high and low values for the soil-air partition coefficient. Other factors reflected in the ranges are differences in vapor pressures and Henry's Law constants for each Aroclor.

Results

The symbol "vs" in Tables 1 and 2 indicates that no upper-bound limit for PCB concentrations in soil can be derived from the exposure evaluation, because the PCB concentration in soil is above the vapor saturation concentration. There are two reasons for such a result. First, the emission rate cannot exceed the upper-bound value which can be expected when the air-phase concentration of PCBs at the contaminated soil surface is maintained at the vapor saturation point. The concentration at the vapor saturation point corresponds to the vapor pressure concentration. Second, when the cover is applied, not only is the emission rate retarded, but also the concentration of PCBs in soil being ingested is controlled by the amount of PCBs adsorbed on soil in equilibrium with the air phase being emitted. Therefore, the concentration of PCBs in the initially clean soil material cannot exceed the concentration in equilibrium with saturated vapor.

In actuality, the "no upper limit" for the level above vapor saturation, designated by vs, should be interpreted with great care. The assumptions used in the ex-

Table 2 Permissible PCB Soil Contamination Levels (25 cm Thick Clean Cover)

Location and Route of Human Exposure	Permissible Levels (ug PCB/g soil) Corresponding to: Noncancer Short-Term[a] Acceptable Intake (ug/day)[b] 100 for Child	700 for Adult	Cancer Risk Specific Doses (ug/day) 0.00175 (10^{-7} Risk)	0.0175 (10^{-6} Risk)	0.175 (10^{-5} Risk)	1.75 (10^{-4} Risk)
On the contaminated site						
-Soil ingestion[c] -Inhalation[d]	110-200[e]	800-1400	0.01-0.2	0.1-2.0	1.17	22-vs
-Soil ingestion[f] -Inhalation[d]	450-vs[g]	3100-vs	0.02-0.8	0.2-8.0	1.0-48	93-vs
-Inhalation only[h]	vs	vs	0.02-1.0	0.2-vs	2.0-vs	770-vs
0.1 km from contaminated site -Inhalation only[h]	vs	vs	1-vs	620-vs	vs	vs
1 km from contaminated site -Inhalation only[h]	vs	vs	vs	vs	vs	vs

[a]Short-term is 10-day intake.
[b]Based on average weights of 10 and 70 kg for a child and an adult, respectively.
[c]Children ages 1-6, with pica (consuming 3 g soil/day).
[d]Children ages 1-6, without pica (consuming 0.6 g soil/day).
[e]Inhalation rates are assumed to be 20 m^3/day for the short-term and longer-term noncancer exposures; all other (more chronic) exposures assumed to be 10 m^3/day as a result of 182 days' exposure per year.
[f]Ranges result in each case because (1) four PCBs (1242, 1248, 1254, 1260) are considered, each with a different vapor pressure...and (2) high and low values for soil-air partition coefficient are used in the calculations.
[g]vs denotes no theoretical upper-bound limit. Practical reasons require no free-flowing PCB liquids for the limit.

posure evaluation are critical. They include but are not limited to (1) no seeking of clean cover by liquid PCBs for the thickness of 25 cm; (2) no disturbance of cover material by construction activities or children digging the ground, (3) no exposure to initial spills when 25 cm of clean cover (Table 2) is assumed; (4) no population enters the area within the respective radius of distances from the site; and (5) the cover material is at least equivalent to soil material.

From a practical point of view, the first assumption is tantamount to ensuring the presence of no free liquids in the soil, which may otherwise result in the phenomenon of "wicking." Since the ranges shown in Tables 1 and 2 are dependent upon the type of Aroclor(s) and the values of the soil-air partition coefficient, site-specific or Aroclor specific information should be used to establish an appropriate level of PCBs for that particular condition. Computer outputs for the selected Aroclors under the ranges and conditions of common environmental concern can be used to find the permissible concentrations in soil suitable to particular situations.

Table 1, for example, can be interpreted as follows:

(1) When the site is amenable to access by children with possibilities of ingesting the contaminated soil exposed to the atmosphere, and when exposure occurring to the children by inhalation and dermal contact is accounted for, the permissible PCB levels in soil should range from 25 to 100 ug/g and 42 to 420 ug/g for prevention of noncancer effects from 10-day exposure for a child with an average weight of 10 kg ingesting soil at the rates of 3 and 0.6 g/day, respectively. For cancer effects, permissible levels in soil for a lifetime exposure to PCBs resulting from ingestion of and dermal contact with contaminated soil and inhalation of contaminated air should range from 0.08 to 0.1 ug/g and 0.1 to 0.8 ug/g, corresponding to an upper-bound risk estimate of 10^{-6} at assumed soil ingestion rates of 3 and 0.6 g/day, respectively. The specific level will depend on the types of Aroclor present, the likely ingestion rate, and the extent of soil-air partitioning. For sites in which there is no possibility of soil ingestion, PCB levels in soil, based on the inhalation route only, should range from 47 ug/g to no limit value for a 10-day exposure for a child with an average weight of 10 kg, and correspond to no limit value for an adult with an average weight of 70 kg. The permissible levels of PCBs in soil, based on the inhalation pathway only, range from 0.1 to 2 ug/g, corresponding to a lifetime AI at a risk factor of 10^{-6}. Again, the level will be dictated by the types of Aroclor present and the specific characteristics of the site involved.

(2) If there is no possibility of a population entering the contaminated site within

a radius of 0.1 km from the site, the PCB levels in soil can remain at no limit value and 90 to 2.2×10^{4} μg/g, without exceeding 10-day AI and lifetime AI at 10^{-6} risk, respectively.

Similar interpretations can be made for the results applicable to sites without affected population up to 1 km from the site, and to the carcinogenic risks listed at 10^{-4}, 10^{-5} and 10^{-7}.

Conclusion

The short-term AI levels (100 μg/g day for a child and 700 μg/g day for an adult) used to develop 10-day advisories based on noncancer effects are derived from animal studies, which collectively indicate that the experimental threshold for adverse effects of Aroclor 1254 is at or near a dose of 1.0 μg/kg body weight. Using this dose as a No Observed Adverse Effect Level and a safety factor of 100, the 10-day AI levels for noncancer effects described above (100 and 700 μg/day) were computed. The permissible concentrations of PCBs in soil are calculated from multimedia exposure assessments by requiring that the total PCBs intake rate from pertinent exposure pathways do not exceed these AIs. Advisory levels for 1-day and lifetime noncancer effects cannot be derived at this time because of the insufficiency of available data. However, in view of the experimental duration, the 10-day advisories may well be used for the 1-day advisories.

The EPA authors Seong T. Hwang (also the EPA Project Officer, see below), James W. Falco, and Charles H. Neuman are with the Office of Health and Environmental Assessment, Washington, DC 20460.

The complete report, entitled "Development of Advisory Levels for Polychlorinated Biphenyls (PCBs) Cleanup," (Order No. PB 86-232 774/AS; Cost: $22.95, subject to change) will be available only from:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Telephone: 703-487-4650

The EPA Project Officer can be contacted at:

Office of Health and Environmental Assessment (RD-689)
U.S. Environmental Protection Agency
Washington, DC 20460

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BIOLOGICAL DATA RELEVANT TO THE EVALUATION OF CARCINOGENIC RISK TO HUMANS

Prepared for
Scientific Advisory Panel,
Safe Drinking Water and Toxic Enforcement Act
State of California

Prepared by
Dr. Raymond D. Harbison
Dr. Robert C. James
Dr. Stephen M. Roberts

Division of Interdisciplinary Toxicology
University of Arkansas
School of Medicine
Little Rock, Arkansas
U.S.A.

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EXECUTIVE SUMMARY

Evaluation of Animal Data

The investigation of PCBs' carcinogenic potential in mice is limited to two short studies, while some eight to ten studies have been reported using various strains of rat. The PCB mixtures tested thus far are : 1) in mice - Kanechlor 300, Kanechlor 400, Kanechlor 500 and Aroclor 1254; and 2) in rats - Kanechlor 300, Kanechlor 400, Kanechlor 500, Clophen A30, Clophen A60, Aroclor 1254 and Aroclor 1260.

PCBs have been found to be tumorigenic in mice with Aroclor 1254 producing hepatomas after 11 months of exposure and Kanechlor 500 (similar in composition to Aroclor 1254) inducing hepatocellular carcinomas after 8 months of exposure. These lesions were shown to be reversible and specific for the dose (500 ppm) and chlorination of the PCB mixture.

In rats, Aroclor 1260 or its equivalent, Clophen A60, have produced hepatocellular carcinomas in three studies at doses of approximately 100 ppm, a dose which appears to represent the maximally tolerated dose for rats. A review of these three studies indicates that the tumors occur very late in the life of the animal, with a significant incidence of tumors only beginning to appear after about two years of exposure. Of interest is the fact that in all three studies the PCB treatment, while increasing the incidence of liver cancer, did not increase the total tumor incidence. The total tumor incidence was not increased in these studies because in each case the incidence of other tumor types had been significantly decreased. This suggestion of antitumor activity of PCBs has also been demonstrated in a study examining the effect of PCB exposure on the final tumor incidence in animals following the transplantation of the Walker 256 sarcoma. The effects of chronic PCB-treatment was not life-shortening, and in fact in two of the studies the morbidity and mortality of the animals was actually decreased by PCB treatment. Furthermore, while the tumors are described as malignant, i.e. hepatocellular carcinomas, in none of the three studies did the liver tumors metastasize to other organs even though metastases would be expected if the tumors were malignant. So from these studies it is evident that PCB-treatment does not increase the total cancer risk in these animals, rather it shifts the incidence of the type of tumors observed by significantly decreasing some tumor types while enhancing the incidence of liver tumors. Lastly, PCB mixtures of lesser chlorination, i.e. Aroclor 1254 and Clophen A30 (similar in composition to Aroclor 1242, see table 1.4, page 8, of Brinkman and DeKok, 1980), have been examined in two separate studies and found not to be carcinogenic. Thus, conclusions to be drawn from the rat data, like the mouse data, are specific for the dose and degree of chlorination of the PCB mixture being tested.

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Possibly because PCBs produce liver hypertrophy, they enhance the tumorigenesis of certain liver carcinogens if given after the carcinogen in question has had an opportunity to initiate tumors. However, if the PCB exposure precedes or is concomitant with exposure to liver carcinogens the tumorigenic response is typically decreased, probably as a result of an enhanced metabolic detoxification of the carcinogen.

To summarize, the qualitative human relevance of the carcinogenic activity of PCBs based on the animal data is limited. The studies providing some evidence of its carcinogenic activity are specific for the degree of chlorination of the PCB mixture, the total tumor incidence is not increased, and the tumors produced occur only very late in the life of the animal and have no adverse effect on the morbidity or mortality of the animal. There are other considerations that limit concern for the carcinogenic data in rats as well. PCBs are not mutagenic, and the mechanism of tumorigenesis for these compounds therefore would appear to involve an epigenetic mechanism. There is also substantial evidence that the doses used to induce tumors in rats are hepatotoxic, and evidence indicating the neoplasms induced by PCBs are reversible if the exposure is terminated before the animal has been exposed for a considerable portion of the animal's lifespan. All of these findings seriously undermine the human relevance of the animal carcinogenicity data. This is particularly true as the human dosages from past and present human exposures are far lower than those used in the animal studies. Given these considerations, it is concluded that the animal data provides *sufficient evidence* of *limited human relevance* that PCBs of 60% chlorine content (e.g. Aroclor 1260/Clophen A60) are carcinogenic in animals. For PCBs having a chlorine composition of 54% (e.g. Aroclor 1254/Kanechlor 500) there is only *inadequate evidence* of carcinogenicity in animals because the larger and longer study in rats was negative, a finding suggesting that the reversible effects reported in mice may have resulted from a promotion of the substantial background incidence of liver tumors occurring in this species. For the remaining commercial PCB mixtures (i.e. Aroclor 1248, Aroclor 1242, Kanechlor 400, Kanechlor 300, and Clophen A30) there is either *no evidence* or *insufficient evidence* for the carcinogenicity of these mixtures in animals.

Evaluation of Epidemiological Evidence

Evidence for human carcinogenicity would be supplied if the two major epidemiological studies of PCB-exposed workers demonstrated a consistent increase in cancer mortality. This increase should show a positive correlation with exposure and evidence of latency. The evidence for carcinogenicity would be strengthened if the incidence of specific types or sites of neoplasms were consistently elevated. In reviewing the data from these two cohorts, none of these conditions are met.

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While Bertazzi et al. (1986), in their study of Italian PCB-exposed workers, found a statistically significant elevation in the rate of cancer mortality among both male and female workers, the much larger study of Brown found no increase in cancer mortality. In the Brown study, there were higher-than-expected incidences of rectal and liver cancer. Evidence for an association between PCB exposure and these malignancy types cannot be considered strong, however, in that: 1) no cases of rectal cancer were observed after the initial report, suggesting that this increased rate was anomalous, 2) the number of cases of liver cancer observed in this study is not appreciably greater than expected when examined without total number of liver neoplasms used by Brown which includes those liver cancers that have metastasized from other organs, 3) in comparison, the study by Bertazzi et al. found only one case of liver cancer and no cases of rectal cancer in their cohort, and 4) the absence of a clear association with latency or relationship with duration of exposure.

The primary sites of neoplasms contributing to the higher-than-expected cancer mortality rates in the Bertazzi studies were located in the digestive system and the hematopoietic and lymphatic systems. These were not increased in the larger cohort reported by Brown. Further, in the Bertazzi cohort, there was no evidence of latency or relationship between cancer mortality and exposure to PCBs. It should also be noted that in the larger of the two subdivisions of their cohort, the female workers, differences in incidences of causes of death presumably unrelated to PCB exposure (viz., increases in accidental death and decreases in deaths from cardiovascular disease) were of similar magnitude as increases in death from malignant tumors. This suggests, at least for this group, that other confounding variables may exist.

In summary, epidemiological evidence for human carcinogenicity of PCBs is at present weak and mostly negative. As such, until larger epidemiological studies can be completed, the data must be considered *inadequate to characterize PCBs as human carcinogens*.

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Summary Table

Aroclor 1260/Clophen A60 :

There is *sufficient evidence* of *limited human relevance* for the carcinogenicity of Aroclor 1260 in animals.

The human evidence for carcinogenicity of this compound is *inadequate*

Aroclor 1254/Kanechlor 500 :

There is *inadequate evidence* for the carcinogenicity of Aroclor 1254 in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

Aroclor 1248/Kanechlor 400 :

There is *no evidence/insufficient evidence* for the carcinogenicity of Aroclor 1248 in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

Clophen A30/Kanechlor 300/Aroclor 1242 :

There is either *no evidence* or *insufficient evidence* for the carcinogenicity of these mixtures in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

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BIOLOGICAL DATA RELEVANT TO THE EVALUATION OF CARCINOGENIC RISK TO HUMANS

1.0 Carcinogenicity and Related Studies In Animals

1.1 Studies in Mice

Nagasaki et al. (1972) initially examined the hepatocarcinogenic effects of Japanese brands of PCB fluids by feeding male mice dietary levels of 100 ppm, 250 ppm, and 500 ppm for 32 weeks. As this particular citation represents a short communication, detailed discussions of the experimental design and histopathological examinations of this investigation were lacking. An increased incidence of liver tumors was found in only one of the treatment groups, those mice receiving the 500 ppm diet of Kanechlor 500, where hepatomas were identified in 58% or 7/12 of the animals. The livers from animals in this group also contained nodular areas and many necrotic foci. In sharp contrast to these findings, no hepatomas and none of these histopathologic changes were observed in animals receiving lower doses of Kanechlor 500 or in any of the animals receiving Kanechlor 400 or Kanechlor 300.

The results of the above study also appear to have been reported in two other journals under Ito et al. (1973a&b). As in the previous study it was reported that male mice of the ddY strain were fed diets containing Kanechlor 300, Kanechlor 400 or Kanechlor 500 at dietary levels of 100, 250 or 500 ppm for 32 weeks. PCBs significantly increased the liver weights of the animals, and at the highest dose of Kanechlor 500 the liver:body weight ratio had increased 3-fold with histopathological examination of the livers revealing a focal hypertrophy in the centrilobular hepatocytes of non-neoplastic areas. Another change observed in all PCB treatment groups, except those receiving 500 ppm of either Kanechlor 500 or 400, was a marked amyloid degeneration of the liver in the space between the sinus endothelium and the hepatocytes. For some reason, the liver tumors in these more recent publications (Ito et al, 1973a&b) have been reclassified, and the tumors reported as hepatomas in the previous Communication (Nagaski et al., 1972) are now listed as carcinomas (Ito et al., 1973 a&b). That is, in the group receiving 500 ppm of Kanechlor 500 (originally described as having hepatomas in 7/12 animals) nodular hyperplasia was found in 7/12 animals (58.3%) while 5/12 of the livers (41.7%) now have well-differentiated hepatocellular carcinomas. The carcinoma cells were reported to be comprised of irregularly shaped cells with pyknotic nuclei and occasionally had mitotic nuclei. The reason for changing the classification of these neoplasms from hepatoma to carcinoma is not provided. Of some interest to discussions of the carcinogenic potential of PCBs is the fact that all of the other doses of all three Kanechlors tested failed to produce even nodular hyperplasia. Thus, the tumorigenicity reported was quite specific for the dose and the extent of chlorination of the Kanechlor being tested.

Kimbrough and Linder (1974) examined the effects of PCBs in

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mice and obtained results consistent with those found for the lesser-chlorinated Kanechlors of the preceding study. Groups of 50 male Balb/cJ mice were fed 300 ppm Aroclor 1254 for either 11 months or for 6 months followed by a 5 month recovery period. The authors pointed out that this dietary level was some 2,500 times the Food and Drug Administration's estimate of the average human daily PCB intake from food during the early 1970's. About one-half of the animals in each PCB treatment group died during the first 4 months, but this problem seems to have been unrelated to the PCB treatment as control animals suffered a similar incidence of mortality. Of the 22 mice surviving the 11 month feeding study, all animals had hepatomegaly with the liver representing approximately 25% of their body weight in comparison to the 5.8% liver:body weight ratio measured for the control animals. Adenofibrosis (i.e. cholangiofibrosis) was observed in all 22 livers taken from mice fed PCBs for 11 months, however 13/68 livers taken from control animals had occasional, small areas of necrosis and fibrosis. Of the livers taken from animals receiving 300 ppm Aroclor 1254 for 11 months, the nuclei were enlarged, hyperchromatic and atypical. The cytoplasm was either smooth or vacuolated, and the Kupffar cells contained a brown pigment. Some of these livers had extensive necrosis and fibrosis. In each of the livers, several areas of hepatocytes had been replaced by proliferating epithelial cells which formed ducts and often produced mucus. In addition to these histological changes, 10 hepetomas were found in 9 of these livers. The tumors were described as well circumscribed and surrounded by compressed parenchyma or strands of fibrosis. In the 24 surviving mice fed PCBs for only 6 months followed by a 5 month recovery period, only one liver contained a hepatoma. Yet, liver fibrosis was observed in two-thirds of these animals and hepatocellular necrosis was evident in most of the livers.

1.2 Studies in Rats

Kimura and Baba (1973) exposed 10 male and 10 female Donryu rats to a variable dietary level of Kanechlor 400 for 400 days. The diet initially contained 38.5 ppm and was fed to the animals for 4 weeks; the dietary level was then doubled and provided for the following 8 weeks; the initial dietary level was then increased 4-fold and provided for 3 weeks; it was then increased 8-fold and fed to the animals for another 3 weeks; finally it was increased to 16 times the initial level and fed to the animals for 3 more weeks. This last increase in the dietary levels of PCBs (a level that was approximately 616 ppm) was found to be too toxic and caused a considerable weight loss in the animals. In response to the toxicity observed at this dose, the dietary level was reduced to 462 ppm for the remaining 32 weeks of the study. Further complicating interpretations of this study is the fact that animals died or were sacrificed at various times throughout the experiment, therefore the total PCB dose each animal received may differ. In general, the total amount ingested was thought to be 1300-1800 mg for the group of male animals and 1100-1500 mg for the female animals. Microscopically the livers of all of the treated animals

contained fatty degenerative changes, and while 6/10 of the livers from female animals had adenomatous nodules, none of the livers of the male animals contained such nodules. However, the liver nodules observed in the female animals do not appear to be related to the PCB treatment as 2/5 (40%) of the livers from the control female animals also contained adenomatous nodules.

In a second study Kimura et al. (1976) fed 12 female Donryu rats diets containing 400 ppm Kanechlor 400 for 6 months. The estimated dose corresponded to a total of 531 mg of PCBs during this period. Eight of the 12 animals were then sacrificed 590 days after the feeding began. None of these animals developed hepatocellular carcinoma, and 9/12 of the livers were normal in appearance, suggesting that the degenerative changes observed in the previous study are reversible.

Ito et al. (1974) fed male Wistar rats Kanechlor 300, Kanechlor 400 or Kanechlor 500 at dietary levels of 100, 500 or 1,000 ppm for up to 52 weeks. No hepatocellular carcinoma was found in the livers of any of the treated rats. The highest dose of all three Kanechlors did produce a cholangiofibrosis of the liver, but this effect was not observed at the lower doses with any of the Kanechlors. Nodular hyperplasia was observed in 30-40% of the rats exposed to the two highest doses of Kanechlor 500 (i.e. doses of 500 ppm and 1,000 ppm) and in animals receiving a diet containing 1,000 ppm of Kanechlor 400. Oval cell proliferation and proliferation of the bile duct cells were observed in all treatment groups. Hypertrophy of the centrilobular cells was also evident in animals receiving the highest dose of the two most heavily chlorinated PCB mixtures. Fatty changes and fibrosis were also observed in the livers of animals of several of the treatment groups. The fatty changes, hypertrophy and fibrosis of the liver all tended to be present and correlate with the observation of nodular hyperplasia, suggesting that these changes may have been contributory factors.

Kimbrough et al. (1975) published the first major positive study demonstrating that Aroclor 1260 can produce hepatocellular carcinoma in the rat. In this study 200 female Sherman strain rats were fed Aroclor 1260 at a dietary level of 100 ppm for approximately 21 months. There was a statistically significant 6-7% decline in the weight gain of the animals exposed to PCBs in this study suggesting that the dose used approximated the maximally-tolerated dose. The incidence of the histopathological findings from this study are summarized in Table 1. The most consistent histopathologic difference in the PCB treatment group was the finding of hyperplastic or neoplastic nodules in 144/184 (78%) of the livers. More importantly, however, was the finding of hepatocellular carcinoma in 26/184 (14%) of the PCB-treated animals. The tumors were well-differentiated neoplasms of the trabecular type, except in three of the animals which had tumors with a glandular, papillary pattern. Foci of coagulative necrosis were occasionally observed in the cancerous areas, but there was no fibrosis or other evidence of chronic degenerative changes. Tumors

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in areas other than the liver were not listed as significantly different, however, in some cases there was a substantial decrease in the tumor incidence of other tissues, e.g.

TABLE 1

Results of Carcinogenesis Bioassay of Aroclor 1260

		Tumor Incidence	
Organ/Tissue	**Tumor Type**	**Control Animals**	**Aroclor 1260 Animals**
Liver	**Hepatocellular carcinoma**	1/173	26/184
	Neoplastic nodules	0/173	144/184
	Areas of cytoplasmic alteration	28/173	182/184
Thyroid gland	**Parafollicular cell tumor**	37/160	18/166
Pituitary gland	**Chromophobe adenoma**	41/153	28/139
Mammary gland	**Fibroadenoma**	17/173	13/184
Ovary	**Granulosa theca cell tumor**	5/149	0/163

Adapted, in part, from Kimbrough et al. (1975)

as in the case of parafollicular cell tumors of the thyroid. The total incidence of extra-hepatic tumors in the Kimbrough et al. (1975) study was 134/173 (74%) in control animals versus 110/183 (60%) in Aroclor 1260 treated animals. So while PCBs had significantly increased the liver carcinoma incidence, the total tumor incidence (78% in control animals -vs- 74% in Aroclor animals) in PCB-treated animals was actually slightly less than the incidence for control animals. The PCB treatment was also not life-shortening; on the contrary, about twice as many control animals had died for various reasons before the experiment was terminated at 23 months.

Calandra (1976) at the 1975 PCB conference sponsored by the EPA reported the findings of several chronic studies performed by a commercial laboratory for Monsanto. While these studies have never been published the results were recently reviewed by Levinskas (1981). In this study 1,000 rats were divided into ten groups of 100 animals (50 of each sex) and nine of these groups were exposed to Aroclors 1242, 1254 or 1260 at dietary levels of 1, 10 or 100 ppm. Apparently five animals of each sex were sacrificed at 3, 6 and 12 months with about 35 animals to be killed at the end of the two year study (EPA, 1980). In the animals sacrificed early, only

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one nodular hyperplasia was observed and it was in the group fed 100 ppm of Aroclor 1260 for 12 months. Mortality in this study was high and approximately one-third of the 105 animals anticipated to be exposed for two years at each dietary level died. Hepatomas were observed in 7/25 livers from animals fed 100 ppm Aroclor 1260, in 4/26 fed Aroclor 1254, 3/19 fed Aroclor 1242, and only 1/156 animals receiving the 1-10 ppm diets. Nodular hyperplasia was twice as prevalent as hepatomas in the high dose animals, particularly in the Aroclor 1254 group.

In 1978 the National Cancer Institute examined the carcinogenic potential of Aroclor 1254 (NCI, 1978). Groups of 24 male and 24 female Wistar rats were fed Aroclor 1254 at dietary levels of 25, 50 or 100 ppm for 105 weeks. Clinical signs of toxicity including hair loss, facial edema and cyanosis occurred by week 72 in the high dose animals and the mean body weights were roughly only 2/3-3/4 that of their respective controls. This decrease in body weight exceeds the no more than 10% weight loss guideline for the estimated maximally tolerated dose that is part of the NCI guideline for cancer bioassays (NCI, 1979). Several histopathologic changes occurred in the livers of animals receiving PCBs that appeared to be related to the PCB treatment, particularly the incidence of hyperplastic nodules and adenomas. Male animals had one hepatocellular carcinoma in the 50 ppm group and only 2 in the 100 ppm group. Although the incidence of these tumors was not significant, the occurrence of proliferative lesions did appear to be dose related. In reviewing this bioassay, the Data Evaluation/ Risk Assessment subgroup of the Clearinghouse on Environmental Carcinogens responsible for providing peer review of NCI studies concluded the following :

> "It is concluded that, under the conditions of the bioassay, Aroclor 1254 was <u>not carcinogenic</u> in Fischer 344 rats; however, a high incidence of hepatocellular proliferative lesions in both male and female rats were related to treatment. In addition, the carcinomas of the gastrointestinal tract may be associated with treatment in both males and females. Based on the liver proliferative lesions in the treated rats and published reports, it is suggested that Aroclor 1254 may be a tissue promoter."

Morgan et al. (1981) have taken the same tissue sections that originated in the NCI bioassay (NCI, 1978), stained the stomach sections for alkaline phosphatase, and then re-sectioned these tissues for histological evaluation in conjunction with those provided in the NCI study itself. The final incidence of alkaline phosphatase rich areas was 6.4% in controls, 10.4% in animals fed 25 ppm Aroclor 1254, 16.7% in the 50 ppm group, and 35.4% in the 100 ppm group. These changes were most often noted in the pyloric region of the stomach and duodenum (88% of the lesions were found in these areas), suggesting a toxicity specific to the cells of these areas. Gastric adenocarcinomas comprised six of the 33 total

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lesions identified in these slices. Three were found in tissues from the 50 ppm treatment group and two in the animal group fed 100 ppm. Thus, the increased incidance of this tumor was not related to the dose of PCBs. The remaining 27/33 lesions identified in this study were described as intestinal metaplasia. The authors concluded that the actual number of lesions they believed should have been observed in the G.I. tract tissue sections of the NCI study was twice the number of lesions reported in the original NCI study. Further, and on the basis of their findings, the authors of this paper concluded that chronic oral Aroclor 1254 exposure may lead to the induction of intestinal metaplasia, and possibly to adenocarcinoma of the glandular stomach of the Fischer 344 rat (Morgan et al., 1981).

Ward (1985) has also published a review of the slides originating from the NCI bioassay. In addition to the aforementioned dose-related depression of body weight, Ward (1985) also discusses, in some detail, the substantial decrease in animal survival that occurred in this study. While the survival rate in control animals and in the treatment group receiving 25 ppm was 92% and 83%, respectively, only 58% of the animals receiving the 50 ppm diet and 46% of the animals fed diets contening 100 ppm survived to the end of the bioassay. Focal hyperplasia was of the eosinophilic type and was only observed in PCB-treated animals. If compression was found on two sides of the neoplasm, Ward diagnosed the lesion as hepatocellular adenoma. A totel of 13 eosinophilic, basophilic or vacuolated adenomas were identified. All of these occurred, with one exception, in those animals fed the two higher dietary levels of Aroclor 1254 and the occurrence of adenomas was slightly greater in the male animals (8/13). Similar to the findings of the NCI (1979) report, only two liver carcinomas were identified, both occurred in male animals receiving the 100 ppm diet. Ward (1985) also reported that Aroclor 1254 increased the incidence of intestinal metaplasia and gastric adenocarcinoma. As in his earlier report with Morgan and Hartman (Morgan et al.,1981), the change in adenocarcinoma wee neither significant nor dose-related. A significant increase in intestinal metaplasia was only observed in the 100 ppm dose group. Thus, the Ward (1985) study is still consistent with the previous NCI (1979) bioassay. No statistically significant increase in liver cancer or cancer of other tissues wae observed, but the 100 ppm dose does lead to significant intestinal metaplasia. Ward mentions the fact that the liver lesions he observed were predominantly of the eosinophilic type rather than the basophilic type generally observed in the control animals. Based on these changes Ward proposes the idea that these data may suggest that PCBs are capable of initiating liver tumors rather than promoting the background tumor incidence. Yet, in contradiction of his suggestion, Ward also makes note of the fact that inducing agents like PCBs and phenobarbital cause a proliferation of the smooth endoplasmic reticulum (SER) of the liver. As a proliferation of the SER gives rise to an eosinophilic appearance of the cytoplasm, the liver hypertrophy and induction of microsomal enzymes associated with PCB exposure provides an obvious explanation for the basophilic to eosinophilic change Ward noted in

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the cellular appearance of the liver tumors of PCB-treated animals.

Schaeffer et al. (1984) used a total of 432 weanling Wistar rats to examine the affects produced by chronically feeding rats Clophen A60 (equivalent to Aroclor 1260) or Clophen A30 (similar in composition to Aroclor 1242; Brinkman and DeKok, 1980). The study consisted of three groups. Group 1, a control group of 139 animals receiving the normal diet, Group 2 with 152 animals receiving a diet containing 100 ppm of Clophen A30, and Group 3 which consisted of 141 animals fed a diet containing 100 ppm of Clophen A60. After day 801 animals were randomly selected and killed, and the experiment was terminated on day 832. The Clophens used in this study were reported to be free of any chlorinated dibenzofuran contamination, but the level of detection for this analysis was not specified. In those animals necropsied prior to day 800, hepatocelluler carcinomas were only identified in the PCB treatment groups, one in Group 2 and a total of 9 were observed in Group 3. This latter number was statistically significant for the Clophen A60 treatment, but represented a liver cancer incidence of only 7% for the entire group. In contrast, the incidence of thymoma was significantly reduced by PCB treatment declining from 12% in the control group to 3-4% in the treatment groups. Likewise the total number of the remaining types of neoplasms was significantly reduced by the PCB treatment, with Clophen A60 causing the greatest reduction (from 52 in controls down to 18 in the Clophen A60 group). The final results of this study are shown below in Table 2. The incidence of hepatocellular carcinoma was significantly increased only in those animals receiving the Clophen A60. Thus, the results of this study were consistent with the previous rat studies, i.e. Aroclor 1260, or its equivalent, was reported to have induced hepatocellular carcinoma in rats while a lesser chlorinated PCB mixture was not carcinogenic.

Table 2

Frequency of Hepatocellular Alterations Induced by Chronic Feeding Studies with Clophen A30 and Clophen A60

	# of Foci	Neoplastic Nodules	Hepatocellular carcinoma
Controls (group 1)	6/131 (4.5%)	5/131 (3.8%)	1/131 (0.8%)
Clophen A30 (group 2)	63/130* (48%)	38/130* (29%)	4/130 (3%)
Clophen A60 (group 3)	3/126 (2.4%)	63/126* (50%)	61/126* (48%)

* denotes a significant difference from the control value ($P<0.05$)

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In a letter to the editor, Young (1985) comments on several additional, interesting and important aspects of the Schaeffer et al. (1984) study that were not noted by the authors of this paper. Young's analysis of this data focused on the effects of PCB exposure on tumor incidence in liver, on tumor incidence in extra-hepatic tissues, and on mortality. The tables generated by Young (1985) are provided below in Table 3.

Table 3

The Incidence of Hepatocellular Carcinoma, Other Neoplastic Lesions, and Mortality by Time Period

Time Interval (days)	Treatment Group: Control	Clophen A30	Clophen A60
A. Hepatocellular carcinoma			
301-400	0/137	0/150	0/135
401-700	0/111	0/122	0/115
701-800	0/92	1/107	9/85*
B. Other Neoplasms			
301-400	0/137	1/150	2/150
401-700	32/111	11/122*	9/115*
701-800	30/92	15/107*	7/85*
C. Incidence and Percentage(%) of Mortality			
101-400	2/139 (1.4%)	2/152 (1.3%)	3/141(2.1%)
401-700	45/137(32.8%)	43/150(28.7%)	23/138(16.7%)
701-800	39/92 (42.4%)	20/107(18.7%)	30/85 (35.3%)
1-800	86/139(61.9%)	65/152(42.8%)*	56/141(39.7%)*

* Different from control value ($P<0.05$), χ^2

Young points out that the Schaeffer et al. (1984) study actually demonstrated three things. These are : 1) that a significant increase in hepatocellular carcinoma occurred only in the animals receiving Clophen A60, 2) that PCB treatment resulted in a significant decrease in other neoplastic lesions, and 3) that PCB treatment significantly increased the chances of survival of the animals. Given these findings, Young states that it is difficult to conclude, given the balance of the data, whether or not the PCB treatment was in fact detrimental to the rats in light of the fact that the PCB treatment significantly enhanced the rate of survival

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and significantly decreased the total tumor load of the exposed rats. In essence, he questions the human relevance of tumors which occur only very late in the life of the animal, are not life-shortening and do not metastasize to other organs of the body. Thus, to quote Young :

> "If the purpose of long-term studies is to extrapolate to humans, then one finds it difficult to infer dire consequences to humans when the treatment is beneficial in the model system. Is the model only useful for inferring bad events? The model should be equally valid for detrimental and beneficial effects."

Lastly, the analysis of Young also calls to question a suggestion made by Schaeffer et al. (1984), which was that the decrease in the incidence of thymoma might be caused by immunosuppressive effects of PCBs. While PCBs cause thymic atrophy at certain doses, any proposed immunosuppressive effect cannot be considered to have a significant clinical impact when the treated animals did not ultimately suffer a greater incidence of morbidity or mortality from either infectious diseases or the cancer induced by this treatment.

The last major rat study reported is that of Norback and Weltman (1985). These investigators fed 70 male and 70 female Sprague-Dawley rats a diet containing 100 ppm Aroclor 1260 for 16 months followed by a reduction to 50 ppm for the next 8 months. The animals were then fed a control diet for the remaining 5 months of their lives. All results were compared to a control group which initially consisted of 126 animals, 63 of either sex. At various time points throughout this study two control animals of each sex and three PCB-treated animals of each sex (10 animals in total) were anesthetized with ether and the medial left lobe of the liver of each animal was surgically removed. These tissue samples were taken at 1, 3, 6, 9, 12, 15, and 18 months. At 24 months a similar group was killed and at the end of 29 months all remaining animals were sacrificed. The induction of liver hypertrophy in the centrilobular area of the lobule was evident at the first observation period made one month after the PCB diet was initiated. By the 18th month the liver:body weight ratio had increased from 4% to 12% in the female animals. Macroscopically these investigators noted evidence characteristic of neoplastic nodules near the capsular surface, hepatocellular carcinomas and adenofibrosis. In the PCB-exposed group, the observed lesions appeared in the following sequence : centrilobular hypertrophy at 1 month, foci of cells appeared at 3 months, foci of altered cells in the centrilobular and midzonal regions at 6-9 months, neoplastic nodules appeared at 12 months, trabecular carcinoma was observed after 15 months and adenocarcinoma at 24 months. Simple cystic cholangioma and adenofibrosis appeared in animals 18-23 months after the exposure began. There was no evidence of metastases to the lungs. All trabecular carcinomas had cell arrangements with a glandular, ductal or cystic pattern and all adenocarcinomas had some elements of the trabecular pattern of growth. The lumens of

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the adenocarcinomas were the apparent result of cellular necrosis.

The incidence of tumors in animals 18 months or older are presented below in Table 4. It should be noted that 7-8 animals

Table 4

Incidence of Hepatocellular Neoplasms

	Incidence or % Tumors Observed (The actual number of animals with tumors)		
	Male	Female	Total
A. Control Animals	**(N=32)**	**(N=49)**	**(N=81)**
Trabecular carcinoma	0%(0/32)	0%(0/49)	0%(0/81)
Adenocarcinoma	0%(0/32)	0%(0/49)	0%(0/81)
Number negative	100%(32/32)	98%(48/49)	99%(80/81)
B. Aroclor 1260 Animals	**(N=46)†**	**(N=47)††**	**(N=93)**
Trabecular carcinoma	4%(2/46)	40%(19/47)	23%(21/93)
Adenocarcinoma*	0%(0/46)	51%(24/47)	26%(24/93)
Neoplastic nodule only	11%(5/46)	4%(2/47)	8%(7/93)
Number negative	85%(39/46)	4%(2/47)	44%(41/93)

† The total number includes 8 animals that had received a partial hepatectomy during the first 18 months.
†† The total number includes 7 animals that had received a partial hepatectomy during the first 18 months.
* Animals with both trabecular carcinoma and adenocarcinoma were placed only in the adenocarcinoma group.

sacrificed after 18 months, i.e. at least 15% of the group of animals in which late developing tumors were observed, had undergone a partial hepatectomy during the first 18 months. The effect of this cannot be determined from this experiment, but partial hepatectomy has been used as a promotional stimulus to increase the incidence of liver tumors induced by other carcinogens. Therefore, it is unfortunate that the authors did not note or describe the possible influence that this might have had on the final tumor incidence measured. Another important factor to consider, and one which is not readily apparent from Table 4, is that almost all of the tumors reported in this study were very late-developing tumors. In Table 1 of their paper, only 4 trabecular carcinomas and only 2 adenocarcinomas had developed between the 18- and 24-month sacrifices. Thus, 35/41 or some 85% of the liver tumors observed in this study developed in the last 25-29 month period of the study. These tumors had not metastasized to other organs, and none appear to have been life-shortening. Concerning this last aspect, unfortunately no information is given concerning the cause of death for any animals dying early, or concerning the number of animals lost. But from the data supplied

it would appear that a number of early deaths occurred only in the group of male control animals. These same observations were also noted by the authors, who stated in the discussion of this paper

> " Although the tumors met the morphological criteria for malignancy, their biologic behavior was relatively unaggressive. The neoplasms did not metastasize to distant organs nor invade blood vessels. Mortality of the animals was not increased. The lack of greater morbidity or mortality is likely due to slow progression of the neoplastic process and late appearance and slow growth of the hepatocellular carcinoma."

The authors further noted that it remains to be established whether PCBs have an initiating effect or whether the neoplasms observed result from the promotion of a background incidence of initiated cells.

1.3 Studies In Other Species

Calandra (1976) reported, in summary form, a carcinogenicity bioassay performed in dogs. Groups containing 4 male and 4 female dogs were fed 1, 10 or 100 ppm of Aroclors 1242, 1254 or 1260 for two years. While this exposure interval is for a period of time that is considerably less than the lifetime of the species being tested, no remarkable findings were reported.

1.4 The Effects of PCBs on Other Liver Carcinogens

PCBs have been tested in numerous studies to determine whether they alter the carcinogenicity of other chemicals. The evidence obtained from such studies is sometimes inconclusive, and in several instances similar studies have produced conflicting results. The results of have been summarized in the following paragraphs and in table 5 located on page 13 :

> • A number of studies indicate that PCBs administered after a carcinogenic dose of a liver carcinogen enhance the incidence of tumors. Nishizumi (1976) found that Kanechlor 500 promotes liver tumors initiated by diethylnitrosamine. Kimura et al. (1976) demonstrated that Kanechlor 400 can promote the liver cancer induced by 3'-methyl-4-dimethylaminoazobenzene (MeDAB). Ito et al. (1978) initiated liver tumors with N-2-fluorenylacetamide and then increased tumor incidence by feeding the rats diets containing 1,000 ppm of PCBs. Preston et al. (1981) have reported that Aroclor 1254 with or without polychlorodibenzofuran contaminants can promote the liver cancer initiated by diethylnitrosamine. Osterle and Deml (1984) demonstrated that this effect can be produced in weanling rats, although the immature animal is less sensitive. Deml et al. (1983) have also found that an initial PCB pretreatment to increase

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oxidative metabolism, followed later by PCB administration for its promotional effects, increased the number of rat liver preneoplastic islands. Similarly, Pereira et al. (1982) demonstrated that Aroclor 1254 promoted the number of diethylnitrosamine-induced enzyme-altered foci in rat livers. Recent work by Deml and Oesterle (1987) has shown that while PCBs are capable of promoting the liver tumors initiated by diethylnitrosamine, the threshold for this effect is about 1 mg/kg/day and correlates strongly to the induction of MFO activity and subsequent liver hypertrophy that the induction of drug metabolism normally produces (Greim et al., 1985).

- In contrast to the above studies, Gans and Pitauro (1986) reported Aroclor 1254 increased the incidence of liver scarring in mice fed diethylnitrosamine, but PCB treatment did not enhance the formation of liver nodules. Arai et al. (1983) also reported that PCBs administered to rats following an initial exposure to dimethylnitrosamine increased the incidence of liver tumors, however, this same dosage regimen decreased the incidence of kidney tumors produced by DEN.

- Conflicting results have been reported in trout where the effect of PCBs is dependent upon the time of PCB administration as well as the carcinogen it is administered with. For example, Hendricks et al. (1980) found that PCBs did not promote the incidence of liver tumors induced by aflatoxin B_1 in trout, even though the trout were fed a diet containing PCBs for 12 months after the aflatoxin B_1 exposure. However, other studies by Shelton et al. (1984a) have demonstrated that PCBs exert an inhibitory effect on the incidence of liver tumors initiated by aflatoxin B1 when PCBs are co-administered with this liver carcinogen. Alternatively, trout fed diets containing 1100 ppm diethylnitrosamine + 100 ppm of either Aroclor 1242 or Aroclor 1254 had a greater incidance of liver cancer than did trout fed diets that only contained 1100 ppm DEN (Shelton et al., 1984b).

- Loury and Byard (1983) observed that Aroclor 1254 enhanced the DNA repair response of amino acid pyrolysate mutagens in primary hepatocyte culture when the PCBs were given three days prior to cell isolation. Thus, it appears that these effects are related to a PCB enhancement of oxidative metabolism. In contrast, Nesnow et al. (1981) found that Aroclor 1254 did not enhance the benzo(a)pyrene-mediated transformation of C3H10T1/2CL8 mouse embryo fibroblasts even though a number of other chemicals known to induce drug metabolism were positive in this test.

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Wistar rats and CD-1 mice from diethylnitrosamine-induced liver tumors (Nishizumi, 1980, Anderson et al., 1983). Likewise Kimura et al. (1976) found that PCBs given before or during MeDAB exposure decreased the incidence of MeDAB-induced liver cancer. Similarly, Makiura et al. (1974) have shown that the co-administration of PCBs with the liver carcinogens MeDAB, N-2-fluorenylacetamide and diethylnitrosamine decreases tumor incidence. Trout fed diets containing PCBs prior to their exposure to aflatoxin had a reduced frequency of liver tumors induced by the aflatoxin (Hendricks et al. 1977). This effect is perhaps explained by Stott and Sinnhuber (1978) who demonstrated that PCBs reduced the bioactivating ability of trout microsomal fractions used to test the mutagenicity of aflatoxin B_1.

- In dermal initiation-promotion assays PCBs have been found to diminish the initiating activity of certain skin carcinogens and to be devoid of any promoting activity (DiGiovanni et al., 1977; Berry et al., 1978). Similarly Hayes et al. (1985) examined the effects of PCBs on the proliferating hepatocytes in livers of young animals or adult animals after partial hepatectomy. They concluded that short-term PCB exposures do not have an initiating action in an *in vivo* assay that detects both hepatic and extra-hepatic initiating carcinogens.

- In contrast to its reportedly adverse effects on the immune system, Kerklivet and Kimeldorf (1977a&b) demonstrated that PCBs administered either in the diet or by injection reduced the size of Walker 256 carcinosarcomas transplanted to rats and increased the lifespan of the PCB-treated animals.

Table 5

Summary of PCB Interactions With Other Carcinogens

Study	Carcinogen	Results
A. PCBs Administered After the Carcinogen :		
Nishizumi (1976)	diethylnitrosamine	promotion (liver tumors)
Kimura et al., (1976)	Me-DAB	promotion (liver tumors)
Ito et al., (1978)	N-2-fluorenylacetamide	promotion (liver tumors)

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Hendricks et al., (1980)	aflatoxin B1	no effect
Preston et al., (1981)	diethylnitrosamine	promotion (liver tumors)
Pereire et al., (1982)	diethylnitrosamine	promotion (liver tumors)
Deml et al., (1983)	benzo(a)pyrene	promotion (liver tumors)
Arai et al., (1983)	dimethylnitrosamine	promotion (liver tumors) inhibition (kidney tumors)
Gans & Pitauro, (1986)	diethylnitrosamine	liver scarring no effect (liver nodules)
Deml & Oesterle, (1987)	diethylnitrosamine	promotion (liver tumors) threshold dose (1 mg/kg/day)

B. PCBs Administered Before or With the Carcinogen :

Makiura et al., (1974)	Me-DAB	less liver tumors
	N-2-fluorenylacetamide	less liver tumors
	diethylnitrosamine	less liver tumors
Kimura et al., (1976)	Me-DAB	less liver tumors
Hendricks et al., (1977)	aflatoxin B1	less liver tumors
Nishizumi (1980)	diethylnitrosamine	less liver tumors
Anderson et al., (1983	diethylnitrosamine	less liver and lung tumors
Shelton et al., (1984a)	aflatoxin B1	less liver tumors
Shelton et al., (1984b)	dimethylnitrosamine	promotion

Me-DAB = 3'-methyl-4-dimethylaminoazobenzene

It is concluded from these studies that the liver hypertrophy induced by PCBs can and does enhance the carcinogenic response of initieting hepetocarcinogens if the PCBs are given some time after the liver cells have been initiated by the other chemical.

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However, this effect has also been demonstrated for phenobarbital and is no doubt also true for most other liver enzyme inducing chemicals that produce a hypertrophy or hyperplasia of the liver. Additionally, recent work by Deml and Oesterle (1987) has shown that the promotional effects of PCBs has a threshold, as one might expect, and this threshold appears to be well above the dose commonly encountered by most persons. In contrast to its promotional effects on liver carcinogens known to be initiators, PCBs also act as anticarcinogens when administered prior to the exposure of an initiating carcinogen. This effect is most probably the result of PCB induction of liver metabolism which then acts to decrease the carcinogenic effects of a number of chemicals by increasing their degradation and elimination.

2.0 Epidemiological Studies of PCB Exposure and Cancer Mortality

Published epidemiological studies addressing the carcinogenic potential of PCBs have been confined to two cohorts, both consisting of employees of plants where PCBs were used in the manufacture of capacitors.(Note : Bahn et al. (1976), in a letter to the editor, reported an analysis of eight deaths among 92 research and development workers at a refinery, and suggested an association between PCB exposure and incidence of malignant melanoma. The extremely limited size of their cohort, the inability to adequately assess exposure of the cohort to other, potentially carcinogenic substances or other known risk factors, and the inconsistency of their observations with the results from the two larger cohorts, precludes any utility of this report in the assessment of the human carcinogenicity of PCBs.)

Brown and Jones (1981) have published a retrospective cohort mortality study of employees from two plants. Minimal exposure period to PCBs was three months, and the types of PCBs used were Aroclors 1016, 1242, and 1254. Workers who had potential exposure to trichloroethylene, which was also used in both plants, were excluded from the cohort. Of the 2567 employee cohort, 163 were known to be deceased and the vital status of 55 (2%) was unknown.

Higher-than-expected incidences of cancer in the rectum (primarily among females in Plant #2) and liver were noted, although the differences were not statistically significant. The overall incidence of malignancies observed was slightly less than expected. None of the causes of death showed a clear association with latency, and no relationship was observed between the duration of employment in jobs involving PCB exposure and risk of mortality due to cancer. The causes of mortality and incidences of specific malignant neoplasms are summarized in Table 6.

The study of mortality in this cohort has recently been updated, with the number of deceased increasing from 163 to 295

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(Brown, unpublished data). There were no additional deaths from cancer of the rectum which brought the observed incidence of this form of neoplasm closer to the expected value. The number of observed malignancies of the liver was significantly greater than expected. However, a number of these malignant neoplasms (3/5) appear to have been the result of metastasis from other sites. Thus, like the rectal cancer the standard mortality rate (SMR) for liver cancer originating in the liver has been substantially lowered by this larger cohort. A higher-than-expected incidence of neoplasms was not noted for any other tissue. The overall incidence of malignancies observed was less than expected. There was no apparent relationship between duration of employment in "PCB-exposed" jobs or total employment and cancer mortality of any type.

Table 6

Major Causes of Death for Plant Workers Exposed to Aroclor 1016, 1242, and 1254

Causes of Death	Observed/Expected	Standard Mortality Rate
	All Causes of Mortality	
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	(80)
Total mortality for 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: Brown and Jones (1981)

The first study of the second major cohort was reported by Bertazzi et al. in 1981. Inclusion in the cohort was limited to workers in the production department who had been employed for at least six months. There were a total of 1310 workers included in

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the study, and exposure was primarily to Aroclor 1254 and Pyralene 1476. While some members of the cohort were also exposed to trichloroethylene, alkylbenzene, and epoxy resins, the number was stated to be few. A total of 27 deaths were observed in the cohort between 1954 and 1978. The overall incidence of cancer observed was significantly higher than expected (14 versus 5.65 expected), contributed primarily by elevated (though not statistically significant) incidences of neoplasms of the digestive organs and lymphatic and hematopoietic systems.

Bertazzi et al. (1986) have recently published an update of their study of PCB-exposed capacitor workers with a modified cohort. Non-production workers at the plant were added to the cohort, and the minimum period of employment was reduced from six months to one week. The size of the cohort was consequently increased to 2100, and the number of deceased to 64. The results from male and female workers were analyzed separately, and are summarized below in Tables 7 and 8.

Table 7

Mortality From Selected Causes of Male Workers Exposed to PCB

		Reference Cohort			
		National Mortality Estimates		Local Mortality	
Estimates Cause of death	Observed	Expected	SMR	Expected	SMR
All causes	30	27.8	108	29.8	101
Malignant tumors	14	5.5	253[a]	7.6	193[b]
Cancer of G.I. tract	6	1.7	346[c]	2.2	274[d]
Lung cancer	3	1.2	250	1.6	187
Hematologic neoplasms	3	0.8	375	1.1	263
Cardiovascular disease	8	7.9	101	9.4	85
Accidents	6	6.8	88	5.8	103

Confidence limits (95%) [a]= 144-415 [c]= 141-721
[b]= 104-300 [d]= 112-572

For males, mortality from cancer was significantly greater than expected (14 versus 5.5 expected). Among specific tissues, the observed incidence of neoplasms of the GI tract was significantly higher than expected, and hematologic neoplasms were also greater

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than expected but not statistically significant. Overall mortality was only slightly greater than expected. Among females, higher-than-expected incidences of overall mortality, mortality from cancer, and incidence of hematologic neoplasms were observed. These differences were of statistical significance when the cohort was compared to local mortality rates but not national mortality rates. While neoplasms were grouped by organ-system for statistical analysis, specific tumor sites were noted. Among both male and female members of the cohort, there was one case of liver cancer and no cases of rectal cancer. There was no apparent association between duration of exposure, latency, and year of first exposure for any of the causes of mortality.

Table 8

Mortality From Selected Causes of Female Workers Exposed to PCB

		Reference Cohort			
		National Mortality Estimates		Local Mortality Estimates	
Cause of death	Observed	Expected	SMR	Expected	SMR
All causes	34	25.8	132	16.5	206[a]
Malignant tumors	12	7.7	156	5.3	226[b]
Hematologic neoplasms	4	1.5	266	1.1	377[c]
Cardiovascular disease	2	4.7	42	3.0	66
Accidents	9	4.0	225	4.0	225

Confidence limits (95%) [a]= 145-288 [c]= 115-877
[b]= 123-389

From Bertazzi et al., 1986

3.0 Other Relevant Human Data

3.1 Health Effects Information from Accidental Ingestion

In 1968, the ingestion of PCB-contaminated rice oil in Japan resulted in an outbreak of chloracne and other symptoms which were later termed "Yusho". A similar large-scale incident of ingestion of contaminated rice oil occurred approximately ten years later in Taiwan with similar symptoms. The most common symptoms observed in rice oil poisoning victims included increased discharge from the eyes, swelling of the eyelids, accompanying visual disturbances, fatigue and malaise, headache, and symptoms suggestive of peripheral neuropathies (numbness of the limbs and pruritis) (Higuchi, 1976; Okumra, 1984; Lu and Wong, 1984). Other notable

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symptoms reported included acneform lesions and hyperpigmentation. The incidence of hyperpigmentation was high (9/10) among offspring born to mothers pregnant during ingestion of the contaminated rice oil (Higuchi, 1976). This hyperpigmentation gradually faded over the 2-5 months after birth. Developmental tooth and bone defects were noted among some of the offspring (e.g. eruption of teeth at birth, larger-than-usual frontal and occipital fontanelles, and maintenance of a wider sagittal suture than usual). However, postnatal physical and mental development of infants born to contaminated rice oil-exposed mothers paralleled that of healthy infants (Higuchi, 1976).

While it was originally assumed that the rice oil was contaminated with only PCBs (Kanechlor 400), subsequent analysis revealed that there was also extensive contamination with polychlorodibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Studies in animals have clearly indicated that PCDFs are more toxic than PCBs, and a number of lines of evidence support the contention that the adverse health effects suffered by the rice oil poisoning victims were a result of PCDF rather than PCB exposure. First, the concentrations of PCBs measured in patients with symptoms of Yusho were substantially lower than those observed in a number of studies of healthy, occupationally-exposed workers (Kunita et al, 1984; Masuda et al, 1985). The occupational studies have also shown workers to have undetectable or minimally-detectable concentrations of PCDFs (Kashimoto et al, 1985), while rice oil victims in Japan and Taiwan had significant concentrations of PCDFs, including a number of extremely toxic isomers. These human observations are supported by a study in which monkeys were fed PCBs with levels of PCDF and PCQ contamination similar to that of the Yusho oils (Kunita et al, 1984). Monkeys fed this diet developed dermatologic symptoms resembling those seen in patients with Yusho. Monkeys fed PCBs without PCDF/PCQ contamination, or fed PCQs alone, did not develop dermatologic lesions. Collectively these observations have led to the conclusion that the symptoms experienced by the rice oil poisoning victims were the result of PCDF rather than PCB exposure (Kuratsune, 1980; Kashimoto et al, 1981; Drill et al, 1982; Masuda et al, 1982; Masuda and Yoshimura, 1984; Chen et al, 1984; Kunita et al, 1985; Miyata et al, 1985, and Bandiera et al, 1984).

3.2 Health Effects Information from Environmental Exposure

A number of studies have attempted to measure health effects from environmental exposure to PCBs. The most common source of environmental exposure in these studies was the consumption of Lake Michigan fish (e.g. Humphrey, 1980; Fein et al, 1984; Kreiss et al, 1981; Smith, 1983), although the results from other sources of environmental exposure have also been studied (e.g. Baker et al, 1980). The results from these studies have generally been negative. Interpretation of the meaning of the few positive observations has been hampered by either the absence of a control population matched for known risk factors for the parameter studied, a strong positive correlation between PCB body burden and the body burden of other

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halogenated organics, or the inability to demonstrate increased PCB body burden in the "exposed" population compared with background body burdens in "non-exposed" controls. The absence of these apparent adverse effects in studies of workers with much higher PCB exposures (see below) casts further doubt on the significance of these findings.

3.3 Health Effects Information from Occupational Exposure

With few exceptions, individuals with the largest and longest exposure to PCBs are found in the occupational setting. For this reason, the study of occupational exposure to PCBs is probably the best source of information regarding their health effects in humans.

A population of 326 workers employed at two capacitor manufacturing plants had been the most studied, and a number of reports concerning their health have appeared in the literature. Though this population had been exposed to Aroclor 1016 during the most recent two year period prior to the initial study (and to a lesser extent to Aroclor 1221), the long-term exposure was primarily to Aroclors 1242 and 1254 (Fischbein et al, 1979). Duration of exposure to PCBs was substantial, as 40% of the workers had been employed for 20 years or longer. Air levels of PCBs varied widely throughout the plants, ranging from 0.007 mg/m^3 to 11.0 mg/m^3 (Fischbein et al, 1982). Wolff et al (1982) analyzed 290 plasma samples and 61 adipose tissue samples from these workers and found plasma concentrations of lesser chlorinated PCBs ranging from 6-2390 ppb, plasma concentrations of higher chlorinated PCBs ranging from 0-546 ppb, adipose levels of lesser chlorinated PCBs of 0.6-414 ppm, and adipose levels of higher chlorinated PCBs from 1-165 ppm. Approximately half of the population had a history of dermatologic symptoms, rash being the most common. A history of non-adolescent acne, a symptom considered characteristic of PCB exposure, was reported by 12% of the workers (Fischbein et al, 1982). Edema of the upper eyelid, eye discharge, and enlargement of the Meibomian glands, common symptoms among patients with Yusho, were each found in 7% or less of the occupationally-exposed workers (Fischbein et al, 1985). Warshaw et al (1979) studied respiratory function in 243 of the workers and found that 14% had abnormal forced vital capacity. From an extensive examination of clinical chemistry parameters in the PCB-exposed worker population, Fischbein et al (1979) concluded :

"... there was a paucity of abnormal results in the biochemical studies. Similar findings were noted in the results of the hematologic tests ... ".

Other occupationally-exposed populations have also been studied, and have been included in a recent review by Gaffey (1983) of the human health effects of PCBs. Gaffey, in surveying the human PCB literature, classified health effect observations into five categories: dermatologic findings, liver function, fat metabolism, blood and blood pressure, and symptoms,illnesses, and other

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conditions. Which respect to each of these categories, the following observations and conclusions were noted:

Dermatological effects: Of 11 studies of PCB-exposed workers which reported dermatologic findings, dermal symptoms were noted in all 11. Correlation of dermal symptoms with blood PCB concentrations were generally poor or non-existent. However, collectively the evidence strongly suggests that chloracne may occur when PCB blood levels exceed 150-200 µg/ml.

Liver function: Some abnormality in liver function indicated by a change in one or more relevant clinical chemistry parameters, was observed in five of seven studies of occupational exposure to PCBs. [Though not mentioned by Gaffey, it should be noted that while differences in some parameters indicative of liver function were observed to be statistically significant in some of these studies, these differences were uniformly quite small. Further, with chemical-induced hepatotoxicity one would expect to find a consistent pattern of abnormalities among overlapping indices of liver function. No such consistent pattern was observed.] In no case was the abnormality associated with any measurable adverse health effect. The remaining two studies found no evidence of liver abnormalities. A ninth study found evidence of induction of drug metabolism among PCB-exposed workers (Alvares et al, 1977).

Fat metabolism: There appears to be a correlation between serum triglycerides and PCB exposure in most studies. Results concerning cholesterol are equivocal, with one study showing an increase, one a decrease, and three no change. Conflicting results have also been observed with HDL-cholesterol. Changes in fat metabolism produced by PCBs, if they exist, do not appear to be of clinical significance.

Blood and blood pressure: None of the five studies which examined blood chemistry noted abnormalities associated with PCB exposure. One study of PCB-exposed workers measured blood pressure, but found no association with PCBs.

Symptoms, illness, and other conditions: Five studies report a variety of symptoms among PCB-exposed workers. Most of these symptoms appear to be unrelated to PCB exposure. None of the reports have found significant clinical effects to be associated with PCB exposure.

3.4 Summary of Non-cancer Human Health Effects of PCBs:

PCBs appear to be of low potency in producing adverse human health effects. Among workers with demonstrated high body burdens

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of PCBs, the only consistently demonstrated clinical finding is dermatological abnormalities. Though one study has found evidence for hepatic enzyme induction in humans, there is no compelling evidence for PCB-induced liver injury despite relatively high levels of exposure. A number of subjective and objective symptoms have been reported for workers exposed to PCBs, and a variety of such symptoms would be expected in examining any population. The appearance of symptoms usually does not correlate with PCB levels or exposures, and no symptom or symptom type (other than dermal) is prominent when the studies are considered collectively. Exposure to PCBs highly contaminated with PCDFs may lead to significant symptomology, but these effects appear to be due to the more toxic PCDFs.

4.0 GENOTOXIC EFFECTS OF PCBS

4.1 Bacterial Mutagenicity Studies

Wyndham and co-workers (1976) were probably the first to test several chlorinated biphenyl mixtures in a bacterial test system. In this study the TA1538 mutant strain of *S. typhimurium* developed by Ames was used as the tester strain of bacteria, and rabbit liver microsomes were apparently added to metabolize the PCBs. Contrary to the authors' report that PCBs were weakly mutagenic under study conditions, a review of their data indicates that only 4-chlorobiphenyl and Aroclor 1221 demonstrated significant activity. Interestingly, Aroclor 1221, which has a chlorine content of 1.15 chlorine atoms per molecule and is therefore largely a monochlorobiphenyl mixture, was considerably less active than 4-chlorobiphenyl. A review of the actual results provided in the report indicate that neither 2,2',5,5'-tetrachlorobiphenyl or Aroclor 1268 are mutagenic.

Subsequent attempts to demonstrate that PCBs might cause mutations in bacterial test systems have failed. In an affadavit from Dr. Safe, senior author of the Wyndham et al (1976) article, he indicates, based on his own inability to reproduce these findings, that 4-chlorobiphenyl should not be considered mutagenic. Additional assays by other scientists also discount any suggestion that PCBs or monochlorobiphenyls are mutagenic in bacterial systems. Heddle and Bruce (1977; Bruce and Heddle, 1979) tested a number of different chemicals in the TA1535, TA1537, TA98, and TA100 strains of *S. typhimurium* , both with and without an S-9 mix to provide metabolism and possible activation of the compounds tested. Aroclor 1254 was not mutagenic in this study. Similarly McMahon et al. (1979) reported results after screening a large number of compounds in a testing scheme incorporating several auxotrophs of *S. typhimurium* and *E. coli* . The only chlorinated biphenyl tested was 4-chlorobiphenyl, but it was found to be negative, i.e. it was not mutagenic, in all 10 tester strains. Based on these studies and other reports in the literature (Schoeny et al., 1979; Rinkus and Legator, 1979; EPA, 1980;

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TABLE 9

Summary of Microbial Mutagenicity Test Results

Product	Tester Strain	S. typhimurium										E. coli	
		C3076	D3052	G46	TA98	TA100	TA1000	TA1535	TA1536	TA1537	TA1538	WP2	WP2uvr
Aroclor 1268		-	-	-	-	-	-	-	-	-	Neg.	-	-
Aroclor 1254		Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	-	Neg.	Neg.	Neg.	Neg.
Kanechlor 500		-	-	-	Neg.	Neg.	-	-	-	-	-	Neg.	-
2,2',5,5'-tetrachloro-biphenyl		-	-	-	Neg.	Neg.	-	Neg.	-	Neg.	Neg.	-	-
Kanechlor 300		-	-	-	Neg.	Neg.	-	Neg.	Neg.	Neg.	Neg.	Neg.	-
Aroclor 1221		-	-	-	-	-	-	-	-	-	Neg.*	-	-
4-chloro-biphenyl		-	-	-	-	-	-	-	-	-	Neg.	-	-

Source: Levinskas (1981)
* Based on re-evaluation of Wyndham et al.(1975) by Dr. Safe.

Levinskas, 1981), all of which have been summarized in Table 9, it is concluded that PCBs are not mutagenic in bacterial test systems.

4.2 Clastogenic/Chromosomal Studies

Several test systems designed to measure chromosomal damage have been used to test the potential genotoxicity of PCBs. The only human cell line tested were humen lymphocytes in the study of Hoopingarner et al. (1972). The test system used phytohemagglutin stimulated cells which were treated with 100 ppm Aroclor 1254 for the first 24 hours, then again during the last eight hours of the S and G_2 stages of the cell cycle and during the three hours of mitosis. Cytological examinations of the cells during these stages of the cell cycle failed to reveal any effect of PCB treatment on chromosomal integrity.

Green et al. (1975a) tested Aroclors 1242 and 1254 for their

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ability to induce chromosomal damage in the bone marrow and sperm cells of rats. Aroclor 1242 was administered either in single doses of 1250, 2500 and 5000 mg/kg, or as four daily doses of 500 mg/kg; Aroclor 1254 was tested using three different dosage regimens, i.e. five daily doses of either 75, 150, or 300 mg/kg. The two highest doses of Aroclor 1254 and all doses of Aroclor 1242 caused a loss of body weight in these animals and the multiple doses of Aroclor 1242 killed half of the test animals. Even though considerable systemic toxicity was observed at these doses, neither Aroclor was found to induce chromosomal damage in sperm cells or bone marrow cells. Oikshith et al. (1975) similarly reported that PCBs do not produce chromosomal abnormalities in the sperm cells of rats exposed to seven daily dosages of 50 mg/kg of Aroclor 1254. The results of these two studies were later reproduced and substantiated by Garthoff et al. (1977). Male rats were fed dietary levels of 5, 50 or 500 ppm of Aroclor 1254 for 5 weeks after which sperm and bone marrow cells were examined for chromosomal damage; no evidence of chromosomal damage to either cell line was obtained.

Several investigators have employed the micronucleus test as a measure of chromosomal damage. Studies using this test system have reported that PCBs do not induce micronuclei in mice injected for five consecutive days with Aroclor 1254 at doses approximating one half of the LD_{50} or at doses representing some fraction thereof (Heddle and Bruce, 1977; Bruce and Heddle, 1979; Jenssen and Ramel, 1980). The doses used in these studies also failed to induce sperm abnormalities believed to be indicative of mutations or chromosomal deletions.

Using Drosophila melanogaster and Bombyx mori as the eukaryote test species, neither of the French PCB mixtures, Clophen 30 or Clophen 50 produced chromosomal aberrations (Nilsson and Ramel, 1974).

In conjunction with a study measuring the effects of PCBs on the breeding success of Ring Doves fed a 10-ppm diet of Aroclor 1254, Peakall et al. (1972) also reported the incidence of chromosomal aberrations in eggs of the birds. The average aberration rate changed from 0.8% in controls to 1.8% in the PCB treated birds. However, the average rate of chromosomal aberrations measured in the eggs of PCB pretreated birds was only higher than the highest control value in 4/17 eggs and the authors indicated that these results were inconclusive. By comparison, Aroclor 1242 has been injected into the eggs of white Leghorn chickens until PCB concentrations reached 20 ppm (Blazak and Marcun, 1975). Even though concentrations were clearly toxic, evidence of chromosomal aberrations was not observed.

4.3 Dominant Lethal tests

Green et al. (1975b) reported that Aroclor 1242 administered as single doses of 625, 1250 and 2500 mg/kg or after five daily dosages of 125 or 250 mg/kg failed to induce dominant lethal

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mutations in the rat. Aroclor 1254 administered for five days at dosages of 75, 150 or 300 mg/kg or at dietary levels of 25 or 100 ppm for 70 days was likewise without effect. Keplinger et al. (1972) and Calandra et al. (1976) tested Aroclors 1242, 1254 and 1260 in mice at dosages of 500 or 1000 mg/kg and also found them to be without dominant lethal effects.

4.4 DNA Damage Studies

On the basis of sedimentation rates, Stadnicki et al. (1979) have reported that the epoxide of tetrachlorobiphenyl caused single-stranded chromosomal breaks in the DNA of L-929 cells at concentrations ranging from 1 ug/ml to 100 ug/ml. A mixture of two hydroxylated metabolites, and to a much lesser extent tetrachlorobiphenyl, caused some damage at 20 ug/ml and what was reported as significant damage at 100 ug/ml. The significance of this single *in vitro* test is questionable, given the fact that the epoxide metabolite was the only chemical species demonstrating a strong activity in this test system. This conclusion has been reached in part because the authors, on the basis of this study, similarly concluded that the epoxide metabolite is the only chemical species of interest with regards to its potential carcinogenicity. However, all mammalian tests as well those *in vitro* tests containing some activation system were negative, indicating that either the epoxide is not genotoxic in other test systems or quantities of the epoxide sufficient to produce genotoxicity are not generated *in vivo*.

4.5 Cell Transformation Studies

Norback et al. (1981) 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 did not. The authors suggested that these results indicate that the effects of PCBs in cell culture may include promotion. In contrast to this study, Pienta (1980) reported Aroclor 1254 did not induce cell transformations after eight days of exposure when utilizing Syrian hamster embryo cells. The highest dose tested was 50 µg/ml, which was five times the highest dose later used by Norbeck et al. (1981).

4.6 Summary

The results of the preceding studies have been summarized on the next page in Table 10. Given the fact that the only test reported as positive is one of questionable significance, the number of times PCBs have been tested and found to be without significant genotoxicity lead inevitably to the conclusion that these compounds should be considered to be without evidence of genotoxic activity.

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Table 10

	Type of Genotoxic Activity			
	DNA damage	Mutation	Chromosomal damage	Cell Transformation
Species				
Prokaryotes		Neg.(28/12)	Neg.(2/2)	
Mammalian cells (*in vitro*)	Pos.?(1/1)		Neg.(6/9)	Neg. (2/2)
Mammals (*in vivo*)			Neg.(3/3)	
Human cells (*in vitro*)			Neg.(1/1)	

The first number in the parentheses indicates the total number of times an Aroclor was tested, the second number in parentheses indicates the total number of times a specific test strain or cell line was tested. Thus, the results followed by the larger numbers in parentheses represent the results most likely to be reproduced further testing is performed in the future.

5.0 Summary of Data Reviewed and Evaluation

5.1 Evaluation of Animal Evidence for Carcinogenicity of PCBs

The investigation of PCBs' carcinogenic potential in mice is limited to two short studies, while some eight to ten studies have been reported using various strains of rat. The PCB mixtures tested thus far are : 1) in mice - Kanechlor 300, Kanechlor 400, Kanechlor 500 and Aroclor 1254; and 2) in rats - Kanechlor 300, Kanechlor 400, Kanechlor 500, Clophen A30, Clophen A60, Aroclor 1254 and Aroclor 1260.

PCBs have been found to be tumorigenic in mice with Aroclor 1254 producing hepatomas after 11 months of exposure and Kanechlor 500 (similar in composition to Aroclor 1254) inducing hepatocellular carcinomas after 8 months of exposure. These lesions were shown to be reversible and specific for the dose (500 ppm) and chlorination of the PCB mixture.

In rats, Aroclor 1260 or its equivalent, Clophen A60, have produced hepatocellular carcinomas in three studies at doses of approximately 100 ppm, a dose which appears to represent the maximally tolerated dose for rats. A review of these three studies indicates that the tumors occur very late in the life of the animal, with a significant incidence of tumors only beginning to appear after about two years of exposure. Of interest is the fact that in all three studies the PCB treatment, while increasing the

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incidence of liver cancer, did not increase the total tumor incidence. The total tumor incidence was not increased in these studies because in each case the incidence of other tumor types had been significantly decreased. This suggestion of antitumor activity of PCBs has also been demonstrated in a study examining the effect of PCB exposure on the final tumor incidence in animals following the transplantation of the Walker 256 sarcoma. The effects of chronic PCB-treatment was not life-shortening, and in fact in two of the studies the morbidity and mortality of the animals was actually decreased by PCB treatment. Furthermore, while the tumors are described as malignant, i.e. hepatocellular carcinomas, in none of the three studies did the liver tumors metastasize to other organs even though metastases would be expected if the tumors were malignant. So from these studies it is evident that PCB-treatment does not increase the total cancer risk in these animals, rather it shifts the incidence of the type of tumors observed by significantly decreasing some tumor types while enhancing the incidence of liver tumors. Lastly, PCB mixtures of lesser chlorination, i.e. Aroclor 1254 and Clophen A30 (similar in composition to Aroclor 1242, see table 1.4, page 8, of Brinkman and DeKok, 1980), have been examined in two separate studies and found not to be carcinogenic. Thus, conclusions to be drawn from the rat data, like the mouse data, are specific for the dose and degree of chlorination of the PCB mixture being tested.

Possibly because PCBs produce liver hypertrophy, they enhance the tumorigenesis of certain liver carcinogens if given after the carcinogen in question has had an opportunity to initiate tumors. However, if the PCB exposure precedes or is concomitant with exposure to liver carcinogens the tumorigenic response is typically decreased, probably as a result of an enhanced metabolic detoxification of the carcinogen.

To summarize, the qualitative human relevance of the carcinogenic activity of PCBs based on the animal data is limited. The studies providing some evidence of its carcinogenic activity are specific for the degree of chlorination of the PCB mixture, the total tumor incidence is not increased, and the tumors produced occur only very late in the life of the animal and have no adverse effect on the morbidity or mortality of the animal. There are other considerations that limit concern for the carcinogenic data in rats as well. PCBs are not mutagenic, and the mechanism of tumorigenesis for these compounds therefore would appear to involve an epigenetic mechanism. There is also substantial evidence that the doses used to induce tumors in rats are hepatotoxic, and evidence indicating the neoplasms induced by PCBs are reversible if the exposure is terminated before the animal has been exposed for a considerable portion of the animal's lifespan. All of these findings seriously undermine the human relevance of the animal carcinogenicity data. This is particularly true as the human dosages from past and present human exposures are far lower than those used in the animal studies. Given these considerations, it is concluded that the animal data provides *sufficient evidence* of *limited human relevance* that PCBs of 60% chlorine content (e.g. Aroclor 1260/Clophen A60)

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are carcinogenic in animals. For PCBs having a chlorine composition of 54% (e.g. Aroclor 1254/Kanechlor 500) there is only *inadequate evidence* of carcinogenicity in animals because the larger and longer study in rats was negative, a finding suggesting that the reversible effects reported in mice may have resulted from a promotion of the substantial background incidence of liver tumors occurring in this species. For the remaining commercial PCB mixtures (i.e. Aroclor 1248, Aroclor 1242, Kanechlor 400, Kanechlor 300, and Clophen A30) there is either *no evidence* or *insufficient evidence* for the carcinogenicity of these mixtures in animals.

5.2 Evaluation of Epidemiological Evidence for Carcinogenicity of PCBs

Evidence for human carcinogenicity would be supplied if the two major epidemiological studies of PCB-exposed workers demonstrated a consistent increase in cancer mortality. This increase should show a positive correlation with exposure and evidence of latency. The evidence for carcinogenicity would be strengthened if the incidence of specific types or sites of neoplasms were consistently elevated. In reviewing the data from these two cohorts, none of these conditions are met.

While Bertazzi et al. (1986), in their study of Italian PCB-exposed workers, found a statistically significant elevation in the rate of cancer mortality among both male and female workers, the much larger study of Brown found no increase in cancer mortality. In the Brown study, there were higher-than-expected incidences of rectal and liver cancer. Evidence for an association between PCB exposure and these malignancy types cannot be considered strong, however, in that: 1) no cases of rectal cancer were observed after the initial report, suggesting that this increased rate was anomalous, 2) the number of cases of liver cancer observed in this study is not appreciably greater than expected when examined without total number of liver neoplasms used by Brown which includes those liver cancers that have metastasized from other organs, 3) in comparison, the study by Bertazzi et al. found only one case of liver cancer and no cases of rectal cancer in their cohort, and 4) the absence of a clear association with latency or relationship with duration of exposure.

The primary sites of neoplasms contributing to the higher-than-expected cancer mortality rates in the Bertazzi studies were located in the digestive system and the hematopoietic and lymphatic systems. These were not increased in the larger cohort reported by Brown. Further, in the Bertazzi cohort, there was no evidence of latency or relationship between cancer mortality and exposure to PCBs. It should also be noted that in the larger of the two subdivisions of their cohort, the female workers, differences in incidences of causes of death presumably unrelated to PCB exposure (viz., increases in accidental death and decreases in deaths from cardiovascular disease) were of similar magnitude as increases in death from malignant tumors. This suggests, at least

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for this group, that other confounding variables may exist.

In summary, epidemiological evidence for human carcinogenicity of PCBs is at present weak and mostly negative. As such, until larger epidemiological studies can be completed, the data must be considered *inadequate to characterize PCBs as human carcinogens*.

8.3 Evaluation

Aroclor 1260/Clophen A60 :

There is *sufficient evidence* of *limited human relevance* for the carcinogenicity of Aroclor 1260 in animals.

The human evidence for carcinogenicity of this compound is *inadequate* .

Aroclor 1254/Kanechlor 500 :

There is *inadequate evidence* for the carcinogenicity of Aroclor 1254 in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

Aroclor 1248/Kanechlor 400 :

There is *no evidence/insufficient evidence* for the carcinogenicity of Aroclor 1248 in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

Clophen A30/Kanechlor 300/Aroclor 1242 :

There is either *no evidence* or *insufficient evidence* for the carcinogenicity of these mixtures in animals.

The human evidence for carcinogenicity is negative but *inadequate*.

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