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SUMMARY OF THE HEALTH EFFECTS OF PCBs

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Prepared for:

CHEMICAL MANUFACTURERS ASSOCIATION

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PREFACE

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

- "The Epidemiology of PCBs" by William Gaffey, a Monsanto publication, (1981).

- "A Review and Evaluation of Carcinogenicity Studies in Mice and Rats and Mutagenicity Studies with Polychlorinated Biphenyls" by George Levinskas, a Monsanto publication, (1981).

- "The Toxicity of Aroclor Products 1242, 1254, and 1260 to the Liver of Albino Rats" by George Levinskas, a Monsanto puolication, (1981).

- "Human Health Effects of Electrical-Grade PCBs" by J.F. Brown, Jr., J.T. Coe, and H.D. Pocock, Jr., a General Electric publication, (1981).

- "Technical Review of the Health Effects of PCBs" by Robert James, Morris Cranmer, and Raymond Harbison, a New England Gas Association publication, (1981).

- "Assessment of Carcinogenic Risks From PCBs in Food" by Kenny S. Grump and Marjory Masterman, prepared for the United States Congress Office of Technology, contract # 933.1350.0, (1979).

The reader will note that, with the exception of the section on risk assessment, the summaries in this report contain no specific references to other documents. Since the documents listed above, which review the pertinent literature on PCB health effects to date, give specific references for further study, it was not thought necessary to repeat these same citations in the body of this report. For a more in-depth review of the pertinent PCB literature and specific citations, it is suggested that the reader refer to the documents listed above.

EXECUTIVE SUMMARY

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

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

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

rats have been reported, but only one study exists to date that suggests PCBs may cause an increase in hepatocellular carcinoma. When the paucity of convincing data is compared to the large number of negative tests, and when other important contributing factors are considered (e.g., the spontaneous rate of liver injury and liver regeneration, thereby promoting aberrant hepatocellular growth; etc.), it is difficult to conclude that PCBs represent a significant cancer risk in man.

Analysis of published animal data leads to the conclusion that, in animals, commercial PCBs represent a low acute exposure hazard; that mutagenic, teratogenic, and reproductive risks are minimal; and that the carcinogenic potential of this compound has not been convincingly demonstrated in an animal model relevant to man. This lack of suggestive risk based on animal data has been further borne out by the fact that neither liver nor other cancers in man have been positively linked to PCB exposure in recent epidemiologic studies utilizing large study populations.

At worst, PCBs at high or elevated doses meet some of the criteria for a chemical promoter, i.e., they enhance tumor growth through epigenetic mechanisms but do not induce new tumor growths. This distinction is of extreme importance and can be made based upon the known mechanisms for genotoxic carcinogens and those for promoting agents. PCBs demonstrate many characteristics of the latter and none of the former. A further importance of this distinction is that PCBs have only been shown to possess a weak promoting activity at most. Therefore, the thresholds both proposed in theory and observed in animal studies suggest that there are safe exposure levels for PCBs.

The occupational exposures are certainly the most extensive and longest-term human PCB exposures that we are currently aware of, and are therefore probably most representative of what adverse effects might be expected. A comparative review of these occupational-exposure studies reveals that, like other chemicals, PCBs can cause adverse health effects, but in many respects these have been minimal While dermatitis and chloracne, which were reversible after discontinuing the exposure, have been noted in some cases, no other significant findings were routinely made. Even though several studies incorporated clinical chemistry analysis as indications of organ

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

In summary, epidemiologic studies have demonstrated that PCBs are not remarkably toxic chemicals after acute exposure, and that when excess exposure does occur, the usual consequences are dermatologic and not of a serious or permanent nature. Chronic exposures have added little or no additional adverse effects of note to this picture. The preponderance of studies has not identified a clinical disease associated with exposure to PCBs, nor has it provided persuasive evidence of health impairment. There is no evidence of an excess in total mortality or in mortality due to cancer, cardiovascular disease, or nervous system disease associated with occupational exposure to PCBs. PCBs have not been linked to any human cancer, and studies to date indicate it is highly unlikely future studies will establish such a link. Therefore, it appears that PCBs are not a remarkable toxicant, but a chemical which requires high doses to produce harmful effects.

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

contaminant, the concern for low level exposures to PCDFs is still expected to be minimal. However, the conclusions reached in this report apply to exposure to commercial PCBs and cannot be applied to all environmental PCB exposures, which may include exposure to concentrated contaminated waste mixtures.

1. MAMMALIAN TOXICOLOGY OF PCBs

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

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

practically nontoxic chemical. Ethyl alcohol is in the same toxicity class. The most consistent pathologic findings associated with the lethality of short-term tests are fatty infiltration of the liver, liver injury, and centrilobular necrosis of the liver. This is not an unexpected finding. Many chlorinated organic chemicals produce liver or kidney injury in mammals. Other effects observed in acute studies include depression and lethargy, decreased pain response, anorexia (loss of appetite), ataxia (unsteady gait), and diarrhea. These are signs of chemical intoxication that are also commonly seen with many other organic chemicals.

PCBs applied directly to the skin of rabbits produce dermal responses such as erythema, hyperkeratosis, blisters, and desquamation. These effects are not a particularly remarkable finding for any organic chemical. In monkeys, the epidermal disorders from oral dosages of 250 to 400 mg/kg are facial edema, hair loss, and acne. While chloracne has been reproduced in humans after high occupational exposures, it can also be produced by exposure to other chlorinated benzene derivatives. Other than discomfort and some scarring in severe cases, it is a reversible effect.

Subchronic studies have revealed other effects. Weight loss and liver injury become a more consistent finding in the rodent species, with liver enlargement and an induction of liver metabolism occurring at lower doses. PCBs are potent inducers of the mixed function oxidase system, more potent in fact than either phenobarbital or DDT, which have been used extensively as experimental tools for this purpose. PCB mixtures are also uniquely capable of inducing both cytochrome P-450 and cytochrome P-448.

The other systemic effects reported are porphyria; increased thyroid metabolism; gastric hyperplasia; increases in triglycerides, cholesterol, and phospholipids; and atrophy of the spleen and thymus. Estrogenic activity for PCBs has been reported in rats, and prolonged menstrual cycles and increased bleeding have been observed in monkeys. Of the above effects, the thymic change and the immunosuppressive effects of PCBs are probably of most concern. Changes in the immune system could lead to increases in the susceptibility to and severity of infectious and neoplastic diseases. However, attempts to verify that the immunosuppressive effects of high doses of PCBs might

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

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

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

negative when tested in the Drosophila melanogaster, negative in cytogenetic analysis of in vitro human lymphocytes, negative in cytogenetic preparations of rat sperm and bone marrow cells, and negative in the dominant lethal assay. Thus, chlorinated biphenyls have not demonstrated any mutagenic potential when tested with the majority of commonly used and well-substantiated mutagenicity procedures.

Attempts to estimate the potential risk of cancer to man caused by PCB exposure using data developed in rodents represents a controversial but crucial dilemma. Numerous studies involving both mice and rats have been reported, but only one study exists to date that suggests PCBs may cause an increase in hepatocellular carcinoma. When the paucity of convincing data is compared to the large number of negative tests, and when other important contributing factors are considered (e.g., the spontaneous rate of liver cancer in rodents; the inductive and cellular growth-promoting potential of PCBs; the potential for PCBs to induce recurrent liver injury and liver regeneration, thereby promoting aberrant hepatocellular growth; etc.), it is difficult to conclude that PCBs represent a significant cancer risk in man. This lack of suggestive risk based on animal data has been further borne out by the fact that neither liver cancer nor other cancers in man have been positively linked to PCB exposure in recent epidemiologic studies utilizing large test populations.

Industrial-grade PCBs may not be just a mixture of chlorinated biphenyls but a mixture that may also contain chemical contaminants, the polychlorinated dibenzofurans (PCDFs). Therefore, when considering all of the data summarized in preceding paragraphs, an assessment of the toxicity and risk to PCB exposure may be complicated by the fairly recent recognition and acknowledgement of PCDF contamination. Tetra-, penta-, and hexachlorodibenzofurans have been measured in Aroclors 1248, 1254, and 1260 in concentrations on the order of 0.1 ppm for each isomer. Studies of Japanese brands of PCBs indicate that they contained concentrations which were several times higher.

Of even more concern is the possibility that dibenzofurans may be formed in significant amounts when PCBs are exposed to high heat and some reactable form of oxygen. This concern was first expressed after the Yusho incident when it was discovered that the PCDF content was

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

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

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

Thus, many of the PCB-induced adverse effects would be expected for a chlorinated organic compound of the PCB type, or at least these effects are consistently produced by many chlorinated organics. These effects include liver injury, liver enlargement, liver enzyme induction, irritation when applied to the skin, chloracne, and possibly a disruption of the estrogenic balance in females because of increased liver metabolism. Although these may indeed be considered adverse effects, all chemicals are capable of altering some physiologic function at a high enough dose. In the more relevant reproductive, teratogenic, mutagenic, and carcinogenic tests, chlorinated biphenyls were consistently negative with only a few exceptions. These exceptions

can be discounted because of inadequate study design, disputable interpretations, and unusual tests Thus, it seems unnecessary to display a disproportionately high concern for those few controversial studies, especially when their findings were not reproduced in subsequent studies under similar or identical conditions. In the vast majority of experiments, the effects were produced by PCBs at high doses. Since the expected and likely human exposure to PCBs is low, the results of the tests using high-exposure conditions are not relevant to the expected human exposure level.

Therefore, it appears that PCBs are not a remarkable toxicant, but a chemical which requires high doses to produce harmful effects and one which clearly represents minimal or no risk to humans because of the limited nature of anticipated human exposure. While PCBs can be toxic, and their toxicity can be dramatically increased by high levels of dibenzofuran contamination, the mammalian toxicity data suggest that, in general, PCB mixtures can be tolerated under most real-world conditions.

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2. THE ROLE OF PCBs IN PRODUCING CANCER

Chemically induced carcinogenesis is a special aspect of toxicology, for the toxicants may or may not observe traditional toxicologic principles. For example, although carcinogens show dose-response relationships, may undergo biotransformation to active or inactive metabolites, and demonstrate specific structure activity relationships as other toxicants do, they may also be unlike other toxicants: they may not demonstrate thresholds and there may exist a long and indefinite latency period between the critical biochemical event and any cellular or physiologic expression.

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

agents (epigenetic chemicals), on the other hand, do have demonstrable threshold levels; thus, there are exposures for which the risk is minimal or the risk exists only for some finite interval after exposure.

For our discussion of the carcinogenic potential of PCBs, we reviewed the data for evidence to determine to which of these two classes of tumorogenic chemicals PCBs belong, and in our discussion we refer to the epigenetic class as promoters (i.e., chemicals that only increase the manifestation of cancer cells) and to the genotoxic class as initiators.

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

There has been great controversy about the relevance and nomenclature of rodent hepatic lesions. Most of this controversy surrounds the criteria used to diagnose cancer. The National Cancer Institute (NCI) has recommended a scheme for the classification of hepatocellular tumors and related lesions in rats. These recommendations have not been universally accepted, but are utilized in many of the reports of PCB carcinogenesis. The NCI classification scheme is extensive and specific in defining neoplastic lesions. It was concluded by NCI that benign hepatic cell tumors, i.e., without potential for malignant behavior, could not be diagnosed consistently. Therefore, terms such as "adenoma," which refers to a benign tumor, were not recommended. It was also determined that the term "hepatoma," used to denote a benign liver tumor, was imprecise in its usage and was not recommended for the description of any of the lesions under discussion. In contrast

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

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

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

content below 52% to 54% did not produce tumors in rats. These results are similar to those for mice. Neither were tumors induced when the average PCB chlorine content was 52% to 54%. The two studies using an average chlorine content of 60% reported no induction of hepatocellular carcinomas.

There is only one report of PCB-induced hepatocellular carcinoma in rats Since this report used the criteria developed by NCI for classifying liver pathology, we must weigh the importance of this report against the majority whose data are negative. As previously stated, utilization of these inclusive cytological criteria to define cancer will define some hepatocellular changes as cancer that will never progress to cancer. Furthermore, investigations have shown that the vast majority of regenerating or hyperplastic nodules reported as cancer disappear upon removing the animals from the chemical exposure. While some investigators have considered the use of the inclusive cytological criteria for classifying hepatocellular lesions, many have rejected this classification scheme because of its lack of diagnostic discrimination. Thus, the single report of PCB-induced cancer in rats uses a pathological description in opposition to the usual terminology for describing a benign tumor.

Chemical carcinogens are those substances capable of initiating cancer. Cancer is defined as the production of life-threatening malignant tumors of potentially unlimited growth that expand locally by invasion and systemically by metastasis. Chemical carcinogens irreversibly initiate and ultimately produce cancer. This is an important distinction and requires careful and accurate evaluation of the kind of tumors produced. Chemicals that promote benign tumors are not carcinogens. Therefore, tumor type is critical to determining whether a compound is a carcinogen. Failure to distinguish between tumor types will place equal importance on test results regardless of whether a malignant or benign tumor is produced as a result of exposure to a chemical. Therefore, it is absolutely essential to define the tumor type associated with chemical exposure to be able to evaluate the outcome and apply the data to humans.

Equally important, it is essential to determine the mechanism by which tumors are produced. Failure to distinguish the mechanism by which tumors are produced will place equal importance on chemicals

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

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

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

spontaneously occurring disease state. To do this, it must be shown that the compound initiates sustained damage to DNA in a dose-dependent manner.

On the other hand, promoters are chemicals that modify gene expression and cellular communication. Promoters can alter the ability to control various genes, thereby providing a selective growth advantage. Promotion is defined as enhancing the selective proliferation of previously initiated cells. By definition, promotion cannot occur until a critical gene is initiated. Wounding, growth stimuli, necrosis, inflammation, and certain chemicals can selectively and rapidly allow cells containing the mutated gene to form a clone of semiinitiated cells. Cell death, cell trauma, and cell hyperplasia are all produced by PCBs and can be expected to yield conditions favoring preferential growth of (promotion of) previously initiated cells. One can safely generalize that the tumorigenic properties of PCBs result, at least, in greatest part from alteration of the homeostasis of control mechanisms. Thus, changes seen in rodents with a high incidence of liver tumors must be interpreted carefully so as not to mistake toxic responses and promotion for initiation. Additionally, processes only promoting cancer in situ would be expected to regress upon removal of the promoter and not change the ratio of metastasizing to nonmetastasizing tumors. It is noteworthy that often such appears to be the case with liver cancer in rodents produced by cyclic chlorinated compounds.

In summary then, it has been documented that PCBs do not increase the incidence of tumors at any site except the rodent liver. Liver tumors are a common part of the natural disease process of rodents. Thus, changes seen in rodents with a natural history of a high incidence of liver tumors must be interpreted carefully so that toxic responses and promotion are not mistaken for initiation. Liver cell death, trauma, and hyperplasia are all produced by PCBs and can be expected to yield conditions favoring preferential growth of cells with dormant neoplastic phenotypes. Therefore, one can safely generalize that the tumorigenic properties of PCBs in the rodent liver result, at least, in greatest part from these alterations of homeostasis. The following summarizes the data delineating PCBs as a potential promoting agent (epigenetic) but not an initiator (genotoxic carcinogen).

Comparison of the Characteristics of Promoting Agents and Effects of PCBs

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

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

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

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

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

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

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

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

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

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

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

12. Promoter effects often require continued presence of the stimulus. Continued presence of PCB is required to sustain neoplastic alterations of the liver.

Comparison of the Characteristics of Carcinogens (Initiators/Genotoxic) and the Effects of PCBs

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

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

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

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

5. Carcinogens produce lethal tumors. PCB-increased liver tumors are not lethal.

6. Carcinogens produce transplantable tumors. PCB-increased liver tumors do not transplant.

7. Carcinogens are often effective at single exposures. PCBs increase liver tumors only after prolonged, continuous exposures.

8. Carcinogens are often active at nontoxic doses. PCBs only increase liver tumors at hepatotoxic doses.

9. Initiators are mutagens. PCBs are not mutagens and therefore are not initiators.

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

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

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

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

They further reiterated this idea by stating:

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

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

single strain, incriminate commercial PCBs as a carcinogen? To answer this question, we have reviewed the pertinent current theories of carcinogens, the scientific body of knowledge which supports these theories, and have provided an analysis of the chemical carcinogenesis testing performed with PCBs. On the basis of the data that have been reported in the last few years, PCBs do not appear to be carcinogens (initiators).

At worst, PCBs at high or elevated doses meet some of the criteria for a chemical promoter, i.e., they enhance tumor growth through epigenetic mechanisms but do not induce new tumor growths. This distinction is of extreme importance and can be made based upon the known mechanisms for initiators and those for promoting agents. PCBs demonstrate many characteristics of the latter and none of the former. A further importance of this distinction is that PCBs have only been shown to possess a weak promoting activity, at most. Therefore, the thresholds both proposed in theory and observed in animal studies suggest that there are safe exposure levels for PCBs.

3

3. RISK ASSESSMENT AS PART OF THE REGULATION OF PCBs: STATEMENT OF PURPOSE, NEED, AND LIMITATION

The increasing use of chemicals and our ever-growing realization of their impacts on human health necessitate a scientific basis from which to determine the largest quantity of a chemical, if any, that could be absorbed over an indefinite period without producing adverse health effects. For this purpose, the toxicologist has long relied on dose-response relationships to guide extrapolation downwards from the observed range to estimate a "safe" dose. A general premise of toxicology has been that the extent of induced adverse effects is closely related to the extent of exposure. Some interested parties have called for an exception to this established toxicological concept, suggesting that chemicals should be considered either as carcinogens or noncarcinogens, regardless of dosage involved. Many toxicologists continue to maintain that carcinogenesis, although complicated, is in fact consistent with classical toxicological concepts. National efforts have been made by several government agencies to develop a data base for evaluating test procedures used in the detection of cancer, as well as to develop methodologies for performing risk estimations for chemically induced cancer.

Undeniably, chemical technology has in a large measure contributed to the achievement of the present standard of living. It has produced many of the tools and resources needed to reduce human suffering and to modify selective pressures of the environment. Accompanying these benefits, however, is the possibility that toxic properties of certain chemicals have the potential to threaten man's health.

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

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

Thresholds

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

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

size in a statistically significant evaluation. This does not mean that thresholds do not exist, nor does it mean that thresholds cannot be estimated in a practical manner It does not mean that bounds cannot be established. It only means that thresholds are not absolute and cannot be defined with absolute certainty. In fact, if known, they might yield little practical relief to our current dilemma, since under the preceding limitations time, rather than dose, may become the critical and determining factor of risk. This stems from our perception that as the dose decreases the latency period increases. Therefore, time is the most appropriate medium to describe the magnitude of excess risk or reduced quality and quantity of life due to neoplastic lesions. Finally, we have demonstrated that PCBs are not genotoxic; therefore, the no-threshold arguments do not apply.

Germane to the modification of risk determinations by combining socially accepted values is the consideration of the hazard/benefit margin. Some chemicals may be considered essential insofar as there is no substitute process considered less hazardous, or for which the requirements of a replacement strategy outweigh or replace the original health concerns. For such chemicals, a relevant approach to controlling the risk is to permit only those uses for which the absence of hazardous exposures of the chemical can reasonably be assured. The cornerstone of this strategy requires that we define the hazard, then determine the amount of exposure which is not expected to be hazardous, which in turn defines the limits of the sensitivity of the analytical methodologies required.

Rephrased, the requirements of the analytical methodology and the limitations of chemical use would be defined toxicologically by the acceptable risk rather than as a function of the state of the art of analytical chemistry. The alternatives, zero-residue rules (such as found in the Delaney Clause) or risk analysis based upon an endless series of conservative presumptions, are inadequate and unusable in several respects. Such alternative approaches provide a false sense of security by ignoring the problem of "false negatives," which may result from chance or inadequate testing. In addition, they encourage poor and limited experimentation, since the less we do and the less precise we are, the less chance we have of determining anything at a statistically significant level. Moreover, these alternative

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

Value Judgement and Emphasis

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

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

Why Are Traditional Models Inapplicable?

When direct measurements are impossible, assumptions must be made if we are to be able to extrapolate a cancer hazard from animal studies at relatively high dose rates to human population cancer hazards at intermittent and low dose rates. Thus, one set of assumptions we must face concerns the description of the function relating the real hazard measured at high dose rates to a theoretically estimated animal risk at low dose rates. The magnitude of low dose risk is highly dependent upon the assumed shape of the dose-response function, and for neoplastic disease we must consider time. Unfortunately, the shape of the curve at low dose rates for most models is much more sensitive to manipulating the extrapolation procedure than to the experimental data. This has led to the discouraging observation that, for most models advanced to date for regulatory purposes, extensive experimentation and quality assurance means less than arbitrary mathematical manipulation, e.g., worst-case confidence limits.

The extreme differences between models for extrapolating to low risks have been reviewed in detail elsewhere and a summary is presented in Table 3-1. The probit, logistic, and one-hit curves can all be shown to calculate that one-fourth of a dose producing a 50% tumor incidence will produce a 16% tumor response. The families of curves generated by these models are indistinguishable in the range usually described by most experiments, that is, the 8% to 92% tumor response. However, several thousand animals would have to be tested in order to distinguish with confidence between predictions by the probit and logistic models in the 2% to 4% response. Hence, extreme differences between the estimated doses generated by the three models are noted when extrapolating to an upper confidence of no more than a one in a million risk.

The "extreme value" curve, another possible model, would generally lie between the probit and logistic, depending on the slopes selected. The choice of an extrapolation model is critical, but the parameters to be adjusted in the use of the model, particularly the slope and upper confidence intervals, are even more critical.

The logistic analysis can also be rejected because the logistic function, as originally proposed by Reed and Berkson in 1929, is an empirical form of a series of at least six equations obtained by data-fitting and not by any form of derivation. In addition, the forms of

Table 3-1

DOSES REQUIRED TO PLACE UPPER LIMITS
ON ESTIMATED RISKS

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

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the logistic are uncertain since different investigators use different equations, and the different slopes and intercepts thus obtained are without physical meaning, even in well-defined chemical or biochemical systems. The logistic equation has a mathematical form similar to the Hill equation that is based on the mass-action law. Thus, there seems to be no reason to use the logistic function.

Even for a particular model, for example the probit, nondata factors influencing the model can produce widely different extrapolation results (Table 3-2). For comparative purposes, dose-reduction factors for a risk not to exceed one in a million are given in Table 3-3 using probit of slope of one.

It is obvious that application of the most refined methods of observation or changing diagnostic criteria can lower any observed threshold. For example, if we consider hyperplasia as the endpoint rather than neoplasia, we shift the threshold. Repeating the bioassay will demonstrate variability even among genetically equivalent individuals. Phenotypic heterogeneity of any population and microenvironments will be expressed and will influence the responses observed. Almost all toxicologists believe that for any compound and for given conditions a "biologically insignificant dose" exists. There is little doubt that this is true; however, so far no acceptable approach has emerged for cancer risk assessment since a consensus on the definition of "insignificant" has not been reached.

Low Dose Models

Most investigators grappling with low dose extrapolation problems agree that we must continue to develop mathematical models describing hazards from carcinogenesis. A more fundamental insight into the relationship which undoubtedly prevails between dose and excess response at low constant dose rates is of critical importance. Much effort has already been expended. Crump et al. (1), Guess et al. (4), and Peto (5) have invoked certain hypotheses of carcinogenesis to argue that the possibility of linear responses at low doses must be considered. For example, Crump et al. (1) and Guess et al. (4) offer the proposition that the probability, $P(d)$, of response at dose rate is given by:

$$P(d) = 1-\exp[-(a_0 + a_1 d + a_2 d^2 + \ldots.)], \; a_1 \geq 0.$$

Table 3-2

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

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

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Table 3-3

FRACTION OF EXPERIMENTAL DOSE USING PROBIT EXTRAPOLATION WITH A SLOPE OF ONE WHICH IS CALCULATED TO PRODUCE AN ESTIMATED UPPER LIMIT RISK NOT TO EXCEED ONE IN A MILLION

Tumors Observed at Dose X	Fraction of Experimental Dosage
0/50	X/2,500
0/100	X/1,140
0/500	X/ 250
0/1,000	X/ 140

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

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

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

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

rates. In both cases, as was predicted, the 90% upper confidence limit on a_1 was positive. It then follows that the upper confidence limits on curves relating limits of possible extra response to dose rate will always appear to be linear at low dose rates. The predictability of false positive prediction of nonexistent risk supports the contention that the value judgement inherent in the use of worst-case confidence limits is not always appropriate. Value judgements should be delineated or completely separated from the quantitative use of mathematical models.

Another example of a mathematical procedure is provided by Gaylor and Kodell (3) in their study of 14 sets of toxicological dose response data previously described by the Scientific Committee of the Food Safety Council (2). The behavior of a gamma multihit model was purported to be compared to the Armitage-Doll multistage model for low dose extrapolation using the technique given by Crump et al. (1). The Gaylor and Kodell Armitage-Doll multistage model results did not exactly agree with the Scientific Committee of the Food Safety Council data because the limits calculated by Gaylor and Kodel did not assume a maximum degree of dose in the exponential term, whereas the limits calculated by the Food Safety Council took the degree of dose as fixed. Gaylor and Kodell (3) concluded that: "Conceptually linear extrapolation would (should) be more conservative, but this is not the case in actuality, apparently because more stringent mathematical assumptions and conditions are required" (by the gamma one-hit model). Selected examples are given in Table 3-4.

The examples given in Table 3-4 reinforce the recommendation made by the Scientific Committee of the Food Safety Council (2) calling for reason when mathematical interpretations affect real-life decisions:

> Although the value judgement involved in the use of conservative risk assessments may seem appropriate in the light of the many scientific unknowns involved, once formalized as a specific mathematical procedure it escapes the control of the decision-maker and can lead to undesirable and unsound results by distorting the balance between risk and benefit. We, therefore, recommend the separation of the mathematical and societal aspects of the problems, with the extrapolation procedure chosen to provide 'best estimates' of risk as well as their upper or lower limits.

The toxicological and mathematical uncertainties associated with extrapolating risks from relatively high experimental dosages in

Table 3-4

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

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

animals to low human exposure levels are often cited as a principal concern of those who call for complete prohibition when a chemical has been "demonstrated" to be a carcinogen. A slight modification of this approach is to use a series of conservative assumptions for data presentation followed by linear extrapolation or equivalent "model" use from upper confidence limits of the experimental results to a zero response at zero dosage. Since rodents, the principal bioassay species, have substantial rates of neoplastic disease at many sites, such an approach invites the option of declaring almost any thoroughly studied compound a carcinogen. PCBs are just such an example when one weighs all the negative studies against the single positive study of Kimbrough.

Evaluation of Criteria and Calculations of Risk from PCBs for Humans by Crump

We have now discussed the lack of mathematical logic supporting use of certain value judgements. In addition, Crump violated his own criteria for justifying the selected model for PCB risk analysis. This can be demonstrated with Crump's own words. Crump states in explaining his approach to risk analysis for PCBs:

> Tumors of so many different types arise in such a diversity of different tissues, their etiology is so little understood, and the agents that cause tumors affect a subject in such diverse ways, that it might seem that no general conclusions can be drawn. However, for a certain broad class of 'directly-acting' chemical carcinogens the range of uncertainty associated with the shape of the dose response curve at low doses can be greatly narrowed. As used in this paper, the term "directly-acting carcinogen" encompasses (Guess, Crump and Peto, 1977) carcinogenic agents for which either the agent itself or a metabolite acts directly at the cellular level and produces a hereditable change which eventually leads to the formation of a tumor. Carcinogens which are carcinogenic by reasons of their mutagenicity should fall into the category of 'directly-acting carcinogens.' Accordingly, carcinogens which test positively using the Ames mutagenicity screening test for carcinogenicity are very likely to be directly-acting.

The available data suggest that even if Crump's statement was true, the concept could not be appropriately applied to PCB risk analysis since PCBs are not direct-acting carcinogens as demonstrated by scientific literature For example, the Ames assay utilizes

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

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

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

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

> A partial solution to the low-dose extrapolation problem for the case of directly-acting chemical carcinogens has been given in Peto (1977), Crump, Hoel, Langley and Peto (1976), and Guess et al. (1976). The key result is that, at least as long as background carcinogenesis is present, we should expect the dose response curve not to be absolutely flat at zero dose. What this means is simply that when risk is plotted against dose response on ordinary linear scales, the tangent line to the dose response curve at zero dose should have a positive slope. When a dose response function has this property we will say it is linear at low dose.

Crump also offers a possible explanation of why the dose response function should be linear at low dose when background is present (Crump, et al. 1976), as does Peto (1977), which will be briefly outlined here. Crump et al. and Peto argue that when background carcinogenesis is present, the cellular mechanisms through which the test agent produces cancer should already be operative in producing background tumors. When this is true, the effect of the test agent is to

add to any already ongoing process. The dose response curve is for all tumors produced through the mechanisms through which the test agents acts. Background carcinogenesis is allowed for by an effective background dose d_0. In this case, the added risk caused by a dose d of the test agent could be expected to increase approximately linearly near d = 0 (i.e., the tangent line at d = 0 will have a positive slope). Implicitly assumed is the fact that an added dose of a carcinogen acting through this mechanism does not produce a smaller risk. If background carcinogenesis is allowed for by positing an effective background dose d_0 estimated from the data, then the wide range of risks obtained using different models effectively disappears (Peto 1977) because they all approach a simple linear model.

The Crump and Peto argument does not apply to PCBs. That the liver cancer rate induced by direct-acting carcinogens is not added to by PCBs has been demonstrated on several occasions. The effects of PCBs on carcinogenicity of various chemicals have been investigated by numerous groups. Kanechlor-500 in combination with 3' methyl-4-dimethylaminoazobenzene, N-2-fluorenylacetamide, and diethylnitrosamine in the diets of rats markedly decreased the formation of hepatocarcinomas. Kimura et al. demonstrated that pretreatment with Kanechlor400 in diets of rats 4 months prior to and 2 months during treatment with 3' methyl-4-dimethyulaminoazobenzene protected the rats against the formation of hepatocarcinomas induced by this carcinogen.

The two-stage system of mouse skin tumorigenesis allows one to evaluate critically the initiation and promotion phases of carcinogenesis individually. This system allows one to study the effects of modifiers on initiation and promotion separately in a skin carcinogenesis assay. The results of Berry et al. demonstrate that PCBs possess the capacity to decrease tumor initiation in a mouse skin assay and that at the doses utilized, PCBs had no initiating or promoting properties. Their study tested PCBs for promoting activity in mouse skin with a high (200 nmol) initiating dose of DMBA. In a 30-week treatment period, the normal DMBA-inititated, TPA-promoted controls yielded approximately 8 papillomas per mouse. PCBs (at doses of 100 µg/mouse given twice weekly) did not promote the development of skin tumors.

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

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

> The evidence for low-dose-linearity given above applies mainly to directly-acting carcinogens. An indirectly acting carcinogen might be one which causes some gross physiological change such as suppression of ovulation which could predispose the subject to cancer. For such carcinogens the shape of the dose response curve at low dose is highly speculative. There could possibly be a threshold dose below which the agent has no carcinogenic effect at all on an individual.

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

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

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

the liver. For example, when male Sprague-Dawley rats were fed a diet containing mixtures of PCB isomers (Aroclor 1248, 1254, and 1260) at a concentration of 100 ppm in the diet for 52 weeks, there was an increase in their serum lipids and cholesterol, and a transient increase in triglycerides accompanied by distinct morphological changes in the liver. Generalized liver hypertrophy and focal areas of hepatocellular degeneration were followed by a wide spectrum of repair processes. The tissue levels of PCB were greater in the animal receiving the high chlorine mixtures and high levels persisted after the PCB treatment had been discontinued.

Summary Supporting the Statement that PCBs Are at Worst Indirect Carcinogens (Promoters)

1. Promoters produce increases of spontaneous tumor at selected sites. PCBs only produce liver tumors in rodents for which there is a spontaneous occurrence.

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

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

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

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

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

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

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

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

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

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

Characteristics of Initiators (Direct-Acting Carcinogens)

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

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

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

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

5. Initiators produce lethal tumors. PCB-increased liver tumors are not lethal.

6. Initiators produce transplantable tumors. PCB-increased liver tumors do not transplant.

7. Initiators are often effective at single exposures. PCBs increase liver tumors only after prolonged continuous exposures.

8. Initiators are often active at nontoxic doses. PCBs only increase liver tumors at hepatotoxic doses.

9. Initiators are mutagens. PCBs are not mutagens and therefore not initiators.

It is apparent that the neoplastic effects of PCBs match the definitions of a promoter and do not match the definitions of an initiator. We have established that the rationale for justifying the technique for analysis of PCBs by Crump is inappropriate when compared against Crump's own criteria.

Conclusions About the Application of Linear Extrapolation and the Equivalent Nonthreshold Models to Risk Analysis of PCBs

We will establish our thesis when we thoroughly analyze the risk analysis offered by Crump. When referring to his modeling efforts, Crump states, "The expected numbers of extra cases of hepatocellular carcinomas per year resulting from a nationwide exposure at a dietary level detected in the 1976 Total Diet Study (3.3 μg/day) would range between 220,000 (288,000 x 70) = 11.1 cases/year and 220,000,000/(764,000 x 70) = 4.1 cases/year."

Crump misleads the reader by suggesting that the mathematical model used to generate these numbers brings logic to the effort. For example, if one simply takes the ratio of animals with and without liver tumors at 100 ppm in the Kimbrough study, divides by the estimated human exposure (1 ppb), then multiplies by the size of the human population in the United States (220 million), and finally divides by the human lifespan of 70 years, one gets the same answer as Crump:

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

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

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

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

The rats in the Kimbrough study were exposed to 10,000 µg/kg/day. Therefore, the ratio of exposure between rats and man is:

Capacitor worker/rat	= .0012
Fish eater/rat	= .00017
General population/rat	= .00005

The chances of dying from liver cancer can be expressed in several ways. For example, 816.3/100,000 Americans die each year from all causes. The incidence of liver cancer disease is 3/100,000. This translates to a .37% chance of liver cancer. Expressed another way, there will be about 2,000,000 deaths in 1981 and 9,400 are estimated to be from liver cancer. Therefore, 9,400/2,000,000 equals a .47% chance that the registered death will result from liver cancer. This estimate will be rounded off to a .5% chance for the purposes of our discussion.

If the risk were linear (and the risk to humans is the same as in rats, or .14), then the risk in man would be .00017 for capacitor workers, .00024 for fish eaters, and .000007 for the general population. Expressed another way, the risk to humans for liver cancer would increase to:

Capacitor worker	.005 + .00517 = .01017
Fish eater	.005 + .000024 = .005024
General population	.005 + .000007 = .005007

Thus, the cancer mortality data suggest that there is only a slight possibility that the actual risk for capacitor workers would be higher; however, the data are far from conclusive. It is also obvious that it would be impossible to determine epidemiologically the tiny increases expected to occur either in the fish-eating population or in the general population.

Let us approach the problem from a different viewpoint. Let us suppose that our risk analysis should be conducted on a relative risk basis. If the relative risk to rats at 100 ppm is 26, and the same exposure ratios between rat and man hold, then the risks are as follows:

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

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

How Did EPA Analyze the Data?

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

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

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

an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5}, for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register Notice of Availability of Draft Ambient Water Quality Criteria, EPA stated that it is considering setting criteria at an interim target risk levels of 10^{-5}, 10^{-6}, and 10^{-7}, as shown in Table 3-5.

If such is the EPA's estimate, 80 µg/day, how does it compare with other EPA statements and those results gathered in the NIOSH and FOA studies? Even when one makes all the conservative assumptions utilized in official PCB cancer risk estimations, one arrives at answers which are so low as to escape our capability of detecting a positive effect via epidemiology. Therefore, one must conclude that mathematical risk estimation, even for the occupationally exposed, yields estimates which are vanishingly small. However, the overzealous use of mathematical models and the assumptions made by the EPA without comparing these results to reality are easily demonstrated. EPA states in the Federal Register Notice of Availability of Draft Ambient Water Quality Criteria that the following risk to cancer from PCBs exists, 10^{-5} cancer risk = 80 ng PCB/day.

Table 3-6 summarizes known human exposures to the risks calculated by an extrapolation of the values.

Using estimates performed on preceding pages calculated from actual cancer rates in the United States, 9,400/2,000,000 equals a .47% chance of dying from liver cancer. This estimate will be rounded off to a .5% chance for the purposes of our discussion. Using these comparisons, it can be seen from the table above that if the EPA estimates are correct then 10% of the liver cancer in the United States would be due to PCB exposure; the Michigan control population would expect a 100% increase in liver cancer incidence, the Michigan fish eaters would have a 3-fold increase, the average capacitor worker would have a 10% incidence of liver cancer or a 20-fold increase, and the highly exposed capacitor worker would have a 25% incidence of liver cancer or a 50-fold increase. No human evidence supports any of

Table 3-5

EPA INTERIM TARGET RISK LEVELS

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

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

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

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Table 3-6

EXTRAPOLATIONS OF EPA RISK LEVELS
TO A HIGHER LEVEL OF HUMAN EXPOSURE

Group	Blood Exposure: Blood	Exposure	EPA Extrapolated Risk
Highly exposed capacitor workers	≥1,000 ppb	2 mg PCB/day	25%
Average capacitor worker	500 ppb	.84 mg PCB/day	10%
Michigan fish eater	70 ppb	.12 mg PCB/day	1.4%
Michigan control population	20 ppb	.035 mg PCB/day	.5%
General population	2 ppb	.0035 mg PCB/day	.05%

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

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

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

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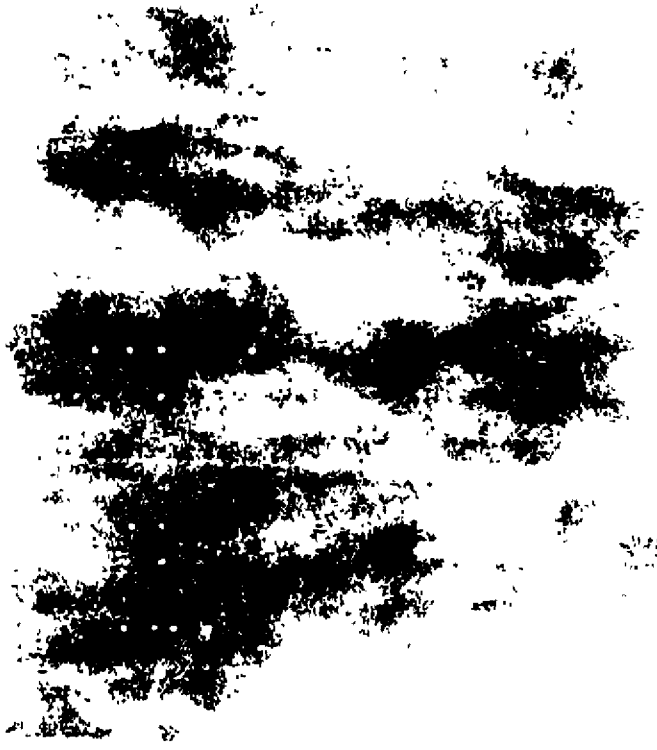

4. SUMMARY AND CONCLUSIONS

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

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

mixtures were apparently the same as those extensively tested over the years. Therefore, the concern for this level of contamination is expected to be no greater than that predicted for what was previously considered to be "pure" PCBs.

It was not the intent of this document to determine the full impact of PCDFs with regard to the hazards associated with PCBs. However, the PCDF content of PCBs may be increased under conditions of high temperatures, and the possibility of increased toxicity by the presence of this contaminant or others should always be considered when dealing with PCB waste mixtures of uncertain origin. Since the consequences of commercial PCB exposure alone were feared and regulated in the past, it was this issue alone which was addressed in this document. Therefore, having brought the above qualifying considerations to the attention of the reader, this report focused only on those health hazards expected to arise from exposure to commercial PCBs alone.

For the benefit of readers whose background and understanding of the field of toxicology, and the principles upon which it is based, is minimal, the following short discussion on safety and hazards is provided to help elucidate the problems involved in extrapolating test data to human consequences.

A poison is an agent that can produce an adverse effect in a biological system. This adverse effect may be an alteration of normal function or the destruction of life. The definition of a poison is broad by necessity and would include most chemicals, if not all. That is, all agents are capable of altering some function or producing death in some biological organism. Thus, classifying a chemical as a poison does not describe the most important feature of poisons, which is those circumstances and conditions under which an adverse effect can be produced. An agent that is a poison produces harm only within prescribed conditions of usage.

The safety of an agent can be defined in terms of its probability for producing an alteration of normal function or causing destruction of life under specified conditions. To determine the safety of an agent, the toxicity of the substance must be determined under controlled circumstances. Assessment of the toxicity of the agent will define the limits and conditions necessary to produce any adverse

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

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

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

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

about 15 micrograms per day (ug/day). However, all evidence now indicates that the level of daily PCB intake by humans is subsiding. Yet these factors have resulted in a major concern for the potential long-term effects of PCBs on human health because many of us still contain low levels of PCBs.

Owing to their low solubility in water and low concentrations in air, PCBs do not present an acute toxicity threat to either birds or aquatic organisms. In other words, the quantity of PCBs necessary to cause death within a short period of time, such as 96 hours, is greater than the amount generally found in natural environments. PCBs can cause major problems for some species, however, because these chemicals are persistent, lipid soluble, and resistant to biodegration and/or excretion. Consequently, PCBs can bioaccumulate (build up in quantity within an organism) as well as biomagnify within food webs (accumulate in larger amounts per group of organisms at each subsequent trophic level). The greatest amounts of PCBs are present in the long-lived predatory fish (e.g., trout, sharks) and birds (e.g., eagles, hawks). Sufficient quantities of PCBs may build up such that physiology or function is disrupted. At high levels, PCBs may decrease resistance to diseases, interfere with reproduction, and disrupt defensive behavior. In the case of birds, increased mortality of embryos can result as a consequence of the thinning of eggshells. Therefore, it has been concluded that PCBs can cause major environmental disruptions, particularly within aquatic habitats. Responding to this problem, the United States Environmental Protection Agency (EPA) has attempted to curtail the release of PCBs into the environment by regulating their use and disposal.

Many aspects must be considered and weighed before the hazards to humans associated with exposure to PCBs can be estimated. The human hazard evaluation and subsequent risk estimation for any chemical must address the data base utilizing thorough comparative toxicologic assessments. This means that the animal and human data available must undergo a careful consideration of 1) the breadth and variety of the toxic responses manifested; 2) the degree of species variation or species consistency in the effects monitored; 3) the possible and/or proposed mechanisms of toxicity; 4) the validity of the tests performed and their relevance for extrapolations to man; 5) the dosage used in

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

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

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

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

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

the large amount of negative data gathered, a suggestion that is becoming increasingly substantiated by human exposures. In the last few years, the reported epidemiologic evidence has not identified PCB exposure as the cause of any form of human cancer.

Therefore, even though there are animal data to demonstrate that PCBs are toxic at high doses, some toxicity at high doses is expected for any chemical. Additionally, while there is some evidence suggesting that the carcinogenic potential of PCBs be considered, the balance of the animal data also suggests that it is unlikely that this single response should become the focus of disproportionate concern usually given to potent carcinogens with definite initiator or genotoxic properties. On the contrary, one might propose that there exist enough animal data to suggest that this finding could be pertinent only to those specific test conditions and the particular mixture of PCBs tested. In summary, when all of the animal data are considered, they suggest that low levels of PCBs do not pose a significant health risk.

At this point in assessing the hazard associated with exposure to PCBs, a more thorough discussion of the carcinogenic potential of PCBs is needed because the risk of cancer from PCB exposure is the most serious concern of the PCB-induced adverse effects. This concern is surely of the utmost importance to the general public. This has been reflected by the stance taken by the EPA, which is manifested by EPA's recent (1980) publication summarizing its concern for PCBs. This ambient water quality criteria document indicates (and we paraphrase) that if PCBs are not carcinogenic, then an allowable daily intake of 210 µg of PCBs per day would be an estimated safe continual exposure. If, however, PCBs are carcinogens, while there may be no safe level, a level of risk approaching a lifetime risk for cancer of only one excess cancer in 100,000 persons exposed would be approximately 2 to 80 nanograms per day (ng/day). By comparison then, the distinction of whether or not PCBs have carcinogenic potential translates into a 2,500- to 100,000-fold difference for what is calculated as an allowable or safe level. Thus, the distinction between whether or not a chemical has carcinogenic potential has a profound impact on how the chemical is perceived by the public as well as how it might be regulated.

While we agree with the concern for and the distinction of chemicals which are carcinogens, it is the conclusion of this review that

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

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

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

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

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

There are four epidemiologic studies addressing the carcinogenetic potential of PCBs. However, the first two studies are being reconsidered and will not be addressed here. The two most recent studies have larger populations with better defined exposure records and therefore more accurately reflect PCB effects. A recently reported NIOSH study by Brown and Jones examined 2,567 workers from two capacitor plants with about half of the cohort having exposure periods of at least 20 years. There was a higher than expected incidence of rectal cancer among the workers, but the higher than normal rectal cancer rates in the geographical area in which the workers lived were not taken into consideration in the experimental design. There was also a statistically insignificant increase in liver cancer deaths. The death rates from all cancers was less than expected (39 as opposed to 43), as was the mortality from all causes. The last study by Bertazzi and coworkers, also just reported this year, examined 1,310 employees with at least six months' employment in a capacitor plant. An excess incidence of digestive cancer was observed, but there were no liver cancer deaths. Again, the total number of deaths was small. The study is continuing and these results may be considered preliminary.

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

A positive correlation between exposure to a chemical and a resultant adverse health effect relies on the following conditions: (1) a positive association must be seen in individuals with known exposures; (2) the positive association cannot be explained by bias in recording, detection, or experimental design; (3) the positive association must be statistically significant; (4) the positive association should show both dose and exposure period dependency; and (5) the positive association must be observed repeatedly in subsequent studies and cannot be a single, confounding, variable observation. To date, the mortality studies concerned with PCB exposures present several problems of interpretation, the most obvious and important of which is the different increases in cancer type reported. Taken as a whole, they provide no support for assertions that PCBs are a cancer-causing chemical. The variety of tumor sites found to be of most concern within each study largely differs from the animal data and is inconsistent with the selectivity of currently known promoting agents.

In summary, epidemiologic studies have demonstrated that commercial PCBs are not remarkably toxic chemicals after acute exposure and that when excess exposure does occur, the usual consequences are dermatologic and not of a serious or permanent nature. Chronic exposures have added little or no additional adverse effects of note to this picture. The preponderance of studies has not identified a clinical disease associated with exposure to PCBs nor has it provided persuasive evidence of health impairment. There is no evidence of an excess

in total mortality or in mortality due to cancer, cardiovascular disease, or nervous system disease associated with occupational exposure to PCBs. PCBs have not been linked to any human cancer, and studies to date indicate it is unlikely that future studies will establish such a link.

The NIOSH epidemiology study demonstrated the absence of any cancer excess among those exposed to far higher levels than the general population has received. The liver cancer rate in the United States is one of the lowest in the world and is not increasing over time. If one were observing a significant effect from PCBs, one would expect to detect a gross rate change, yet such is not the case.

Even when one makes all the conservative assumptions utilized in the official PCB cancer risk estimations, one arrives at answers which are so low as to escape our capability of detecting a positive effect via epidemiology. One must conclude that mathematical risk estimation, even for the occupationally exposed, yields estimates which are vanishingly small. The data provided by recent studies do not support the current assumptions by EPA. The EPA, in the Federal Register Notice of Availability of Draft Ambient Water Quality Criteria, estimates that the following risk to cancer from PCBs as: 10^{-5} cancer risk = 80 ng PCB/day. When this estimate is compared to the NIOSH and the FDA studies, one finds a large disparity between those results that would be predicted by this value and those that were actually measured.

The following table summarizes estimated exposures and the risk calculated based upon the EPA calculated risk at lower doses, as proposed in EPA's ambient water quality criteria document (45 FR 79320).

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

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

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