
TECHNICAL REPORT -- EXECUTIVE SUMMARY
A WEIGHT-OF-EVIDENCE EXECUTIVE SUMMARY REVIEW OF THE
HUMAN STUDIES OF THE POTENTIAL CANCER EFFECTS OF PCBs

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I. INTRODUCTION

To date, EPA has derived cancer potency factors (CPFs) for polychlorinated biphenyls (PCBs) based solely upon the results of laboratory bioassays. As discussed in this Report, this approach to assessing the potential cancer risks posed by PCBs is inconsistent with the modern risk assessment practice of using a weight-of-evidence approach to assess chemical toxicity. Although not yet applied by EPA to PCBs, the weight-of-evidence approach has been endorsed by EPA in the Agency's Proposed Guidelines for Carcinogen Risk Assessment (1996) ("*Proposed Guidelines*").

This Report provides a thorough assessment of animal studies and human epidemiological evidence relevant to determining whether PCBs cause cancer in humans. The assessment focuses on the 19 human mortality studies that sought to determine whether PCBs are associated with an increased risk of any type of cancer in humans, 21 studies that have sought an association between PCBs and human breast cancer, and two studies that have sought an association between PCB exposure and human endometrial cancer. To assure that the review would be as objective as possible, the analyses presented in this Report were performed using a formal weight-of-evidence evaluation utilizing what has become known as "*causation analysis*" to answer the ultimate question of whether exposure to PCBs causes an increased risk of human cancer. As described below, this Report concludes that the collective weight-of-evidence demonstrates that there is little credible evidence that PCBs have caused cancer in highly-exposed occupational cohorts and that there is virtually no evidence that PCBs could cause cancer in humans at environmental exposure levels.

II. EXECUTIVE SUMMARY

This Report presents an exhaustive review of the world's literature pertaining to a possible association between human environmental and/or occupational exposure to PCBs and various forms of cancer. This Report uses the principles of "*causation analysis*" to determine the strength of the evidence associating exposure to PCBs with specific cancer mortality. Causation analysis methodology is well-recognized by EPA (USEPA, 1996), as well as by the general scientific community, as a valid approach for distilling complex and diverse study results into a meaningful weight-of-evidence determination for risk assessment and risk management decisions.

The Report begins with reviews and critical analyses of the bioassays that have reported associations between high dose PCB exposure and cancer in laboratory animals, primarily rodents. These studies as a whole demonstrate that high dose exposure to commercial PCB mixtures promotes liver cancer in certain species and strains of rodents, usually in a sex-dependent manner. Although these studies support the biological plausibility that PCBs may promote liver cancer in humans, the uncertainty concerning the species, strain and sex specificity of the mechanism of the PCB-induced carcinogenicity, combined with the sometimes equivocal observations reported among the different PCB animal bioassays, raise questions regarding the extent to which the animal data fulfill the criteria of specificity of association and biological plausibility.

The Report then reviews all of the relevant human cancer studies published on or before March 30, 2000. Included are 19 cancer mortality studies, 21 breast cancer studies and 2 endometrial cancer studies. The studies have identified several cancer types as possible candidates for

association with PCBs. These cancers are: hepatobiliary cancer, malignant melanoma, rectal cancer, gastrointestinal cancer, pancreatic cancer, several hematological cancers, breast cancer, endometrial cancer, and all cancer combined.

As described in detail within this Report, the various studies differ substantially in quality and their relative contribution to the overall weight of evidence. Such factors as size of the study group, availability of PCB exposure measurements, latency period from first exposure, length and extent of follow-up, and adequacy of control for confounding factors, can all impact the overall contribution of an individual study to the weight-of-evidence assessment. The breadth and variability of the PCBs data set for humans require that risk assessment decisions be based on a total weight-of-evidence analysis, rather than relying on individual studies as conclusive or substantial evidence for an effect, to the exclusion of all others.

The Report evaluates the cancer mortality studies separately from the breast cancer (and endometrial cancer) studies. Within each section, each of the studies is evaluated to determine the extent to which the fundamental criteria for causation analysis are satisfied. The fundamental criteria are: strength of association, dose-response relationship, specificity of association, consistency of association, temporally correct association, and biological plausibility. With the exception of temporality, none of the criteria are considered necessary to establish causation. Causation (or the lack thereof) is established by the weight-of-evidence and the extent to which all six criteria are satisfied by the available data.

A. The Animal Bioassays

A number of bioassays have shown that high, chronic exposure to PCB mixtures can induce hepatic tumors in rodent species, particularly certain strains of rats. This fact had led EPA to consider PCBs as probable human carcinogens. However, there are well recognized uncertainties in extrapolating such data to humans (Squire, 1984), particularly if tumor formation is secondary to cellular changes caused by high-dose testing or involves a threshold dependent mechanism. At present, certain features of the data from the PCB animal bioassays, as well as the inconsistent findings among different studies,¹ raise questions as to the overall human relevance of the animal data. Uncertainties regarding whether the findings of the animal studies can be extrapolated to man arise from the following considerations:

- PCBs are not genotoxins, but appear to increase hepatic tumor incidence in rats via an as yet incompletely defined promotional or epigenetic mechanism. This fact portends the possibility that the animal findings might not be relevant for humans, especially if human exposures do not exceed the threshold for promotion. Several of the studies suggest there may be a threshold in animals at doses relatively close to the MTD or highest dose tested. In Mayes et al. (1998), the one study designed to provide dose-response information, the steep dose-response curves suggest that the risk of carcinogenicity may be negligible at the low exposure levels that occur from the environment.

¹ For example, although Mayes et al. (1998) reported that all Aroclor mixtures tested (i.e., 1016, 1242, 1254 and 1260) were hepatic carcinogens in female rats, earlier investigations had reported a lack of significant carcinogenicity for PCB mixtures of 42% and 54% average chlorine content (NCI, 1978; Schaeffer et al., 1984; IEHR, 1991). In addition, Mayes et al. (1998) reported that the Aroclor 1254 mixture they tested was about twice as potent as the Aroclor 1260 and 1242 mixtures they tested. Previously, only PCB mixtures with an average chlorine content of 60% (Aroclor 1260 and Clophen-A60) had yielded positive results.

- Several studies, including Mayes et al. (1998), Kimbrough et al. (1975) and NCI (1978), suggest that the tumorigenicity of PCBs is sex- and strain-dependent in some rats. Because males typically have greater capacity for oxidative metabolism, this feature raises questions for any proposed genotoxic mechanism requiring the bioactivation of PCB congeners to reactive metabolites. A sex-linked mechanism in some, but not all, rat strains also confounds extrapolation of the rat study findings to humans.
- The tumors induced in the animal studies were largely benign and the survival rates of PCB-treated animals were generally equal to or greater than those of controls. The tumors occurred relatively late in the lives of the animals, indicating a low tumorigenic potency. In addition, evidence indicates that PCB-treatment reduces the incidence of other tumors. Some studies have shown that PCB-treated animals have lower rates of nonhepatic tumors, causing the total tumor incidence of treated and untreated groups to either not differ significantly (Kimbrough et al., 1975; Schaeffer et al., 1984), or to be less in treated than untreated animals (Mayes et al., 1999). Moreover, shorter term studies indicate PCB-treatment can significantly reduce the growth of certain types of malignant tumors (Kerklivet and Kimeldorf, 1977a,b). This may explain the lack of an increase in total cancer risk and/or the increased longevity of PCB-treated animals that has been observed in some studies. When these results are considered together with the facts that PCBs are not genotoxic and that at high doses recurrent hepatotoxicity would be expected, the relevance of the animal findings to humans is questionable.

In light of these findings, the relevance of the rodent bioassays for assessing the carcinogenicity of PCBs to humans is dubious. This uncertainty raises questions regarding the extent to which the animal data fulfill the criterion of biologic plausibility, and the weight that the animal data should be given in assessing the potential for PCBs to cause cancer in humans. If no other data existed from which one could assess the human carcinogenicity of PCBs, one might be constrained to assume that PCBs may be human carcinogens. However, as discussed below, substantial additional data exist. There is a large and growing body of epidemiological information that can serve as a better basis for assessing the likely human cancer risks posed by PCBs.

B. Human Cancer Mortality Studies

Human mortality studies suggest the possibility that seven types of cancer (other than breast cancer) may be associated with exposure to PCBs: hepatobiliary cancer, malignant melanoma, rectal cancer, gastrointestinal tract cancer, pancreatic cancer, endometrial cancer, and hematological cancers. The causation criteria, as a whole, are not well satisfied for any of these endpoints.

One of the causation criteria is likely satisfied for all of the seven cancer types and another criterion may be satisfied as to one cancer type. Temporality of association is probably satisfied for all the cancer types because the study subjects were likely exposed to PCBs before onset of disease. Moreover, liver cancer, which is within the grouping of hepatobiliary cancer, may be biologically plausible because bioassays have shown that PCBs promote this type of cancer in some rodent species and strains. However, none of the epidemiological studies found that primary liver cancer was associated with PCB exposure.

Whether the remaining causation criteria are satisfied for any other cancer types is discussed below:

Consistency of Association and Specificity of Effect

As shown in the following table, the consistency of association and specificity of effect criteria are not satisfied for any of the cancer types.

Study	Cancer Type						
	Hepatobiliary Cancer	Malignant Melanoma	Rectal Cancer	Pancreatic Cancer	Hematologic Cancer	GI Tract Cancer	All Cancers
Brown and Jones (1981)			X ¹				
Brown (1987)	X						
Nicholson (1987)							
Taylor (1988)							
Kimbrough et al. (1988)							
Bertazzi et al. (1982)							X ²
Bertazzi et al. (1987)					X ³	X ⁴	X
Tironi et al. (1996)							
Loomis et al. (1997)		X					
Gustavsson et al. (1986)							
Gustavsson and Hogstedt (1997)							
Sinks et al. (1992)		X					
Yassi et al. (1994)				X			
Greenland et al. (1994)							
Hoppin et al. (2000)				X			
Zach and Musch (1982)							
Rothman et al. (1997)					X		
Bahn et al. (1976, 1977)		X					
NIOSH (1977)							X
Hardell et al. (1996)					X		

¹ In female workers at one of two plants. ² In males. ³ In females. ⁴ In males.

In the above table, studies of the same cohort are listed consecutively in bold. "Xs" indicate that the study reported a statistically significant association between exposure to PCBs and a type of cancer. Bold "Xs" indicate that the finding was not observed in a follow-up study.

As the above table indicates, there is no consistency of association or specificity of effect for any of the cancer types. Hepatobiliary cancer, rectal cancer, and gastrointestinal tract cancer were reported in only one study each. "All cancer" should be deemed to have been reported in only one cohort (studied twice) because the results reported by Bertazzi et al. (1982, 1987) were not confirmed in a third follow-up study by Tironi et al. (1996). Malignant melanoma should be deemed to have been reported in only two studies because Bahn et al. (1976, 1977) was not really a study, but rather a letter to the editor of a journal reporting on a very small (N=72) cohort of workers at a refinery who may not even have been significantly exposed to PCBs. Moreover, this finding was not reported by NIOSH (1977), which also provided mortality data for the cohort. Hematological cancer should also be deemed to have been reported in only two studies because the results of Bertazzi et al. (1987) were not confirmed on follow-up in Tironi et al. (1996). Pancreatic cancer likewise was only reported in two studies.

Strength of Association

The evidence for an association between PCB exposure and hepatobiliary cancer is very weak because this finding was reported in only one study, was based on a small number of cases (5 grouped liver/biliary/gallbladder cancer deaths observed vs. 1.9 expected), and is likely a random finding based on grouping of distinct cancers into the group "hepatobiliary cancer." Such grouping of cancer types is scientifically suspect because different cancers likely result through different mechanisms. Only one of the cancers was a primary liver cancer, the type that might be considered biologically plausible.

The strength of association for malignant melanoma is weak because none of the three studies reporting an excess of malignant melanoma adequately controlled for exposure to sunlight. One of the studies also did not control for exposure to mineral oil, a known skin carcinogen. Moreover, as noted previously, the results of Bahn et al. (1976) should be given little, if any, weight.

Strength of association is similarly weak for rectal cancer. Rectal cancer was seen in only one study with small numbers (3 rectal cancer deaths observed vs. 0.5 expected). Moreover, rectal cancer was not elevated in a follow-up study of that cohort.

Pancreatic cancer was reported associated with PCB exposure in only two studies. In one of the studies (Yassi et al., 1994), the authors did not claim that PCBs caused the cancer because the workers had little exposure to PCBs and were exposed to many different chemicals. In the other study, a small case/control study, it is likely that the higher PCB concentrations in the cancer cases resulted from, rather than caused, the disease (due to loss of fat, resulting in increased concentration of PCBs in remaining fat) (Hoppin et al., 2000).

There is also little strength in the reported association between PCB exposure and hematologic cancer. Non-Hodgkin's lymphoma (NHL) was really seen in only two studies, since hematologic cancer was not seen on follow-up in Tironi et al. (1996). Rothman et al. (1997) was a small study (N=74) in which the authors seriously questioned whether there was a causal relation between PCBs and NHL due to possible confounding and other factors. Hardell et al. (1996) was an even smaller (N=27) case/control study in which the higher PCB concentrations in the NHL cases likely resulted from, rather than caused, the disease.

There is no strength in the association between gastrointestinal tract cancer and PCB exposure because it was seen in only one study, and was not seen on follow-up.

Finally, any association between PCB exposure and “all cancers” is very weak. The elevated “all cancer” findings of Bertazzi et al. (1982) and (1987) were not seen in follow-up in Tironi et al. (1996). Moreover, NIOSH (1977) is not even a study, but rather a two paragraph reference to a small cohort of workers at a refinery who may not even have been significantly exposed to PCBs.

Dose-Response Relationship

The dose-response criterion is not satisfied for hepatobiliary cancer because this cancer type was seen in only a single study and the authors specifically noted the lack of dose-response.

There is very little data supporting a dose-response relationship for PCBs and malignant melanoma. Sinks et al. (1992) found no evidence of dose-response. Loomis et al. (1997) claimed a dose-response relationship, but the finding is very questionable because of lack of any direct measurements of PCB exposure, simultaneous exposure to a known human skin carcinogen, and failure to consider exposure to sunlight.

Rectal cancer was only observed in a single study and analysis of the data by length of employment failed to support a dose-response relationship.

Pancreatic cancer was seen in one occupational exposure study and one small case/control study. In the occupational study (Yassi et al., 1994), there was no clear evidence of dose-response and the authors did not claim that PCBs caused the cancer because the workers had little exposure to PCBs. In the case/control study (Hoppin et al., 2000), a dose-response relationship was claimed, but is doubtful because it is likely that the higher PCB concentrations in the cancer cases resulted from, rather than caused, the disease.

There is only weak evidence for dose-response with respect to hematologic cancer. Rothman et al. (1997) reported a dose-response relationship in their small study (N=74), but the authors seriously questioned a causal relationship between PCBs and NHL due to possible confounding and other factors. In Hardell et al. (1996), an even smaller (N=27) study, there was no analysis for dose-response.

Gastrointestinal tract cancer should not be considered a valid finding because the association reported by Bertazzi et al. (1987) was not seen in follow-up in Tironi et al. (1996). Moreover, Bertazzi et al. (1987) provides no evidence of dose-response because three of the six gastrointestinal tract cancer cases had very little PCB exposure.

Similarly, “all cancers” should not be considered a valid finding because the findings of Bertazzi et al. (1982) and (1987) were not seen in follow-up in Tironi et al. (1996) and because NIOSH (1977) should not be given little, if any, weight. The results reported by Bertazzi et al. (1982) were based on so few deaths (N=14) that no dose-response analysis is possible. In Bertazzi et al. (1987), seven of the 26 deceased individuals had PCB exposure for one year or less, suggesting that a dose-response relationship was not present.

A summary of how well the causation criteria are satisfied for the seven cancer endpoints in provided in the following table.

Cancer Endpoint	<u>Causation Criteria</u>					
	Consistency of Association	Specificity of Association	Strength of Association	Dose-Response	Biological Plausibility	Temporally Correct Association
Liver	No	No	No	No	Yes	Yes
Rectal	No	No	No	No	No	Yes
Pancreatic	No	No	No	No	No	Yes
Melanoma	No	No	No	No	No	Yes
Hematologic	No	No	No	No	No	Yes
GI Tract	No	No	No	No	No	Yes
All Cancers	No	No	No	No	No	Yes

C. Breast Cancer

There are 21 clinical studies that have sought associations between human body burdens of PCBs and breast cancer. Several of the early studies reported associations between PCB body burdens and breast cancer, while others did not. The studies reporting associations were generally based on fewer than 20 cases of breast cancer, their results are subject to considerable chance variation, and often known risk factors for breast cancer were not taken into account. Also, the studies investigated active cases of breast cancer where disease-induced weight loss or other metabolic changes might explain the reported association between concentrations of PCBs in the body and breast tumors. Nevertheless, reviews of the literature based on the data available up until about 1994 concluded that an association between exposure to PCBs and breast cancer was unlikely.

Several large clinical studies conducted since 1994 have not detected a statistically significant increased risk of breast cancer associated with PCBs. Many of these were prospective in design, thereby eliminating the possible confounding effect of disease-related alterations in PCB concentrations. While a few of the post-1994 studies found an association between PCBs (or select PCB congeners) and breast cancer or related conditions in some population subgroup, the results from these studies have either not been replicated or are based on a small cohort of women with invasive breast cancer, thereby casting doubt on the reported association due to the unknown effects of invasive breast cancer on PCB levels in breast tissue.

There are 20 mortality studies of occupational cohorts that were highly exposed to PCBs. None of the studies found a statistically significant association between PCB exposure and increased deaths due to breast cancer. In fact, a meta-analysis of many of the studies found that the number of deaths due to breast cancer was less than expected.

Application of the causation criteria to all of the breast cancer studies reveals that there is little credible evidence that PCBs cause this type of cancer.

Strength of Association and Consistency of Association

Twelve of the 21 clinical breast cancer studies, including six of the largest, most recent, and best-performed studies, found no association between PCB exposure and breast cancer. The nine studies that reported some association between PCBs and breast cancer in fact provide

little evidence of such an association, much less of a causal relationship, due to the limited nature of their findings and serious flaws in study design. Six of the nine studies are very small. In the majority of the nine studies it is likely that the higher PCB concentrations in the individuals with breast cancer resulted from, rather than caused, the disease. In three of the studies, the authors stated that their data were inadequate for drawing conclusions or that the weight-of-evidence does not support a link between PCBs and breast cancer. In three of the studies, the authors did not control for known breast cancer risk factors.

Finally, six of the nine studies reporting associations found associations only for certain PCB congeners, certain types of breast cancer, or certain metastases, not associations between total PCB exposure and breast cancer *per se*. There is virtually no consistency to the associations reported. None of the congeners were associated with an outcome more than once. There is no consistency in the types of cancer or metastases, or the affected populations. The reported associations are therefore likely to be chance occurrences resulting from multiple comparisons (the more comparisons that are made, the higher the likelihood that associations will appear due to chance alone). Thus, strength of association and consistency of association between PCB exposure and breast cancer is weak.

Dose-Response Relationship

The dose-response criterion is not satisfied because there is no relation between PCB exposure and increased risk of breast cancer, even at the high levels of exposure experienced by occupational cohorts. Only one clinical breast cancer study reported a marginally significant dose-response trend. Four other clinical studies which sought evidence of dose-response found no statistically significant dose-response pattern.

Temporally Correct Association

No temporally correct association has been demonstrated by the breast cancer studies because none of the studies in which PCBs were measured in blood collected prior to a diagnosis of breast cancer (i.e., in a temporally correct sequence) demonstrate any association between exposure to PCBs and increased risk of breast cancer.

Biological Plausibility

It has been postulated that PCBs could cause breast cancer by acting as "classical nongenotoxic carcinogens" or by acting as weak estrogens to cause an increase in breast cancer. The first hypothesis is not supported by the evidence. While rat studies have shown PCBs to promote liver tumors, there are no data from animal studies suggesting an increased incidence of mammary tumors.

The second hypothesis is not well supported. First, it is doubtful that exposure to exogenous estrogen increases breast cancer risk. The most obvious source of exogenous estrogen is use of oral contraceptives. A meta-analysis of a large number of epidemiological studies observed overall no increase in the risk of breast cancer for women of all ages combined who had ever used oral contraceptives.

It is even less likely that PCBs can act as weak estrogens to cause an increase in breast cancer. It has been determined that some PCB congeners act as estrogens and others act as anti-estrogens. In his review of whether organochlorines act as environmental estrogens, Safe (1995) assessed the relative estrogenic potency of the chemicals people might be exposed to

from their daily environment and determined that the net effect of one's total persistent organochlorine exposure would, if anything, be anti-estrogenic and therefore inhibit estrogen-sensitive breast cancer. Thus, it is not biologically plausible that PCBs cause breast cancer.

Specificity of Association

Since all of the studies investigating potential associations between PCBs and breast cancer were designed to address only this endpoint, the specificity of association criterion is moot.

The following table summarizes the extent to which the causation criteria are satisfied by the breast cancer studies:

Criterion	Extent Satisfied
Consistency of the association	Very Weak
Strength of the association	Very Weak
Evidence of a dose-response relationship	Not present
A temporally correct association	Not proven
Biological plausibility of the effect	Weak
Specificity of the effect	Moot

Thus, the collective weight-of-evidence is that exposure to PCBs is not a risk factor for breast cancer.

Finally, the potential association between endometrial cancer and PCBs has been studied by two investigative teams, Sturgeon et al. (1998) and Weiderpass et al. (2000). Both of these studies concluded that there was no evidence for an association between PCB exposure and endometrial cancer.

* * *

In summary, a vast body of human epidemiological literature investigating the potential link between PCB exposure and cancer has been published. These studies include both highly exposed worker populations as well as populations exposed to lesser environmental background levels. In all instances where isolated instances of cancer have been reported and putatively associated with exposure to PCBs, subsequent studies that were better designed, more appropriately controlled for potential confounders, statistically more powerful, encompassing longer latency periods, and otherwise more robust, did not confirm the original findings. Therefore, the weight-of-evidence clearly supports the conclusion that PCBs are not a human carcinogen at exposure concentrations that have been encountered in either occupational settings or from the environment.

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