

*Editorial***Understanding Population and Individual Risk Assessment: The Case of Polychlorinated Biphenyls**

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Abstract

Decisions about how to improve or protect the public health can be, and sometimes necessarily are, made on imprecise science. The regulation of potential human carcinogens in the environment entails a population-risk assessment process intended to reduce risks to less than one additional cancer in 100,000 or 1,000,000 persons. These risk assessment processes, however, may be miscommunicated or misinterpreted in the context of individual cancer risks by scientists, regulators, the lay media, and the public. This commentary will review methods for establishing a causal relationship between carcinogen exposures and cancer risk. It will use the case of polychlorinated biphenyls (PCB) as an example of how to place scientific data into the context of human exposure and cancer risk. PCBs are widespread environmental contaminants and most people have detectable levels of PCBs in their bodies. The primary source for exposure in the general population is through the diet. PCBs are carcinogens in experimental animal models, but how this information can be extrapolated to human risk remains uncertain. PCB experimental studies provide data that are used to regulate and control human exposure, although the epidemiologic evidence fails to establish PCBs as human carcinogens. Thus, what is used for population-

risk assessment may not be appropriate for individual-risk assessment or concluding that a causal relationship exists between PCB exposure and cancer risk. The hazards from a carcinogen designated by regulatory and review agencies as a "probable" human carcinogen is often misunderstood out of context about the magnitude of the risk and in what settings. How scientists communicate their results in scientific articles can strongly influence how others interpret their data. Misunderstandings from both the use of regulatory and review-agency opinions and the conclusions espoused by scientists occur in the media, among private physicians counseling their patients about cancer risk, and in the legal settings where plaintiffs seek compensation for exposure and alleged harm (or future harm). This can lead to false conclusions about what caused a cancer in a specific patient, undue anxiety about future cancer risk, inappropriate cancer screening, and attendant increased morbidity due to increased uses of the medical system and complication rates from medical procedures. The communication of research findings by scientists must be presented with caution, resisting the temptation to extrapolate, inappropriately, research data to the general population. (*Cancer Epidemiol Biomarkers Prev* 2006;15(5):830-9)

Introduction

Public health is improved by sound science. Decisions about how to improve public health can be, and sometimes necessarily are, made on imprecise science. Assumptions are made, with the recognition that data are not available. Population-risk assessment is the process used by regulators to control hazardous exposures, including for environmental and workplace carcinogens. Individual-risk assessment considers if a specific exposure has led to the development of cancer in a person, and may involve medical or legal opinions. It may also lead to future cancer screening. Interpretation of published research data drives, but does not control, the process of individual- and population-risk assessment and subsequent interpretations of causality, opinions, uses, processes, and agendas. Nonetheless, how researchers present and interpret their data can have great effect in venues outside of the scientific arena.

Both individual- and population-risk assessment begin with the determination of potential cancer causation, which considers whether a chemical can cause cancer at any dose and whether the chemical has been found to, or can, cause cancer at levels of human exposure. Several U.S. and international agencies provide opinions on the potential of an exposure to cause cancer (Table 1). Their processes used to develop the determinations are intended for controlling cancer risks in the population, for example, the Environmental Protection Agency regulates carcinogen exposure to levels that would cause no more cancers than one in 10^5 or 10^6 persons. However, these determinations are often misunderstood by scientists, medical practitioners, media, and the public, and the magnitude of the risks can be miscommunicated. Agencies may use descriptive terms for classifying a carcinogen such as "known," "probable," and "possible," where these terms can be indistinguishable to the uninformed, and the media can portray risks as though they were as high as for known human carcinogens (e.g., smoking, alcohol, and some chemotherapy). Lifetime cancer risk is about one in two for males and one in three for females, and most persons with cancer do not have identifiable risk factors (other than age). In contrast, the risks that are the concern of regulatory authorities are more on the order of magnitude of the risk for being struck by lightning: 1 in 280,000.¹ It is human nature to

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Note: The author has served as a consultant for chemical and electrical equipment manufacturers and has participated as an expert witness in litigation cases.

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¹ www.lightningsafety.com.

Table 1. Carcinogen classification for risk assessment regulatory and review authorities

Agency	Classification
Environmental Protection Agency	A—Human carcinogen; B—probable human carcinogen: B1—limited evidence from epidemiologic studies, B2—sufficient evidence from animal studies but inadequate for epidemiology; C—possible human carcinogen, limited evidence in animals; D—not classifiable, inadequate human and animal evidence, or no data available
IARC	1—Carcinogenic in humans; 2A—probably carcinogenic to humans; 2B—possibly carcinogenic to humans; 3—unclassifiable; 4—probably not carcinogenic
National Toxicology Program	K—Known to be a human carcinogen; R—reasonably anticipated to be a human carcinogen or sufficient evidence from animal studies
American Conference of Governmental Industrial Hygienists	A1—Confirmed human carcinogen: The agent is carcinogenic in humans based on the weight of evidence from epidemiologic studies; A2—suspected human carcinogen: Human data are accepted as adequate in quality but are conflicting or insufficient to classify the agent as a confirmed human carcinogen, or the agent is carcinogenic in experimental animals; A3—confirmed animal carcinogen with unknown relevance to humans; A4—not classifiable as a human carcinogen; A5—not suspected as a human carcinogen
National Institute for Occupational Safety and Health	Ca—Potential occupational carcinogen, with no further classification

seek explanations for a cancer diagnosis and to fear the disease. However, it is important that scientists properly convey risks, help focus public health strategies, and do not overstate risks; this last can lead to inappropriate anxiety and resultant overuse of screening tests.

Polychlorinated biphenyls (PCB) comprise a closely related group of synthetic chlorinated compounds manufactured in the United States under the trade name Aroclor, and elsewhere under other trade names. PCBs were used by the electrical utility industry for capacitors and transformers, but also have been used in hydraulic fluids, fluorescent light fixtures, flame retardants, inks, adhesives, carbonless copy-paper, paints, pesticide extenders, plasticizers, wire insulators, and some microscope immersion oils. During the 1970s, concern regarding the continued unrestricted use of PCBs surfaced because of their environmental persistence and toxicity data generated in experimental laboratory models. Monsanto, the manufacturer of PCBs in the United States, voluntarily halted production in 1977 and, in 1979, the Environmental Protection Agency banned further manufacture. PCBs are currently regulated by many governmental agencies as probable human carcinogens because they are carcinogenic in animal studies and not because of sufficient data in humans. There are numerous human studies of highly exposed workers that are inconsistent, and there is no consistent increase of any single tumor. Given these data, communicating cancer risks inferred from experimental animal studies in the context of what is known about human risk can be challenging. This is compounded by analogy to dioxin, where 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, which is classified by the IARC as a known human carcinogen, because dioxins and PCBs share some similar toxicological effects in laboratory studies (PCB congeners are less potent than dioxins in experimental studies). This analogy adds to the miscommunication of PCB-related risks because epidemiologic studies of dioxins provide results very different from PCBs.

Cancer Causation. The evaluation of cancer causation requires examination of multiple different types and sources of data. A cause of a specific disease event, as defined by Rothman and Greenland (1), is “an antecedent event, condition, or characteristic that was necessary for the occurrence of the disease at the moment it occurred.” They further clarify that the disease would not have occurred at all, or until sometime later, if the cause had not existed before the disease. Moreover, causality is not qualitative, but quantitative (i.e., given uncertainty and/or insufficiency of data, the determination of causality is a measurement, rather than a yes-no determination). Published guidelines exist for assessing causality, such as those proposed by Sir Austin

Bradford-Hill (2). It should be noted that although the Bradford-Hill statements are usually called criteria, Bradford-Hill himself called them viewpoints. Similar principles were used in the first Surgeon General’s Report on smoking and health, which concluded that smoking caused lung cancer in men (3). It has been argued that such criteria are difficult to apply (1), but there is an appeal for having the best possible framework to guide research agendas and study design (4, 5). Some have argued that a statistical model derived from epidemiologic observations cannot determine causation (5) and that providing the statistics is sufficient and doing more is not supportable scientifically (6). Parascandola and Weed (5) argue that a probabilistic model or one that does not require that an exposure be necessary to cause a disease (counterfactual) is the most practical approach for epidemiologists; another is a deterministic component-cause model that considers disease as a result of multiple causes, all of which occur before the disease, although in any order (4). Some models reflect a scientific perspective, whereas others are derived for public-health purposes. Whatever the model, opinions about causality are demanded by the public, patients, and the courts, so scientists must provide clear communication about the strengths and limitations of the data that provide a basis for assessing causality.

There are several different criteria to consider when evaluating the scientific literature for causality assessment and determining which studies will contribute to a conclusion regarding carcinogenicity in humans. Thygesen et al. (7) opined that the Bradford-Hill criteria were consistent with each of the different models described above, depending on the individual criterion. Herein, I argue that, although not all of the criteria are required, there are some that, if violated, would exclude the likelihood of causation; conversely, fulfilling some may not lead to a conclusion of causality without considering other criteria.

Among the most important criteria is consistency among well-done epidemiology studies (i.e., several well-designed studies lead to similar findings in different populations). No single observational study is definitive and no report is properly considered out of the context of all others, duly noting the role of chance, bias, and confounding. Further, not only should there be a consistent association across studies, the type of cancer should be the same across human studies. With only a few exceptions, chemicals exert organ-specific carcinogenic effects in humans and animals. Target organ specificity is common and biologically plausible. Exposure routes allow for greater or lesser exposure at the cellular level in the target organ (i.e., different blood flow or prevention of exposure by the blood-brain barrier). Different

tissues express different metabolizing and phase 2 proteins, such as cytochrome P450s and glutathione *S*-transferases, and have different DNA repair and apoptosis capacities. Target organ specificity is demonstrable in people who have sufficient exposures, e.g., predictable second cancer patterns following specific chemotherapy or acute myelogenous leukemia following benzene exposure. Cigarette smoke might be considered an exception, but it contains >60 human carcinogens. Alcohol may be an exception, as it increases the risk for liver, oropharyngeal, and esophageal cancers, but it, too, is a complex mixture. Although lack of consistency might not rule out the capability of a chemical to cause cancer (1), the lack of consistent human data precludes a causal relationship.

A fundamental tenet of toxicology is the dose-response relationship; greater exposure leads to more disease; studies used for cancer-causation assessments must consider dose-response relationships. Although some studies might be small and lack power, absence of a dose-response relationship is problematic for causality. If a study examines a dose-response relationship and lower exposure is associated with higher risk, an explanation of why toxicologic principles are violated is needed.

Another consideration is strength of association: Is the reported association believable (e.g., not too high or too low)? What do other studies show? Making judgments on the basis of a small study with a high-risk estimate, when larger and better-designed studies do not show the same association at similar levels of exposure, can lead to wrong conclusions. The First Surgeon General's report and Bradford-Hill argued that higher-risk estimates for an exposure were more likely demonstrating a causal relationship. However, today, we know that high-risk estimates, e.g., as reported for coffee drinking and pancreatic cancer (8), are often not correct, especially where the high prevalence of exposure does not intuitively match the low incidence of the cancer.

An evaluation of temporality considers whether the exposure sufficiently preceded the cancer to allow for latency. Positive associations reported in cohort studies that include cases with recent enrollment, or case-control studies that evaluate only recent exposures, might be the result of confounding or chance. Some studies, such as occupational studies reporting standardized mortality ratios (SMR) within an industry, helpful for understanding risks in persons with high levels of exposure, may include persons with only 1 day of exposure who develop cancer within 1 year. This is a technique commonly used to improve statistical power. For all types of cancers, it is highly unlikely that such a short time of exposure and time to cancer are indicative of an exposure-related risk.

Other criteria exist for helping to determine the potential for a chemical to cause cancer in humans: specificity, coherence among research methods (e.g., epidemiology, animal studies, cell-culture models), and analogy (do similar chemicals behave similarly?).

Regulatory and Review Agencies for Cancer Risk Assessment

Regulatory and review processes, and the conclusions derived therein, are not necessarily and directly applicable

to assessing past and future risk for individuals or groups of individuals, such as patients, and for communicating risks to individuals in a community or in litigation. These agencies are classifying agents to prioritize risk assessments; they consider population cancer risks as a probability (e.g., in thousands or millions of people) and do not provide conclusions regarding individual or small-group risks. Their conclusions are focused on protecting the public health, including the need to acknowledge that there are limitations in the scientific data and some risks might not be measurable. Their methods lead to an interpretation of data in ways that err on the side of caution. Although this is an important process to protect humans before we learn whether a chemical may cause cancer in people, these agency methods and findings are, thus, not appropriate to support a conclusion of cancer causation in a particular individual, to predict individual risk, or to decide whether the chemical is carcinogenic in humans at all. Moreover, a conclusion of possible or probable carcinogenic potential for one type of cancer in a target organ does not imply that the chemical can cause cancer in other organs.

Polychlorinated Biphenyls

Several review and regulatory agencies have considered the carcinogenic potential for PCBs (Table 2). For PCBs, in particular, no agency has, to date, determined that PCBs are human carcinogens; rather, a lower designation is given, such as probable or reasonably anticipated; the human evidence is considered insufficient to warrant a stronger qualifier. Thus, PCBs are not accorded a classification among the most potent carcinogens, such as tobacco products, asbestos, oral contraceptives, alcoholic beverages, and cancer chemotherapies.

Genotoxicity and Experimental Animal Studies. The effects of PCBs at the genetic level have been widely investigated. Overwhelming evidence shows that the PCBs are not mutagenic (9). DNA binding has been reported in some crude studies (10), although a specific nucleotide adduct has not been identified (11-15).

The target organ for PCB tumorigenicity in animals is the liver (see discussion below for initiation-promotion models). Four studies report that Aroclor 1260 induces hepatocellular carcinomas in laboratory mice and rats exposed to large doses over a lifetime (16-19). A reevaluation of published studies (20) using uniform pathologic criteria indicates that the potency of the PCB mixtures depends on the chlorination, and not all exposures should be considered equivalent. The Mayes et al. study (19) indicated that only Aroclor 1260 induced neoplasms in male rats, but Aroclor 1254, 1260, 1242, and 1016 induced neoplasms in female rodents, in that order of potency. (The actual incidence of mammary tumors was decreased; ref. 19). There are, however, many pathologic dissimilarities between experimental animal tumors induced by PCBs and human liver cancer. In spite of the morphologic appearance of cancer in animals, these lesions do not otherwise display malignant behavior. For example, animals with PCB-related tumors live longer than controls and metastases have not been shown (17, 18). It also should be noted that some methods in animal studies reduce the reliability of extrapolating to human cancer risk, such as

Table 2. Classification for PCBs and carcinogenic potential designations by review agencies

Agency	Classification
Environmental Protection Agency	B2—Sufficient evidence from animal studies but inadequate for epidemiology
IARC	2A—Probably carcinogenic to humans
National Toxicology Program	R—Reasonably anticipated to be a human carcinogen or sufficient evidence from animal studies

Table 3. Summary of selected PCB occupational studies

	Brown (61)	Tironi (62)	Loomis (59)	Kimbrough (60)	Mallin (63)	Ruder (58)
Publication year	1987	1996	1997	2003	2004	2005
No. subjects						
Males	258	594	NR*	4,062	1,178	2,817
Females	1,309	1,556	0	3,013	1,707	852
Minimal employment	3 months	7 days	6 months	3 months	1 day	1 day
Years traced	42	36	38	52	56	43
No. deaths						
Males	141	45	2,536	1,022	478	461
Females	154	47	0	632	721	86

Abbreviation: NR, not reported.

*Not reported for only the exposed workers.

exposures that are substantially higher than potential human exposure.

Laboratory animal studies also show that PCBs can act as modifying agents following exposure to known carcinogens, acting as both tumor promoters and inhibitors: PCBs have been shown to promote hepatocellular tumors and preneoplastic lesions following ingestion of *N*-nitrosamines (21-26) and azo dyes (27); lung and colon tumors following exposure to *N*-nitrosamines (28, 29) and 1-nitropyrene (30); and mammary tumors following exposure to 7,12-dimethylbenz(*a*)anthracene (31). In contrast, PCBs inhibit tumorigenesis when animals are treated before carcinogen exposure (22, 32-35). Because of this complexity, and the fact that PCBs are not multiorgan initiators, these promotion studies cannot be used to defend the hypothesis that PCBs are a multiorgan carcinogen. Thus, for both exposure to PCBs as a single agent and in tumor promotion studies, we see target-organ specificity in laboratory animals.

Absorption, Metabolism, Excretion, and PCB Body Burdens. PCBs are detectable in most people. They are absorbed through skin, lungs, and gastrointestinal tract. Dermal absorption is the major route in occupational groups (36). Ingestion is the major route for environmental exposures in the general population (37-39). The major dietary source is fish. PCBs are transported by the bloodstream mostly to adipose tissue. An equilibrium is established under which partitioning among tissues remains relatively constant for a given species. Elimination of PCBs is slow, and even low levels of absorption can lead to bioaccumulation. The input-output equation for ingestion and excretion shows the potential for bioaccumulation in humans, and this is dependent on amount of adipose and on weight changes (40). As people gain weight in later life, input-output equation for different congeners will change: Some congeners will bioaccumulate and some will be excreted. Some congeners are absorbed more efficiently than others. Older people excrete more PCBs, but this may be due to higher body burdens (41). The half-life of PCBs in humans varies by congener, shorter in experimental animals than humans ranging from 1 to 26 years (42). In a small group of occupationally exposed persons, the serum half-life was reported to be 6 to 7 months for Aroclor 1242 and ~34 months for Aroclor 1260 (43). In other studies, the half-life in workers was 1.8, 3.3, and 4.1 years for Aroclors 1242, 1254, and 1260, respectively (44, 45). The elimination rate of PCBs in the body also might be related to the body burden: Higher levels are cleared faster (42, 46). Biological half-life increases over time (47).

The measurement of PCB levels in the blood is a well-accepted method for determining exposure and body burden; it is the most frequent biomarker used. Body burdens in humans depend on many factors, including route and length of exposure, sex, age, and possibly alcohol consumption (38, 48-53). The Agency for Toxic Substances Disease Registry

Toxicological Profile for PCBs² provides data from different studies for nonoccupationally exposed persons who are not fish eaters over a 20-year period. The arithmetic means have generally been decreasing for the most recent studies. Generally, background levels for persons without obvious sources of PCB exposure are <10 ppb. The mean values reported for nonoccupationally exposed persons may vary, but these differences will be trivial in the context of worker studies; occupationally exposed persons can have PCB blood levels up to 3,300 ppb (54), typically have mean levels of >30 ppb and often >100 ppb not lipid-adjusted (52, 54, 55). In communities with demonstrable exposure to environmental PCBs, such as those surrounding PCB manufacturing plants, the mean was 14.3 ppb, with an upper level of 210 ppb (56). As noted earlier, toxicology principles argue that, if there were a measurable cancer risk from PCBs in humans, these should be observable among workers who have orders of magnitude higher levels of exposure than the general population.

Human PCB Cancer Studies. There are >40 human studies of PCB exposure and cancer risk, including persons with high occupational exposures over long periods of time (i.e., capacitor and transformer workers), evidenced by the very high blood levels and histories of PCB-related skin effects. Multiple follow-ups of some cohorts have been undertaken. There are more than six separate occupational groups where the all-cause cancer mortality has been found not to be increased and, in some cases, decreased for individual cancers (57-63). The largest occupational studies are summarized in Tables 3 and 4. Taken together, these reports fail to show consistently increased death rates either for all causes of death, cancer deaths, or any individual cause of death, when compared with the expected number for the general population.

Commonly, cohort studies investigating multiple cancer rates can find a statistically significant positive association with a particular cancer, at a rate of 5 associations per 100 examined, because of a multiple comparison issue. Thus, in the evaluation of causality, both consistency and dose-response relationships must be shown, as stated above. In the case of PCB studies, there are, indeed, individual studies reporting associations that are not replicated in other studies, but examination of Table 4 shows for any single positive association reported in a published study, the other studies (usually larger or with longer follow-up) are null.

The largest study to date assessing risks related to PCB exposure was published by Kimbrough et al. (60). There were 7,075 PCB-exposed capacitor workers studied with 235,984 person-years of observation and 1,654 deaths. The workers were studied in a number of different ways,

² <http://www.atsdr.cdc.gov/toxprofiles/tp17.html>.

providing evidence of internal consistency. The study found no associations with cancer and all cancer-combined mortality was actually decreased. This study had the most power and used a 3-month entry criteria that is more relevant for causation assessment compared with most of the other studies that included workers with shorter work times. Other advantages of this study are that it had excellent follow-up, uncontested use of large amounts of PCBs in the two plants, and classification of exposure-potential by job. Notwithstanding its advantages, limitations of this study have been noted (64-66). However, most of the limitations are generic and germane to almost all occupational studies. For example, it is opined that the healthy-worker effect obscures a statistically significant increase for cancer risk (64). But, a biological reason for the healthy-worker effect related to cancer is not apparent for studies with long length of follow-up. Nonetheless, whether a healthy worker effect exists or not, the lack of a positive association precludes a conclusion in support of causality. The Kimbrough et al. study (67) also has been criticized for exposure misclassification, but the methods are typical, or better, than most other occupational studies, and studies of workers in the same plant clearly indicate high levels of exposure (48, 55, 67). The study also allowed for subset analysis of the most highly exposed in the plants.

Coherence has been sought with animal studies of liver cancer. An initial report by Brown (61) suggested an increased risk of the combined tumors of the liver, biliary tree, and gallbladder, and other studies have examined this. The initial Brown report (61) indicated a SMR of 280 based on five observed cases and 1.9 expected cases. However, it was statistically significant only with a one-sided *P* value, and an examination of the cancers by pathology showed that one case was a metastatic cancer to the liver from a different organ and one was not pathologically confirmed. Further, four of the five cases were exposed to PCBs for <1.5 years, and three of them were exposed for <1 year. None was specifically liver cancer. Finally, the rationale for grouping these cancers was based on convenience of coding and not for biological reasons. Thus, it is highly improbable that these cases were caused by the PCB exposure. In fact, risk factors for human liver cancer are well known, and gall bladder cancer is not caused by similar factors (e.g., specific viruses and alcohol drinking). In a separate

study, Bertazzi et al. reported an SMR in men for cancer of the gastrointestinal tract of 253 [95% confidence interval (95% CI), 144-415], compared with national rates and of 274 (95% CI, 112-572) compared with local rates (68). However, there clearly was no consistent type of cancer within this category. In fact, only one case among the six was a liver cancer, and one was a biliary tract cancer. For women, there was no increase at all. Thus, the Bertazzi study does not provide supportive evidence of an increased risk for liver, biliary tree, and gallbladder cancers. Importantly, the mortality data for this same cohort were reported for an additional 10-year follow-up, in the Italian scientific literature, and there was no increased rate for the overall category of digestive system cancer (62). A recent publication by Mallin et al. (63) reported results for 2,885 capacitor workers used between 1944 and 1977; there was an SMR reported for liver, gallbladder, and biliary tree of 227 for women (95% CI, 104-431) and 260 for men (95% CI, 84-609). Among women, the risks seemed to increase with numbers of years working. This was based on nine total cancers, only one to two were liver cancers (one reported as liver cancer and the other as hepatocellular carcinoma), five gallbladder cancers, and one each cancer of the common duct and cholangiocarcinoma. In this study, the authors attempted to verify the cause of death, but were unable to do so. Importantly, four of the nine subjects worked ≤ 6 months, and one subject worked 1.3 years. Further, the authors postulate that because the plant initially used chlorinated naphthalenes, this chemical might have had a contributing role. There has been a total of eight different publications from five different worker groups, and every one other than Brown (61) and Mallin (63) was null. Indeed, Loomis et al. (59) reported a decreased risk for the relationship for the separate categories of liver, biliary passages, and gallbladder (SMR = 0.73; 95% CI, 0.57-0.93).

Another sometimes proposed causal relationship is with increased melanoma risk. The hypothesis that melanoma might be related to PCB exposure was first raised in a letter by Bahn et al. (69). Subsequently, Sinks et al. (70) reported an SMR of 4.1 (95% CI, 1.8-8.0; eight observed and two expected), with no dose response. The 4.1-fold effect is actually a huge magnitude of risk and so not believable in the context of both widespread exposure and other null studies. If this were true, an increased risk in most of the other PCB studies would have been seen. Further, three cases probably should not have been

Table 4. PCB worker studies—risk estimates

	Brown (61)	Tironi (62), male/female	Loomis (59)	Kimbrough (60), (male/female)	Mallin (63), (male/female)	Ruder (58)
No. subjects	2,588	2,150	NR*	7,075	2,885	3,643
No. deaths	295	92	2,536	1,654	1,199	547
Risk estimates (standardized to reference group = 100)						
All cancers combined	89	81/137	86	98/110	114/108	90
Liver, gall bladder, and biliary tree	280 [†]	NR (digestive system NS)	73 [†]	89/103	260/227*	51
Skin (melanoma)	NR	NR	104	124/117	83/111	243 [†]
Hematologic	46	202/141	82 [†]	NR (lymphoma 92/65; leukemia 78/74)	57/113	108
Colon	99	NR (digestive system 195/92)	93	100/153 (Rectum 100/142)	84/144	94
Kidney	NR (urinary tumors 143)	NR	0.76 [†]	117/72	1.8/1.76	0.38
Breast	102	NR	80	88	-/124	83
Non-Hodgkin's lymphoma	NR	177	77	92/65	None/153	123
Pancreas	53	NR	84	124/102	93/76	106
Thyroid	NR	NR	NR	None/222	1,522*/None	NR
Gastric	60	NR	67	104/113	225*/0.59	123
Prostate	NR	NR	89	125	107	NR

NOTE: Risk estimates revised for consistency using 100 to indicate no increased risk.

Abbreviation: NS, not statistically significant.

*Not reported as such; can be inferred as null.

[†]Statistically significantly different than 100.

included in analysis due to limited opportunity for exposure.¹ There was no dose, duration, or latency relationship. It also is unclear to what extent Sinks et al. accounted for sunlight exposure. The Sinks study has recently been updated by Ruder (58); although the risk for melanoma was still increased, the estimate has decreased to 2.4 (95% CI, 1.1-4.6). The new report had only one additional case in 14 years of additional follow-up (versus eight in the first 29 years). Importantly, there still was no dose-response relationship and the highest risk was in the lowest exposed. In a separate study, Loomis et al. (59) reported an increased relative risk for melanoma in a subgroup of workers with the greatest years of exposure and a lag period >10 years, but a dose-response relationship was not clear and the overall SMR (=1.04) was not statistically significant. A significant association was found for mechanics with 0 to 5 years of work, but not for longer work time or for workers with greater exposure. There also was no association for total career exposure. Thus, the data are not internally consistent and the sunlight exposure assessment was poor. The remainder of the literature fails to support a melanoma risk. There are many null studies and studies that must surely have examined the cancer risk for this category that were likely null, although they did not list the risk estimate in the article (57, 60-63, 68).

There has been recent attention focused on the risk of non-Hodgkin's lymphoma and PCB exposure in environmentally exposed persons. In heavily exposed workers, the largest studies examining this association of heavily exposed workers have been null or shown a decreased risk (Table 4). Loomis et al. (59) reported a decreased risk with an SMR of 0.82 (95% CI, 0.75-0.91) for neoplasms of the lymphatic and hematopoietic tissue, and an SMR of 0.77 (95% CI, 0.60-0.97) for lymphosarcoma and reticulosarcoma. Mallin et al. (63) reported no males with non-Hodgkin's lymphoma and the SMR for women was statistically nonsignificant. Other studies also have been null (57, 60). Bertazzi et al. (68) reported that women had an SMR of 377 (95% CI, 145-285) for all hematologic malignancies using local rates and a nonstatistically significant increase using national rates (SMR = 266; 95% CI not reported). These SMRs were for four cases and only one had non-Hodgkin's lymphoma. For men, there was a statistically nonsignificant increase with only three cases. The mortality data for this same cohort were reported for an additional 10-year follow-up, in Italian, and the increased rate for this category was specifically reported and found not to be statistically significantly increased (62). The focus of attention for lymphoma risk began with a report by Rothman et al. (71) who published a nested case-control study examining 74 persons with non-Hodgkin's lymphoma from a prospective cohort of 25,802 adults with a mean duration of follow-up of 12.1 years; a dose-response relationship was found between non-Hodgkin's lymphoma and lipid-corrected serum PCB concentration. The relative risk in the highest quartile was 4.1 (95% CI, 1.4-11.9). This is a very large risk and seems implausible given the rarity of this tumor in the general population and the commonality of exposure. Another environmental-exposure study also reported a positive association for lymphoma and PCB exposure using house dust samples as a surrogate for exposure, although no dose-response relationship was found (72). There were some positive associations within dose levels for the individual congeners they studied (PCBs 105, 138, 153, 170, and 180), although not with dose-response trends, except for PCB congener 180 (OR, 1.7; 95% CI, 1.1-2.6). They also found an increased risk for DDE, which suggests that the PCB relationship might be confounded. One limitation of this study might have been survival bias. They also had a high rate of refusal and unlocatability, and it has been separately reported that house dust is not a good surrogate for body burden in persons with probably environmental exposure (e.g., residents living near PCB-manufacturing plants; ref. 56). Also, as noted by the authors, carpet dust is not likely to be an important

source for PCB exposure. There also is a very small case-control study of 82 cases reporting an increased risk in persons without occupational exposure, suggesting bias as cancer cases bioconcentrate PCBs as a result of cachexia (73). An important question about these studies reporting positive associations for PCB and nonoccupational exposure is how these studies could be positive, when studies of highly exposed workers are not. Until a mechanistic reason is established for the absence of a dose-response relationship for PCBs and lymphoma, a causal association cannot be inferred. It also should be noted that Quinanta et al.'s (74) recently studied total adipose PCB levels in 175 non-Hodgkin's lymphoma cases compared with 481 controls. This study was limited in that cases and controls were mostly autopsy subjects, matched on sex, race, and residence. Nonetheless, there was no relationship to adipose tissue PCB levels and lymphoma risk.

There are other reported positive associations for non-occupationally exposed persons and cancer, which are not corroborated by large studies of highly exposed workers. These include pancreas (75) and prostate cancer (76, 77).

Among the most commonly studied cancer for PCB exposure is breast cancer. The initial interest began when Wolff et al. (78) published the report of a nested case-control study of women enrolled in the New York University Women's Health Cohort Study. They found that, in 68 cases compared with 171 matched controls from 14,290 women in a screening project, serum PCBs were borderline elevated in cases (mean difference, 1.0 ng/mL), but the paired difference was not statistically significantly different. There were several methodologic limitations to this study and almost all subsequent cohort and case-control studies have been null (79-84). In an early article, there was a positive association for PCB exposure among parous women who had never lactated (85). Subsequently, the issue of breast cancer risk in general, and for parous women who never lactated in particular, was addressed in a large pooled analysis of five studies that included the positive report (80). There was no increased risk for either. The occupational studies, as indicated in Table 4, are also null. Thus, there has been extensive investigation of a PCB-related breast cancer risk and the literature is consistently null.

Although the risk of exposure to PCBs, as they would occur from real-life exposure, has not been shown to increase breast cancer risk, there also are several studies examining risks for individual PCB congeners in blood and adipose tissue. The hypothesis is that some congeners might confer an increased risk, because PCB congeners have different toxicologic properties in experimental studies. However, this is a particularly difficult way to study PCB risks because there are intercorrelations of congener levels in the environment and the body (PCBs were manufactured as mixtures) and they covary with other lipophilic organochlorines (86, 87). Because most congeners are highly correlated (88), it is not likely that a congener-specific analysis will yield more information than total PCB levels, and more likely to provide for false positives due to multiple comparison analyses. For breast cancer, even if there is some biological plausibility that individual congeners might increase risk through a hypothesized estrogenic effect, there are other congeners that act antagonistically and could negate this effect. In fact, this probably happens more often [reviewed in ref. 89 and others (90-92)]. Synergistic effects have been studied and have not been demonstrable (89, 93). Nonetheless, there are a sufficient number of congener-specific studies that allow for the conclusion that the consistent finding in the epidemiologic literature is that individual congeners are not associated with breast cancer. A representative summary of the literature, if not all published studies, is shown in Table 5. This table shows that congener-specific analyses (blood or adipose tissue) for breast cancer risk was not any more informative than total PCB analysis. Hoyer et al.

Table 5. Selected examples of congener-specific analysis and breast cancer risk

Reference	Study design (n)	Tissue	Congener (P, NS if null)				
			99	105	118	156	126
Demers (97)	Case-control; Canada (314/523)	Serum	0.02	NS	0.03	0.006	NR
Ward (114)	Cohort; Norway (150/25,431)	Serum	0.12	0.96	0.46	0.23	0.70
Moysich (85)	Case-control (154/192)	Serum	NS	NR	NS	NS	NR
Hoyer (94)	Cohort; Denmark (240/7712)	Serum	NS	NS	NS	NS	NR
Gammon (82)	Case-control (646/429)	Serum	NR	NR	NS	NR	NR
Dorgan (95)	Cohort; Missouri (105/7224)	Serum	0.99	0.99	0.25	0.74	NR
Laden (96)	Prospective, Nurses Health (372/121,700)	Serum	NR	NR	0.66	NR	NR
Zheng (79)	Case-control (475/502)	Serum	NR	NR	NS	NS	NR
Holford (87)	Case-control (304/186)	Serum	NS	NS	NS	NS	NR
Charlier (115)	Case-control (60/60)	Serum	NR	NR	NR	NR	NR
Raaschou-Nielsen (116)	Cohort (409/409)	Serum	NS	NS	NS	NS	NR
Aronson (117)	Case-control (217/213)	Adipose	NS	NS	NS	NS	NR
Zheng (118)	Case-control (304/186)	Adipose	NS	NS	NS	NS	NR
Lilegren (119)	Case-control (43/35)	Adipose	NR	NR	NR	NR	NS

(94) reported a large and well-conducted nested case-control study within a prospective cohort of 7,712 women from the Copenhagen City Heart Study, whose blood serum was sampled 17 years earlier. There were 268 women with breast cancer. This study found no relation between total PCBs and breast cancer, or for 28 PCB individual congeners. There was clearly no dose-response relationship ($P_{\text{trend}} = 0.77$). Other cohort studies also failed to find an association with breast cancer risk and specific congeners (95, 96). This also is true for case-control studies (87). In fact, for PCB 156, an inverse association was reported (87). The exception to the bulk of the literature is a study reported by Demers et al. (97). They conducted a case-control study in Canada with 314 cases and 523 controls. Three of the 14 congeners that they measured showed a statistically significant difference between premenopausal cases and controls (PCB 99, 118, and 156, but not 105). Notably, these were not chosen *a priori* as those more likely to have an effect. As would be expected from multiple comparison analyses at least, it also has been reported that some congeners are inversely associated with breast-cancer risk (87).

Toxic Equivalency Factors

Potential PCB toxic effects are sometimes considered in relation to dioxins as a probability of cancer from mixed PCB and dioxin exposures in a population-risk assessment process (98-102). Individual congeners are assigned a toxicologic potency value in relation to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, as determined mostly by *in vitro* and sometimes experimental animal studies. There are different ways to calculate toxic equivalency factors (TEF; ref. 100). TEFs for PCBs are derived generally from noncancer end points, such as enzymatic aryl hydrocarbon hydroxylase activity in cell cultures, which is considered a surrogate for "toxic effects." In some cases, a tumor promotion assay is used, but there are no data from classic carcinogenic bioassays available to be used for calculating TEFs. (The most potent PCB by TEFs, congener 126, is not tumorigenic in a 2-year rodent bioassay; ref. 103.) For a mixture of TEF compounds, a total toxic equivalency value is calculated from the sum of the TEF times the concentration of the components. This has been considered an interim research method (100) and remains in use as such. Today, it is recognized that there are substantial limitations for the use of TEFs in population-risk assessment, and has no validation or precedent for use in individual-risk assessment (or recommendations for cancer screening and early detection). It is unknown whether the experimental studies used for the determination of TEFs can be extrapolated to humans and what is the appropriateness of these toxicologic noncancer end

points for predicting human cancer risk (195, 196). Whether the mechanistic relationship of PCBs to tumorigenesis in animals is due solely to aryl hydrocarbon hydroxylase pathways also remains speculative; non-aryl hydrocarbon hydroxylase-inducing congeners can behave as tumor promoters (104). The TEF approach assumes that there is no interspecies difference in toxicity, which is not true (105, 106), and some data show that humans are less sensitive than rodents (107). Also, enzymatic induction can vary depending on tissue and dose (108). The TEF approach assumes an additive effect and, for PCBs, this is known not to be the case, especially when the mixtures contain PCBs that are thought not to contribute to the TEF ("nondioxin-like"; refs. 98, 100, 109), and antagonists can block the effects of agonists (28, 109-111). For example, in a study of three different congeners (126, 105, and 153) in a rat tumor promotion assay using *N*-nitrosodiethylamine as the initiator, a weak antagonistic effect was seen (109). In another study, using a cell-culture model, congener 153 almost completely antagonized the effects of tetrachlorodibenzo-*p*-dioxin and PCB congener 126 had no additive effect over tetrachlorodibenzo-*p*-dioxin (110). In yet another study using altered hepatic foci as an intermediate marker for a tumor endpoint following *N*-nitrosodiethylamine exposure, there was less than an additive effect for different combinations of congeners 126 and 153, although the authors showed increasing levels of these congeners in the adipose and liver tissues (111). There also are data to show that the mixture of organochlorine compounds with high TEF particularly overestimates the promoting effects (100, 104, 110). Further, the TEF approach assumes that dose-response curves are parallel. To illustrate the limitations, Harris et al. (112) assessed actual versus calculated aryl hydrocarbon hydroxylase induction capacity based on rodent studies and estimated toxic equivalencies, respectively. The two were poorly related (calculated values overestimated the tumor-inducing effect), and the PCBs with the greatest tumorigenicity potential (Aroclor 1254 and 1260) had low toxic equivalencies. The net effect of the TEF research method is to overstate PCB toxicity (104). Nonetheless, some epidemiologists have attempted to identify a relationship for PCBs to human cancer risk, conducting a congener-specific analysis and determining risk estimates for congeners with high TEFs; the results for PCBs and lymphoma were null (113). TEFs also were applied to a breast cancer study calculating a toxic equivalency using only those congeners with statistically positive associations, although this was an arbitrary use of congener data (97). Unless new data establish the relevance of the TEF approach for cancer risk in humans, it should not be applied to understanding causality and PCB-related cancer risk. Congener-specific risk assessment should also not be applied in the clinical setting.

Perspective

There are sufficient data to indicate that PCBs are carcinogens in experimental animal studies, but how this information can be extrapolated to human risk remains uncertain. PCB experimental studies provide data that are used to regulate and control human exposure, although the epidemiologic evidence fails to establish PCBs as human carcinogens. This has been an extensively studied topic in the occupational setting, and more recently in the general population. There are reported positive associations in some studies, but the literature fails to identify a consistent target organ and the animal studies do not indicate that PCBs are multiorgan carcinogens. Some cancer relationships from environmental studies are not consistent with studies of highly exposed workers. Blood and adipose testing for total PCBs and individual congeners are reliable biomarkers of long-term exposure, and so misclassification is reduced. Molecular epidemiologic approaches, using congener-specific analysis, have failed to indicate that these will identify unique risks and, further, such approaches are problematic because humans are necessarily exposed to mixtures of congeners and not individual congeners. Weighting a toxicologic response and then adding these scores is conceptually appealing, but there are significant problems with the assignment of scores; it is questionable for population-risk assessment and irrelevant for individual risk and epidemiologic studies.

Scientists communicate research findings and their interpretation through publications. Public health advocates and governmental authorities, as well as the media and the general public, use the data to infer cancer risk for population and individuals, and rely heavily on the interpretations by the scientists. The distinction between classification of carcinogens for protecting public health through the risk assessment process, and the determination that a chemical has a high likelihood for causing cancer, is often not well understood by the public and the media. There are numerous lawsuits in the United States relating to claims regarding cancers in persons, fear of future cancer in the community, and future medical costs. The fear of cancer also leads to the misperceptions about the need for cancer screening. The misinterpretation of risks can also lead to untoward anxiety among individuals and communities. The PCB literature exemplifies how the same scientific data can be used differently in various venues, where a human cancer risk suggested by experimental animal data is not borne out by human studies. Most importantly, these risks should be placed into the context of known risk factors for cancer.

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