Assessing the Cancer Risk from Environmental PCBs

Vincent James Cogliano

U.S. Environmental Protection Agency, National Center for Environmental Assessment, Washington, D.C. 20460 USA

A new approach to assessing the cancer risk from environmental polychlorinated biphenyls (PCBs) considers both toxicity and environmental processes to make distinctions among environmental mixtures. New toxicity information from a 1996 cancer study of four commercial mixtures strengthens the case that all PCB mixtures can cause cancer, although different mixtures have different potencies. Environmental processes alter PCB mixtures through partitioning, chemical transformation, and preferential bioaccumulation; these processes can increase or decrease toxicity considerably. Bioaccumulated PCBs are of greatest concern because they appear to be more toxic than commercial PCBs and more persistent in the body. The new approach uses toxicity studies of commercial mixtures to develop a range of cancer potency estimates and then considers the effect of environmental processes to choose appropriate values for representative classes of environmental mixtures. Guidance is given for assessing risks from different exposure pathways, less-than-lifetime and early-life exposures, and mixtures containing dioxinlike compounds. *Key words*: bioaccumulation, cancer, mixtures, partitioning, PCBs, persistence, polychlorinated biphenyls, risk assessment. *Environ Health Perspect* 106:317–323 (1998). [Online 13 May 1998]
http://ehpnet1.niehs.nih.gov/docs/1998/106p317-323cogliano/abstract.html

Twenty years after their manufacture was halted, polychlorinated biphenyls (PCBs) remain a major environmental concern. Standards often have been based on cancer risk, yet before 1996 only commercial mixtures with 60% chlorine had been adequately tested. Different assumptions were made for other mixtures: sometimes all PCB mixtures were considered carcinogenic and sometimes only mixtures with high chlorine content. A quantitative potency estimate derived from mixtures with 60% chlorine was applied to any PCB mixture regarded as carcinogenic. The overlapping compositions of different mixtures (Table 1) show the problem with treating all mixtures the same or creating a false dichotomy of carcinogenic and noncarcinogenic mixtures.

New information is making possible a more rational approach for distinguishing among PCB mixtures. A recent study compared the cancer potential of the commercial mixtures Aroclors 1016, 1242, 1254, and 1260 (*1*). Its results strengthen the case that all PCB mixtures can cause cancer, although different mixtures have different potencies. Potency is also affected by the environmental processes that alter PCB mixtures. These processes diminish the similarity of environmental mixtures to commercial mixtures and can markedly increase or decrease a mixture's toxicity.

As the Aroclor comparisons became available, the EPA developed a new approach to assessing the cancer risk from environmental PCBs, considering both toxicity and environmental processes (*2*). A range of estimates now characterizes the potency of different mixtures, and information on environmental processes is used to choose appropriate values for representative classes of environmental mixtures. There is also guidance for assessing different exposure pathways, less-than-lifetime and early-life exposures, and mixtures containing dioxinlike compounds. The use of several kinds of information fulfills the intent of the EPA's proposed cancer guideline revisions (*3*) as well as the instruction of the EPA's mixture guidelines (*4*) to consider mixture composition. The new approach was reviewed by a panel of independent experts on the carcinogenicity of PCBs at a public peer review workshop (*5*).

Summary of Cancer Evidence for PCBs

Four commercial PCB mixtures, Aroclors 1016, 1242, 1254, and 1260, have been tested in rats for their potential to cause cancer. All mixtures induced liver tumors when fed to female rats; Aroclor 1260 also induced liver tumors in male rats (*1*). Several of these tumors were hepatocholangiomas, a rare biliary tract tumor seldom seen in control rats. These mixtures contain overlapping groups of congeners that, together, span the range of congeners most often found in environmental mixtures. Previously, lifetime dietary exposure to commercial mixtures with 60% chlorine induced liver tumors in three rat strains (*6–9*). Although many of these tumors were benign, sequential morphologic analyses have demonstrated the eventual progression of the benign liver lesions to malignant carcinomas (*8*). Commercial mixtures with 54% chlorine induced gastrointestinal tumors (*10–12*). Less-than-lifetime dietary exposure to commercial mixtures with 42–60% chlorine induced precancerous liver lesions in rats and mice (*13–18*).

Epidemiologic studies have reported similar tumor sites, although the same specific response was not seen across all studies. Capacitor manufacturing workers exposed to a series of commercial mixtures with 41–54% chlorine had increased mortality from liver, gall bladder, and biliary tract cancers (*19*), gastrointestinal tract cancers (*20*), or malignant melanoma (*21*). An analysis of these and a smaller study (*22*) found the combined results significant for liver, gall bladder, and biliary tract cancers and for malignant melanoma (*23*). Earlier, petrochemical refinery workers exposed to Aroclor 1254 and other chemicals had significantly increased mortality from malignant melanoma (*24*). More recently, electric utility workers exposed to PCBs had significantly increased mortality from malignant melanoma and brain cancer (*25*). Recent case–control studies have found a significant association between non-Hodgkin's lymphoma and PCB concentrations in adipose tissue (*26*) and serum (*27*). In a general population, dietary consumption of rice oil accidentally contaminated with PCBs and chlorinated dibenzofurans, which can be formed when PCBs are heated above 270°C (*28*), was associated with significantly increased mortality from liver cancer and lung cancer (*29*).

Mechanistic studies have demonstrated tumor-promoting activity in liver or lung

Address correspondence to V.J. Cogliano, U.S. Environmental Protection Agency, 401 M Street, SW (8623-D), Washington, DC 20460 USA.
The author gratefully acknowledges the contributions of all who commented on the EPA's assessment, including the peer review panel and many scientists in the EPA's program, regional, and research organizations. Their efforts truly improved the final product.
The views expressed in this paper are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.
Received 22 May 1997; accepted 9 February 1998.

from Aroclor 1254 and some congeners with four to six chlorines: tetrachlorobiphenyl congeners PCB-47, -49, -52, and -77 [International Union of Pure and Applied Chemistry (IUPAC) numbering]; pentachlorobiphenyl congeners PCB-105, -118, and -126; and the hexachlorobiphenyl congener PCB-153 (*30*). Toxicity of some congeners is correlated with induction of mixed-function oxidases: some congeners are phenobarbital-type inducers, some are 3-methylcholanthrene-type inducers, and some have mixed inducing properties (*31–33*). The latter two groups most resemble chlorinated dibenzo-*p*-dioxins and dibenzofurans in structure and toxicity (*33,34*). These congeners contributing to cancer induction can be present in mixtures with either high or low chlorine content (Table 1).

PCBs are absorbed through ingestion, inhalation, and dermal exposure, after which they are transported similarly through the circulation (*35*), providing a reasonable basis for expecting similar internal effects from different exposure routes. Quantitatively, dermal exposure poses lower risks because PCBs are substantially but incompletely absorbed through the skin (*36–39*).

Recent research is suggesting mechanisms by which PCBs can contribute to cancer at other sites. One experiment raises concern for PCBs of low chlorine content, finding that dihydroxy metabolites of PCBs with low chlorine content are activated to reactive intermediates that produce oxidative DNA damage (*40*). These results provide a possible mechanism to support the hypothesis that environmental PCBs may contribute to human breast cancer. Among the case–control studies of non-Hodgkin's lymphoma, one study found an association with both dioxinlike and nondioxinlike congeners (*26*), and the other found a multiplicative interaction with seropositivity for the Epstein-Barr virus early antigen (*27*). Because PCBs suppress the immune system and immunosuppression is an established risk factor for non-Hodgkin's lymphoma, immune system suppression may be a possible mechanism for PCB-induced cancer. Other research has associated both dioxinlike and nondioxinlike congeners with toxicity due to endocrine disruption (*41,42*).

Table 1. Typical composition of some commercial PCB mixtures

	Aroclor 1016	Aroclor 1242	Aroclor 1248	Aroclor 1254	Aroclor 1260
Mono-CBs	2	1	–	–	–
Di-CBs	19	13	1	–	–
Tri-CBs	57	45	21	1	–
Tetra-CBs	22	31	49	15	–
Penta-CBs	–	10	27	53	12
Hexa-CBs	–	–	2	26	42
Hepta-CBs	–	–	–	4	38
Octa-CBs	–	–	–	–	7
Nona-CBs	–	–	–	–	1
Deca-CB	–	–	–	–	–
PCDFs (ppm)	ND	0.15–4.5	NR	0.8–5.6	0.8–5.6
Chlorine content	41	42	48	54	60
Production, 1957–1977	13	52	7	16	11

Abbreviations: PCB, polychlorinated biphenyl; CBs, chlorinated biphenyls; PCDFs, polychlorinated dibenzofurans; ND, not detected; NR, not reported. Values shown are percent of weight except where noted.
Data from Silberhorn et al. (*30*), the Agency for Toxic Substances and Disease Registry (*35*), and Brown et al. (*43*).

Table 2. Reported composition of commercial mixtures tested in the 1996 rat study

	Aroclor 1016	Aroclor 1242	Aroclor 1254	Aroclor 1260
Mono-CBs	0.83	0.08	–	–
Di-CBs	17.64	14.48	0.12	0.15
Tri-CBs	54.98	42.83	0.66	0.48
Tetra-CBs	25.84	33.49	19.67	2.41
Penta-CBs	0.69	6.64	45.33	11.96
Hexa-CBs	0.01	1.70	31.38	39.28
Hepta-CBs	–	0.10	2.76	36.38
Octa-CBs	–	0.01	0.07	7.67
Nona-CBs	–	–	0.02	1.59
Deca-CB	–	–	–	0.07
PCB-77 (3,3′,4,4′-TetraCB) (ppm)	66.0	3340.0	918.0	31.0
PCB-126 (3,3′,4,4′,5-PentaCB) (ppm)	0.95	44.0	134.3	0.0
PCB-169 (3,3′,4,4′,5,5′-HexaCB) (ppm)	0.0	0.0	1.52	0.0
PCDFs (ppm)	0.05	2.2	0.13	5.5
TEQ from PCBs (ppm)	0.14	8.1	46.4	7.1
TEQ from PCDFs (ppm)	0.002	0.1	0.01	0.08

Abbreviations: CBs, chlorinated biphenyls; PCB, polychlorinated biphenyl; PCDFs, polychlorinated dibenzofurans; TEQ, toxic equivalent. Values shown are molecular percent except where noted.
Data from Brown et al. (*43*).

Differences in Cancer Potential of Commercial PCB Mixtures

The recent study comparing Aroclors 1016, 1242, 1254, and 1260 (*1*) provides the best information for distinguishing the cancer potential of different mixtures. Composition of the tested mixtures was reported by homologues, plus three dioxinlike congeners and total chlorinated dibenzofurans (Table 2; compare with Table 1). Prior to the study, the polychlorinated dibenzofurans were removed from the Aroclor 1254 fed to the rats because of "unusually high" dibenzofuran concentrations (*43*). Despite this pretreatment, the resulting mixture was reported to have double the usual dioxin toxic equivalents (*43*).

Concentrations of the three dioxinlike congeners reported lie within the historical range. One historical analysis found each of these congeners below 500 ppm in each Aroclor, except for 4500 ppm PCB-77 in Aroclor 1242 and 500 ppm PCB-169 in Aroclor 1260 (*44*). Another analysis found 2700–3300 ppm PCB-77 in Aroclor 1242, 300–2000 ppm PCB-77 in Aroclor 1254, and up to 200 ppm PCB-126 in Aroclor 1254 (*45*). In sharp contrast, however, an earlier analysis found 15,900 ppm PCB-126 in Aroclor 1260 (*35,46*). These and other variations provide evidence of significant lot-to-lot variability among similar mixtures. Striking lot-to-lot differences have been found for Aroclors 1248 and 1254, due primarily to numerous congeners with four to six chlorines being created and altered during the chlorination process by which Aroclors are manufactured, and also to differences in the chlorination processes that can be used (*45*). These lot-to-lot differences highlight the importance of characterizing and reporting mixture composition, both in toxicity testing and in environmental samples.

In the recent cancer study (*1*), groups of 50 male or female Sprague-Dawley rats were fed diets with 50, 100, or 200 ppm Aroclor 1016; 50 or 100 ppm Aroclor 1242; or 25, 50, or 100 ppm Aroclor 1254

or 1260. There were 100 controls of each sex. Exposure began when the rats were 6–9 weeks old, and the animals were killed 104 weeks later. Complete histopathologic evaluations were done for control and high-dose groups; for low- and mid-dose groups, evaluations were done for liver, brain, mammary gland, and male thyroid gland. Statistically significant increased incidences of liver tumors were found in female rats for all Aroclors and in male rats for Aroclor 1260 (Table 3). Fewer than a quarter of the tumors were malignant, but the proportion of tumors that were malignant increased with dose. In female rats, Aroclor 1254 appeared most potent, followed by Aroclors 1260 and 1242, with Aroclor 1016 markedly less potent. In male rats, only Aroclor 1260 caused liver tumors.

To investigate tumor progression after exposure stops, this same study exposed groups of 24 female rats for 52 weeks; exposure was then discontinued for an additional 52 weeks before the rats were killed. For 52 weeks exposure to Aroclors 1242 or 1254, tumor incidences were approximately half those for 104 weeks exposure, that is, nearly proportional to exposure duration. In contrast, there were no tumors from 52 weeks exposure to Aroclor 1016, while for Aroclor 1260 incidences were generally greater than half those for 104 weeks exposure (Table 4). For 100 ppm Aroclor 1260, the incidence from 52 weeks exposure was greater than that from 104 weeks, 71 and 48%, respectively.

Different patterns may hold for other cancers. In the study just described (*1*), thyroid gland follicular cell adenomas or carcinomas were increased in males for all Aroclors, and statistically significant trends were noted for Aroclors 1242 and 1254. The increases did not continue proportionately above the lowest dose, and no thyroid trends were apparent in females.

Modeling Results for Commercial PCB Mixtures

Under the EPA's proposed cancer guideline revisions (*3*), dose–response assessment first considers developing a biologically based model, that is, one whose mathematical structure reflects the ascertained mode of action and whose parameters are experimentally measured. Few PCB congeners or mixtures, however, have been tested to measure the rate parameters that would be used in a biologically based model. Consequently, the information available at this time is more suited to empirical modeling, in which a flexible default model—allowing either linearity or nonlinearity—is fitted to describe tumor incidence as a function of dose in the experimental range.

The EPA's new assessment (*2*) fitted a linear-quadratic dose–response model [that is, a model of the form $P(d) = 1\text{-}\exp(-q_1 d - q_2 d^2)$, where $P(d)$ is the probability of response at dose d, and q_1 and q_2 are parameters] to the liver tumor incidences in female Sprague-Dawley rats fed Aroclors 1016, 1242, 1254, or 1260 (Table 3). Dose was expressed as a lifetime daily average, calculated from weekly body weight measurements and food consumption estimates. Doses were scaled to humans using a factor based on the three-fourths power of relative body weight (*3*). Response was taken as the incidence of hepatocellular adenomas or carcinomas. Combining adenomas and carcinomas reflects the guidance of the National Toxicology Program (*47*) and the progression of hepatocellular adenomas to carcinomas in female Sprague-Dawley rats (*8*). To reflect lot-to-lot variability among similar mixtures, the EPA also modeled earlier results in female Sprague-Dawley rats fed from a different lot of Aroclor 1260 (Table 5).

In the experimental range, the EPA described the cancer potency of each mixture by an estimated dose associated with 10% increased incidence (ED_{10}) and its 95% lower confidence bound (LED_{10}), expressed as equivalent human doses (Table 6). ED_{10}s have been used both for potency ranking and as a starting point for low-dose extrapolation (*48,49*). The EPA recently proposed using an LED_{10} for these purposes, while inviting public comment on the alternative of using 1% for tumor responses (*3*).

To gauge the potential risk at environmental exposure levels, the EPA extrapolates to doses below the experimental range. Extrapolation considers both linear and nonlinear approaches, with a linear default if there is not sufficient information to support a sublinear model (*3*). This policy rests, in part, on some general considerations. Low-dose linear models are appropriate when a carcinogen acts in concert with other exposures and processes leading to a background incidence of cancer (*50,51*).

Table 3. Liver tumor[a] incidences from the 1996 rat study

Mixture	Dose (ppm)	Females	Males
Aroclor 1260	Control[b]	1/85 (1%)*	7/98 (7%)*
	25	10/49 (20%)	3/50 (6%)
	50	11/45 (24%)	6/49 (12%)
	100	24/50 (48%)	10/49 (20%)
Aroclor 1254	Control[b]	1/85 (1%)*	7/98 (7%)
	25	19/45 (42%)	4/48 (8%)
	50	28/49 (57%)	4/49 (8%)
	100	28/49 (57%)	6/47 (13%)
Aroclor 1242	Control[b]	1/85 (1%)*	7/98 (7%)
	50	11/49 (24%)	1/50 (2%)
	100	15/45 (33%)	4/46 (9%)
Aroclor 1016	Control[b]	1/85 (1%)*	7/98 (7%)
	50	1/48 (2%)	2/48 (4%)
	100	6/45 (13%)	2/50 (4%)
	200	5/50 (10%)	4/49 (8%)

Data from Brunner et al. (*1*), and reported by the EPA (*2*).
[a]Hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in rats alive when the first tumor was observed.
[b]One control group supported all experiments.
*Statistically significant ($p<0.05$) by Cochran-Armitage trend test.

Table 4. Liver tumor[a] incidences in female rats from less-than-lifetime exposure

Mixture	Dose (ppm)	Less-than-lifetime[b] exposure	Lifetime[c] exposure
Aroclor 1260	Control[d]	1/85 (1%)*	1/85 (1%)*
	25	4/24 (17%)	10/49 (20%)
	50	3/24 (12%)	11/45 (24%)
	100	17/24 (71%)	24/50 (48%)
Aroclor 1254	Control[d]	1/85 (1%)*	1/85 (1%)*
	25	5/24 (21%)	19/45 (42%)
	50	7/24 (29%)	28/49 (57%)
	100	6/24 (25%)	28/49 (57%)
Aroclor 1242	Control[d]	1/85 (1%)*	1/85 (1%)*
	50	3/24 (12%)	11/49 (22%)
	100	6/24 (25%)	15/45 (33%)
Aroclor 1016	Control[d]	1/85 (1%)	1/85 (1%)*
	50	0/24 (0%)	1/48 (2%)
	100	0/24 (0%)	6/45 (13%)
	200	0/24 (0%)	5/50 (10%)

Data from Brunner et al. (*1*), and reported by the EPA (*2*).
[a]Hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas.
[b]Dosed for 52 weeks and killed after 104 weeks.
[c]Dosed for and killed after 104 weeks (from Table 3).
[d]One control group supported all experiments.
*Statistically significant ($p<0.05$) by Cochran-Armitage trend test.

Table 5. Liver tumor[a] incidences from the Norback rat study

Mixture	Dose	Females	Males
Aroclor 1260	Control	1/45 (2%)*	0/31 (0%)
	100/50/0 ppm[b]	41/46 (89%)	5/40 (12%)

Data from Norback and Weltman (*8*), reevaluated by Moore et al. (*9*).
[a]Hepatocellular adenomas or carcinomas.
[b]Dosing was decreased after 16 and 24 months.
*Statistically significant ($p<0.05$) by Fisher exact test.

Table 6. Human potency estimates (mg/kg/day) derived from liver tumors in female Sprague-Dawley rats

Mixture	ED_{10}	LED_{10}	Reference
1016	2.4	1.4	(1)
1242	0.38	0.27	(1)
1254	0.086	0.067	(1)
1260	0.24	0.19	(1)
1260	0.062	0.046	(8)

Abbreviations: ED_{10}, estimated dose associated with 10% increased incidence; LED_{10}, 95% lower confidence bound on an ED_{10}.
Data from the EPA (2).

Moreover, even when the mode of action indicates a nonlinear dose–response curve in homogeneous animal populations, the presence of genetic and lifestyle factors in a heterogeneous human population tends to make the population dose–response curve more linear (51). This is because genetic and lifestyle factors contribute to a wider spread of human variability, which extends and straightens the dose–response curve over a wider range. Although these considerations provide a reasonable argument for a model that is linear at low doses, the relation of the low-dose slope to one from the experimental range is uncertain, an uncertainty that increases with distance below the experimental range.

For PCBs, genetic activity testing is generally negative (35), raising the possibility of a sublinear dose–response curve. At the low end of the experimental range (25–50 ppm), however, dose–response curves are not sublinear for Aroclors 1242, 1254, and 1260 (Table 3). Below the experimental range, some PCB congeners add to the considerable background of human exposure to dioxinlike compounds and augment processes associated with dioxin toxicity, providing a linear component to the dose–response curve. There is also considerable background exposure to nondioxinlike congeners, so additional PCB exposure can augment other carcinogenic processes that may be operating. Lacking a dose range in which a sublinear dose–response curve has been observed, the information available at this time is more suited to linear extrapolation.

Extrapolation below the ED_{10} follows a line with slope $0.10/ED_{10}$. An upper bound on the slope is $0.10/LED_{10}$. (Note that slopes are inversely proportional to ED_{10}s; high potency is indicated by high slopes but low ED_{10}s.) Slope estimates can be multiplied by lifetime average daily dose estimates (in milligrams per kilogram body weight per day) to obtain a plausible upper bound on the increased cancer risk. The slope estimates (Table 7) reflect experimental uncertainty and lot-to-lot variability of commercial mixtures, but not human heterogeneity or differences between commercial and environmental mixtures. Environmental processes have profound effects that can increase or decrease toxicity, so an Aroclor tested in the laboratory is not necessarily the best surrogate for assessing that Aroclor as altered in the environment.

Table 7. Human slope estimates (per mg/kg/day)

Mixture	Central slope	Upper-bound slope	Reference
1016	0.04	0.07	(1)
1242	0.3	0.4	(1)
1254	1.2	1.5	(1)
1260	0.4	0.5	(1)
1260	1.6	2.2	(8)

Data from the EPA (2).

Environmental Alteration of PCB mixtures

In the environment, PCBs occur as mixtures whose compositions differ from the commercial mixtures. This is because after release into the environment, mixture composition changes over time through partitioning, chemical transformation, and preferential bioaccumulation.

Partitioning refers to processes by which different fractions of a mixture separate into air, water, sediment, and soil. PCBs adsorb to organic materials, sediments, and soils; adsorption tends to increase with chlorine content of the PCBs and organic content of the other material (52). PCBs can volatilize or disperse as aerosols, providing an effective means of transport in the environment (52). Congeners with low chlorine content tend to be more volatile and also more soluble in water (52). Vaporization rates and water solubility of different Aroclors and individual congeners vary over several orders of magnitude (53,54).

Chemical transformation can occur through biodegradation of PCB mixtures in the environment. Anaerobic bacteria in sediments can selectively remove chlorines from *meta* and *para* positions, appearing to reduce the toxicity and bioaccumulation potential of residues; the occurrence and extent of these dechlorinations can be limited by sediment PCB concentrations (55–57). Dechlorination is not synonymous with detoxication, as congeners having carcinogenic activity can be formed through dechlorination. Aerobic bacteria can remove chlorines from PCBs with low chlorine content and break open the carbon rings through oxidation (55). PCBs with higher chlorine content are extremely resistant to oxidation and hydrolysis (52). Photolysis can slowly break down congeners with high chlorine content (52). Overall, however, dechlorination processes are slow, and altered PCB mixtures persist in the environment for many years.

Preferential bioaccumulation occurs in living organisms. PCBs are highly soluble in lipids and are absorbed by fish and other animals. Rates of metabolism and elimination are slow and vary by congener (58). Each species in the food chain retains persistent congeners that prove resistant to metabolism and elimination (59). Bioaccumulation through the food chain tends to concentrate congeners of higher chlorine content, producing residues that are considerably different from the original Aroclors (59–61). PCB residues in fish and turtles, changed through environmental or metabolic alteration, cannot be characterized by Aroclor 1242, 1248, 1254, or 1260 standards (60). Congener distributions in several species, including humans, do not resemble any Aroclor (33).

In humans, too, bioaccumulated PCBs also appear to be more persistent in the body (62). This is significant because in animals bioaccumulated PCBs appear to be more toxic than Aroclors (63). A study comparing mink fed a given quantity of Aroclor 1254 with mink fed Great Lakes fish contaminated with one-third that quantity of bioaccumulated PCBs (plus other chemicals) found similar liver and reproductive toxicity (64).

Assessing Risks from Environmental PCBs

Consensus has emerged on the fallacy of assessing environmental PCBs as if they were Aroclors. Safe (34) wrote, "Regulatory agencies and environmental scientists have recognized that the composition of PCBs in most environmental extracts does not resemble the composition of the commercial products." When assessing risks from environmental PCBs, the EPA now considers how environmental processes alter mixture composition (2).

Through partitioning, different portions of a PCB mixture are encountered through each exposure pathway. The mixture fraction that adsorbs to sediment or soil tends to be higher in chlorine content and persistence than the original mixture; it also tends to be less inclined to metabolism and elimination and, thus, higher in persistence and toxicity. (Persistence is not synonymous with toxicity; however, in the absence of testing of most congeners, it is reasonable to assume some correlation between persistence and toxicity.) Consequently, ingesting contaminated sediment or soil or inhaling contaminated dust can pose relatively high risks. On the

other hand, the mixture fraction that dissolves in water or evaporates into air tends to be lower in chlorine content and persistence, so risks from ingesting water-soluble congeners or inhaling evaporated congeners would tend to be lower, in the absence of contaminated sediment or dust.

Preferential bioaccumulation can have even more pronounced effects, as each species in the food chain retains persistent congeners that prove resistant to metabolism and elimination. Bioaccumulated PCBs appear to be more toxic than Aroclors and more persistent in the body. The Aroclors tested in laboratory animals were not subject to prior selective retention of persistent congeners through the food chain. For exposure through the food chain, therefore, risks can be higher than those estimated in this assessment.

To reflect these environmental processes, the EPA now provides a tiered approach that considers how partitioning and bioaccumulation affect each exposure pathway or situation. Three tiers are provided:

- High risk and persistence (upper-bound slope, 2 per mg/kg/day; central-estimate slope, 1 per mg/kg/day). The highest slope from Table 7 is used for pathways in which environmental processes tend to increase risk: food chain exposure, sediment or soil ingestion, dust or aerosol inhalation, exposure to dioxinlike, tumor-promoting, or persistent congeners, and early-life exposure (all pathways and mixtures).
- Low risk and persistence (upper-bound slope, 0.4 per mg/kg/day; central-estimate slope, 0.3 per mg/kg/day). A lower slope is appropriate for pathways in which environmental processes tend to decrease risk: ingestion of water-soluble congeners and inhalation of evaporated congeners. Dermal exposure is also included because PCBs are incompletely absorbed through the skin; however, if an internal dose has been calculated by applying an absorption factor to reduce the external dose, then the highest slope would be used with the internal dose estimate.
- Lowest risk and persistence (upper-bound slope, 0.07 per mg/kg/day; central-estimate slope, 0.04 per mg/kg/day). The lowest slope from Table 7 is used when congener or homologue analyses verify that congeners with more than four chlorines comprise less than one-half percent of total PCBs.

The key finding supporting the lowest tier is the lower potency of Aroclor 1016 compared with 1242 (Table 3). Though these mixtures have similar chlorine content, Aroclor 1016 has virtually no congeners with more than four chlorines (Table 1). Thus, the lowest slope, derived from the Aroclor 1016 study, is appropriate only for mixtures free of congeners with more than four chlorines.

The key assumption supporting lower-tier risks for water-soluble or evaporated congeners is that partitioning has reached equilibrium. Congener or homologue analysis of environmental samples can verify whether equilibrium has been achieved. For example, if water samples contain congeners of high chlorine content, this could indicate a continuing release into the environment, a recent release without sufficient time to partition as expected, a past release with high chlorine content, or the presence of stirred-up sediment with adsorbed congeners of high chlorine content. Judgment should be used to choose a higher slope in these situations.

Because the potency range for Aroclors (Tables 6 and 7) can underestimate the range for environmental mixtures, congener analysis can be an important tool in risk assessment, providing information on the presence in environmental samples of specific congeners that contribute to cancer induction. When concentrations of dioxinlike congeners are available, risk estimates can be refined using toxic equivalency factors developed for dioxinlike PCB congeners (*65*); the EPA provides an example of this (*2*). Congener analysis can also reveal composition changes for persistent or tumor-promoting congeners that are not dioxinlike. Among these, PCB-153 (2,2′,4,4′,5,5′-hexachlorobiphenyl) is of particular interest, as it shows tumor promoting activity, is highly persistent, and comprises 12 and 21% of PCBs in human milk and fat, respectively (*33*).

Early-life exposure is treated with special concern because of the potential for higher exposure during pregnancy and nursing (*66,67*) and the possibility of greater perinatal sensitivity. Metabolic pathways are not fully developed in human infants; for example, some nursing infants receive a steroid in human milk that inhibits the activity of glucuronyl transferase, reducing PCB metabolism and elimination (*68*). In animals, Aroclor 1260 induced high incidences of liver tumors when exposure began early in life and lasted a short time (*18*). Perinatal exposure to polybrominated biphenyls enhanced susceptibility to liver tumors in female rats also exposed as adults and in male and female mice not further exposed (*69*). It is, therefore, important to assess early-life exposure through human milk and other pathways.

For less-than-lifetime exposure, current practice typically assumes that effects are proportional to exposure duration, yet there is evidence that cancer risks can be higher for persistent mixtures. Tumor incidences in rats from 52 weeks exposure to Aroclor 1260 were comparable to those from lifetime exposure (Table 4). This confirms earlier findings that some PCBs persist in the body and retain biological activity after exposure stops (*70*). Thus, current practice can underestimate risks from persistent mixtures.

Some Implications and Research Needs

The EPA's new approach highlights how environmental processes—partitioning, chemical transformation, and preferential bioaccumulation—alter the cancer potential of environmental mixtures. Bioaccumulated mixtures are of greatest concern because they appear to be more toxic than commercial mixtures and more persistent in the body. Two highly exposed populations are exposed to bioaccumulated mixtures. One is nursing infants, for whom average intake of total PCBs was estimated at 1.5–27 μg/kg/day (*35*), 3–11 μg/kg/day (*46*), or 2.1 μg/kg/day (*71*), compared to 0.2 μg/kg/day estimated for adults (*46,71*). Dietary intake varies widely, often depending on proximity to where PCBs were released into the environment (*35,46*). This gives rise to another highly exposed population: people who derive much of their diet from local sources that happen to be contaminated, for example, subsistence anglers and their families who frequently eat fish from a contaminated source.

One prominent research need is a cancer study comparing commercial and bioaccumulated mixtures. The EPA's assessment warns that risks from exposure through contaminated food can be underestimated, but the extent is not quantified. Also needed is a method for using lifetime studies to assess risks from less-than-lifetime exposure to persistent agents. The EPA's assessment warns that assuming risk and exposure duration are proportional can underestimate risks from persistent mixtures, but the extent is not quantified. For persistent agents, delivered dose might be a better dose metric than the lifetime average daily dose.

The next question is how environmental processes alter the potential for noncancer toxicity and adverse ecological effects. This requires a separate analysis, as different sets of congeners may be associated with cancer and other effects. Characterizing the effects of environmental processes can improve assessments of these other effects. The same may be true when assessing complex environmental mixtures other than PCBs.

Additionally, the new assessment may change the way analytical laboratories characterize environmental samples. The prevailing practice has been to describe environmental

samples in terms of Aroclors, even though environmental processes make the composition of environmental mixtures considerably different from Aroclor mixtures. Congener and homologue analysis may become preferred for the ability to estimate the dioxin toxic equivalence of an environmental mixture or verify whether PCBs found in water or air are, as expected, of low chlorine content and persistence. In particular, analysis of dioxinlike congeners may be warranted for exposure through contaminated food; recently, PCB–126 (3,3′,4,4′,5-pentachlorobiphenyl), the PCB congener with the highest dioxin toxic equivalency factor (*65*), was found in all of 63 samples of beef back fat (*72*).

Finally, the EPA's assessment proves that good research can indeed improve risk assessments. The recent study of four Aroclors strengthened the case that all PCB mixtures can cause cancer, resolving questions about the cancer hazard from different PCB mixtures and providing key information that now enables risk assessors to quantify differences in cancer potency.

References and Notes

1. Brunner MJ, Sullivan TM, Singer AW, Ryan MJ, Toft JD II, Menton RS, Graves SW, Peters AC. An Assessment of the Chronic Toxicity and Oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor-1254, and Aroclor-1260 Administered in Diet to Rats. Battelle Study No SC920192. Columbus, OH:Battelle, 1996.
2. U.S. EPA. PCBs: Cancer Dose–Response Assessment and Application to Environmental Mixtures. EPA/600/P–96/001F. Washington, DC:U.S. Environmental Protection Agency, 1996.
3. U.S. EPA. Proposed guidelines for carcinogen risk assessment; notice. Fed Reg 61(79):17960–18011 (1996).
4. U.S. EPA. Guidelines for the health risk assessment of chemical mixtures. Fed Reg 51(185):34014–34025 (1986).
5. U.S. EPA. Report on Peer Review Workshop on PCBs: Cancer Dose–Response Assessment and Application to Environmental Mixtures. Washington:U.S. Environmental Protection Agency, 1996.
6. Kimbrough RD, Squire RA, Linder RE, Strandberg JD, Montali RJ, Burse VW. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. J Natl Cancer Inst 55:1453–1459 (1975).
7. Schaeffer E, Greim H, Goessner W. Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. Toxicol Appl Pharmacol 75:278–288 (1984).
8. Norback DH, Weltman RH. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ Health Perspect 60:97–105 (1985).
9. Moore JA, Hardisty JF, Banas DA, Smith MA. A comparison of liver tumor diagnoses from seven PCB studies in rats. Regul Toxicol Pharmacol 20:362–370 (1994).
10. National Cancer Institute. Bioassay of Aroclor 1254 for Possible Carcinogenicity. Carcinogenesis Technical Report Series 38. Washington, DC:National Cancer Institute, 1978.
11. Morgan RW, Ward JM, Hartman PE. Aroclor 1254-induced intestinal metaplasia and adenocarcinoma in the glandular stomach of F344 rats. Cancer Res 41:5052–5059 (1981).
12. Ward JM. Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254. Environ Health Perspect 60:89–95 (1985).
13. Kimbrough RD, Linder RE, Gaines TB. Morphological changes in livers of rats fed polychlorinated biphenyls: light microscopy and ultrastructure. Arch Environ Health 25:354–364 (1972).
14. Kimbrough RD, Linder RE. Induction of adenofibrosis and hepatomas of the liver in BALB/cJ mice by polychlorinated biphenyls (Aroclor 1254). J Natl Cancer Inst 53(2):547–552 (1974).
15. Kimura NT, Baba T. Neoplastic changes in the rat liver induced by polychlorinated biphenyl. Gann 64:105–108 (1973).
16. Ito N, Nagasaki H, Arai M, Makiura S, Sugihara S, Hirao K. Histopathologic studies on liver tumorigenesis induced in mice by technical polychlorinated biphenyls and its promoting effect on liver tumors induced by benzene hexachloride. J Natl Cancer Inst 51(5):1637–1646 (1973).
17. Ito N, Nagasaki H, Makiura S, Arai M. Histopathological studies on liver tumorigenesis in rats treated with polychlorinated biphenyls. Gann 65:545–549 (1974).
18. Rao CV, Banerji AS. Induction of liver tumors in male Wistar rats by feeding polychlorinated biphenyls (Aroclor 1260). Cancer Lett 39:59–67 (1988).
19. Brown DP. Mortality of workers exposed to polychlorinated biphenyls—an update. Arch Environ Health 42(6):333–339 (1987).
20. Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C. Cancer mortality of capacitor manufacturing workers. Am J Ind Med 11:165–176 (1987).
21. Sinks T, Steele G, Smith AB, Watkins K, Shults RA. Mortality among workers exposed to polychlorinated biphenyls. Am J Epidemiol 136(4):389–398 (1992).
22. Gustavsson P, Hogstedt C, Rappe C. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med 10:341–344 (1986).
23. Nicholson WJ, Landrigan PJ. Human health effects of polychlorinated biphenyls. In: Dioxins and Health (Schecter A, ed). New York:Plenum, 1994;487–524.
24. Bahn AK, Rosenwaike I, Herrmann N, Grover P, Stellman J, O'Leary K. Melanoma after exposure to PCBs [letter]. N Engl J Med 295:450 (1976).
25. Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. Occup Environ Med 54:720–728 (1997).
26. Hardell L, van Bavel B, Lindström G, Fredrikson M, Hagberg H, Liljegren G, Nordström M, Johansson B. Higher concentrations of specific polychlorinated biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. Int J Oncol 9:603–608 (1996).
27. Rothman N, Cantor KP, Blair A, Bush D, Brock JW, Helzlsouer K, Zahm SH, Needham LL, Pearson GR, Hoover RN, et al. A nested case–control study of non-Hodgkin lymphoma and serum organochlorine residues. Lancet 350:240–244 (1997).
28. Morita M, Nakagawa J, Rappe C. Polychlorinated dibenzofuran (PCDF) formation from PCB mixture by heat and oxygen. Bull Environ Contam Toxicol 19:665–670 (1978).
29. Masuda Y. The Yusho rice oil poisoning incident. In: Dioxins and Health (Schecter A, ed). New York:Plenum, 1994;633–659.
30. Silberhorn EM, Glauert HP, Robertson LW. Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. Crit Rev Toxicol 20(6):439–496 (1990).
31. Buchmann A, Kunz W, Wolf CR, Oesch F, Robertson LW. Polychlorinated biphenyls, classified as either phenobarbital- or 3-methylcholanthrene-type inducers of cytochrome P-450, are both hepatic tumor promoters in diethylnitrosamine-initiated rats. Cancer Lett 32:243–253 (1986).
32. Buchmann A, Ziegler S, Wolf A, Robertson LW, Durham SK, Schwarz M. Effects of polychlorinated biphenyls in rat liver: correlation between primary subcellular effects and promoting activity. Toxicol Appl Pharmacol 111:454–468 (1991).
33. McFarland VA, Clarke JU. Environmental occurrence, abundance, and potential toxicity of polychlorinated biphenyl congeners: considerations for a congener-specific analysis. Environ Health Perspect 81:225–239 (1989).
34. Safe S. Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. Crit Rev Toxicol 24(2):87–149 (1994).
35. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Polychlorinated Biphenyls. Atlanta,GA:Agency for Toxic Substances and Disease Registry, 1997.
36. Wester RC, Bucks DAW, Maibach HI, Anderson J. Polychlorinated biphenyls (PCBs): dermal absorption, systemic elimination, and dermal wash efficiency. J Toxicol Environ Health 12:511–519 (1983).
37. Wester RC, Mobayen M, Maibach HI. *In vivo* and *in vitro* absorption and binding to powdered stratum corneum as methods to evaluate skin absorption of environmental chemical contaminants from ground and surface water. J Toxicol Environ Health 21:367–374 (1987).
38. Wester RC, Maibach HI, Bucks DAW, McMaster J, Mobayen M. Percutaneous absorption and skin decontamination of PCBs: *in vitro* studies with human skin and *in vivo* studies in the rhesus monkey. J Toxicol Environ Health 31:235–246 (1990).
39. Wester RC, Maibach HI, Sedik L, Melendres J, Wade M. Percutaneous absorption of PCBs from soil: *in vivo* rhesus monkey, *in vitro* human skin, and binding to powdered human stratum corneum. J Toxicol Environ Health 39:375–382 (1993).
40. Oakley GG, Devanaboyina U, Robertson LW, Gupta RC. Oxidative DNA damage induced by activation of polychlorinated biphenyls (PCBs): implications for PCB-induced oxidative stress in breast cancer. Chem Res Toxicol 9(8):1285–1292 (1996).
41. Birnbaum LS. Endocrine effects of prenatal exposure to PCBs, dioxins, and other xenobiotics: implications for policy and future research. Environ Health Perspect 102(8):676–679 (1994).
42. Birnbaum LS, DeVito MJ. Use of toxic equivalency factors for risk assessment for dioxins and related compounds. Toxicology 105(2-3):391–401 (1995).
43. Brown JF Jr, Silkworth JB, Mayes BA. Characterization of PCB Composition, Tissue Accumulation, and Correlations with Tumorigenicity in Chronically Dosed Male and Female Sprague-Dawley Rats. Battelle Study No SC920192. Columbus, OH:Battelle, 1997.
44. Schulz DE, Petrick G, Duinker JC. Complete characterization of polychlorinated biphenyl congeners in commercial Aroclor and Clophen mixtures by multidimensional gas chromatography-electron capture detection. Environ Sci Technol 23(7):852–859 (1989).
45. Frame GM, Cochran JW, Bøwadt SS. Complete PCB congener distributions for 17 Aroclor mixtures determined by 3 HRGC systems optimized for comprehensive, quantitative, congener-specific analysis. J High Resolut Chromatogr 19:657–668 (1996).
46. WHO. Polychlorinated Biphenyls and Terphenyls. 2nd ed. Environmental Health Criteria 140. Geneva:World Health Organization, 1993.
47. McConnell EE, Solleveld HA, Swenberg JA, Boorman GA. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J Natl Cancer Inst 76(2):283–289 (1986).
48. Cogliano VJ. The U.S. EPA's methodology for adjusting the reportable quantities of potential carcinogens. In: Proceedings of the 7th National Conference on Management of Uncontrolled Hazardous Wastes (Superfund '86), December 1986, Washington, DC. Washington, DC:Hazardous Materials Control Research Institute, 1986; 182–185.
49. National Research Council. Issues in Risk Assessment. Washington, DC:National Academy Press, 1993.
50. Crump KS, Hoel DG, Langley CH, Peto R. Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Res 36:2973–2979 (1976).
51. Lutz WK. Dose–response relationship and low dose extrapolation in chemical carcinogenesis. Carcinogenesis 11(8):1243–1247 (1990).
52. Callahan MA, Slimak MW, Gabel NW, May IP, Fowler CF, Freed JR, Jennings P, Durfee RL, Whitmore FC, Maestri B, et al. Water-related Environmental Fate of 129 Priority Pollutants, Vol 1. EPA–440/4–79–029a. Washington,DC:U.S. Environmental Protection Agency, 1979.
53. Hutzinger O, Safe S, Zitko V. The Chemistry of PCB's. Boca Raton, FL:CRC Press, 1974.
54. Erickson MD. Analytical Chemistry of PCBs. Boston, MA:Butterworth, 1986.

55. Abramowicz DA. Aerobic and anaerobic biodegradation of PCBs: a review. Biotechnology 10(3):241–251 (1990).
56. Brown JF Jr, Wagner RE. PCB movement, dechlorination, and detoxication in the Acushnet Estuary. Environ Toxicol Chem 9:1215–1233 (1990).
57. Lake JL, Pruell RJ, Osterman FA. An examination of dechlorination processes and pathways in New Bedford Harbor sediments. Marine Environ Res 33:31–47 (1992).
58. Matthews HB, Anderson MW. Effect of chlorination on the distribution and excretion of polychlorinated biphenyls. Drug Metab Dispos 3(5):371–380 (1975).
59. Oliver BG, Niimi AJ. Trophodynamic analysis of polychlorinated biphenyl congeners and other chlorinated hydrocarbons in the Lake Ontario ecosystem. Environ Sci Technol 22:388–397 (1988).
60. Schwartz TR, Stalling DL, Rice CL. Are polychlorinated biphenyl residues adequately described by Aroclor mixture equivalents? Isomer-specific principal components analysis of such residues in fish and turtles. Environ Sci Technol 21:72–76 (1987).
61. Lake JL, McKinney R, Lake CA, Osterman FA, Heltshe J. Comparisons of patterns of polychlorinated biphenyl congeners in water, sediment, and indigenous organisms from New Bedford Harbor, Massachusetts. Arch Contam Toxicol 29:207–220 (1995).
62. Hovinga ME, Sowers M, Humphrey HEB. Historical changes in serum PCB and DDT levels in an environmentally-exposed cohort. Arch Environ Contam Toxicol 22:362–366 (1992).
63. Aulerich RJ, Ringer RK, Safronoff J. Assessment of primary vs. secondary toxicity of Aroclor 1254 to mink. Arch Environ Contam Toxicol 15:393–399 (1986).
64. Hornshaw TC, Aulerich RJ, Johnson HE. Feeding Great Lakes fish to mink: effects on mink and accumulation and elimination of PCBs by mink. J Toxicol Environ Health 11:933–946 (1983).
65. Ahlborg UG, Becking GC, Birnbaum LS, Brouwer A, Derks HJGM, Feeley M, Golor G, Hanberg A, Larsen JC, Liem AKD, et al. Toxic equivalency factors for dioxin-like PCBs. Chemosphere 28(6):1049–1067 (1994).
66. Dewailly É, Weber J-P, Gingras S, Laliberté C. Coplanar PCBs in human milk in the province of Québec, Canada: are they more toxic than dioxin for breast fed infants? Bull Environ Contam Toxicol 47:491–498 (1991).
67. Dewailly É, Ryan JJ, Laliberté C, Bruneau S, Weber J-P, Gingras S, Carrier G. Exposure of remote maritime populations to coplanar PCBs. Environ Health Perspect 102(suppl 1):205–209 (1994).
68. Calabrese EJ, Sorenson AJ. The health effects of PCBs with particular emphasis on human high risk groups. Rev Environ Health 2:285–304 (1977).
69. National Toxicology Program. Toxicology and Carcinogenesis Studies of Polybrominated Biphenyls (CAS No. 67774–32–7) (Firemaster FF–1) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). TR 398. Research Triangle Park, NC:National Toxicology Program, 1993.
70. Anderson LM, Fox SD, Dixon D, Beebe LE, Issaq HJ. Long-term persistence of polychlorinated biphenyl congeners in blood and liver and elevation of liver aminopyrine demethylase activity after a single high dose of Aroclor 1254 to mice. Environ Toxicol Chem 10:681–690 (1991).
71. Kimbrough RD. Polychlorinated biphenyls (PCBs) and human health: an update. Crit Rev Toxicol 25(2): 133–163 (1995).
72. Winters D, Cleverly D, Lorber M, Meier K, Dupuy A, Byrne C, Deyrup C, Ellis R, Ferrario J, Leese W, et al. Coplanar polychlorinated biphenyls (PCBs) in a national sample of beef in the United States: preliminary results. Organohalogen Compounds 28:350–354 (1996).