Assessment of Potential Cancer Risk from Consumption of PCBs Bioaccumulated in Fish and Shellfish

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We evaluated the potential cancer risk to adults from ingesting polychlorinated biphenyls (PCBs) in fish and shellfish using an equilibrium partitioning model of PCB bioaccumulation in the aquatic animal. Estimated potential cancer risk to humans increased exponentially with increasing hydrophobicity of the PCB. However, the addition of food-chain sources of PCBs was necessary to cause potential cancer risk to exceed 10^{-6}. Environmental degradation of the PCB reduced cancer risk by reducing the exposure concentration; 3.3 degradation half-lives were required to reduce cancer risk estimates by one order of magnitude. PCB biotransformation to nongenotoxic metabolites (no increase in the cancer slope factor) by the aquatic animal reduced cancer risk by reducing the steady-state concentration of PCBs in the edible tissue. Even relatively slow biotransformation (e.g., metabolic half-life of 100 days) reduced cancer risk estimates under the default model conditions. Nonequilibrium conditions, such as limited exposure time, reduced potential cancer risk by reducing contaminant concentrations in the aquatic animal. Risk assessment using toxic equivalency factors predicted substantially greater potential risk for specific congeners than for PCB mixtures. Our evaluation demonstrates that deviation from conventional assumptions used in risk assessment (e.g., negligible biotransformation and degradation; steady-state equilibrium) can significantly affect cancer risk estimates. *Key words:* bioaccumulation, biotransformation, degradation, equilibrium partitioning, polychlorinated biphenyls, risk assessment, toxic equivalency factors. *Environ Health Perspect* 102:562–567 (1994)

Polychlorinated biphenyls (PCBs) are a class of chlorine-substituted aromatics consisting of 209 possible congeners. PCBs were sold commercially and entered the environment as various mixtures of individual congeners (e.g., Aroclor in the United States, Kanechlor in Japan). The physical-chemical properties and toxicity of PCBs vary with the degree of chlorine substitution, number of vicinal unsubstituted carbons, and steric configuration (*1*). PCBs have become significant environmental contaminants because they are persistent, ubiquitous, bioaccumulative, and potentially carcinogenic. Currently PCBs are considered to be class B2 carcinogens because of sufficient weight of evidence in animals (hepatocellular carcinoma), but inadequate weight of evidence in humans (*2*). Although the carcinogenic potency of PCBs remains uncertain, the assessment of potential cancer risk of PCBs in environmental media remains a requisite component of risk assessment (*3*).

Risk assessment generally involves estimating potential risk from intake rate and the carcinogenic potency of the chemical. Estimates of carcinogenic potency are published as cancer slope factors (*3*) after evaluation of data from animal studies, genotoxicity and mutagenicity assays, and epidemiologic studies. Intake rates are typically calculated from the measured concentration in the edible tissue and normalizing the dose for body weight and exposure time using standardized parameter values and exposure models (*3,4*). In the absence of direct measurements, tissue concentrations can be predicted from the chemical concentration in the environmental media and pharmacokinetic or equilibrium partitioning models (*5*). Whether predicted or measured tissue concentrations are used to calculate intake, an invariant tissue concentration is usually assumed in estimating risk.

The objective of the present study was to evaluate the relationship between estimated cancer risk and factors controlling PCB concentrations in tissues of aquatic animals. We evaluated potential cancer risk from ingestion of PCBs in fish and shellfish using a standard oral exposure model for adults. PCBs in edible tissue were predicted using an equilibrium partitioning model of PCB bioaccumulation in the aquatic animal. The equilibrium partitioning model and risk analysis model were coupled to quantify the effect of PCB bioaccumulation in fish and shellfish on estimates of potential cancer risk. Factors evaluated in this study included PCB hydrophobicity and food chain contributions, environmental degradation of PCBs, biotransformation by the aquatic animal, and nonequilibrium exposure conditions. Additionally, the potential cancer risk from ingestion of individual PCB congeners was assessed because risk is usually assessed from total concentrations of PCBs rather than the specific congeners present.

Methods

We predicted PCB concentrations in fish and shellfish using an equilibrium partitioning model of PCB bioaccumulation in the aquatic animal (*5*):

$$\mathrm{BCF} = k_1/k_2\,, \qquad (1)$$

where BCF is the ratio of the PCB concentration in the aquatic animal to exposure water at equilibrium, and k_1 and k_2 are first-order uptake and elimination constants, respectively. Inherent assumptions of the equilibrium partitioning model include steady-state conditions, negligible biotransformation, and contaminant uptake by the aquatic animal solely from water.

We estimated potential cancer risk (RISK) to adult humans from ingestion of PCB-contaminated fish and shellfish using the reported (*6*) carcinogenic potency (cancer slope factor; CSF) and the standard oral exposure model (*3*):

$$\mathrm{RISK} = I \times \mathrm{CSF}\,. \qquad (2)$$

Intake (I) was calculated from:

$$I = \frac{C_T \times a \times \mathrm{IR} \times \mathrm{EF} \times \mathrm{ED}}{\mathrm{BW} \times \mathrm{AT}}\,, \qquad (3)$$

where default model parameters are defined in Table 1. The contaminant concentration in edible tissue (C_T) was calculated by applying BCF to the ambient water concentration (C_W):

$$C_T = \mathrm{BCF} \times f \times C_W\,. \qquad (4)$$

The edible tissue fraction (f) was included in Equation 4 to normalize C_T to the PCBs present in tissue ingested by humans (*7*).

The relationship between chemical hydrophobicity and potential cancer risk was evaluated using BCFs estimated from the relationship between octanol-water partition coefficient (K_{ow}) and BCF in fish (*8*):

$$\mathrm{BCF} = 0.79 \times (\log K_{ow}) - 0.40\,. \qquad (5)$$

The effect of PCB bioaccumulation in aquatic animals from food-chain sources (trophic transfer) was evaluated by applying a hydrophobicity-dependent food chain multiplier (FCM) to the hydrophobicity-dependent BCF from Equation 5:

$$\mathrm{BAF} = \mathrm{FCM} \times \mathrm{BCF}\,. \qquad (6)$$

The calculated bioaccumulation factor (BAF) was then substituted for BCF (in

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We thank R. Crane and M. Boyajian for assistance in preparing the manuscript.
Received 2 February 1994; accepted 4 May 1994.

Table 1. Model parameters and default values used in estimating potential cancer risk from tissue consumption

Parameter	Definition	Default
BCF	Bioconcentration factor	Calculated
k_1	Uptake clearance constant	700 l × day^{-1}
k_2	Elimination rate constant	0.007 day^{-1}
CSF	Cancer slope factor	7.7 (mg × kg^{-1} × day^{-1})$^{-1}$
C_T	Concentration in edible tissue	Calculated
a	Absorption efficiency	1
IR	Ingestion rate	0.0065 kg × day^{-1}
EF	Exposure frequency	350 days × year^{-1}
ED	Exposure duration	30 years
BW	Body weight	70 kg
AT	Averaging time	25,550 days
C_W	Water concentration	0.1 ng/l
FCM	Food chain multiplier	From U.S. EPA (*9*)
BAF	Bioaccumulation factor	Calculated
f	Edible tissue fraction	0.4
TEF	Toxicity equivalency factor	From Safe (*1*)

Equation 4) to estimate C_T. FCMs used in Equation 6 were for the fourth trophic level (top predators) developed by EPA (*9*) from the food chain model of Thomann (*10*).

We evaluated the effect of environmental degradation (e.g., photolysis, hydrolysis, biodegradation) in determining potential cancer risk from ingestion of bioaccumulated PCBs by modeling degradation as a single first-order rate constant (k_d). C_T, which declined over time due to declining C_W, was calculated by substituting k_1 and k_2 for BCF (Eq .1):

$$C_T = (k_1/k_2) \times f \times C_W \times e^{-kdt} . \quad (7)$$

We set k_d at 0.001, 0.01, or 0.1 day^{-1}, corresponding to PCB degradation half-lives of 693, 69.3, and 6.93 days, respectively.

PCB biotransformation by the aquatic animal was modeled as a separate parameter for biotransformation (k_M; the metabolic rate constant) to assess the effect on potential cancer risk. The equation for C_T substituted k_1 and k_2 for BCF (Eq. 1):

$$C_T = C_W \times f \times k_1/(k_2 + k_M) . \quad (8)$$

Total elimination was set equal to (k_2 + k_M), and k_M was varied over the range of 0.0001 to 0.1 day^{-1} (corresponding to half-lives between 6930 to 6.93 days).

We evaluated the effect of nonequilibrium conditions on the potential cancer risk of PCBs bioaccumulated in fish and shellfish by calculating C_T with increasing PCB exposure time (*11*):

$$C_T = C_W \times f \times (k_1/k_2) \times (1 - e^{-k2t}) ; \quad (9)$$

k_1 and k_2 were substituted for BCF (Eq. 1).

The potential cancer risk resulting from the ingestion of individual PCB congeners was estimated by substituting the congener-specific cancer slope factor ($CSF_{specific}$) for CSF in Equation 2. $CSF_{specific}$ was calculated from:

$$CSF_{specific} = CSF_{TCDD} \times TEF , \quad (10)$$

where CSF_{TCDD} [CSF for 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (TCDD)] was equal to 1.5×10^5 (*12*) and the TEFs (toxic equivalency factors) for individual congeners were from Safe (*1*) or Kafafi et al. (*13*). The TEF normalizes the potency of an individual congener to the potency of TCDD (TEF = 1) (*1*). Tissue concentrations (C_T) were estimated using the congener-specific hydrophobicity (K_{ow}) from Hawker and Connell (*14*) to calculate BCF (Eq. 5).

Results and Discussion

Model Assumptions

Potential cancer risk from ingestion of PCBs in fish and shellfish was estimated using a standard oral exposure model for adults and the product of carcinogenic potency and chemical intake. The concentration of PCBs in edible tissue was calculated from an equilibrium partitioning model, rather than using measured tissue concentrations, to evaluate the dependence of cancer risk estimates on model assumptions. Using a fixed cancer slope factor (Table 1), estimated potential cancer risk was directly proportional to the predicted tissue concentration in the aquatic animal.

To calculate tissue concentrations, we chose representative default conditions (Table 1) for aquatic animals and PCBs. The default value for the uptake constant was 700 l/day, which was in the range of 1–1000 l/day reported for fish by McKim and Heath (*15*). The default value for the elimination constant was 0.007 day^{-1}, corresponding to an elimination half-life of 99 days. Niimi and Oliver (*16*) reported that the elimination half-lives of PCB congeners from trout (*Oncorhynchus mykiss*) muscle ranged from less than 5 days to 127 days. The edible tissue fraction (f) was used to adjust PCB concentrations in the whole body of the aquatic animal to the edible tissue concentration. The value for f (0.4) was calculated from the ratio of PCBs in muscle to whole fish of Lake Ontario salmonids (*7*) and appeared to vary with fish species and the congeners present (*7*). We used the relationship between hydrophobicity (K_{ow}) and BCF (*8*) to estimate tissue concentrations of PCBs in fish and shellfish; this relationship was established with fish of a mean lipid content of 7.6% (*9*). Lipid contents were not normalized for species or trophic level, although lipid content and composition are variable in aquatic animals (e.g., 1–10% of tissue mass), even within a specific tissue (*17*). The default water concentration (0.1 ng PCB/l) was constant (Table 1). This concentration is below the range of reported background water concentrations in diverse aquatic environments (*18*) and approximated the ambient water quality criteria (*19*) corresponding to 10^{-6} excess cancer risk for the ingestion of PCB contaminated fish and shellfish.

The majority of the default assumptions of the oral exposure model for adult humans were conservative and thus may result in an overestimate of risk. For example, absorption efficiency in humans was set at 1 (100% bioavailability), as recommended by EPA (*3*). However, animal studies have shown a general trend of decreasing absorption efficiency for higher chlorinated congeners (*20*). Ingestion of PCB-contaminated fish and shellfish was assumed to occur for 350 days/year for 30 years (*3*). Intake was estimated assuming an average ingestion rate of 6.5 g contaminated tissue per day, as recommended by EPA (*3*). The 6.5 g/day value represents a national average for populations with a diversified diet of animal products, while human populations consuming only contaminated fish and shellfish may have ingestion rates in excess of 180 g/day (*4*).

Carcinogenic potency was quantified using the published CSF for PCBs (*6*), with the implicit assumption that all PCB congeners and mixtures are carcinogenic and have the same potency. However, the actual carcinogenic potency of PCB congeners and mixtures remains controversial because of the absence of direct evidence of PCB-caused carcinogenesis in humans (*2*). PCBs exhibit tumor-promoting activity in rodents, but do not appear to be mutagenic or genotoxic. Application of a single potency value may be inappropriate because commercial mixtures of PCBs appear to exhibit differences in carcinogenic potency. For example, Smith et al. (*21*) argued that the

PCB mixture Aroclor 1260 is carcinogenic in animals, but lower-chlorinated Aroclors (e.g., 1242, 1254) may have limited, if any, carcinogenicity. Thus, actual cancer risk from consumption of contaminated fish and shellfish may be overestimated by conventional risk assessment methodology.

Bioconcentration

Bioconcentration is the process of accumulation of waterborne contaminants by aquatic organisms through nondietary routes (*22*). Predicting PCB bioconcentration in the edible tissues of fish and shellfish from equilibrium partitioning resulted in increasing potential cancer risk estimates with increasing chemical hydrophobicity (Fig. 1). This increase occurred because the evaluation used a fixed cancer slope factor (7.7) and assumed equilibrium partitioning was the sole process controlling tissue concentrations. The relationship between hydrophobicity and potential cancer risk was evaluated for log K_{ow} between 4 and 6.5 because this range spanned the lower limit of PCB hydrophobicity (*14*), and hydrophobicity may not control bioconcentration at log K_{ow} greater than 6.5 (*9*). Under the default conditions (e.g., water concentration of 0.1 ng PCB/l), potential cancer risk was not estimated to exceed 10^{-6}. Water concentrations in excess of 10 ng PCB/l and log K_{ow} greater than 5.5 would be required to cause potential cancer risk to exceed 10^{-5}. Thus, there appears to be limited cancer risk from ingestion of PCB contaminated fish and shellfish when accumulation is restricted to bioconcentration.

Cancer risks estimated from predicted tissue concentrations must be interpreted with caution because chemical accumulation in aquatic animals does not appear to be solely dependent on equilibrium partitioning. Evidence includes the dependence of PCB bioconcentration on the fish species and exposure regime (*22*), nonlinearity of the relationship between log BCF and log K_{ow} for PCBs (*23*), and large variation in BCFs for PCB isomers. For example, Mackay et al. (*24*) reported that BCFs for tetrachlorobiphenyl ranged from 8,900 to 62,000. Bioconcentration may be limited because of rate-limiting barriers to uptake imposed by physiological flow (epithelial blood perfusion, ventilation, water) limitations, or to diffusive barriers due to steric hindrance (*25*). Steric effects, caused by the orientation of chlorine atoms on the biphenyl moiety, appear to be important in controlling PCB accumulation. For example, chlorine substitution in the *ortho* position decreases aryl hydrocarbon (Ah) receptor affinity (*13*) and may increase elimination (*20*). BCFs calculated from PCB hydrophobicity will overestimate cancer risk from ingestion of PCB-contaminated fish and shellfish if the assumption of equilibrium partitioning is violated.

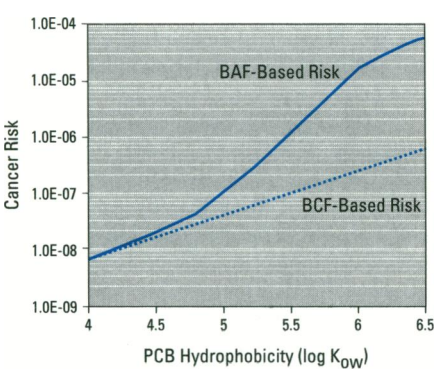

Figure 1. Relationship between PCB hydrophobicity and estimated potential cancer risk in humans consuming contaminated fish. Potential cancer risk was estimated using fish tissue concentrations calculated using hydrophobicity-dependent bioconcentration factors (BCF-based risk) or food chain bioaccumulation factors (BAF-based risk).

Food Chain Bioaccumulation

For many persistent chemicals, dietary (food chain) sources of a contaminant contribute significantly to contaminant concentrations in aquatic animals (*26*). PCBs enter the aquatic food chain by partitioning between algae and water or from filtration and ingestion of sediment-associated PCBs by benthic organisms (*27–31*). Food chain contributions of PCBs are the dominant source of PCBs bioaccumulated in tissues of aquatic animals in many aquatic ecosystems (*30,32*). Thus, the use of BCFs alone is inappropriate to estimate potential cancer risk from PCB ingestion of contaminated fish and shellfish. A bioaccumulation factor (BAF) or biota-to-sediment factor (BSF) is required to predict tissue concentrations in the absence of measured concentrations. The BAF or BSF accounts for exposure from food chain sources and normalizes concentrations in edible tissue to concentrations in the ambient water or sediment, respectively.

BAFs can be estimated from field or laboratory measurements (assuming equilibrium conditions) or may be estimated by applying kinetic models of simplified food chains. To estimate potential cancer risk resulting from food chain bioaccumulation, BAFs were calculated from the product of BCF and a food chain multiplier (FCM). The FCMs used in estimating potential cancer risk were hydrophobicity dependent and were for the fourth trophic level (top predator) (*9*). This simplistic approach used generic FCMs developed by EPA (*9*) from the food chain model of Thomann (*10*). The Thomann model did not specifically account for accumulation of sediment-associated PCBs (*10*). FCMs developed from the refined Thomann et al. (*30*) model were not available.

Greater potential cancer risk was estimated from food-chain-bioaccumulated PCBs than from bioconcentration alone (Fig. 1). Food chain bioaccumulation caused the potential cancer risk estimates to exceed 10^{-6} for log K_{ow} >5.5. Potential cancer risk was not estimated above log K_{ow} of 6.5 because of high variability in FCMs (*9*). Lower cancer risk would be predicted from ingestion of species at a lower trophic level (e.g., filter-feeding-shellfish) because FCMs are lower (*9*). When food chain bioaccumulation is important, application of BCFs alone to predict tissue concentrations will underestimate potential cancer risk from ingestion of contaminated fish and shellfish. The trophic level and the feeding behavior of the ingested species will also be important determinants of potential cancer risk.

Environmental Degradation and Biotransformation

Conventional assumptions in risk assessment usually include the absence of significant biotransformation or degradation of contaminants. However, significant environmental degradation (e.g., hydrolysis or photolysis, biodegradation), or metabolism (e.g., biotransformation to polar metabolites) of the chemical may result in lower tissue concentrations in the aquatic animal. Environmental degradation of PCBs generally involves dechlorination, chlorobenzoic acid formation, and ring cleavage (*33,34*). Degradation of PCBs in environmental media may reduce cancer risk by reducing contaminant concentrations in the ambient water or sediment (driver compartment). Evaluations using the default parameters for PCBs (Table 1) showed that relatively rapid degradation (e.g. half-lives <70 days) was necessary to substantially reduce driver compartment concentrations and thus reduce potential cancer risk (Fig. 2). Independent of the default parameters, the relationship between driver compartment concentration (e.g., C_w) and tissue concentration (Eq. 7) predicted that 3.3 degradation half-lives were required to reduce potential cancer risk by one order of magnitude.

Biotransformation of PCBs by aquatic animals generally proceeds by P450-mediated oxidation of unsubstituted carbon atoms in non-*ortho* positions (*35*). Biotransformation is favored by vicinal unsubstituted *meta-para* carbon atoms and provides a site for epoxidation (*35*). Conjugation of hydroxylated metabolites is limited (*33*). Chlorine substitution at the *meta-para* carbon atoms results in "enrichment," whereas *ortho*-chlorine substitution

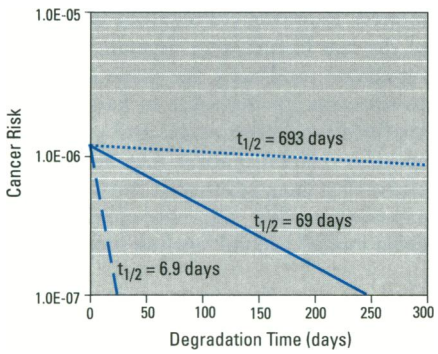

Figure 2. Relationship between the rate of environmental degradation (e.g, half-life, $t_{1/2}$) of PCBs and estimated potential cancer risk in humans consuming contaminated fish.

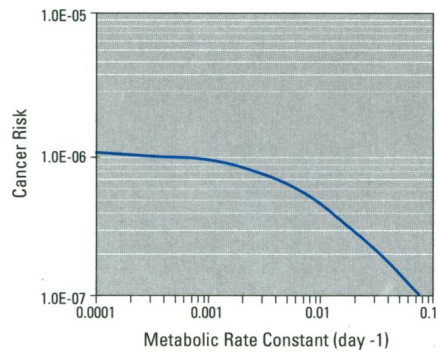

Figure 3. Relationship between the rate of PCB biotransformation in the aquatic animal (as the metabolic rate constant) and estimated potential cancer risk in humans consuming contaminated fish.

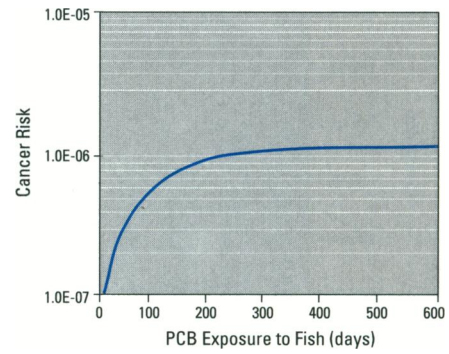

Figure 4. Relationship between duration of PCB exposure to the aquatic animal and estimated potential cancer risk in humans consuming contaminated fish.

favors elimination (*20*). For example, Tanabe et al. (*20*) found that the elimination half-life of trichlorobiphenyl in fish decreased from 94 days to 3 days with increasing *ortho*-chlorine substitution, presumably due to increased biotransformation (*17*). There also appears to be a general inverse relationship between the rate of PCB metabolism and the extent of chlorination (*16*).

Biotransformation was modeled as a first-order rate constant with half-lives from 7000 to 7 days and assumed transformation to nongenotoxic metabolites (no increase in CSF; Fig. 3). Evaluations using the default conditions (Table 1) indicated that even slow metabolism (e.g., metabolic half-life of 100 days) in the aquatic animal reduced tissue concentrations and substantially reduced potential cancer risk (Fig. 3). Prior exposure to PCBs and related chemicals will increase the rate of biotransformation by induction of P450 isozymes. For example, prior PCB exposure to aquatic animals favors metabolism of coplanar non-*ortho* chlorine-substituted congeners (*35*). Induction of biotransformation in the aquatic animal may further reduce potential cancer risk by reducing PCB concentrations in the tissues of aquatic animals. Carcinogenic metabolites of PCBs are less likely to be transferred to humans (*36*).

Nonequilibrium Conditions

Equilibrium partitioning models (e.g., BCF, BAF) are frequently used to estimate tissue concentrations in aquatic animals. Cancer risk estimates developed from these models inherently assume that equilibrium conditions exist. However, this assumption is not valid if the exposure conditions do not allow establishment of a steady-state equilibrium. Nonequilibrium conditions may be caused by variations in exposure to the aquatic animal (e.g., mobile population, intermittent discharge, or dilution), or variations in chemical uptake or elimination by the aquatic animals (e.g., changes in temperature, body size, or biotransformation).

Under conditions of constant chemical exposure, uptake, and elimination, contaminant concentrations in aquatic animals exhibit an exponential approach to steady-state equilibrium. The elimination constant of the aquatic animal then determines the exposure time required to reach steady-state equilibrium (*11*). Under conditions of constant exposure, 3.3 elimination half-lives are required to reach 90% of steady state. For example, with the default parameter as 0.007 day^{-1} ($t_{1/2}$ = 99 days), approximately 1 year was required to reach 90% of steady state (Fig. 4). A reduction in exposure time will reduce the estimated cancer risk (Fig. 4). Aquatic animals with short life spans relative to the elimination half-life may never reach steady state (*32*).

Potential cancer risk cannot be accurately estimated if the predicted or measured tissue concentrations are not representative of average contaminant concentrations in the aquatic animal during the ingestion period. For example, a seasonal increase in contaminant exposure may cause transient increases in tissue concentrations; this may be less of a concern for slowly eliminated chemicals such as PCBs. Ultimately, pharmacokinetic models coupled to environmental fate models may be required to more accurately estimate risk from ingestion of PCBs in tissues of aquatic animals.

Congener-specific Risk

Potential cancer risk from PCB ingestion is usually assessed from total concentrations of PCBs rather than a congener-specific analysis. Congener-specific assessment is important because individual congeners may preferentially accumulate in aquatic animals relative to PCBs in the exposure media. For example, Niimi and Oliver (*7*) found that 10 congeners represented approximately 52% of the total PCBs in Lake Ontario salmonids. Oliver and Niimi (*27*) observed that the proportion of higher-chlorinated congeners increased with increasing trophic level. Preferential accumulation (enrichment) may be due to biotransformation, environmental degradation, or limited absorption or equilibrium partitioning of specific congeners. Thus, cancer risk estimates based on total PCB concentrations in tissues may be inappropriate.

CSF recommended by EPA for evaluating potential cancer risk of specific PCB congeners are not available. However, CSFs can be estimated for specific PCB congeners by applying TEFs, which normalize the potency of an individual congener to the potency of 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (*1*). Safe (*1*) has estimated TEFs from an integration of toxicity, carcinogenicity, and enzyme induction studies. In general, TEFs are very conservative, have large confidence limits, and are based on both cancer and noncancer endpoints (*1*). Thus, interpretation of potential cancer risk estimated with TEFs warrants caution.

Application of the TEFs developed by Safe (*1*) resulted in potential cancer risk estimates in excess of 10^{-5} for coplanar and mono-*ortho*-substituted coplanar PCB congeners (Fig. 5). Of the congeners evaluated, only di-*ortho* substituted coplanar PCBs (e.g., congeners 128, 190, 205) had cancer risk estimates below 10^{-5} (Fig. 5). Alternatively, application of TEFs developed from Ah receptor binding (*13*) resulted in an order of magnitude lower estimated risk for the majority of PCB congeners evaluated (Fig. 6). In comparison, potential cancer risk estimates for the PCB mixture Aroclor 1254 (log K_{ow} of 4.65) (*22*) estimated from hydrophobicity (Fig. 1) was less than 10^{-7}. Potential cancer risk estimates developed from chemical

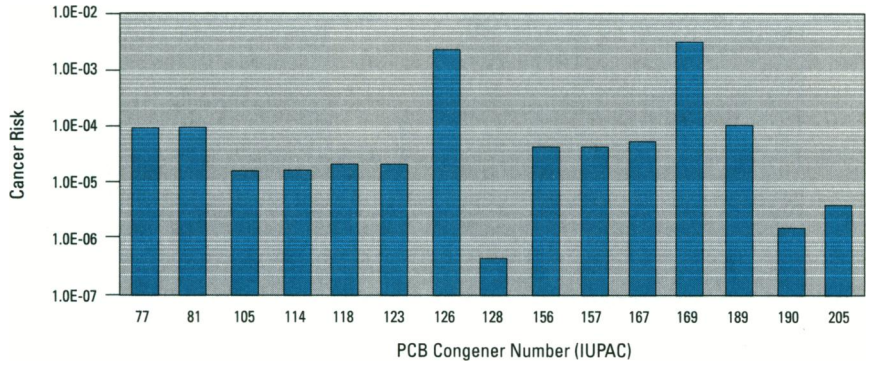

Figure 5. Estimated potential cancer risk in humans consuming contaminated fish for specific PCB congeners (identified by congener number). Toxic equivalency factors used in estimated cancer risk (see text) were from Safe (*1*).

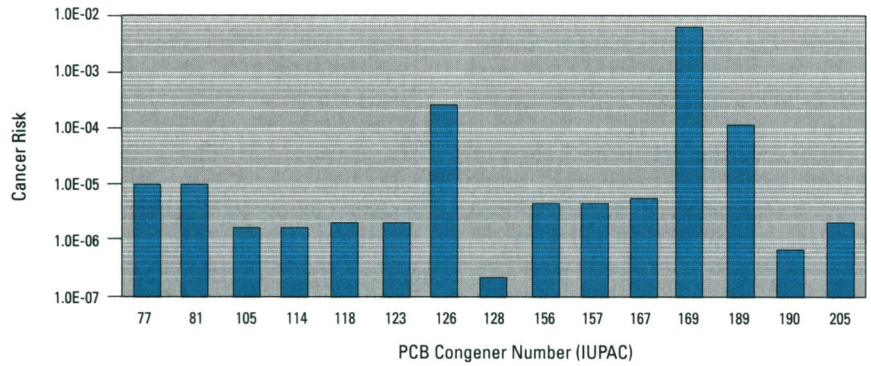

Figure 6. Estimated potential cancer risk in humans consuming contaminated fish for specific PCB congeners (identified by congener number). Toxic equivalency factors used in estimated cancer risk (see text) were from Kafafi et al. (*13*).

hydrophobicity were also limited for other PCB mixtures. Thus, risk assessment of PCBs bioaccumulated in fish and shellfish indicated substantially greater potential risk from individual congeners than from the total PCB concentration (*37*). Specific PCB congeners may also contribute greater potential toxicity than other contaminants bioaccumulated in fish (*38*). However, the carcinogenic potency of specific PCB mixtures or congeners remains uncertain (*2,21*). Despite limitations, congener-specific analysis and application of TEFs may eventually improve the risk assessment of the ingestion of PCBs in tissues of aquatic animals.

Conclusions

Tissue concentrations in fish and shellfish predicted from an equilibrium partitioning model showed an exponential increase in potential cancer risk to humans with increasing hydrophobicity of the PCB. However, the addition of food-chain sources of PCBs were necessary to cause potential cancer risk to exceed 10^{-6}. Environmental degradation of PCBs reduced estimated cancer risk by reducing the aquatic animal exposure concentration. A total of 3.3 degradation half-lives were required to reduce cancer risk estimates by one order of magnitude. PCB biotransformation to nongenotoxic metabolites (no increase in the cancer slope factor) by the aquatic animal reduced cancer risk by reducing the steady-state concentration of PCBs in the edible tissue. Even relatively slow biotransformation (e.g., metabolic half-life of 100 days) reduced cancer risk estimates under the default model conditions. Simulations of environmental degradation and biotransformation did not account for selective loss or bioaccumulation of specific congeners.

Nonequilibrium conditions, such as limited exposure time, reduced potential cancer risk by reducing contaminant concentrations in the aquatic animal. Risk assessment using toxic equivalency factors predicted substantially greater potential risk for specific congeners than for PCB mixtures. The evaluation demonstrated that deviation from conventional assumptions used in risk assessment (e.g., negligible biotransformation and degradation; steady-state equilibrium) can significantly affect cancer risk estimates.

The potential cancer risk estimates developed in this evaluation were specific to the simulation conditions (i.e., standard default conditions and PCB-specific parameters). However, although the magnitude of the risk factors were dependent on the simulation conditions, the observations and conclusions are intended to have general applicability. Site-specific and congener-specific risk estimation may be accomplished by integration with more complex exposure models (e.g., site-specific food chain model) and risk analysis models.

References

1. Safe S. Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). Crit Review Toxicol 21:51–88 (1990).
2. Silverhorn EM, Glauert HP, Robertson LW. Carcinogenicity of polychlorinated biphenyls: PCBs and PBBs. Crit Rev Toxicol 20:439–496 (1990).
3. U.S. EPA. Risk assessment guidance for superfund, vol I. Human health evaluation manual, part A. EPA/540/1-89/002. Washington, DC:Environmental Protection Agency, 1989.
4. U.S. EPA. Assessing human health risks from chemically contaminated fish and shellfish: a guidance manual. EPA/503-8/89-002. Washington, DC:Environmental Protection Agency, 1989.
5. Barron MG. Bioconcentration. Environ Sci Technol 24:1612–1618 (1990).
6. U.S. EPA. Integrated risk information system. Washington, DC:Environmental Protection Agency, 1993.
7. Niimi AJ, Oliver BG. Distribution of polychlorinated biphenyl congeners and other halocarbons in whole fish and muscle among Lake Ontario salmonids. Environ Sci Technol 23:83–88 (1989).
8. Vieth GD, Kosian P. Estimating bioconcentration potential from octanol/water partition coefficients. In: PCBs in the Great Lakes (Mackay D, Patterson R, Eisenreich S, Simmons M, eds). Ann Arbor, MI:Ann Arbor Science, 1983.
9. U.S. Environmental Protection Agency. Water quality guidance for the Great Lakes system. Fed Reg 58:21010–2104 (1993).
10. Thomann RV. Bioaccumulation model of organic chemical distribution in aquatic food chains. Environ Sci Technol 23:699–707 (1989).
11. Barron MG, Stehly GS, Hayton WL. Pharmacokinetic modeling in aquatic animals. I. Models and concepts. Aquat Toxicol 18:61–86 (1990)
12. U.S. EPA. Health effects assessment summary tables. EPA 540-R-93-058. Washington, DC:Environmental Protection Agency, 1993.
13. Kafafi SA, Afeefy HY, Ali AH, Said HK, Kafafi AG. Binding of polychlorinated biphenyls to the aryl hydrocarbon receptor. Environ Health Perspect 101:422–428 (1993).
14. Hawker DW, Connell DW. Octanol-water partition coefficients of polychlorinated biphenyl congeners. Environ Sci Technol 22:382–387 (1988).
15. McKim JM, Heath EH. Dose determinations for waterborne 2,5,2′,5′-(C-14)tetrachlorobiphenyl and related pharmacokinetics in two species of trout (*Salmo gairdneri* and *Salvelinus fontinalis*): a mass balance approach. Toxicol

Appl Pharmacol 68:177–187 (1983).
16. Niimi AJ, Oliver BG. Biological half-lives of polychlorinated biphenyl (PCB) congeners in whole fish and muscle of rainbow trout (*Salmo gairdneri*). Can J Fish Aquat Sci 40:1388–1394 (1983).
17. Phillips DJH. Use of organisms to quantify PCBs in marine and estuarine environments. In: PCBs in the environment, vol 2 (Waid JS, ed). Boca Raton, FL:CRC Press, 1986; 127–181.
18. Macdonald CR, Metcalfe CD. Concentration and distribution of PCB congeners in isolated Ontario lakes contaminated by atmospheric deposition. Can J Fish Aquat Sci 48: 371–381(1991).
19. U.S. EPA. Ambient water quality criteria for polychlorinated biphenyls. EPA 440/5-80-068. Washington, DC:Environmental Protection Agency, 1980.
20. Tanabe S, Maruyama K, Tatsukawa R. Absorption efficiency and biological half-life of individual chlorobiphenyl in carp (*Cyprinus carpio*) orally exposed to Kanechlor products. Agric Biol Chem 46:891–898(1982).
21. Smith MA, Curley WH, Moore JA. Revised cancer slope factors (CSF) for specific polychlorinated biphenyls (PCB) based on current pathology nomenclature. Toxicologist 12:99 (1992).
22. Vieth GD, DeFoe DL, Bergstedt BV. Measuring and estimating the bioconcentration factor of chemicals in fish. J Fish Res Bd Can 36:1040–1048 (1979).
23. Shaw GR, Connell DW. Factors controlling bioaccumulation of PCBs. In: PCBs in the environment, vol I (Waid JS, ed). Boca Raton, FL:CRC Press, 1986;121–141.
24. Mackay D, Shiu WY, Ma KC. Illustrated handbook of physical-chemical properties and environmental fate for organic chemicals. vol I. Monoaromatic hydrocarbons, chloro-benzenes and PCBs. Ann Arbor, MI:Lewis Publishers, 1990.
25. Hayton WL, Barron MG. Rate-limiting barriers to xenobiotic uptake by the gill. Environ Toxicol Chem 9:151–157 (1990).
26. Barron MG. Bioaccumulation and biomagnification. In: Handbook of ecotoxicology (Hoffman D, ed). Ann Arbor, MI:Lewis Publishers, in press.
27. 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).
28. Rubinstein NI, Gilliam WT, Gregory NR. Dietary accumulation of PCBs from a contaminated sediment source by demersal fish (*Leiostomus xanthurus*). Aquat Toxicol 5:331–342 (1984).
29. Connolly JP. Application of a food chain model to polychlorinated biphenyl contamination of the lobster and winter flounder food chains in New Bedford harbor. Environ Sci Technol 25:760–770 (1991).
30. Thomann RV, Connolly JP, Parkerton TF. An equilibrium model of organic chemical accumulation in aquatic food webs with sediment interaction. Environ Toxicol Chem 11: 615–629 (1992).
31. Macdonald CR, Metcalfe CD, Balch GC, and Metcalfe TL. Distribution of PCB congeners in seven lake systems: interactions between sediment and food-web transport. Environ Toxicol Chem 12:1991–2003 (1993).
32. van der Oost R, Heida H, Opperhuizen A. Polychlorinated biphenyl congeners in sediments, plankton, mollusks, crustaceans, and eel in a freshwater lake: implications of using reference chemicals and indicator organisms in bioaccumulation studies. Arch Environ Contam Toxicol 17:721–729 (1988).
33. Menzie CM. Metabolism of pesticides update III. Special scientific report—wildlife no. 232. Washington, DC:U.S. Department of the Interior, 1980.
34. Brown JF, Wagner RE, Feng H, Bedard DL, Brennan MJ, Carnahan JC, May RJ. Environmental dechlorination of PCBs. Environ Toxicol Chem 6:579–593 (1987).
35. Borlakoglu JT, Haegele KD. Comparative aspects on the bioaccumulation, metabolism and toxicity with PCBs. Comp Biochem Physiol 100C:327–338 (1991).
36. Varanasi U, Stein JE. Disposition of xenobiotic chemicals and metabolites in marine organisms. Environ Health Perspect 90:93–100 (1991).
37. Williams LL, Giesy JP, DeGalan N, Verbrugge DA, Tillitt DE, Ankley GT. Prediction of concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents from total concentrations of polychlorinated biphenyls in fish fillets. Environ Sci Technol 26:1151–1159 (1992).
38. Niimi AJ, Oliver BG. Assessment of relative toxicity of chlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in Lake Ontario salmonids to mammalian systems using toxic equivalency factors (TEF). Chemosphere 18:1413–1423 (1989).

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ABSTRACT DEADLINE: JUNE 29, 1994

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