Manuscript submitted to: Volume 2, Issue 1, 21-41.

AIMS Environmental Science DOI: 10.3934/environsci.2015.1.21

Received date 1 December 2014, Accepted date 26 January 2015, Published date 2 February 2015

Review

The use of biomonitoring equivalents for interpreting blood concentrations in population studies: a case for polychlorinated biphenyls

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Abstract: A number of exposure guideline values for environmental contaminants are established by various agencies for risk assessment purposes. Biomonitoring equivalents are conversions of external guideline values to internal doses, against which biomonitoring data can be directly compared. Several biomonitoring equivalents have been developed for the interpretation of blood concentrations of environmental contaminants, but none has yet been developed for polychlorinated biphenyls (PCBs). In this paper, we describe information needed to develop biomonitoring equivalents for PCBs and discuss anticipated challenges. We provide a broad overview of PCB absorption, distribution, metabolism and excretion, PCB guideline values, and PCB pharmacokinetic modeling efforts in animals and humans. We also provide strategies to address anticipated challenges in deriving biomonitoring equivalents for this complex contaminant. Biomonitoring equivalents will be useful for the interpretation of the PCB biomonitoring data that is currently available for populations around the globe through national surveys and research of specific populations.

Keywords: risk assessment; biomonitoring equivalent; polychlorinated biphenyls; pharmacokinetic modeling

Abbreviations:

ADME = absorption, distribution, metabolism, excretion
ATSDR = Agency for Toxic Substances and Disease Registry
BMD = benchmark dose
CHMS = Canadian Health Measures Survey
DDE = dichlorodiphenyldichloroethylene
DDT = dichlorodiphenyltrichloroethane
GerES = German Environmental Survey
LOAEL = lowest observed adverse effect level
MRL = minimum risk level
NHANES = National Health and Nutrition Examination Survey
NOAEL = no observed adverse effect level
PBDE = polybrominated diphenyl ether
PBPK = physiologically-based pharmacokinetic
PCB = polychlorinated biphenyl
PCDD = polychlorinated dibenzo-p-dioxins
PCDF = polychlorinated dibenzofurans
RfC = reference concentration
RfD = reference dose
TCDD = tetrachlorodibenzodioxin
TDI = tolerable daily intake

1. Introduction

Guideline values for environmental contaminants describe exposure thresholds likely to have minimal risk of adverse effects in humans. The Environmental Protection Agency, for example, uses the concept of reference dose (RfD) or reference concentration (RfC), which are estimates of daily oral or inhalational exposures, respectively, in humans that are likely to have no adverse non-cancer effects over a lifetime. These estimates take into consideration effects of chemicals on sensitive human subpopulations [1,2]. The Agency for Toxic Substances and Disease Registry (ATSDR) defines minimum risk level (MRL) of acute (1–14 days), intermediate (15–364 days), or chronic duration (1 year or longer) to describe oral and inhalational exposures without risk for adverse non-cancer effects [3]. Tolerable daily intakes (TDI) are used by Health Canada to describe oral exposures without adverse non-cancer effects over a lifetime [4]. Guideline values are often derived by applying uncertainty factors to estimates of no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL) or benchmark dose (BMD) from toxicological studies in animals. Uncertainty factors may account for uncertainties in extrapolating from animal data to humans, extrapolating from a LOAEL to a NOAEL, length of exposure (e.g. from acute to chronic), and variation among human populations [5].

The magnitude of internal exposure has often been inferred based on estimates of external intake. While this method provides a rough estimate of exposure it may not be representative of the dose that ultimately arrives in the bloodstream or at target organs where toxicity occurs [6].

Chemicals are known to undergo processes of absorption, distribution, metabolism, and excretion—these pharmacokinetic processes will transform the external dose into a chemical-specific internal dose, which is the true parameter of interest in characterizing risk. A biomonitoring equivalent is the conversion of an external guideline value, such as a RfD, MRL, or TDI, to an internal dose against which biomonitoring data can be directly compared [7,8]. Biomonitoring equivalents have been developed for several environmental contaminants, such as polybrominated diphenyl ether (PBDE) -99 [9], dichlorodiphenyldichloroethylene (p,p'-DDE) and dichlorodiphenyltrichloroethane (DDT) [10], toluene [11], hexachlorobenzene [12], and 2,4-dichlorophenoxyacetic acid [13].

To our knowledge, biomonitoring equivalents have not yet been developed for polychlorinated biphenyls (PCBs), a ubiquitous class of environmental contaminant. Levels of PCBs have been measured in human populations around the world. In a risk assessment context, biomonitoring equivalents for PCBs could more accurately guide the interpretation of the available human biomonitoring data. Polychlorinated biphenyls contain up to 209 congeners and each congener has different chemical properties, such as biological half-life. Therefore, the development of biomonitoring equivalents for PCBs is a challenge. In this paper we provide a broad overview of the information needed to develop biomonitoring equivalents for PCBs. We begin by describing background information and worldwide PCB biomonitoring data, followed by a summary of ADME (absorption, distribution, metabolism, excretion) processes, external guideline values, and pharmacokinetic modeling studies of PCBs in animals and humans. Lastly, we present some strategies to address anticipated research challenges in the development of biomonitoring equivalents for this complex contaminant.

2. Background on polychlorinated biphenyls

Although the production, use, and trade of PCBs was prohibited under the Stockholm Convention since 2004 [14] and international production stopped since 1993 [15], these chemicals persist in air, water, soil, biota, and human tissues. PCBs are synthetic materials that were produced for coolant and lubricant properties in electrical equipment, such as capacitors and transformers, and in plasticizers, oils, inks, paints, adhesives, and waxes [15]. Breivik et al. estimated that total global production of PCBs amounted to about 1.3 million tons, of which greater than 70 percent were tri-, tetra-, and pentachlorinated homologues [16]. About half of this production came from the United States and nearly all consumption occurred in the Northern hemisphere [16].

Individual PCB congeners vary in the degree and position of chlorine atoms, resulting in 209 possible congeners. The industrial manufacture of PCBs was mostly in the form of complex commercial PCB mixtures defined by degree of chlorination patterns, such as Aroclors in the United States, Kanechlors in Japan, and Clophens in Germany. The number and positioning of chlorine atoms on the biphenyl ring will determine potential for atmospheric volatilization, environmental degradation, bioaccumulation, and metabolism. Generally, the higher chlorinated PCB congeners are more resistant to environmental breakdown and bioaccumulate in biota [5]. In addition, the positioning of the chlorine atoms will determine toxic effects. Dioxin-like congeners, for example, have a coplanar structure with no or maximum of one chlorine atom in the ortho positions. These congeners act through the aryl hydrocarbon receptor and cause toxicity similar to 2,3,7,8-tetrachlorodibenzodioxin (TCDD) [17].

Exposure to PCBs has been shown to have many adverse effects in wildlife and humans and, therefore, their persistence in the environment is of high concern. Most effects in humans have been observed in the settings of occupational exposures or poisoning incidents and include increase in liver enzymes, gastrointestinal symptoms, increased thyroid gland volume and risk for goiter, upper respiratory tract symptoms, joint pain, skin irritation and chloracne, hematological and immunological effects, neurological effects, reproductive effects, and cancer [5]. The International Agency for Research on Cancer has classified PCBs as Group 2A, probably carcinogenic to humans [18].

3. Worldwide biomonitoring data

PCB biomonitoring data for children, adolescents, and adults are available from several countries through national surveys, such as the National Health and Nutrition Examination Survey (NHANES) in the United States, the Canadian Health Measures Survey (CHMS), and the German Environmental Survey (GerES). Table 1 presents data from United States, Canada, Australia, Germany, Spain, and Belgium. In addition, monitoring of PCBs in remote populations, such as the Inuit, has been conducted [20,21]. Table 2 shows the sum of PCB congeners detected in breast milk samples around the world. Biomonitoring equivalents could be used to interpret this worldwide PCB biomonitoring data.

4. Absorption, distribution, metabolism, and excretion (ADME)

The ATSDR contains comprehensive data on the ADME of PCB congeners in animals and humans. The information described in this section comes mostly from that report [5,22]. The primary route of human exposure to PCBs is through oral ingestion from contaminated foods, drinking water, and breast milk. Other minor routes of exposure are inhalational and dermal absorption [22]. PCBs are lipophilic chemicals and, therefore, absorption from the gastrointestinal tract to blood lipids occurs passively. Once PCBs are absorbed they distribute preferentially to adipose tissue and liver where they may remain for years. Commonly detected congeners in human tissues are PCB-138, 153, and 180 [22].

PCBs can be metabolized by cytochrome P450 isozymes to polar metabolites which can then undergo phase 2 metabolism by conjugation with glutathione and glucuronic acid. Arene oxides of PCBs are formed by CYP 1A1, CYP 1A2, CYP 2B1, CYP 2B2, and CYP 3A and are transformed to hydroxylated aromatic compounds or methylsulfonyl metabolites. The rate of metabolism decreases with higher chlorinated congeners. Phenolic metabolites predominate, although other metabolites such as trans-dihydrodiols, polyhydroxylated congeners, and methyl ether derivatives may also be formed. Hydroxylated metabolites accumulate in lung, liver, and kidneys. Due to metabolism of parent compounds and selective retention of certain congeners in body tissues (e.g. PCB-153), the original mixture of PCBs ingested will not be the same as the congeners subsequently detected in serum, adipose, and breast milk.

PCBs are primarily eliminated in feces as parent form and as metabolites in urine and bile. Elimination half-lives vary greatly depending on congener; for example, half-life for PCB-28 is estimated at 1.4 years whereas the half-life for PCB-163 is more than 20 years. Other congeners have been found to have infinite half-lives, indicating repeated exposures or absence of decline over the experimental duration.

Table 1. Worldwide biomonitoring data.

Country	Population	Sample Size	Congener(s)	Level	Source
United States*	NHANES: 12+ years (2003–2004)	1896	PCB-153	GM (95% CI) (ng/g lipid): 19.8 (18.8, 20.9)	[21]
Canada*	CHMS: 20–79 years (2007–2009)	1666	PCB-118	GM (95% CI) (ng/g lipid): 4.43 (3.78, 5.20)	[22]
			PCB-138	10.13 (8.92, 11.51)	
			PCB-146	2.02 (1.76, 2.32)	
			PCB-153	18.31 (15.83, 21.16)	
			PCB-156	2.64 (2.40, 2.92)	
			PCB-163	3.22 (2.85, 3.65)	
			PCB-170	4.60 (4.09, 5.17)	
			PCB-180	15.21 (13.52, 17.11)	
			PCB-187	3.72 (3.21, 4.31)	
			PCB-194	2.91 (2.59, 3.29)	
			PCB-201	2.60 (2.33, 2.89)	
			PCB-203	2.25 (2.04, 2.47)	
Canada	Adult IHS: 18+ years (2007–2008)	2162	∑PCB	GM (95% CI) (ng/g lipid): 409 (389, 430)	[20]
Australia*	Pooled samples: 61+ years (2011–2012)	4 pools of 100 samples	PCB-138	AM (95% CI) (ng/g lipid): 13.4 (11.0, 15.7)	[69]
			PCB-153	18.9 (16.9, 20.9)	
			PCB-180	18.5 (15.3, 21.6)	
Germany*	GerES: 18–69 years (1998)	2823	PCB-138	GM (95% CI) (μg/L w.b.): 0.42 (0.41, 0.43)	[70]
		2818	PCB-153	0.68 (0.66, 0.70)	
		2822	PCB-180	0.44 (0.42, 0.45)	
Spain (Catalonia)*	CHIS: 18–74 years (2001–2002)	919	PCB-118	GM (range) (ng/g lipid): 17.4 (0.7, 465.0)	[71]
			PCB-138	63.5 (0.7, 1829.7)	
			PCB-153	91.2 (0.7, 1912.1)	
			PCB-180	75.1 (2.6, 2047.2)	
Belgium (Flanders)*	FLEHS: newborns (2002–2003)	1051	PCB-118	GM (95% CI) (ng/g lipid): 10.5 (10.1, 11)	[72]
		1054	PCB-138	15.3 (14.6, 16.2)	
		1065	PCB-153	25.9 (24.5, 27.5)	
		1050	PCB-170	7.7 (7.5, 8.0)	
		1071	PCB-180	20.4 (19.5, 21.3)	
	FLEHS: adolescents (2002–2006)	1645	∑PCB	GM (95% CI) (ng/g lipid): 68.0 (66.0 ,70.0)	[73]
	FLEHS: 50–65 years (2002–2006)	1530	∑PCB	333.0 (325.0, 341.0)	

Abbreviations: AM = arithmetic mean; CHIS = Catalan Health Interview Survey; CHMS = Canadian Health Measures Survey; CI = confidence interval; FLEHS = Flemish Environment and Health Survey; GerES = German Environmental Survey; GM = geometric mean; IHS = Inuit Health Survey; NHANES = National Health and Nutrition Examination Survey; PCB = polychlorinated biphenyl; w.b. = whole blood

* Data for PCB-138, PCB-153, and PCB-180 stratified by age groups presented in Aylward et al. [69].

Table 2. Worldwide biomonitoring data—breast milk (∑PCB).

Country	Population	Sample Size	Level (ng/g lipid)	Source
Canada	National Canadian Study (1992)	497	Mean: 238	[5]
Canada (Northern)	Women from Keewatin (1996–1997)	12	Mean: 247	[5]
United States —Akwesasne	Mohawk women residing near three hazardous waste sites (1991–1992)	40	Mean: 254	[5]
United States (rural New York)	Caucasian women (1991–1992)	45	Mean: 318	[5]
United States (New York)	Women residing in counties adjacent to Lake Ontario(1991–1993)	213	Mean: 271	[5]
Sweden	National Sweden Study (1992)	380	Mean: 380	[5]
Finland (urban)	Women giving birth in a maternity clinic in Helsinki (1992–1994)	20	Mean: 296	[5]
Finland (rural)	Women giving birth in a maternity clinic in Kuopio (1992–1993)	64	Mean: 198	[5]
Germany	Women 27–31 years, primiparous	14	Median: 450	[5,74]
Croatia	Women nursing hospitalized children (1994–1995)	45	Median: 212	[5]
Russia (industrialized)	Women from Murmansk (1993)	15	Mean: 429.4	[5]
Russia (industrialized)	Women from Monchegorsk (1993)	15	Mean: 490.5	[5]

Abbreviations: PCB = polychlorinated biphenyl; SD = standard deviation.

5. Guideline values

Guideline values for PCBs were collected from sources of the World Health Organization, European and North American jurisdictions (e.g. French Food Safety Agency, Health Canada, Environmental Protection Agency), and occupational organizations (e.g. National Institute for Occupational Safety and Health) (Tables 3 and Table 4) [5,22,24-30]. The reference values pertain to total PCBs, total non-dioxin like PCBs, dioxin-like PCBs, or PCB mixtures (e.g. Aroclor 1254) and ingestion through food, water or breast milk. The maximum reference value for ingestion is 5 μg/kg/day based on toxic effects of Phenochlor-DP6 in rats (CSHPF 1991). More recent sources have lowered ingestion references values, ranging from a low of 0.01 μg/kg/day for seven PCB indicators in food (AFSSA 2007) to a high of 0.13 μg/kg/day for total non-dioxin like PCBs (Health Canada 2010). For dioxins, a reference value of 2.33 pg TEQ/kg/day has been specified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 2001). A theoretical TDI for dioxin-like

PCBs is 1.63 pg TEQ/kg/day, given that these PCBs constitute 70% of dioxin mixtures [29]. The European Food Safety Authority 2005 indicated benchmark dose lower confidence limits in breast milk of 0.63–0.71 μg/g lipid for total PCBs based on cognitive outcomes in children exposed prenatally and 65 pg TEQ/g lipid for dioxin-like PCBs, polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF) based on neurological and immune effects with perinatal exposures. Three occupational reference standards for inhalational and dermal exposures were identified for Aroclor 1242 and Aroclor 1254 of either 0.5 mg/m^3 or 1 mg/m^3.

Table 3. Non-occupational PCB reference values.

Source	Route of Exposure	Reference Value
AFSSA 2013	All	Critical Concentration Threshold (vulnerable populations - pregnant women, women of child-bearing age, lactating women, and children under 3 years of age): 0.7 μg total PCB/g plasma lipids (rest of population): 1.8 μg total PCB/g plasma lipids
Health Canada 2010	Ingestion	TDI (total NDL-PCBs): 0.13 μg/kg/d
AFSSA 2007	Ingestion	TDI: 0.01 μg/kg/d (PCB indicators in food)
WHO 2003	Ingestion	TDI: 0.02 μg/kg/d (Aroclor 1254)
JECFA 2001	Ingestion	TDI (dioxins): 2.33 pg TEQ/kg/d Theoretical TDI for DL-PCBs (based on 70% of dioxin mixture): 1.63 pg TEQ/kg/d
EPA 2000	Ingestion	RfD Aroclor 1254: 0.02 μg/kg/d Aroclor 1016: 0.07 μg/kg/d Aroclor: 1248: not verifiable
ATSDR 2000	Ingestion	MRL (intermediate duration): 0.03 μg/kg/d MRL (chronic duration): 0.02 μg/kg/d (Aroclor 1254)
CSHPF 1991	Ingestion	TDI: 5 μg/kg/d (Phenochlor-DP6)
EFSA 2005	Ingestion (breast milk)	BMD: 0.94–1.05 μg total PCB/g lipid BMDL: 0.63–0.71 μg/g lipid
EFSA 2005	Ingestion (breast milk)	BMDL (PCDD/PCDF/PCB TEQ): 65 pg TEQ/g lipid

Abbreviations: AFSSA = French Food Safety Agency; ATSDR = Agency for Toxic Substances and Disease Registry; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; CSHPF = French High Council for Public Hygiene; DL-PCBs = dioxin-like polychlorinated biphenyls; EFSA = European Food Safety Authority; EPA = Environmental Protection Agency; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MRL = minimal risk level; NDL-PCBs = non dioxin-like polychlorinated biphenyls; PCB = polychlorinated biphenyl; PCDD = polychlorinated dibenzo-p-dioxins; PCDF = polychlorinated dibenzofurans; RfD = reference dose (oral); TDI = tolerable daily intake; TEQ = toxic equivalent; WHO = World Health Organization.

Table 4. Occupational PCB reference values.

Source	Route of Exposure	Reference Standard
NIOSH 2000	Inhalation	REL (10-hour)
		Chlorodiphenyl (42% or 54% Cl): 1 μg/m^3
ACGIH 1998	Inhalation, dermal	TLV (8 hour)
		Aroclor 1242: 1 mg/m^3
		Aroclor 1254: 0.5 mg/m^3
OSHA 1998	Inhalation, dermal	PEL (8-hours)
		Aroclor 1242: 1 mg/m^3
		Aroclor 1254: 0.5 mg/m^3

Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; Cl = chlorine; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure level; REL = recommended exposure limit; TLV = threshold limit value.

6. Pharmacokinetic modeling

The conversion of an external PCB reference value to a corresponding internal dose requires the use of a pharmacokinetic model that describes the absorption, distribution, metabolism and excretion of a chemical in the body. The model description can vary from simple relationship between dose exposure and internal metrics to highly complex structures with saturable processes. The level of detail in the model structure will depend on the quality and quantity of data available.

6.1. Modeling in animals

Several pharmacokinetic modeling studies of PCBs have been conducted in wildlife species, such as marine mammals, birds, and polar bears [31-39]. Pharmacokinetic modeling of PCBs has also been carried out in experimental animals, such as rats, mice and fish [40-49] and in swine and sheep [49]. PCB-153 has been most commonly modeled, although some work has also been done with other congeners and with PCB mixtures, such as Aroclor 1242, 1254, and 1260. One study focused on dioxin-like PCBs and their transfer from feed and soils to eggs of laying hens [50].

Models of various complexities have been developed with the simplest using a single compartment model that represented the whole organism [48]. In the single compartment model, bioaccumulation and elimination of Aroclor 1254 was studied in striped bass and parameters for absorption rate constant and elimination rate constant were estimated. Several studies employed a two-compartment model to represent, for example, blubber and rest of body in pilot whales [30], gut and rest of body in ringed seal [33], central and fat in laying hens [50], and yolk + albumen and embryo in herring gulls [36]. The most complex scheme was a physiologically-based pharmacokinetic (PBPK) model that incorporated multiple compartments to represent lungs, blood, perfused adipose, deep adipose, bone, brain, muscle, kidney, liver, and intestine in East Greenland polar bears [38]. A risk quotient analysis was conducted by estimating critical body residues of many contaminants, including PCBs, based on reproductive endpoints and then comparing observed contaminant levels measured in polar bears with the critical body residues to determine the proportion at risk for reproductive toxicity [38]. Other studies introduced greater complexity by modeling pregnancy, birth, and lactational processes in females [35] and incorporating

time-dependent variations in pharmacokinetic parameters [38,43,46,52].

The pharmacokinetic models were used to estimate lifetime exposure and bioaccumulation [31,32,33,36,37,52], influence of blubber temperature gradients on PCB concentrations [33], mother-offspring transfer of PCBs [35,36,41], protein binding [39], interactions between congeners [41,43], and the effect of chlorine position on PCB kinetic behaviour [43].

6.2. Modeling in humans

Pharmacokinetic modeling of PCBs has been conducted in pregnant women [52], lactating women [54,55,56], infants and children [57,58,59], women with breast cancer [60,61], Inuit [56,58,59,62,63,64] workers in a contaminated building [64], and general populations [66-69] (Table 5). As with animal modeling studies, the human pharmacokinetic models varied in complexity from simple one-compartment models [55,63,66,68,69], two-compartment models representing maternal and fetal lipids or liver and fat [53,64], to a 22 compartment model in lactating women [53]. The most commonly modeled congener was PCB-153, although other congeners, such as PCB-28, PCB-99, PCB-138, PCB-180, and PCB-199 were also examined. In breast cancer studies, pharmacokinetic models were used to estimate lifetime exposure or exposure during susceptible time windows, which may more accurately represent exposures at the time of cancer diagnosis [60,61]. Similarly, pharmacokinetic modeling was used to simulate exposures during specific time periods (i.e. prenatal, lactational, postnatal) and their association with mental and psychomotor development or behaviour in infants and children [57,58].

The modeling studies conducted for Inuit estimated PCB-153 intake through breast milk using reverse dosimetry [55], simulation of PCB-153 prenatal and postnatal exposures [57], infant exposure to PCB-138, 153, and 180 through placental transfer and breast feeding [58], fate of PCB-99 and PCB-153 in blood and other tissues using a generic PBPK model [61], estimation of PCB-153 cancer risk based on prenatal, postnatal, and lifetime exposures [62], and estimation of daily intake doses of PCB-77, PCB-126, PCB-153, and PCB-169 with comparison to a reference value [63].

7. Addressing challenges for the development of biomonitoring equivalents

The development of biomonitoring equivalents using pharmacokinetic modeling is complex for PCBs because of the presence of multiple congeners with different pharmacokinetic and toxicological properties. In addition, there are multiple pathways of exposure (e.g. ingestion, inhalation, dermal absorption, placental and lactational transfer), species differences in kinetics, and adverse endpoints which must be taken into consideration when modeling PCB pharmacokinetics.

The following is a list of procedural steps that needed to be followed to develop useful biomonitoring equivalents based on existing information:

1. Deciding which congeners to model: A list of PCB congeners that are abundant in biota and/or have high potential for toxicity, are shown in Box 1. These congeners fall under five homologue groups (i.e. tri-, tetra-, penta-, hexa-, and hepta-). Prioritization should be given to developing biomonitoring equivalents for these congeners as they are most relevant for risk assessments.

Table 5. Pharmacokinetic modeling of PCBs in humans.

Population	Model Purpose	Congener	Methods	Compartment	Selected Results	Reference
Pregnancy						
Pregnant women	Influence of pharmacokinetics on the association between prenatal PCB-153 exposure and reduced birthweight	PCB-153	Monte Carlo simulations run on model and simulated data used in linear regression analyses to estimate association between PCB-153 and birthweight	*n* = 2 Maternal lipids Fetal lipids	Model validated with observed data in 10 pregnant women Association was confounded by effects of gestational weight gain	[52]
Lactation						
Italian women	To estimate exposure scenarios	PCB-138 PCB-153 PCB-180	PBPK Model: Food was only source of exposure considered	*n* = 22	Model adequately predicted observed results for PCB-153 and PCB-180, but not for PCB-138	[53]
Mother-infant birth cohort from Slovakia	To use longitudinal measurements in development of exposure metrics	PCB-153	System type model	*n* = 1 Fat	PCB body burden was associated with duration of breast feeding in most children	[54]
Women (25-year old)	Population-scale lactational model	PCB-153	PBPK Model: Derived from a model in pregnant and lactating mice Reverse dosimetry to estimate PCB intake in Canadian Inuit	*n* = 5 Liver Fat Mammary tissue Blood Rest of body Flow-limited	Model predicted human biomonitoring data of milk content from all over the world Estimated intake in Canadian Inuit 0.294 µg/hr/kg—this intake generated milk levels similar to those reported	[55]

Infants and Children						
Spanish children	To investigate if lactational exposure is associated with effects on mental and psychomotor development; To compare with prenatal exposure	PCB-153	PBPK Model: To simulate prenatal and postnatal PCB-153 exposure Association between simulated PCB-153 concentrations and mental/psychomotor scores estimated with linear regression model	Same as Verner 2009 [58]	No association found between postnatal exposure and mental or psychomotor scores Prenatal exposure was associated with worse mental and psychomotor score	[56]
Inuit infants from Arctic Quebec	To simulate PCB levels during specific pre- and postnatal periods and assess association with infant behaviour	PCB-153	PBPK Model: To simulate prenatal and postnatal PCB-153 exposure Association between simulated PCB-153 concentrations and behavioural measures estimated with linear regression model	Same as Verner 2009 [58]	Pre- and postnatal exposures associated with inattention and increased activity at 11 months of age—inattention related to prenatal exposure and activity with postnatal exposure Strongest association during 4th month of life	[57]
Mothers and infants—validation with data from Nunavik population	Development of a generic PBPK for POPs to estimate infant exposure through placental transfer and breast feeding	PCB-138 PCB-153 PCB-180	PBPK Model: Absorption assumed to be 100% and direct input to liver	Mother: $n = 9$ Liver Brain Fat Richly-perfused Poorly-perfused Mammary tissue Uterus Placenta	Model predicted observed concentrations in mothers and infants from a Northern Quebec Inuit population	[58]

				Fetus Infant: $n = 5$ Liver Fat Richly-perfused Poorly-perfused Brain		
Women with Breast Cancer						
French women	To estimate lifetime pharmacokinetic profile of PCB-153 and compare with levels measured at the time of breast cancer diagnosis	PCB-153	PBPK Model: Exposure via oral intake, assuming complete bioavailability from GI tract and direct input to liver Area under lipid-adjusted blood concentration vs. time curve for each decade (proxy for total internal exposure) compared with measured concentrations	Same as Verner 2008 [60]	Single point PCB levels measured at time of diagnosis do not fully represent early-life exposures	[59]
Women in general	To estimate lifetime POP blood/tissue exposure during any time window of susceptibility for breast cancer (from 0–55 years of age)	PCB-153 PCB-180	PBPK Model: Exposure via oral intake, assuming complete bioavailability from GI tract and direct input to liver To simulate exposures throughout life, compartment size, blood flow, and biochemical properties change	$n = 9$ Fetus Placenta Uterine tissue Brain Fat Richly-perfused Slowly-perfused Liver Mammary	Lactation periods and weight profile had greatest impact on lifetime pharmacokinetic profile	[60]

			as a function of age, body weight, body height, and pregnancy periods	tissue—all perfused by blood circulation		
Inuit						
Greenlandic Inuit	To estimate fate of POPs in liver, blood, muscle, fat tissue	PCB-99 PCB-153	PBPK Model: General model for POPs	Based on model by Cahill (2003)	PCB-99 estimated mean: Blood—0.03 ng/g Fat—5.3 ng/g Liver—0.3 ng/g Muscle—0.2 ng/g PCB-153 estimated mean: Blood—1.4 ng/g Fat—313 ng/g Liver—18 ng/g Muscle—13 ng/g	[61]
Inuit	To estimate human lifetime health risks using pharmacokinetic modeling	PCB-153	Pharmacokinetic Model: PCB-153 concentration in total body lipid modelled as a function of age and calendar time Three life stages—prenatal exposure, postnatal exposure, lifetime exposure Non-cancer (HQ) and cancer risks estimated	$n = 1$ Fat	HQ > 1 between 1955–1987 for 90th population percentile and during 1956–1984 for 50th population percentile Cancer risk ranged from 4.6×10^{-5} to 1.8×10^{-6} for 90th percentile and 3.6×10^{-5} to 1.4×10^{-10} for 50th percentile with upper bound slope factor	[62]

Inuit (Arctic Quebec)	To estimate daily intake dose based on milk fat content and compare with reference intake	PCB-153 Non-ortho PCBs (PCB-77, 126, 169)	Modeling and comparison with reference intake	Based on model by Carrier (1991)[c] $n = 2$ Liver Fat	Estimated daily intake: PCB-153: 0.04 μg/kg/d PCDD/PCDF/NOC PCB: 7×10^{-6} μg/kg/d Calculated PCB-153 exceeds acceptable daily intake	[63]
Workers						
Contaminated building	To develop pharmacokinetic model for degradation in adult humans based on data from workers in a contaminated building	PCB-28 PCB-52	Model—first order elimination kinetics: $y_t = y_o (1 - e^{-kt})$	N/A	Estimated half-lives: PCB-28: 2.18 (95% CI: 1.91–2.54) y PCB-52: 3.95 (95% CI: 3.55–4.45) y	[64]
General Populations						
General	To estimate chemical half-lives	PCB-199	Whole body primary biotransformation half-life (HL_B) estimated from whole body total elimination half-life (HL_T) using a one-compartment model	$n = 1$	Half-life of 83 000 days calculated Low rates of predicted passive chemical elimination (HL_B approximates HL_T)	[65]
General	To develop a generic model that estimates bioaccumulative potential of a chemical (hBCF)	PCB-77 PCB-80 PCB-136 PCB-153 PCB-155	PBPK Model: Assumed 100% intestinal absorption	$n = 4$ Absorption compartment Portal vein Systemic compartment Liver	Model was validated for several chemicals by comparing model simulations with literature human data and PBPK model results	[66]

General	To estimate intrinsic human elimination half-lives of PCBs (i.e. correcting for body weight and ongoing exposure) using population data	PCB-28 PCB-52 PCB-105 PCB-118 PCB-138 PCB-153 PCB-170 PCB-180 PCB-187	PBPK Model: Described changes in body concentrations as function of age and calendar time (incorporated age-dependent growth of body and lipid mass, age- and body-weight dependent dietary intake) Derived from Ritter 2009 [75]	$n = 1$	Intrinsic half-lives derived e.g. PCB-153: 14.4 y PCB-170: 15.5 y PCB-180: 11.5 y Distinction is needed between apparent and intrinsic half-lives	[67]
General	To model POPs burden and clearance throughout a lifetime, taking into account changes in age, body composition, and environmental concentrations	PCB-101	Simple model with an age-dependent function allowing for growth in body fat and subsequent compound dilution with age	$n = 1$ Fat	Model reconstructed lifetime exposure in UK population born between 1920 and 1980	[68]

Abbreviations: CI = confidence interval; GI = gastrointestinal; hBCF = human bioconcentration factor; HQ = hazard quotient; NOC = non-ortho coplanar; PBPK = physiologically-based pharmacokinetic; PCB = polychlorinated biphenyl; PCDD = polychlorinated dibenzodioxin; PCDF = polychlorinated dibenzofuran; POP = persistent organic pollutant; UK = United Kingdom.

Box 1. Abundant and/or toxic PCB congeners.

PCB-28 (2,4,4^{I} trichlorobiphenyl)	PCB-105 (2,3,3^{I},4,4^{I} pentachlorobiphenyl)	PCB-156 (2,3,3^{I},4,4^{I},5 hexachlorobiphenyl)
PCB-52 (2,2^{I},5,5^{I} tetrachlorobiphenyl)	PCB-118 (2,3^{I},4,4^{I},5 pentachlorobiphenyl)	PCB-163 (2,3,3^{I},4^{I},5,6 hexachlorobiphenyl)
PCB-74 (2,4,4^{I},5 tetrachlorobiphenyl)	PCB-125 (2^{I},3,4,5,6^{I} pentachlorobiphenyl)	PCB-168 (2,3^{I},4,4^{I},5^{I},6 hexachlorobiphenyl)
PCB-77 (3,3^{I},4,4^{I} tetrachlorobiphenyl)	PCB-126 (3,3^{I},4,4^{I},5 pentachlorobiphenyl)	PCB-169 (3,3^{I},4,4^{I},5,5^{I} hexachlorobiphenyl)
PCB-100 (2,2^{I},4,4^{I},6 pentachlorobiphenyl)	PCB-128 (2,2^{I},3,3^{I},4,4^{I} hexachlorobiphenyl)	PCB-170 (2,2^{I},3,3^{I},4,4^{I},5 heptachlorobiphenyl)
PCB-101 (2,2^{I},4,5,5^{I} pentachlorobiphenyl)	PCB-138 (2,2^{I},3,4,4^{I},5^{I} hexachlorobiphenyl)	PCB-180 (2,2^{I},3,4,4^{I},5,5^{I} heptachlorobophenyl)
PCB-104 (2,2^{I},4,6,6^{I} pentachlorobiphenyl)	PCB-153 (2,2^{I},4,4^{I},5,5^{I} hexachlorobiphenyl)	PCB-190 (2,3,3^{I},4,4^{I},5,6 heptachlorobiphenyl)

2. Choosing a guidance value: As described in Tables 3 and Table 4, different organizations have formulated various guideline values based mostly on mixtures of PCB congeners rather than individual congeners. Therefore, it will be necessary to make assumptions about the constitution of these mixtures so that biomonitoring equivalents for individual congeners can be derived.

3. Parameterization of pharmacokinetic models: A full PBPK model requires input of several parameters. Where possible, these parameters should be based on human data to minimize species differences. However, in the absence of such data, animal data or theoretical structural equations, both of which introduce greater degrees of uncertainty in the models, can be used. The ATSDR contains data on the absorption, distribution, metabolism, and excretion of PCB congeners as described previously [5,22]. In addition, Parham et al. devised structural regression formula to calculate blood-adipose partition coefficients and metabolic rates for any of the 209 congeners based on structural characteristics [66,67]. An important component of the modeling process will be to evaluate and transparently declare the confidence in the inputted parameters.

4. Minimizing complex scenarios: Depending on the research question, initial modeling attempts should focus on the most common routes of exposure. In general populations, ingestion of contaminated foods will be the primary exposure pathway. For lactating women, elimination of PCBs through breast milk should additionally be considered.

8. Conclusion

Biomonitoring equivalents for PCBs will be useful from a risk assessment standpoint because they can be used to interpret the biomonitoring data collected from populations around the globe. The percentage within and exceeding guidance values can be calculated for full survey samples, as well as for sensitive sub-populations, such as children, pregnant women, women of childbearing age and the elderly. These comparisons will help to contextualize the results of biomonitoring surveys and provide evidence on which to base public health interventions for the percentage of the population exceeding guidelines. In this paper we have reviewed key information and challenges for deriving biomonitoring equivalents for PCBs. Modelers, environmental epidemiologists, and risk assessors can make use of this information to evaluate worldwide PCB biomonitoring data and develop international guidelines.

Acknowledgments

We would like to thank Stella Chen for assisting with literature acquisition, organization, and data retrieval. We also acknowledge support from the Northern Contaminants Program (NCP), Canada Research Chair, and Health Canada.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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