WHO FOOD ADDITIVES SERIES: 71-S1

Prepared by the eightieth meeting of the
Joint FAO/WHO Expert Committee
on Food Additives (JECFA)

Safety evaluation of certain food additives and contaminants

Supplement 1:

Non-dioxin-like polychlorinated biphenyls

Food and Agriculture Organization of the United Nations

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PREFACE

The monograph contained in this volume was prepared at the eightieth meeting of the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA), which met at FAO headquarters in Rome, Italy, on 16–25 June 2015. This monograph summarizes the data on one contaminant group reviewed by the Committee. Monographs on seven food additive groups discussed at the meeting have been published in WHO Food Additives Series 71, and a monograph on a second contaminant group will be published as a separate supplement in WHO Food Additives Series 71.

The eightieth report of JECFA has been published by WHO as WHO Technical Report No. 995. Reports and other documents resulting from previous meetings of JECFA are listed in Annex 1. The participants in the meeting are listed in Annex 3 of the present publication.

JECFA serves as a scientific advisory body to FAO, WHO, their Member States and the Codex Alimentarius Commission, primarily through the Codex Committee on Food Additives, the Codex Committee on Contaminants in Food and the Codex Committee on Residues of Veterinary Drugs in Foods, regarding the safety of food additives, residues of veterinary drugs, naturally occurring toxicants and contaminants in food. Committees accomplish this task by preparing reports of their meetings and publishing specifications or residue monographs and dietary exposure and toxicological monographs, such as that contained in this volume, on substances that they have considered.

The monograph contained in this volume is based on a working paper that was prepared by JECFA experts. A special acknowledgement is given at the beginning of the monograph to those who prepared this working paper. The monograph was edited by M. Sheffer, Ottawa, Canada.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the organizations participating in WHO concerning the legal status of any country, territory, city or area or its authorities, or concerning the delimitation of its frontiers or boundaries. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the organizations in preference to others of a similar nature that are not mentioned.

Any comments or new information on the biological or toxicological properties of or dietary exposure to the compounds evaluated in this publication should be addressed to: WHO Joint Secretary of the Joint FAO/WHO Expert Committee on Food Additives, Department of Food Safety and Zoonoses, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.

Non-dioxin-like polychlorinated biphenyls

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1. Explanation

1.1 Introduction

Polychlorinated biphenyls (PCBs) are chemically stable aromatic chlorinated hydrocarbons. They were first produced commercially around 1930 and for the next 5 decades found a wide range of industrial applications as a result of their physicochemical properties of low electrical conductance, fire resistance, resistance to thermal breakdown and chemical inertness. Their main uses included dielectric fluids in electrical equipment such as transformers and capacitors, heat transfer agents in mechanical operations, plasticizers (e.g. in carbonless copy paper), lubricants, inks and surface coatings. The manufacture, distribution and use of PCBs have been widely discontinued or banned, but PCBs may be found in equipment still in use today. Environmental contamination by PCBs from open, partially closed or closed uses and from disposal has been widespread (UNEP, 1999). The most abundant PCBs are readily biodegradable. However, some PCBs are very persistent in the environment; hence, they are present as contaminants, especially in fatty foods, and they bioaccumulate in the adipose tissue of exposed animals and humans. As a consequence of environmental contamination by PCBs and their toxicity, many countries restricted the marketing and use of PCBs in the 1970s and 1980s. In 2001, PCBs were classified as persistent organic pollutants (POPs) under the Stockholm Convention on POPs; signatories agreed to ban all production of PCBs, to promote control and reduction of exposures and risks and to eliminate all uses by 2025 (Stockholm Convention, 2009).

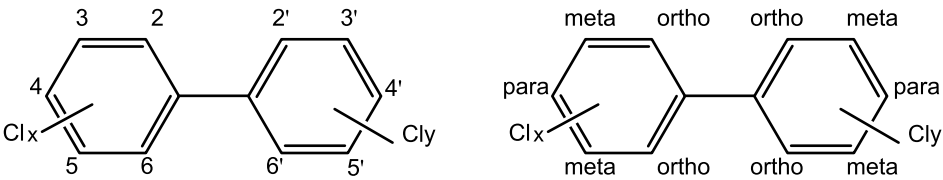
The Committee was requested to undertake an assessment of the non-dioxin-like polychlorinated biphenyls (NDL-PCBs) by the Codex Committee on Contaminants in Foods. The Committee has not previously evaluated NDL-PCBs specifically. The Committee previously reviewed PCBs at its thirty-fifth meeting, when it concluded that it was impossible to establish a precise numerical value for a tolerable intake in humans because of limitations in the available data and the ill-defined nature of the materials that were used in feeding studies (Annex 1, reference *88*). Dioxin-like PCBs (DL-PCBs), together with polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), were reviewed by the Committee at its fifty-seventh meeting (Annex 1, reference *154*).

NDL-PCBs were comprehensively reviewed in 2005 by the European Food Safety Authority (EFSA, 2005) and by the United States Agency for Toxic Substances and Disease Registry (ATSDR, 2000, 2011), and the present Committee used these reviews as a starting point for its evaluation, taking particular account of new studies published subsequent to the reviews.

1.2 Compounds considered and nomenclature

PCBs are a class of chemicals that have a biphenyl structure of two linked benzene rings in which 1–10 chlorine atoms substitute the hydrogen atoms on the rings (Erickson, 1986) (Fig. 1). There are 209 possible congeners in total, based on the substitution positions along the phenyl rings.

Fig. 1
General structure of PCBs



where x + y = 1–10

PCBs were manufactured as complex mixtures of congeners by the progressive chlorination of batches of biphenyl until a target percentage of chlorine by weight was achieved. Of the 209 congeners that are theoretically possible, only about 130 have been identified in commercial products that were marketed. Commercial PCBs were sold not as specified compositions of congeners, but on the basis of their physical properties, in particular per cent chlorination and molecular weight. The absolute congener composition of commercial PCB mixtures, as well as the content of impurities, such as PCDFs, naphthalenes and quaterphenyls, varied from batch to batch.

To standardize the identification of the individual PCB congeners, a numbering system was developed by Ballschmiter & Zell (1980), following the International Union of Pure and Applied Chemistry (IUPAC) rules for characterization. A couple of octachlorinated congeners were initially misnumbered, but these were subsequently corrected (Ballschmiter, Schäfer & Buchert, 1987). In this scheme, a number, called the "BZ number", is attributed to each individual congener. This number correlates the structural arrangement of the PCB congener and ascending order of number of chlorine substitutions within each sequential homologue, as shown in Table 1. Thus, congeners are numbered from PCB 1 to PCB 209, a useful shorthand nomenclature. However, it is important to note that it obscures the chemical identity of the congener and does not strictly follow the IUPAC rules.

Table 1

PCB congeners showing the BZ number[a] and correspondence between the positions of chlorine atoms on each phenyl ring of the PCBs[b]

Position of chlorine atom on each ring	2	3	4	2,3	2,4	2,5	2,6	3,4	3,5	2,3,4	2,3,5	2,3,6	2,4,5	2,4,6	3,4,5	2,3,4,5	2,3,4,6	2,3,5,6	2,3,4,5,6
None	1	2	3	5	7	9	10	12	14	21	23	24	29	30	38	61	62	65	116
2′	4	6	8	16	17	18	19	33	34	41	43	45	48	50	76	86	88	93	142
3′		11	13	20	25	26	27	35	36	55	57	59	67	69	78	106	108	112	160
4′			15	22	28	31	32	37	39	60	63	64	74	75	**81**	**114**	115	117	166
2′,3′				40	42	44	46	56	58	82	83	84	97	98	122	129	131	134	173
2′,4′					47	49	51	66	68	85	90	91	99	100	**123**	137	139	147	181
2′,5′						52	53	70	72	87	92	95	101	103	124	141	144	151	185
2′,6′							54	71	73	89	94	96	102	104	125	143	145	152	186
3′,4′								**77**	79	**105**	109	110	**118**	119	**126**	**156**	158	163	190
3′,5′									80	107	111	113	120	121	127	159	161	165	192
2′,3′,4′										128	130	132	138	140	**157**	170	171	177	195
2′,3′,5′											133	135	146	148	162	172	175	178	198
2′,3′,6′												136	149	150	164	174	176	179	200
2′,4′,5′													153	154	**167**	180	183	187	203
2′,4′,6′														155	168	182	184	188	204
3′,4′,5′															**169**	**189**	191	193	205
2′,3′,4′,5′																194	196	199	206
2′,3′,4′,6′																	197	201	207
2′,3′,5′,6′																		202	208
2′,3′,4′,5′,6′																			209

[a] The revised PCB numbering system, including the revised numbering of congeners 107–109 and 199–201. For a number of PCB congeners, the indicated (truncated) structural names do not strictly adhere to the IUPAC rules (primed and unprimed numbers are interchanged). A comprehensive survey of PCB nomenclature, including IUPAC names, is given in Mills, Thal & Barney (2007). The names of the PCB congeners can be obtained directly from the table. For example, PCB 74 is 2,4,4′,5-tetrachlorobiphenyl, PCB 99 is 2,2′,4,4′,5-pentachlorobiphenyl, PCB 138 is 2,2′,3,4,4′,5′-hexachlorobiphenyl, PCB 153 is 2,2′,4,4′,5,5′-hexachlorobiphenyl, PCB 170 is 2,2′,3,3′,4,4′,5-heptachlorobiphenyl, PCB 180 is 2,2′,3,4,4′,5,5′-heptachlorobiphenyl, PCB 194 is 2,2′,3,3′,4,4′,5,5′-octachlorobiphenyl, PCB 206 is 2,2′,3,3′,4,4′,5,5′,6-nonachlorobiphenyl and PCB 209 is 2,2′,3,3′,4,4′,5,5′,6,6′-decachlorobiphenyl. The PCB congeners will be referred to only by number in the remainder of this monograph.

[b] Dioxin-like PCBs are indicated in grey shading and bold type.

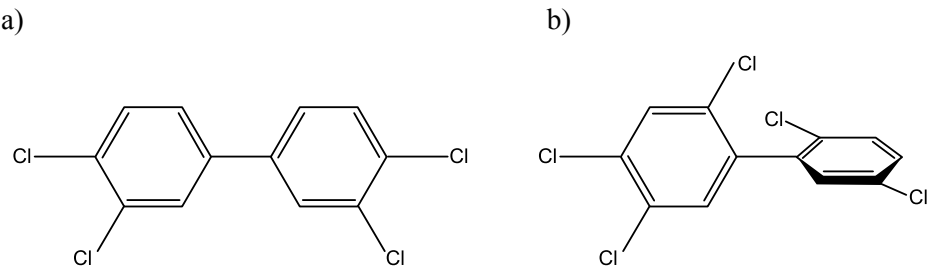
Source: Adapted from IARC (2015)

International bodies have identified seven PCBs that can be used to characterize the presence of PCB contamination. Six of these seven are NDL-PCBs (PCB 28, PCB 52, PCB 101, PCB 138, PCB 153 and PCB 180), and one is a DL-PCB (PCB 118). These seven PCBs are often called "indicator PCBs" (European Commission, 1999). In this monograph, which is concerned only with NDL-PCBs, the term "indicator PCBs" includes only the six NDL-PCBs.

PCBs exhibit different toxicological effects depending on the site of chlorine substitution on the phenyl rings. Congeners with no chlorine substitution in the *ortho* position (PCBs 77, 81, 126 and 169) or those congeners having only *ortho* substitution in one position (i.e. mono-*ortho*-substituted PCBs 105, 114, 118, 123, 156, 157, 167 and 189) have toxicological activity similar to that of the PCDDs and PCDFs owing to their ability to adopt a similar planar structure (see Fig. 2a) and to bind strongly to the aryl hydrocarbon receptor (AhR). Hence, these 12 PCBs are referred to as DL-PCBs. The remaining 197 congeners – that is, those not conforming to the planar structure (see Fig. 2b) – are referred to as NDL-PCBs. The NDL-PCBs have different toxicological activity compared with the DL-PCBs and PCDDs/PCDFs, the end-points most sensitive to NDL-PCB exposure being toxicity to the liver and thyroid (Bjermo et al., 2013). A few of the NDL-PCBs have hybrid activity, showing both dioxin-like and non-dioxin-like activities. In the present evaluation, only those congeners with non-dioxin-like activity are considered.

Fig. 2

Examples of a) a planar PCB (PCB 77) and b) a non-planar, di-*ortho*-substituted PCB (PCB 101)



Commercial mixtures of PCBs have been marketed in the past with various tradenames, depending on the country (e.g. Aroclors, Kanechlors, Clophens, Fenclors, Phenoclors). They comprise mainly coplanar DL-PCBs and are not further discussed, except in some toxicity studies in which their effects are compared with those of NDL-PCBs.

1.3 General considerations on exposure sources and exposure measurements

The major source of exposure to PCBs for the general population is through consumption of contaminated foods in the diet, which accounts for more than 90% of total exposure. NDL-PCBs account for the majority of the total PCB contamination in food, the remainder being DL-PCBs. Dermal and inhalation routes of exposure are of minor importance, except for occupationally exposed individuals (ATSDR, 2000; EFSA, 2005).

Some lower chlorinated PCB congeners are readily metabolized, but some higher chlorinated congeners are more stable and accumulate within the food-chain, particularly in foods of animal origin. Fish and fish products, including fish oils, generally contain the highest concentrations of PCBs, followed by milk, eggs and dairy products and meat and meat products. Cereals and cereal products, fruits and vegetables contain only low amounts of PCBs. Breastfeeding is a major route of exposure for infants. Ingestion of contaminated soil or dust can be a minor route of exposure for children (EFSA, 2005; Elabbas et al., 2013).

The Stockholm Convention on POPs recommends measurement of the six indicator PCBs (PCB 28, PCB 52, PCB 101, PCB 138, PCB 153 and PCB 180) to characterize contamination by PCBs (UNEP, 2013). These are all NDL-PCB congeners, and they were chosen because they are found at high concentrations in the environment, in food or in human fluids/tissues.

2. Biological data

2.1 Biochemical aspects

2.1.1 Absorption, distribution and elimination

PCB congeners are lipid soluble. They are generally well absorbed from the gastrointestinal tract by passive diffusion in laboratory rodents, monkeys and humans. Absorption and excretion of PCBs from the diet are congener specific; the major determinants of the amount of a particular congener that is absorbed and excreted are the existing concentration in blood and the body burden of the congener at the time of the exposure. In rats, lower chlorinated congeners with six or fewer chlorine atoms have greater than 90% absorption, and higher chlorinated congeners have about 75% absorption (Albro & Fishbein, 1972; ATSDR, 2000; EFSA, 2005).

Dietary exposures are to mixtures of PCB congeners. The profile of PCB congeners in human serum immediately following an exposure reflects that of the exposure source, but the profile begins to change within 4–24 hours as a result of selective metabolism, excretion and deposition. Thus, in most cases, the PCB profile in adults represents a steady-state body burden that does not match the profile of commercial PCB mixture formulations (ATSDR, 2000).

PCBs are rapidly distributed to all body compartments and particularly to highly perfused areas, such as liver and muscle. The toxicokinetics of PCBs is similar in humans and experimental animals. However, the rates of metabolism and excretion may be slower in humans, as indicated by the longer half-lives of certain congeners in humans (Chen et al., 1982; Bühler, Schmid & Schlatter, 1988).

Some PCBs have apparent half-lives in blood as short as a week or so, but the high lipid solubility of many PCBs results in much longer half-lives, with retention and accumulation in adipose tissue. Higher chlorinated PCB congeners with only isolated non-chlorinated carbons show the longest half-lives, and therefore the greatest accumulation; for example, PCB 138, PCB 153 and PCB 180 have half-lives of several years in humans, as shown in Table 2. It should be noted that Table 2 shows apparent half-lives. These reflect the overall effect of intrinsic elimination, ongoing exposure and body weight changes on concentrations as a function of time (Ritter et al., 2011). As can be seen from Table 2, apparent half-lives are subject to considerable variability, much more so than intrinsic half-lives, which reflect only interindividual variability of intrinsic elimination at similar concentrations. Ritter et al. (2011) proposed intrinsic half-lives at background levels for several PCBs and recommended the following values for five of the six indicator PCBs: PCB 28, 5.5 years; PCB 52, 2.6 years;

PCB 138, 10.8 years; PCB 153, 14.4 years; and PCB 180, 11.5 years. Ritter et al. (2011) recommended that these intrinsic half-lives be used to translate between exposure and body concentration when pharmacokinetic models are used.

Table 2
Indicative apparent half-lives of the six indicator PCBs

		Estimated half-life (years)					
Study	***n***	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**
Yakushiji et al. (1984)	8	3.0	–	–	–	–	–
Brown et al. (1989)	194	1.4	–	–	–	–	–
Wolff, Fischbein & Selikoff (1992)	165	4.8	–	–	–	–	–
Ritter et al. (2011)	229	5.6	–	–	–	–	–
Wolff, Fischbein & Selikoff (1992)	165	–	5.5	–	–	–	–
Ritter et al. (2011)	229	–	2.6	–	–	–	–
Wolff, Fischbein & Selikoff (1992)[a]	165	–	–	5.7	–	–	–
Chen et al. (1982)	17	–	–	–	32	–	–
Chen et al. (1982)[b]	17	–	–	–	20	–	–
Yakushiji et al. (1984)	8	–	–	–	16.3	–	–
Brown et al. (1989)	194	–	–	–	6–7	–	–
Wolff, Fischbein & Selikoff (1992)	165	–	–	–	16.7	–	–
Ryan et al. (1993)	16	–	–	–	3.4	–	–
Masuda (2001)[c]	8	–	–	–	4.5	–	–
Masuda (2001)[c]	8	–	–	–	12.8	–	–
Ritter et al. (2011)	229	–	–	–	8.4	–	–
Chen et al. (1982)	17	–	–	–	–	47	–
Chen et al. (1982)[b]	17	–	–	–	–	26	–
Yakushiji et al. (1984)	8	–	–	–	–	27.5	–
Brown et al. (1989)	194	–	–	–	–	12.4	–
Ryan et al. (1993)	16	–	–	–	–	3.8	–
Masuda (2001)[c]	8	–	–	–	–	4.2	–
Masuda (2001)[c]	8	–	–	–	–	9.1	–
Ritter et al. (2011)	229	–	–	–	–	13.8	–
Wolff, Fischbein & Selikoff (1992)	165	–	–	–	–	–	9.9
Ryan et al. (1993)	16	–	–	–	–	–	4.3
Masuda (2001)[c]	8	–	–	–	–	–	6.0
Masuda (2001)[c]	8	–	–	–	–	–	16.7
Ritter et al. (2011)	229	–	–	–	–	–	5.5

[a] Co-elution with PCB 99.
[b] Recalculated by Shirai & Kissel (1996).
[c] Same patients (Yusho), but observations are from different time intervals after the exposure event.
Source: Adapted from Ritter et al. (2011)

It can be seen from Table 2 that estimates of PCB half-lives in humans, derived from successive body burden measurements, vary widely. As discussed by Shirai & Kissel (1996), differences in physiological processes among individuals and in congener properties are to be expected, but these factors do not appear to explain all the variation. Very short half-lives (<1 year) are unlikely for congeners most frequently found in human blood, because the exposures required to sustain observed body burdens are too large. Very long half-lives (>10 years) may be artefacts of confounding by ongoing exposures, which is a common effect at low body burdens.

PCB parent compounds and methyl sulfone PCB metabolites are lipophilic and are associated with lipoproteins in plasma and persistence in tissue lipids. Methyl sulfone metabolites are slightly less lipophilic than their parent compounds and are present only at low concentrations in human blood. However, for some methyl sulfone metabolites, their accumulation is cell and tissue specific (liver and lung), and some are present in adipose tissue at concentrations higher than those of their respective parent compounds. In contrast, the more polar hydroxy metabolites of PCBs are transported via blood proteins and are more readily excreted. The highest amounts of PCBs are usually found in the liver, fat, skin and breast milk (ATSDR, 2000; EFSA, 2005; Elabbas et al., 2013).

Distribution of PCBs from the maternal to the fetal compartment is by passive diffusion across the placenta, and there is a correlation between maternal and cord serum concentrations (ATSDR, 2000). However, body burdens are lower in the fetus than in the mother because of the lower blood lipid and body fat content in the fetus (EFSA, 2005). In an ex vivo human placental transfer model, PCB 52 and PCB 180 were shown to transfer across the placenta within 2.5 hours, transfer of PCB 180 being more rapid (Correia Carreira et al., 2011). Hydroxy metabolites of PCBs are efficiently transferred from maternal to fetal blood via the placenta (Grimm et al., 2015).

Postnatally, the amounts of PCB parent compounds and methyl sulfone PCB metabolites transferred to suckling animals are higher than the amounts transferred to the fetus, whereas transfer of the hydroxy-PCB metabolites through maternal milk is low (ATSDR, 2000; EFSA, 2005). In the breastfed human infant exposed to typical levels of NDL-PCBs in maternal milk, a rate of absorption of greater than 90% of the PCB content has been demonstrated (McLachlan, 1993; Abraham et al., 1994; Dahl et al., 1995; ATSDR, 2000). In human milk, concentrations of PCBs are highest in primiparous women and generally decline with duration of breastfeeding (ATSDR, 2000).

The major routes of excretion are through the faeces for the PCB parent compounds and lipophilic methyl sulfone metabolites and through the urine and faeces for the hydroxy metabolites. For the majority of PCB excretion, biotransformation is required (ATSDR, 2000). There is significant elimination

of unchanged PCBs and their methyl sulfone metabolites via breast milk (EFSA, 2005).

2.1.2 Biotransformation

The metabolism of PCBs has been recently reviewed by Grimm et al. (2015). Rates of metabolism vary greatly across species. Rates of PCB metabolism also vary with the number and position of the chlorine atoms in the different congeners. In all species studied, PCB congeners with adjacent unsubstituted (vicinal) carbon atoms in the *meta* and *para* positions are more readily metabolized, whereas congeners without such adjacent unsubstituted carbon atoms are generally metabolized and cleared very slowly. PCBs with higher numbers of chlorine atoms are generally metabolized more slowly, and the PCBs that are not readily metabolized and cleared concentrate in adipose tissue. In humans, PCB 153 is often the most prevalent congener detected because of its occurrence in exposure media and its slow rate of biotransformation (Matthews & Dedrick, 1984; ATSDR, 2000).

Biotransformation of PCBs involves oxidation by cytochrome P450 (CYP) enzymes. Exposure to PCBs generally induces the enzymes that metabolize them. NDL-PCBs are metabolized by CYP2B or by CYP2C and CYP3A, whereas DL-PCBs are metabolized by CYP1A (James, 2013; Quinete et al., 2014).

NDL-PCBs have several routes of metabolism. They can be oxidized across the aromatic ring, the *meta* and *para* positions being the preferred sites, to one or more unstable, intermediate arene oxides. These can then spontaneously rearrange to produce a hydroxy metabolite. Arene oxides of PCBs are reactive electrophilic intermediates that may also form adducts to biomacromolecules (DNA and proteins) and to lipids. PCBs that oxidize to more stable arene oxides are subsequently reduced by epoxide hydrolase to dihydroxy metabolites, also known as dihydrodiols. Dihydrodiols can then be aromatized and form catechol metabolites, which are in equilibrium with their oxidized form, the corresponding hydroquinone and quinone. Hydroquinones and quinones are reactive intermediates with the potential for adduct formation (EFSA, 2005).

Approximately 40 different hydroxy-PCBs have been identified in human blood. Hydroxy-PCB concentrations in human plasma or serum are in a range similar to those of many parent PCB congeners, except for those PCBs that are the most prevalent or persistent; for example, plasma concentrations of the most abundant hydroxy-PCB congeners reach about 30% of those determined for PCB 153, with a variation among studies of 11–82%. Thus, hydroxy-PCBs present at the highest concentrations always exceed the concentrations of a large number of individual PCB congeners (Grimm et al., 2015).

In the case of PCB congeners that do not easily form arene oxides, there is an alternative metabolic pathway of direct insertion of a hydroxyl group to form a monohydroxy metabolite, usually at an open *meta* position (Bandiera, 2013). Hydroxy metabolites are excreted as such or can be conjugated with glucuronide or sulfate by uridine diphosphate-glucuronosyltransferase (UGT), although there is little evidence that the higher chlorinated metabolites are conjugated (James, 2013). Of the 50 or so potential hydroxy metabolites, only five are retained in the blood and are bound to transthyretin, which normally binds thyroxine (T_4). Hydroxy-PCBs that are substituted in the *para* position with chlorine atoms on each side of the hydroxyl group are known to be strongly retained in human blood (Letcher, Klasson-Wehler & Bergman, 2000), binding to transthyretin with an affinity that is, in general, greater than that of the natural ligand, T_4 (Lans et al., 1993). The concentrations of hydroxy metabolites in blood are around 5–10 times lower than those of the most persistent PCB congeners (EFSA, 2005; Quinete et al., 2014).

Another route of metabolism for PCBs with non-chlorinated *meta/para* positions on at least one of the phenyl rings is rapid metabolism to a methyl sulfone. This occurs in a multistep pathway involving glutathione conjugation catalysed by glutathione *S*-transferase (GST), degradation via the mercapturic acid pathway, and excretion into the bile and the large intestine, followed by cleavage by microbial C–S lyase. The thiols formed are methylated, reabsorbed and further oxidized on the sulfur atom to the corresponding methyl sulfone, which can then be distributed to the tissues through the blood. This enterohepatic recirculation may account for some of the long retention times of methyl sulfone metabolites (ATSDR, 2000; James, 2013). Fifty or more methyl sulfone PCB metabolites have been detected in human serum, but so far the majority of these have not been structurally identified (Grimm et al., 2015). Methyl sulfone PCB metabolites are present primarily in body lipids and accumulate with high selectivity in certain tissues, such as the liver and lung. In humans, those that have been identified are generally present only at low concentrations of 1% or less, compared with parent PCB concentrations (Grimm et al., 2015).

In a recent study, the association between serum levels of 16 PCBs and genotype was analysed in 922 individuals 70 years of age from Uppsala, Sweden, focusing on CYP2B6 variation, to determine whether differences in metabolism might identify susceptible persons. The study included seven DL-PCBs and nine NDL-PCBs; the NDL-PCBs were PCB 74, PCB 99, PCB 138, PCB 153, PCB 170, PCB 180, PCB 194, PCB 206 and PCB 209. PCB concentrations were similar, or comparable, to those in other general European populations. The relationship was complex, with effects on mapping to CYP2B6 mediated predominantly through PCB 99, an NDL-PCB, and PCB 118, a DL-PCB. There were weaker associations with PCB 138 and PCB 153, but these were extinguished after adjusting for PCB

99 levels, suggesting that the association for these two PCBs is mediated through PCB 99 (Ng et al., 2015).

Both hydroxylated and methyl sulfone PCB metabolites can have biological activity. For example, methyl sulfone metabolites can have anti-estrogenic activity, bind to glucocorticoid receptors, reduce blood thyroid hormone levels and affect reproduction (Letcher et al., 2002). Thus, for those parent PCB congeners that are rapidly metabolized to persistent methyl sulfone metabolites, it is more relevant to assess the effects of those metabolites with the highest retention potential than to assess the effects of parent congeners, as the latter are present in only trace or non-detectable amounts (EFSA, 2005; James, 2013). Similarly, the most relevant hydroxy-PCBs are those that are persistent – that is, generally those with chlorine atoms on the adjacent carbons to the hydroxyl group and containing five or more chlorine atoms – which can exert toxicological effects on the thyroid (ATSDR, 2000; Quinete et al., 2014).

2.1.3 Receptor interactions and relationship to toxicity

Interactions with several nuclear receptors have been reported for PCBs, and these strongly depend on the number of chlorine atoms and their positions in the molecule. The binding of PCBs to AhR is by far the best studied, and structure–activity relationships (SARs) for the binding of PCBs are well known. PCBs lacking *ortho*-substituted chlorine atoms (e.g. PCBs 77, 81, 126 and 169) have the highest binding affinity for AhR and induce the typical dioxin-like activity seen at very low dose levels (Safe, 1984, 1993). With increasing chlorine substitution in the *ortho* position, the affinity for AhR rapidly decreases. As a result, congeners with two or more *ortho* chlorine atoms are considered to be NDL-PCBs (e.g. PCB 153). PCBs with one *ortho* chlorine atom (e.g. PCBs 105, 114, 118, 123, 156, 157, 167 and 189) do still bind to AhR and exert biological and toxicological effects that are similar to those of dioxins, but they also share biological and toxicological properties with the NDL-PCBs. These SARs between dioxin-like compounds, including some PCBs, and AhR are the basis for the WHO toxic equivalency factors (TEFs) approach that is now widely used for risk assessment (van den Berg et al., 1998). It is important to note that NDL-PCB congeners are not included in this WHO TEF concept, with the exception of some so-called mono-*ortho*-substituted PCBs that exhibit (moderate) AhR-mediated effects (van den Berg et al., 2006). Although there are observations of AhR-mediated responses to PCBs containing multiple *ortho*-substituted chlorines, there is an uncertainty regarding the possible dominating role of low-level contamination with potent dioxin-like agonists.

The constitutive androstane receptor (CAR) and pregnane X receptor (PXR) are nuclear hormone receptors, and NDL-PCBs, at levels approximating

human serum levels, can directly activate both receptors, with subsequent gene transcription (Al-Salman & Plant, 2012; Gahrs et al., 2013). In particular, PCBs containing multiple *ortho* chlorine substitutions can have a profound agonistic effect on these nuclear receptors, which indicates that this substitution pattern plays a dominant role in binding to PXR or CAR. So far, the biological implications of chronic activation of PXR and/or CAR by NDL-PCBs remain unclear. However, it should be noted that activation of both receptors is associated with adverse health effects, such as metabolic dysfunction and changed hormone metabolism (Kretschmer & Baldwin, 2005; Al-Salman & Plant, 2012).

Studies on possible interactions of PCBs with other (nuclear) receptor proteins are much more limited and usually involve a few congeners (Luthe, Jacobus & Robertson, 2008). For peroxisome proliferator–activated receptors (PPARs), it has been reported that only DL-PCBs act as antagonists (Ariyoshi et al., 1998; Robertson et al., 2007). Thus, based on these observations, it can be expected that NDL-PCBs may not interact with this receptor.

In contrast, NDL-PCBs with multiple *ortho* chlorine atoms show a specific binding affinity to and activation of ryanodine receptors (RyRs). These receptors play a crucial role in calcium (Ca^{2+}) signalling and neurotoxicity (Pessah et al., 2006) and are involved in numerous cellular and subcellular neuronal processes, such as exocytosis, cell death and mitochondrial function (Llansola et al., 2010; Pessah, Cherednichenko & Lein, 2010). This mechanism of action is thought to be one of the major pathways leading to the neurotoxicity of NDL-PCBs. Furthermore, the observed SARs between NDL-PCBs and these RyRs may potentially provide an alternative TEF system for these compounds, with neurotoxicity as an end-point (Pessah et al., 2006). A comparable SAR was found for NDL-PCBs and a decrease in dopamine levels (Seegal, Bush & Shain, 1990; Shain, Bush & Seegal, 1991). Although the actual mechanism is still unknown, it may be related to decreased dopamine synthesis, an inhibition of tyrosine hydroxylase or L-aromatic amino acid decarboxylase, or a decreased uptake of dopamine into vesicles (Angus et al., 1997; Choksi et al., 1997; Mariussen, Morch Andersen & Fonnum, 1999).

A wide range of NDL-PCBs and their most common hydroxylated and methyl sulfone metabolites have also been studied for their agonistic and antagonistic effects on the glucocorticoid receptor (GR). Although the parent PCBs can interact with GR, the inhibitory potency of the hydroxy-PCBs is much higher. These observations point towards an indirect mechanism of action via interactions of this receptor with metabolites of NDL-PCBs (Antunes-Fernandes et al., 2011). In addition, methyl sulfone PCB metabolites also act as agonists with GR in a structure-dependent way (Johansson, Nilsson & Lund, 1998; Johansson et al., 1998b). This interaction occurs at relatively low dose levels and is important, owing to the role of GR in many endocrine and physiological processes.

2.1.4 Effects on enzyme activities

PCBs have been identified as potent inducers of phase I and II enzymes in many vertebrate species, including humans (Safe, 1984). This enzyme induction is directly related to their binding to specific nuclear receptors (AhR, PXR, CAR). Traditionally, the differentiation between DL- and NDL-PCBs was based on the type of cytochrome P450 isoforms that are induced (Safe, 1993; Connor et al., 1995). Furthermore, metabolism of PCBs has usually been considered to be a detoxification process, because it facilitates (slow) elimination of these compounds from the body. However, during the last decades, it has become clear that common hydroxy-PCB and methyl sulfone PCB metabolites have additional mechanistic actions that can cause endocrine or toxic effects on, for example, thyroid hormone homeostasis, neuronal development and functioning, the adrenals and steroidogenesis.

As mentioned above, the DL-PCBs show a high binding affinity to AhR, and this results, among other things, in the induction of CYP1A1, CYP1A2 and CYP1B1 in various tissues of the body. The lack of induction by NDL-PCBs of CYP1A1, CYP1A2 and CYP1B1 has generally been used to structurally define this category of congeners in comparison with DL-PCBs (Safe, 1984; van den Berg et al., 2006). NDL-PCBs bind to PXR and CAR, which can result in the induction of the CYP3A and CYP2B isoforms in rodents and humans (Petersen et al., 2007; Al-Salman & Plant, 2012). These enzymes also play a major role in the biotransformation and elimination of PCBs, which depend on the number and position of the chlorine atoms that are present in the molecules. To date, the involvement of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in the biotransformation of PCBs has been reported (Ariyoshi et al., 1995; McGraw & Waller, 2006; Warner, Martin & Wong, 2009; Yamazaki et al., 2011). The metabolism of NDL-PCBs in humans and rodents is generally thought to involve CYP2A, CYP2B, CYP2C and CYP3A isoforms, which play a major role in the formation of hydroxy-PCB metabolites. The relationship between adverse health effects and the induction of CYP2B and CYP3A enzymes still remains unclear, but it should be noted that these enzymes play a significant role in steroid metabolism and bioactivation of xenobiotics to genotoxic compounds. In addition, some of these hydroxy-PCB metabolites interfere significantly with thyroid hormone homeostasis at the receptor and transport protein (transthyretin) level, for which the presence of a hydroxyl group in the *para* position is important (Brouwer et al., 1998).

In addition to the interaction of NDL-PCBs with the above cytochrome P450 isoforms that are involved with xenobiotic metabolism, several studies have reported effects on cytochrome P450 isoforms that are involved with the endogenous synthesis of (sex) hormones. These interactions with steroidogenic

cytochrome P450 isoforms in various cell types have been reported for both DL- and NDL-PCBs and include parent compounds as well as hydroxy metabolites or methyl sulfone metabolites (Johansson, Nilsson & Lund, 1998; Johansson et al., 1998; Heneweer et al., 2005; Xu et al., 2006; Li, 2007; Antunes-Fernandes et al., 2011). In vitro studies have indicated effects of NDL-PCBs and their metabolites on steroidogenic pathways involved with corticosteroid and sex hormone synthesis, including upregulation of CYP11A, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, 3β-hydroxysteroid dehydrogenase type 1 (3β-HSD1), 3β-HSD2 and 17β-HSD1 (Xu et al., 2006).

PCBs are also known to induce various isoforms of phase II enzymes, such as UGTs, GSTs and sulfotransferases (SULTs). The induction of various isoforms of these enzymes depends on the binding and activation of the nuclear receptors mentioned previously. Although not studied in detail, it can be expected that NDL-PCBs binding to PXR and CAR may cause the induction of UGTs, GSTs and SULTs (Gardner-Stephen et al., 2004; Chai, Zeng & Xie, 2013; Runge-Morris, Kocarek & Falany, 2013). In addition, DL-PCBs binding to AhR are also capable of inducing these phase II enzymes, and similar isoforms of UGT1A can be induced via both types of receptor (Zhou, Zhang & Xie, 2005). This indicates that UGT activation cannot be used as a discriminative marker between DL- and NDL-PCBs. UGT plays an important role in the metabolism and elimination of hydroxy-PCBs. Moreover, it has been found that the specific role of the UGT1A1, UGT1A6 and UGT2B1 isoforms depends on the position of the hydroxy groups in the PCB molecule and type of tissue (Tampal et al., 2002; Daidoji et al., 2005). From an endocrine point of view, it should be noted that UGT induction by these PCBs can lead to an increased elimination of thyroid hormones via the liver. This can have a distinct impact on neuroendocrine and neurobehavioural function (Vansell & Klaassen, 2002; Kato et al., 2004; Richardson et al., 2008).

SULTs are another group of phase II enzymes for which an interaction with PCBs has been found. From a mechanistic point of view, there is a relationship with AhR as well as PXR and CAR. It appears that dioxin-like compounds are capable of downregulating SULT1A1 and SULT2A expression via an AhR-mediated process (Runge-Morris, Kocarek & Falany, 2013). Such an effect could also be expected for DL-PCBs, but not for the NDL-PCBs, which lack AhR agonistic properties. PXR and CAR also play a role in the expression of SULT, and therefore NDL-PCBs can likely interact with SULT, but so far experimental evidence is lacking. However, evidence for interaction with these enzymes is available for hydroxy-PCB metabolites, which can significantly inhibit the activity of several SULT isoforms. The extent of interaction depends on the position of the hydroxyl groups in the molecule; the presence of a hydroxyl group in the *para* or *meta* position is important, with *ortho*-hydroxy-PCBs being much

weaker inhibitors (van den Hurk et al., 2002; Liu et al., 2006, 2009; Ekuase et al., 2011, 2014).

Limited information is available on the interaction of PCBs with GSTs. PXR and CAR are both involved in the regulation of these enzymes (Chai, Zeng & Xie, 2013). Consequently, interaction of NDL-PCBs with GSTs is a mechanistic possibility, but is not yet supported by experimental evidence. However, two studies indicate that induction of GSTs is most relevant for DL-PCBs, although their induction potency decreases with increasing *ortho* chlorine substitution (Aoki et al., 1992; Dragnev et al., 1995).

2.2 Toxicological studies

The focus of the toxicological information in this monograph is on data from oral toxicity studies on individual NDL-PCB congeners. Test samples of individual NDL-PCB congeners may potentially be contaminated with dioxin-like compounds, and so the purity of test samples has been described when such information was available. Studies on technical or reconstituted mixtures are not reviewed in detail. As EFSA (2005) noted in its opinion, experimental studies using technical or reconstituted mixtures or human data on exposure to the mixtures that occur in food and in the environment are not suitable for the evaluation of the effects of NDL-PCBs because, in most instances, no distinction can be made between the effects caused by NDL-PCBs and those caused by DL-PCBs or PCDDs/PCDFs. It should also be noted that environmental mixtures may also contain other PCB congeners or other contaminants that are able to induce the same types of effects.

2.2.1 Acute toxicity

No reports on the acute toxicity of individual NDL-PCB congeners were found. The acute toxicity of single oral doses of commercial PCB mixtures in the rat and mink is low, with median lethal dose (LD_{50}) values ranging from 1000 to 4000 mg/kg body weight (bw) (ATSDR, 2000).

2.2.2 Short-term studies of toxicity

(a) Mice

(i) PCB 153

The effects of PCB 153 (purity 99.9%) on liver weight, histology and gene expression were investigated in mice and compared with those of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a classical AhR ligand (Kopec et al., 2010). Groups of five immature female ovariectomized mice were given a single dose of PCB 153 at 300 mg/kg bw or sesame oil vehicle (controls) by oral gavage and sacrificed 4, 12,

24, 72 or 168 hours later. Other mice were given PCB 153 at 1, 3, 10, 30, 100 or 300 mg/kg bw or sesame oil and sacrificed after 24 hours. Significant increases in relative liver weights were induced with PCB 153 at 300 mg/kg bw between 24 and 168 hours, accompanied by slight vacuolation and hepatocellular hypertrophy. Comparative analysis with TCDD suggested that the differential gene expression elicited by PCB 153 was not mediated by AhR. Protein expression of CAR/PXR-regulated genes, including CYP2B10, CYP3A11, Ces2, Insig2 and Abcc3, was dose-dependently induced by PCB 153.

In a follow-up study (Kopec et al., 2011), groups of five immature female ovariectomized mice were given TCDD at 30 µg/kg bw, PCB 153 (purity 99.9%) at 300 mg/kg bw, a mixture of TCDD at 30 µg/kg bw with PCB 153 at 300 mg/kg bw (MIX) or sesame oil vehicle as single oral gavage doses and were sacrificed after 4, 12, 24, 72 or 168 hours. In the 24-hour dose–response study, animals were gavaged with TCDD (0.3, 1, 3, 6, 10, 15, 30 or 45 µg/kg bw), PCB 153 (3, 10, 30, 60, 100, 150, 300 or 450 mg/kg bw), MIX (0.3 + 3, 1 + 10, 3 + 30, 6 + 60, 10 + 100, 15 + 150, 30 + 300 or 45 µg/kg bw TCDD + 450 mg/kg bw PCB 153, respectively) or vehicle. All three treatments significantly increased relative liver weights, with MIX eliciting significantly greater increases compared with TCDD and PCB 153 alone. MIX induced hepatocellular hypertrophy, vacuolation, inflammation, hyperplasia and necrosis, a combination of TCDD and PCB 153 responses. Hepatic triglycerides were significantly increased by MIX and TCDD treatments, but not by PCB 153. Hepatic PCB 153 levels were also significantly increased by TCDD co-treatment. Microarray analysis for gene expression changes identified more than 100 unique, differentially expressed genes elicited by each of TCDD (n = 167), PCB 153 (n = 185) and MIX (n = 388). Thus, TCDD and PCB 153 co-treatment elicited specific, non-additive gene expression effects consistent with the liver changes observed.

(b) **Rats**

(i) Twenty-eight-day studies

PCB 52

The short-term toxicity of PCB 52 in rats was investigated (unpublished data[1] provided to WHO by study authors of the Assessing the Toxicity and Hazard of Non-dioxin-like PCBs Present in Food [ATHON] project; see also the ATHON Final Report at http://cordis.europa.eu/publication/rcn/11432_en.html and Elabbas et al., 2013). The experimental protocol followed Organisation

[1] Liver and thyroid pathology data were made available for the JECFA meeting from the European Union project ATHON (Assessing the Toxicity and Hazard of Non-dioxin-like PCBs Present in Food). Results from the study are still under evaluation and are not yet published.

for Economic Co-operation and Development (OECD) Test Guideline 407 (Repeated Dose 28-day Oral Toxicity Study in Rodents). In order to improve the assessment of dose–response relationships at the lower end of the study dose range, the number of dose groups was increased to eight, whereas the number of rats of each sex per dose group was reduced to five. The protocol was optimized for dose–response evaluation by the benchmark dose (BMD) modelling approach and used a loading/maintenance dose protocol in order to reach steady-state conditions more rapidly. It was also enhanced to detect effects on the endocrine system. Animals were 6 weeks of age at the start of treatment. The purity of the PCB 52 used was 99.9%, and the analysed level of dioxin-like impurities, as represented by the sum of WHO toxic equivalents (TEQ), was 0.5 ng TEQ_{WHO}/g PCB 52. Groups of five male and five female rats were administered PCB 52 dissolved in corn oil or corn oil only (controls) by oral gavage at 4 mL/kg bw. Loading doses were administered on days 0–4, and maintenance doses were administered 3 times a week over 3 weeks. The total doses of PCB 52 administered over the 28-day period were 0, 3, 10, 30, 100, 300, 1000 and 3000 mg/kg bw. Selection of the highest dose was based on a pilot study. The rats were observed for clinical signs twice daily on weekdays and once daily on weekends and were weighed every second day during the loading dose period and at least once weekly thereafter. Feed consumption and water consumption per cage were recorded once weekly. For determination of the stage of the estrous cycle, vaginal smears were collected from female rats daily starting from day 23 of the study. This was done to ensure that the females were at the diestrous stage during necropsy. A complete necropsy (macroscopic observations, tissue sampling for molecular biology, biochemistry, histopathology, analytical chemistry and organ weights) was performed on each rat. In addition, perirenal adipose tissue and liver were stored at −20 °C for determination of PCB 52 tissue concentration. Activities of UGT, pentoxyresorufin-*O*-deethylase (PROD) and ethoxyresorufin-*O*-deethylase (EROD) and messenger RNA (mRNA) expressions of CYP1A1, CYP1A2, CYP1B1, CYP2B1 and CYP3A1 were measured in the liver. Hepatic retinoids, DNA damage markers and bone densitometry parameters were analysed. Observations were evaluated for exposure-related changes by analysis of variance (ANOVA). All significant exposure-related findings were further evaluated by dose–response modelling in order to establish the critical effect doses (CEDs) and the lower bounds of the confidence interval on the critical effect dose (CEDLs) at the default (5%) or end-point-specific critical effect sizes (CESs).

The main effects observed were on liver and thyroid. Slightly increased relative liver weights were observed in females at the highest dose of 3000 mg/kg bw. Blind reading of the histopathology across the full dose range showed a significant, dose-dependent increase in centrilobular hepatocellular hypertrophy

in male livers (Table 3). In females, hepatocellular hypertrophy was generally more localized in the periportal area, but without a dose-dependent distribution (Table 3). In male rats, CEDs could be calculated for the progression of the average animal from score 1 to 2 (BMD = 0.056 mg/kg bw) and from score 2 to 3 (CED = 0.658 mg/kg bw). In the thyroid, an increase in reduced follicle size was observed in both sexes (Table 4). Dose–response analysis revealed that this decrease occurred at a lower dose in male rats (CED = 6.5 mg/kg bw at CES = 5%) than in female rats (CED = 325 mg/kg bw at CES = 5%). The thyroid follicle size effect was not accompanied by follicular cell activation. The basal (control) average content of large follicles was lower in males than in females. Plasma free T_4 was dose-dependently decreased in males at and above 300 mg/kg bw. Serum free triiodothyronine (T_3) was not affected in either sex. There were no effects on reproductive organs, other endocrine organs or hormone levels in males or females.

PCB 180

The short-term toxicity of PCB 180 was investigated in a 28-day repeated-dose toxicity study in young adult rats (Roos et al., 2011; Viluksela et al., 2014) as part of the ATHON project. The experimental protocol followed OECD Test Guideline 407 (Repeated Dose 28-day Oral Toxicity Study in Rodents), which was enhanced for detection of endocrine, neurotoxicity, retinoid, bone and DNA damage end-points. In order to improve the assessment of dose–response relationships at the lower end of the study dose range, the number of dose groups was increased to eight, whereas the number of rats of each sex per dose group was reduced to five. The animals were 6 weeks of age at the start of treatment. The purity of PCB 180 was 98.9%, and the analysed level of dioxin-like impurities, as represented by the sum of WHO-TEQ, was 2.7 ng TEQ_{WHO}/g PCB 180. PCB 180 was dissolved in purity-controlled (0.2 pg TEQ_{WHO}/g) corn oil, corn oil also serving as control, and administered by oral gavage in a volume of 4 mL/kg bw. Groups of five male and five female rats were given total doses of PCB 180 of 0, 3, 10, 30, 100, 300, 1000 or 1700 mg/kg bw using a loading dose/maintenance dose regimen. To rapidly achieve the kinetic steady state, the total dose was divided into six daily loading doses and three weekly maintenance doses. Loading doses were administered on days 0–5 of the study, and maintenance doses were administered on days 10, 17 and 24. The rats were observed for clinical signs twice daily on weekdays and once daily on weekends, and they were weighed every second day during the loading dose period and at least once weekly thereafter. Feed consumption and water consumption per cage were recorded once weekly. For determination of the stage of the estrous cycle, vaginal smears were collected from female rats daily starting from day 23 of the study. This was done to ensure that the females

Table 3

Histological liver changes in rats treated with individual PCB congeners in 28-day repeated-dose toxicity studies[a]

		Incidence of hypertrophy[c]																	
		Males									Females								
PCB congener no.	Centrilobular hypertrophy stages[b]	0 mg/kg bw	3 mg/kg bw	10 mg/kg bw	30 mg/kg bw	100 mg/kg bw	300 mg/kg bw	1 000 mg/kg bw	1 700 mg/kg bw	3 000 mg/kg bw	0 mg/kg bw	3 mg/kg bw	10 mg/kg bw	30 mg/kg bw	100 mg/kg bw	300 mg/kg bw	1 000 mg/kg bw	1 700 mg/kg bw	3 000 mg/kg bw
52[d]	0	1	1	2	4	3	–	–		–	1	1	2	1	2	4	5		2
	1	1	1	–	1	1	1	1		–	1	2	1	1	2	–	–		3
	2	3	3	3	–	1	3	3		1	3	2	1	3	1	1	–		–
	3	–	–	–	–	–	1	1	na	4	–	–	–	–	–	–	–	na	–
	4	–	–	–	–	–	–	–		–	–	–	–	–	–	–	–		–
	5	–	–	–	–	–	–	–		–	–	–	–	–	–	–	–		–
180[e]	0	5	5	3	–	–	–	–	–		5	5	4	5	5	1	–	–	
	1	–	–	–	–	–	–	–	–		–	–	1	–	–	3	4	1	
	2	–	–	–	–	–	–	–	–		–	–	–	–	–	1	1	3	
	3	–	–	2	5	1	5	1	1	na	–	–	–	–	–	–	–	–	na
	4	–	–	–	–	4	–	4	3		–	–	–	–	–	–	–	–	
	5	–	–	–	–	–	–	–	–		–	–	–	–	–	–	–	–	

na: dose not used

[a] Doses given are total doses during study.

[b] Hypertrophy stages 0–5 represent absent, slight, mild, moderate and severe, respectively. No other histopathology was observed.

[c] Scores are actual counts per group, with $n = 5$ in all groups, except for PCB 52 females, 10 mg/kg bw, $n = 4$.

[d] CED_{05} for mild hypertrophy in males was calculated at 0.056 mg/kg bw; no effect in females.

[e] CED_{05} for mild hypertrophy was 14.8 and 205 mg/kg bw in males and females, respectively.

Source: Unpublished data provided to WHO by ATHON project study authors (PCB 52); Roos et al. (2011) and Viluksela et al. (2014) (PCB 180)

Table 4

Histological thyroid changes in rats treated with individual PCB congeners in 28-day repeated-dose toxicity studies[a]

		Incidence of thyroid change																	
		Males									Females								
PCB congener no.	Thyroid histopathology	0 mg/kg bw	3 mg/kg bw	10 mg/kg bw	30 mg/kg bw	100 mg/kg bw	300 mg/kg bw	1 000 mg/kg bw	1 700 mg/kg bw	3 000 mg/kg bw	0 mg/kg bw	3 mg/kg bw	10 mg/kg bw	30 mg/kg bw	100 mg/kg bw	300 mg/kg bw	1 000 mg/kg bw	1 700 mg/kg bw	3 000 mg/kg bw
52[b]	Reduced follicle size[c]	2	5	5	4	5	5	4	na	5	2	2	2	2	2	2	3	na	4
	Epithelial hypertrophy[d]																		
	Stage 0	4	3	3	4	3	5	5	na	3	1	ns	ns	ns	ns	ns	ns	ns	1
	Stage 1	1	2	2	1	2	–	–		2	4								4
	Stage 2	–	–	–	–	–	–	–		–	–								–
180[e]	Reduced follicle size[c]	1	3	4	3	2	5	5	5	na	2	5	2	5	4	4	4	3	na
	Epithelial hypertrophy[d]																		
	Stage 0	–	–	–	–	–	–	–	–	na	5	2	3	2	2	1	2	–	na
	Stage 1	3	1	3	–	1	–	3	2		–	3	2	3	3	3	3	4	
	Stage 2	2	4	2	5	4	5	2	3		–	–	–	–	–	1	–	1	

na: dose not used; ns: dose not scored

[a] Doses given are total doses during study.

[b] CED_{05} for reduced follicle size was calculated to be 6.5 and 325 mg/kg bw for males and females, respectively. Thyroid epithelial hypertrophy was not affected in either sex (only control and top dose scored in females).

[c] Reduced follicle size is represented as the count of animals scoring below the average of control.

[d] Thyroid epithelial hypertrophy stages 0–2 represent absent, mild and moderate, respectively. Scores are actual counts per group, with $n = 5$ in all groups. No other histopathology was observed.

[e] CED_{05} for reduced follicle size was calculated to be 131 mg/kg bw for females; no effect in males. Thyroid epithelial hypertrophy was increased in females only, but no CED was calculated.

Source: Unpublished data provided to WHO by ATHON project study authors (PCB 52); Roos et al. (2011) and Viluksela et al. (2014) (PCB 180)

were at the diestrous stage during necropsy. All observations were evaluated for exposure-related changes by ANOVA, and significant exposure-related findings were further evaluated by dose–response modelling in order to establish CEDs and CEDLs at the default (5%) or end-point-specific CESs.

Body weight gain was reduced at 1700 mg/kg bw during the loading dose period in both sexes, but recovered thereafter. There were no observed general pathologies, with the exception of hyperplasia of the mammary glands, which was observed in six out of 10 assessed males, including controls.

The most sensitive end-point was altered open-field behaviour in females. On study day 24 (test day 1), there were statistically significant, dose-related increases in the percentages of time and distance moved in the inner zone (CED = 0.35 mg/kg bw, 1.55 mg/g lipid, and CED = 0.87 mg/kg bw, 4.12 mg/g lipid, respectively, for CES = 5%). Conversely, there were decreases in the percentages of time and distance moved in the outer zone of the open field. These differences ameliorated across the 5 days of testing, as demonstrated by significant interactions between exposure and test days for both measures, indicating differences in habituation between groups. As a consequence, dose–response relationships were no longer statistically significant on day 28. The increased activity and distance moved in the inner zone of an open field suggest altered emotional responses to an unfamiliar environment and impaired behavioural inhibition. No significant dose–response relationships in open-field behaviour were found in exposed males.

Absolute liver weights were dose-dependently increased at doses of 300 mg/kg bw and higher in both sexes. The increases were greater in males than in females, with CED values of 11.6 and 225 mg/kg bw (42.3 and 512 µg/g lipid, respectively) and maximum increases of 66% and 45% in males and females, respectively. The liver of exposed animals showed centrilobular hypertrophy (see Table 3). BMD analysis showed CEDLs of 9 and 138 mg/kg bw in males and females, respectively, for progression of hepatocellular hypertrophy to stage 1. Males were more sensitive to the induction of hypertrophy, in terms of both the CEDL and severity. The centrilobular hypertrophy observed in the liver was associated with the induction of hepatic cytochrome P450 enzymes, including significant increases in liver PROD activity, CYP2B1 and CYP3A1 mRNA levels, as well as CYP2B1/2 and CYP3A1 protein levels in both male and female rats, with males being more sensitive. A significant induction of hepatic EROD activity was observed in both male and female rats, with males being more sensitive. CYP1A1 mRNA and protein levels were induced at the higher dose levels. In contrast, CYP1B1 and CYP1A2 were not affected at the mRNA level, although slight inductions of protein levels were observed at the higher doses. These findings suggest that PCB 180 acts as a CAR and PXR agonist and as a weak inducer of AhR-mediated CYP1A1 expression and activity. A significant dose-related

decrease in liver retinoids was also observed after exposure to PCB 180 regarding both amount, with CEDs of 257 mg/kg bw in females and 148 mg/kg bw in males, and concentration, with CEDs of 123 mg/kg bw in females and 21.6 mg/kg bw in males. Taken together, quantification of liver histopathology, hepatic cytochrome P450 enzyme assays and hepatic retinoid levels were confirmative, as males were more sensitive than females to PCB-induced changes for all three end-points. In contrast, expressions of the tumour suppressor protein p53 and the DNA damage signalling proteins p53 Ser15, γH2AX Ser139 and pChk2 Thr68 were dose-dependently increased in livers of female rats, whereas expression of pMdm2 Ser166 was not affected. These in vivo results are in line with findings in the human hepatocellular carcinoma cell line HepG2 (Al-Anati, Högberg & Stenius, 2009).

Other dose-dependent changes due to PCB 180 exposure included decreased serum thyroid hormone levels with associated histopathological changes (see Table 4). The weight of the thyroid gland was dose-dependently increased in males, but decreased in females. Plasma free T_4 level was dose-dependently decreased in both sexes, compared with controls: in males, it was decreased at doses of 100 mg/kg bw and higher, reaching statistical significance at 300 mg/kg bw and higher; in females, it was decreased at 300 mg/kg bw, reaching statistical significance at 1700 mg/kg bw. The effect was more pronounced in males than in females, with a maximal reduction of 69% in males compared with 50% in females. Plasma free T_3 concentrations were significantly decreased only in males at 1000 mg/kg bw. Histopathology revealed increased thyroid follicular cell vacuolation, suggestive of thyroid activation, and there was a dose-dependent decrease of large follicles in females, indicating depletion of follicle contents. Male thyroids had a lower proportion of large follicles at the control and low doses compared with females, comparable with the level in females exposed to high doses. The area of large follicles was estimated as a percentage of the total area of the section, and the data for the females were used for dose–response and BMD analyses. These analyses revealed a CED of 131 mg/kg bw, with a corresponding CEDL of 81 mg/kg bw. The follicular epithelial cells showed hypertrophy, which increased in a dose-dependent way in females. Males had a higher basal score for hypertrophy, and no significant increase was observed with treatment.

In the adrenals, cells in the zona fasciculata showed dose-dependent hypertrophy. Females were more sensitive than males, showing progression of hypertrophy to further stages, and they also had a lower CED (2.0 mg/kg bw) than did males (594 mg/kg bw). There was also hypertrophy and vacuolation in cells of the zona reticularis, with a significant dose–response relationship in females. The inner zones of the cortex occasionally also showed hyperaemia, with a significant dose–response relationship in females, but not in males.

Cauda epididymal sperm counts were analysed in the controls and the highest-dose group, but no differences were observed. Serum testosterone levels in males and estradiol and progesterone levels in females were not affected by the treatment. However, serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels showed significant decreasing trends in males. LH levels were not affected in females.

(ii) Ninety-day studies

PCB 28

The short-term toxicity of PCB 28 was investigated in a 90-day dietary exposure study in rats (Chu et al., 1996a). The purity of PCB 28 was greater than 99%, and contamination with PCDDs and PCDFs was found to be less than 0.1 mg/kg. Groups of 10 male and 10 female weanling rats were administered PCB 28 in the diet at 0, 0.05, 0.50, 5.0 or 50.0 mg/kg feed for 13 weeks. The corresponding calculated exposures to PCB 28 were 0, 2.8, 36, 359 and 3783 µg/kg bw per day for male rats and 0, 2.9, 37, 365 and 3956 µg/kg bw per day for female rats. Corn oil was used to dissolve the test substance prior to mixing with the diet, and control groups received the diet containing an equivalent amount of corn oil (4% weight per weight [w/w]) only.

Feed consumption and body weights were determined weekly. Observations for clinical signs of toxicity were made daily. Brain, liver, heart, lung, spleen, thymus and kidney weights were recorded at termination of the experiment. Haematology, clinical chemistry and full histopathology were performed. Liver aminopyrine *N*-demethylase (APDM), UGT and EROD activities and uroporphyrin levels were determined. Biogenic amines (dopamine, norepinephrine, serotonin, 3,4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylacetic acid, 5-hydroxyindoleacetic acid) and total protein were analysed in several sections of the right hemisphere of the brain. Vitamin A content of liver, lung and kidneys and ascorbic acid in urine samples were analysed. PCB 28 residues were analysed in several tissues.

Growth rate and feed consumption were not affected by treatment, and no clinical signs of toxicity were observed. Liver and thyroid gland showed treatment-related histopathological changes in both male and female rats. Liver pathology was mild to moderate in nature, and treatment-related changes generally occurred at 5.0 mg/kg feed and above (Table 5). Several thyroid gland changes were present at 0.05 mg/kg feed; however, the authors judged that only the thyroid gland changes at 5.0 mg/kg feed and above were biologically significant (see Table 6). Morphological changes were also seen in the kidney and thymus of treated groups; these changes were mild even at the highest dose. No treatment-related histopathological changes were found in other tissues, and no

Table 5

Histological changes in liver of rats treated with individual PCB congeners in 90-day repeated-dose toxicity studies

PCB congener no.	Liver histopathology	Incidence of histological changes in liver[a]									
		Males					Females				
		Control	0.05 mg/kg feed	0.50 mg/kg bw	5.0 mg/kg bw	50.0 mg/kg bw	Control	0.05 mg/kg bw	0.50 mg/kg bw	5.0 mg/kg bw	50.0 mg/kg bw
28	Liver cytoplasm										
	Increased portal density	4/9 (0.6)	8/10 (1.4)	5/10 (1.1)	3/10 (0.4)	5/9 (0.7)	3/10 (0.4)	5/9 (0.8)	8/10 (0.9)	8/10 (1.5)	8/10 (1.1)
	Periportal vacuolation	0/9	1/10 (0.3)	7/10 (1.1)	6/10 (0.8)	6/9 (1.3)	4/10 (0.4)	5/9 (1.3)	2/10 (0.5)	5/10 (1.1)	2/10 (0.4)
	Midzonal vacuolation	2/9 (0.4)	3/10 (0.3)	3/10 (0.3)	9/10 (0.6)	8/9 (1.0)	7/10 (0.6)	6/9 (0.6)	6/10 (0.6)	4/10 (0.3)	6/10 (0.4)
	Increased perivenous homogeneity	5/9 (0.7)	10/10 (2.0)	10/10 (2.4)	10/10 (2.4)	9/9 (2.3)	3/10 (0.2)	3/9 (0.2)	8/10 (1.0)	8/10 (1.6)	6/10 (0.7)
128	Liver cytoplasm										
	Increased portal density	0/10	1/10 (0.10)	0/10	0/10	5/10 (0.7)	3/10 (0.2)	8/10 (0.6)	10/10 (1.3)	8/10 (1.2)	7/10 (0.8)
	Midzonal vacuolation	2/10 (0.25)	3/10 (0.15)	7/10 (0.45)	8/10 (0.4)	7/10 (0.9)	0/10	4/10 (0.2)	3/10 (0.35)	3/10 (0.4)	7/10 (0.7)
	Increased perivenous homogeneity	10/10 (0.9)	10/10 (0.9)	9/10 (1.7)	9/10 (2.0)	7/10 (2.1)	1/10 (0.05)	7/10 (0.35)	10/10 (0.6)	10/10 (1.2)	8/10 (1.8)
153	Liver cytoplasm										
	Midzonal vacuolation	3/10 (0.4)	9/10 (0.4)	7/10 (0.6)	9/10 (1.3)	5/10 (1.3)	6/10 (0.6)	3/10 (0.3)	4/10 (0.5)	6/10 (0.8)	10/10 (0.9)
	Increased perivenous homogeneity	6/10 (0.5)	10/10 (0.8)	10/10 (1.9)	10/10 (3.0)	1/10 (0.3)	4/10 (0.2)	7/10 (0.5)	10/10 (1.5)	10/10 (2.5)	3/10 (0.9)

[a] Data denote (number of animals showing changes/number of animals examined). Figures in parentheses denote the severity of histology gradings, which were as follows: 1 = minimal; 2 = mild; 3 = moderate; 4 = severe. The overall scores are obtained by dividing the sum of total scores by the number of tissues examined.

Source: Chu et al. (1996a) (PCB 28); Lecavalier et al. (1997) (PCB 128); Chu et al. (1996b) (PCB 153)

Table 6
Histological changes in thyroid of rats treated with individual PCB congeners in 90-day repeated-dose toxicity studies

PCB congener no.	Thyroid histopathology	Incidence of histological change in thyroid[a]									
		Males					Females				
		Control	0.05 mg/kg feed	0.50 mg/kg feed	5.0 mg/kg feed	50.0 mg/kg feed	Control	0.05 mg/kg feed	0.50 mg/kg feed	5.0 mg/kg feed	50.0 mg/kg feed
28[b]	Reduced follicle size	3/9 (0.6)	7/10 (1.2)	9/10 (1.7)	9/10 (1.7)	8/10 (1.8)	4/10 (0.6)	8/10 (1.6)	8/10 (1.3)	8/9 (1.6)	7/10 (1.6)
	Follicle collapse/angularity	6/9 (0.9)	8/10 (0.7)	9/10 (1.0)	8/10 (0.7)	7/10 (0.7)	2/10 (0.2)	9/10 (0.8)	7/10 (0.7)	5/9 (0.4)	9/10 (1.7)
	Thyroid epithelium										
	Increased height	4/9 (0.6)	5/10 (0.8)	9/10 (1.4)	10/10 (1.5)	10/10 (2.5)	4/10 (0.4)	9/10 (0.8)	10/10 (0.6)	9/9 (1.2)	9/10 (1.4)
	Cytoplasmic vacuolation	8/9 (1.2)	10/10 (1.0)	10/10 (1.4)	10/10 (1.1)	10/10 (1.5)	5/10 (0.2)	9/10 (0.7)	6/10 (0.6)	9/9 (1.2)	10/10 (1.3)
	Nuclear vesiculation	0/9	2/10 (0.2)	9/10 (1.0)	9/10 (1.7)	10/10 (2.0)	5/10 (0.3)	8/10 (0.7)	8/10 (0.9)	9/9 (1.3)	10/10 (1.6)
	Colloid density	0/9	2/10 (0.1)	2/10 (0.2)	4/10 (0.2)	3/10 (0.5)	0/10	4/10 (0.1)	4/10 (0.1)	2/9 (0.1)	3/10 (0.3)
128[c]	Reduced follicle size	3/10 (0.65)	9/10 (1.50)	8/10 (1.25)	7/10 (1.50)	9/10 (1.58)	3/10 (0.45)	6/10 (0.68)	6/10 (0.75)	8/10 (1.20)	8/10 (1.33)
	Thyroid epithelium										
	Increased height	10/10 (1.2)	9/10 (1.3)	10/10 (1.8)	10/10 (2.3)	10/10 (2.4)	5/10 (0.48)	7/10 (0.43)	9/10 (0.6)	10/10 (1.5)	8/10 (1.7)
	Papillary proliferation	0/10	1/10 (0.13)	3/10 (0.10)	5/10 (0.63)	7/10 (0.68)	0/10	0/10	0/10	1/10 (0.03)	2/10 (0.30)
	Nuclear vesiculation	1/10 (0.18)	0/10	4/10 (0.40)	9/10 (0.93)	10/10 (1.8)	0/10	6/10 (0.20)	8/10 (0.78)	10/10 (1.58)	9/10 (1.75)
153[d]	Reduced follicle size	1/10 (0.08)	3/10 (0.35)	8/10 (1.3)	9/10 (1.4)	10/10 (2.5)	2/10 (0.3)	4/10 (0.8)	5/10 (1.0)	5/10 (0.9)	10/10 (1.9)
	Follicle collapse	1/10 (0.03)	1/10 (0.05)	5/10 (0.7)	5/10 (0.8)	5/10 (0.8)	2/10 (0.1)	5/10 (0.7)	9/10 (1.3)	10/10 (0.7)	10/10 (1.6)
	Thyroid epithelium										
	Increased height	0/10	2/10 (0.1)	2/10 (0.3)	9/10 (1.4)	10/10 (2.0)	1/10 (0.2)	5/10 (0.5)	8/10 (1.2)	10/10 (1.4)	10/10 (2.3)
	Cytoplasmic vacuolation	8/10 (0.8)	10/10 (0.6)	10/10 (1.6)	10/10 (1.6)	10/10 (2.0)	8/10 (0.8)	10/10 (1.1)	10/10 (1.2)	10/10 (1.7)	10/10 (1.4)
	Nuclear vesiculation	0/10	3/10 (0.1)	3/10 (0.2)	10/10 (1.3)	10/10 (1.8)	2/10 (0.3)	7/10 (0.9)	10/10 (1.4)	8/10 (1.2)	10/10 (2.5)

[a] Data denote (number of animals showing changes/number of animals examined). Figures in parentheses denote the severity of histology gradings, which were as follows: 1 = minimal; 2 = mild; 3 = moderate; 4 = severe. The overall scores are obtained by dividing the sum of total scores by the number of tissues examined.

[b] Comments and conclusions by the authors of the study on PCB 28 (Chu et al., 1996a):
Low magnification: treatment-related follicle size and colloid density and collapse of follicles. At cytological level: increased epithelial height, cytoplasmic vacuolation and nuclear vesiculation.
0.05 mg/kg feed: moderate and irregular reduction in follicle size + vacuolation + mildly reduced colloid density.
0.50 mg/kg feed: no comment.
5.0 and 50.0 mg/kg feed: biologically significant changes in both sexes.

50.0 mg/kg feed: marked reduction in follicle size and colloid density.
Conclusions: Dose/treatment-related effect. Severity at 0.05 and 0.50 mg/kg feed was considered minimal. A broader spectrum of histological changes was observed only at 5.0 mg/kg feed and above. NOAEL = 0.50 mg/kg feed (equal to 36 µg/kg bw per day).

[c] Comments and conclusions by the authors of the study on PCB 128 (Lecavalier et al., 1997):
Treatment-related histological changes consisted of reduced follicle size with papillary proliferation and nuclear vesiculation of the epithelium. Incidence and severity were dose dependent and were rated minimal in the low-dose groups. Changes became progressively more severe as the dose increased.
Conclusions: More severe changes occurred at 5.0 mg/kg feed and above. NOAEL = 0.50 mg/kg feed (equal to 42 µg/kg bw per day).

[d] Comments and conclusions by the authors of the study on PCB 153 (Chu et al., 1996b):
Minimal dose-dependent reduction in follicle size in the low-dose group (0.05 mg/kg feed). Changes of moderate degree in the high-dose group. Dose-dependent reduction in follicle size and increased epithelial height and nuclear vesiculation. Epithelial cells changed from low cuboidal to columnar shape, with females being more sensitive and effects occurring from 0.50 mg/kg feed.
Cytoplasmic vacuolation occurred also at high rate in control animals; thus, considered not to be treatment related.
Conclusions: NOAEL = 0.50 mg/kg feed (equal to 34 µg/kg bw per day).

Source: Chu et al. (1996a) (PCB 28); Lecavalier et al. (1997) (PCB 128); Chu et al. (1996b) (PCB 153)

haematological changes were observed. An increase in urinary ascorbic acid and minimal induction of hepatic EROD activity were observed in both sexes of the 50.0 mg/kg feed group. A significant decrease in dopamine concentrations in the substantia nigra region of the brain was observed in female rats at 0.50 mg/kg feed and above. Vitamin A content in liver, lung and kidneys was not affected by PCB 28 treatment. PCB 28 residues were found in fat, liver, kidney, brain and spleen and accumulated in a dose-dependent fashion, with the PCB concentrations in fat being at least 20- to 40-fold higher than those in other tissues. Based on these data, the authors of the study concluded that the no-observed-adverse-effect level (NOAEL) for PCB 28 was 0.50 mg/kg feed (equal to 36 µg/kg bw per day).

PCB 128

The short-term toxicity of PCB 128 was investigated in a 90-day dietary exposure study in rats (Lecavalier et al., 1997). The purity of PCB 128 was greater than 99%, and no detectable levels of PCDDs or PCDFs were found (limit of detection [LOD] of 1 mg/kg). Groups of 10 male and 10 female weanling rats were administered PCB 128 in the diet at 0, 0.05, 0.50, 5.0 or 50.0 mg/kg feed for a period of 13 weeks. The corresponding calculated exposures to PCB 128 were 0, 4.2, 42, 425 and 4210 µg/kg bw per day for male rats and 0, 4.5, 45, 441 and 4397 µg/kg bw per day for female rats. Corn oil was used to dissolve the test substance prior to mixing with the diet, and control groups received the diet containing an equivalent amount of corn oil (4% w/w) only.

Feed consumption and body weights were determined weekly. Observations for clinical signs of toxicity were made daily. Brain, liver, heart, lung, spleen, thymus and kidney weights were recorded at termination of the experiment. Haematology, clinical chemistry and full histopathology were performed. Liver aniline hydroxylase (AH), APDM, PROD and EROD activities and total protein and uroporphyrin levels were determined. Selected biogenic amines and metabolites (i.e. dopamine, norepinephrine, serotonin, 3,4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylacetic acid,

5-hydroxyindoleacetic acid) and total protein were analysed in several sections of the right hemisphere of the brain. Vitamin A content of liver, lung and kidneys and ascorbic acid in urine samples were analysed. PCB 128 residues were analysed in several tissues.

Growth rate and feed consumption were not affected by treatment, and no clinical signs of toxicity were observed. The highest-dose group of female rats had an increased liver to body weight ratio. Liver and thyroid gland showed treatment-related histopathological changes in both male and female rats, with female rats seemingly more sensitive (see Tables 5 and 6). Several liver and thyroid changes were present at 0.05 mg/kg feed, although they were mostly of minimal severity; the authors of the study judged that more severe changes occurred at 5.0 mg/kg feed and above.

An increase in urinary ascorbic acid was observed in the 50.0 mg/kg feed group of both sexes. Hepatic EROD activity was induced in both male and female rats starting from doses of 0.5 mg/kg feed in female rats, whereas APDM activity was increased at only the highest dose level in both male and female rats. PROD activity data were not presented. Decreased dopamine concentrations were found in the frontal cortex and hippocampus of female rats. Although a dose-related trend in dopamine levels in the hippocampus was observed, there was no dose-related trend in the levels in the frontal cortex, as even the lowest dose, 0.05 mg/kg feed, resulted in the same level of dopamine reduction. Hepatic vitamin A content was decreased at the highest dose level in female rats only. PCB 128 residues were found in fat, liver, kidney, brain, spleen and serum and accumulated in a dose-dependent fashion, with the PCB concentrations in fat being markedly higher than those in other tissues. PCB 128 concentrations in fat, kidneys and brain were higher in female rats than in male rats by a factor of about 2. Based on these data, the authors of the study concluded that the NOAEL for PCB 128 was 0.50 mg/kg feed (equal to 42 µg/kg bw per day).

PCB 153

The short-term toxicity of PCB 153 was investigated in a 90-day dietary exposure study in rats (Chu et al., 1996b). The purity of PCB 153 was greater than 99% (authors wrote in error <99%) and contained less than 1% (authors wrote in error >1%) of PCDDs/PCDFs (LOD 1 mg/kg). Groups of 10 male and l0 female weanling rats were administered PCB 153 in the diet at 0, 0.05, 0.50, 5.0 or 50.0 mg/kg feed for a period of 13 weeks. The corresponding calculated exposures to PCB 153 were 0, 3.6, 34, 346 and 3534 µg/kg bw per day for male rats and 0, 4.2, 42, 428 and 4125 µg/kg bw per day for female rats. Corn oil was used to dissolve the test substance prior to mixing with the diet, and control groups received the diet containing an equivalent amount of corn oil (4% w/w) only.

Feed consumption and body weights were determined weekly. Observations for clinical signs of toxicity were made daily. Brain, liver, heart, lung, spleen, thymus and kidney weights were recorded at termination of the experiment. Haematology, clinical chemistry and full histopathology were performed. Liver AH, APDM and EROD activities and total protein and uroporphyrin levels were determined. Selected biogenic amines and metabolites (i.e. dopamine, norepinephrine, serotonin, 3,4-dihydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylacetic acid, 5-hydroxyindoleacetic acid) and total protein were analysed in several sections of the right hemisphere of the brain. Vitamin A content of liver, lung and kidneys and ascorbic acid in urine samples were analysed. PCB 153 residues were analysed in several tissues.

Growth rate and feed consumption were not affected by treatment. Clinical signs of toxicity were not observed. Enlarged, fatty liver was observed in treated male rats at all dose levels and in females only at the highest dose level. Liver and thyroid gland showed treatment-related histopathological changes in male and female rats. Several liver and thyroid changes were present at 0.05 mg/kg feed, although they were mostly of minimal severity; the authors judged that more severe changes occurred at 5.0 mg/kg feed and above (Table 5). Details of histopathological changes in the thyroid are shown in Table 6.

An increase in urinary ascorbic acid was observed in both sexes of the 50.0 mg/kg feed group, and increased liver uroporphyrin levels were observed in females only at the highest dose level. Hepatic AH, APDM and EROD activities were induced in both sexes starting from doses of 0.05 and 0.50 mg/kg feed in female and male rats, respectively. Changes in brain biogenic amines and intermediate products were observed mainly in female rats. Observations included decreased dopamine and 5-hydroxytryptamine concentrations in the frontal cortex region at 5.0 and 50.0 mg/kg feed and decreased dihydroxyphenylacetic acid in the caudate nucleus region, which was significantly reduced at 0.50 mg/kg feed. Thus, female rats appeared to be more sensitive than males to the neurotoxic effects of PCB 153. Treatment-related reductions in hepatic and pulmonary vitamin A were seen in the highest-dose group of both sexes. PCB 153 residues were found in fat, liver, kidney, brain, spleen and serum and accumulated in a dose-dependent fashion, with the PCB concentrations in fat being markedly higher than those in other tissues. PCB 153 concentrations in all tissues except for liver were higher in females than in males. Based on these data, the authors of the study concluded that the NOAEL for PCB 153 was 0.50 mg/kg feed (equal to 34 μg/kg bw per day).

(iii) PCB metabolites

Reduced thyroid hormone levels were found in serum of rats treated with four consecutive daily doses of each of the 3-methylsulfonyl metabolites of

the congeners PCB 132, PCB 141 and PCB 149 and with the 4-methylsulfonyl metabolite of PCB 149. All four metabolites (20 μmol/kg bw, intraperitoneal injection, once per day for 4 days) reduced the serum concentration of total T_4 by 22–44% on days 2, 3, 4 and 7 after the last dose. Concentrations of total T_3 were reduced by 37% on day 7 after treatment with the 4-methylsulfonyl metabolite of PCB 149. A 30% increase in thyroid weight was seen after treatment with the 3-methylsulfonyl metabolite of PCB 141. The data suggest that these 3- and 4-methylsulfonyl metabolites act on the thyroid, but probably through different mechanisms (Kato et al., 1998). A similar study conducted with the 3-methylsulfonyl metabolites of PCB 49, PCB 70, PCB 87 and PCB 101 and the 4-methylsulfonyl metabolite of PCB 101 found that all five methylsulfonyl metabolites of PCBs influence thyroid hormone metabolism (Kato et al., 1999). A further study by this group demonstrated that the 3-methylsulfonyl metabolites of PCB 49, PCB 70, PCB 89, PCB 101, PCB 132, PCB 141 and PCB 149 and the 4-methylsulfonyl metabolite of PCB 101 induced hepatic UGT in male rats. The increase in hepatic glucuronidation of T_4 after the administration of the eight test compounds was the probable cause of the reduced serum concentration of T_4 (Kato et al., 2000).

2.2.3 Long-term studies of toxicity and carcinogenicity

Studies on the carcinogenicity of commercial mixtures of PCBs, individual PCB congeners, combinations of specified congeners and PCB metabolites have been described in detail by IARC (2015).

(a) Commercial mixtures of PCBs

Early studies on commercial PCB mixtures containing both DL- and NDL-PCBs administered orally in the diet were summarized in Ahlborg, Hanberg & Kenne (1992). Various Aroclor, Kanechlor and Clophen mixtures have been tested in mice and in several strains of rats at doses of 5 mg/kg bw per day or more. They induced hepatocellular carcinomas and/or hepatic foci and neoplastic nodules in both sexes of both species. Several of these early bioassays for cancer were re-evaluated by a panel of pathologists, applying the then-accepted classification for liver pathology (IEHR, 1991). The outcome of the evaluation was that only Aroclor 1260 and Clophen A60 were considered to give a clear carcinogenic response. However, in many of the other studies, there were high incidences of hepatocellular proliferative lesions in both male and female rats that were related to the administration of the various mixtures. PCB mixtures are also effective tumour promoters in mouse and rat liver when given in conjunction with known carcinogens, such as 2-acetylaminofluorene, benzene hexachloride, 3′-methyl-

4-dimethylaminoazobenzene, *N*-methyl-*N′*-nitrosoguanidine or nitrosamines (Ahlborg, Hanberg & Kenne, 1992; ATSDR, 2000; IARC, 2015).

Later studies on commercial mixtures have been summarized in ATSDR (2000) and IARC (2015). They confirmed that several commercial mixtures increased the incidences of hepatocellular adenomas and carcinomas, hepatocholangiomas and hepatocholangiocarcinomas, and thyroid follicular cell adenomas and carcinomas in rats. Increases in hepatocellular carcinomas were also confirmed in three mouse studies (liver was the only tissue examined and reported on).

In its opinion, EFSA (2005) commented on whether the liver carcinogenicity of technical PCB mixtures is due to the dioxin-like compounds present in these mixtures. For example, in a comparative chronic carcinogenicity study in rats administered four different Aroclor mixtures (1016, 1242, 1254 and 1260), the total TEQ doses associated with dioxin-like constituents within the technical mixtures, but not the doses of total PCBs, were mainly, if not exclusively, responsible for the development of liver neoplasms (Mayes et al., 1998). EFSA (2005) also did a quantitative comparison of the data from Mayes et al. (1998) with those from a chronic carcinogenicity study with TCDD in female rats (Kociba et al., 1978), which showed that for induction of hepatic neoplasms in female rats, the dose–response curves for the total TEQs in the various technical PCB mixtures were similar to that for TCDD. EFSA (2005) commented that these findings suggest that in rats, NDL-PCBs, administered together with DL-PCBs in technical mixtures, play a minor role – if any – as carcinogens.

(b) **Individual NDL-PCB congeners**

Few studies on the chronic toxicity and carcinogenicity of individual NDL-PCB congeners have been published to date.

(i) PCB 153

The United States National Toxicology Program (NTP) carried out a carcinogenesis bioassay on PCB 153, which is the PCB that is present at the highest concentrations in human samples on a molar basis (NTP, 2006a). Groups of 80–82 female rats were given PCB 153 in corn oil:acetone (99:1) by oral gavage for 14, 31 or 53 weeks or 2 years. Analytical checks of the test material for purity showed an overall purity of greater than 99%, no contamination with DL-PCBs and only minor contamination with PCB 101 (0.21%) and PCB 180 (0.002%). PCB 153 dose levels of 0 (vehicle only), 10, 100, 300, 1000 and 3000 μg/kg bw per day were administered on 5 days/week for up to 105 weeks. A stop-exposure group of 50 female rats was administered 3000 μg/kg bw per day for 30 weeks and then vehicle only for the remainder of the study. In addition to the usual

histopathological observations, PCB concentrations in fat, liver, lung and blood were measured, and specific end-points that might be affected by PCBs, such as cytochrome P450 levels in liver and lung, thyroid hormone levels and hepatic cell proliferation, were investigated.

Detectable levels of PCB 153 in fat were found at 14, 31 and 53 weeks and at the end of the 2-year study in the vehicle controls. Measurable concentrations of PCB 153 were also found in the lungs of vehicle control rats at 31 and 53 weeks and at 2 years. No measurable concentrations of PCB 153 were found in the liver of vehicle controls at any time point. The finding of PCB 153 in fat and lung of the vehicle control group is likely attributable to the presence of low levels of PCB 153 in the laboratory chow of rats (Feeley & Jordan, 1998; Jordan & Feeley, 1999). NTP (2006a) estimated that the background intake of PCB 153 from the chow was 1–3 orders of magnitude less than the lowest dose of PCB 153 administered. In the groups dosed with PCB 153, concentrations of PCB 153 in fat and liver increased with increasing dose and exposure duration. In fat, these doses resulted in a linear increase in concentrations; at the end of the study, concentrations were approximately 440, 20 000, 160 000, 520 000, 1 600 000 and 4 300 000 ng/g lipid for the 0, 10, 100, 300, 1000 and 3000 μg/kg bw per day dose groups, respectively. Concentrations of PCB 153 in lung and blood increased with increasing dose at each time point, and concentrations in blood increased with duration of exposure. In liver, lung and blood of rats in the 3000 μg/kg bw per day stop-exposure group, PCB 153 concentrations were slightly above or below those found in the 1000 μg/kg bw per day group.

There were no dose-related effects on survival. Mean body weights were unaffected by treatment except in the 3000 μg/kg bw per day core study rats, which had lower mean body weight than vehicle controls after week 69 of the study. Absolute and/or relative liver weights in the rats given 1000 or 3000 μg/kg bw per day were significantly higher than those of vehicle controls at 14 and 31 weeks. At week 53, absolute and relative liver weights were significantly higher in rats given 100 μg/kg bw per day or more compared with vehicle controls. Absolute kidney weights of all groups exposed to PCB 153 and the relative kidney weight of 3000 μg/kg bw per day rats were significantly increased at week 53. There were no effects on thyroid weight.

There were significant increases in the incidences of hepatocyte hypertrophy in the rats given 1000 or 3000 μg/kg bw per day at 14 weeks and in all groups administered 300 μg/kg bw per day or more at 31 and 53 weeks. At 2 years, the incidence of hepatocyte hypertrophy was significantly increased in all dosed groups. There were significant increases in diffuse fatty change in the liver in the groups given 300 μg/kg bw per day or more and in bile duct hyperplasia in those given 300 or 3000 μg/kg bw per day (core and stop-exposure groups). Oval cell hyperplasia and pigmentation of the liver were significantly increased in

the 3000 μg/kg bw per day core study group. At 2 years, two cholangiomas in the 1000 μg/kg bw per day group and two cholangiomas in the 3000 μg/kg bw per day stop-exposure group were seen. A single hepatocellular adenoma was seen in the 3000 μg/kg bw per day core study group. Hepatic cell proliferation, as measured by hepatocellular labelling index, was not significantly different between the vehicle control and dosed groups at any of the interim evaluations.

At 2 years, there were significant increases in chronic active inflammation in the ovary and oviduct in the 1000 and 3000 μg/kg bw per day core study groups. Suppurative inflammation of the uterus in the 1000 μg/kg bw per day group and chronic active inflammation in the 3000 μg/kg bw per day core study group were significantly increased compared with vehicle controls.

Sporadic incidences of minimal to mild follicular cell hypertrophy of the thyroid gland were seen at 53 weeks in all groups, except at 10 μg/kg bw per day. At 2 years, the incidences of minimal to mild follicular cell hypertrophy were significantly increased in the 300 μg/kg bw per day group and in the 3000 μg/kg bw per day (core and stop-exposure) groups.

In the thyroid hormone assessments, serum total T_4, free T_4 and total T_3 concentrations were significantly lower in the 3000 μg/kg bw per day group than in vehicle controls at the 14-week interim evaluation. At the 31-week interim evaluation, no significant differences were observed in serum total T_4, free T_4, total T_3 or thyroid stimulating hormone (TSH) concentrations. At the 53-week interim evaluation, serum total T_4 and free T_4 concentrations in the 3000 μg/kg bw per day group were significantly lower than in vehicle controls.

At PCB 153 dose levels of 100 μg/kg bw per day or more, large, significant and dose-related increases in hepatic PROD activities were found, with activities increased by 136-, 140- and 40-fold, compared with vehicle controls, at 14, 31 and 53 weeks, respectively. Increased PROD activity is characteristic of NDL-PCBs that induce the CYP2B subfamily of cytochrome P450 enzymes. However, there was also up to a 2-fold increase in EROD and acetanilide-4-hydroxylase (AHH) activities in the groups of PCB 153–dosed animals compared with vehicle controls at 14 and 31 weeks. Increases in EROD and AHH activities are characteristic of induction of the CYP1A subfamily of cytochrome P450 enzymes by compounds with dioxin-like activity that bind to AhR. However, this should be compared with the much higher increases of 50- to 100-fold in EROD activity and of 5-fold in AHH activity that were induced in a parallel NTP bioassay on PCB 126, a DL-PCB (NTP, 2006c), indicating that if there was some contamination with DL-PCBs, it was very low.

The overall NOAEL for effects on liver and thyroid for PCB 153 appears to be 10 μg/kg bw per day, equivalent to approximately 7 μg/kg bw per day if adjusted for 5 days/week dosing.

NTP (2006a) concluded that under the conditions of this 2-year gavage study, there was equivocal evidence of carcinogenic activity of PCB 153 in female rats, based on the occurrences of cholangioma of the liver. Although the numbers of cholangiomas were small, the occurrence of bile duct hyperplasia and oval cell hyperplasia could have contributed to cholangioma formation, and so the tumours may have been treatment related (NTP, 2006a).

(ii) PCB 153 plus PCB 126

In a parallel carcinogenesis bioassay in female rats, NTP (2006b) evaluated the effects of combined treatment with PCB 153, an NDL-PCB, and PCB 126, a DL-PCB. This mixture study was conducted because previous studies had demonstrated interactions between PCB 153 and dioxin-like compounds on pharmacokinetics and biological effects.

Groups of 80–81 female rats were given mixtures of PCB 126 and PCB 153 in corn oil:acetone (99:1) by oral gavage for 14, 31 or 53 weeks or 2 years. Both PCBs had an overall purity of greater than 99%. The mixture was given either as a constant ratio of PCB 126 (in ng/kg bw per day) to PCB 153 (in µg/kg bw per day) of 10/10, 100/100, 300/300 or 1000/1000 or varying ratios of PCB 126 at 300 ng/kg bw per day to PCB 153 at 100, 300 or 3000 µg/kg bw per day. Dosing was on 5 days/week for up to 105 weeks.

The main non-neoplastic finding was a significant increase in the incidence and severity of hepatotoxicity at 14, 31 and 53 weeks and 2 years. There were also numerous increases in the incidences of non-neoplastic lesions, notably in the lung, pancreas, adrenal cortex, thyroid gland, thymus, kidney, nose and forestomach, at 14, 31 and 53 weeks and/or 2 years.

Neoplastic findings were increased incidences of hepatocholangiocarcinoma, hepatocholangioma and hepatocellular neoplasms (predominantly adenomas), squamous neoplasms of the lung (predominantly cystic keratinizing epithelioma) and gingival squamous cell carcinoma of the oral mucosa. Increased incidences of pancreatic acinar neoplasms were also considered to be treatment related. Increased incidences of uterine squamous cell carcinoma were possibly treatment related.

NTP (2006b) concluded that under the conditions of this 2-year gavage study, there was clear evidence of carcinogenic activity of a constant ratio binary mixture of PCB 126 and PCB 153 in female rats. NTP (2006b) did not draw any direct comparisons with the NTP study on PCB 126 alone (NTP, 2006c) or discuss in general terms the impact of PCB 153 on the overall tumour response. ATSDR (2000) commented that some of the effects observed in other studies using an initiation–promotion model in which PCB 153 was administered as a promoting agent are consistent with the results of this NTP (2006b) study,

noting that in initiation–promotion studies, PCB 153 induces hepatic EROD and PROD activities and hepatocyte hypertrophy, but does not affect hepatocyte proliferation.

It has been suggested that the development of thyroid follicular cell tumours in PCB-treated rats is attributable to a non-genotoxic mechanism whereby decreasing thyroid hormone levels after PCB treatment result in increased TSH levels, but other mechanisms may also be involved (EFSA, 2005; Knerr & Schrenk, 2006). This mode of action is considered a risk factor for the development of thyroid cancer in rodents, but not in humans (Capen, 1997; EFSA, 2005).

(c) Hydroxylated PCBs

Two hydroxylated PCBs, 2′,4′,6′-trichloro-4-biphenylol (hydroxy-PCB 30) and 2′,3′,4′,5′-tetrachloro-4-biphenylol (hydroxy-PCB 61), which have relatively high estrogenic activity in vitro and in vivo, have been tested in the neonatal mouse model to examine the relationship between the estrogenicity and carcinogenicity of hydroxylated PCB congeners. The model used was the BALB/cCrgl female mouse, which has a low incidence of mammary tumours and well-documented neonatal responses to 17β-estradiol. Groups of 24–43 mice were given subcutaneous injections of 17β-estradiol and/or one or both of the hydroxylated PCBs every 24 hours for 5 days, beginning within 16 hours of birth, in the following doses and combinations: 5 μg 17β-estradiol alone; 2.5 μg 17β-estradiol plus 100 μg hydroxy-PCB 30; 20 μg hydroxy-PCB 30; 200 μg hydroxy-PCB 30; 40 μg hydroxy-PCB 61; 400 μg hydroxy-PCB 61; 10 μg hydroxy-PCB 30 plus 10 μg hydroxy-PCB 61; or 100 μg hydroxy-PCB 30 plus 100 μg hydroxy-PCB 61. Negative controls were given the sesame oil vehicle. The mice were followed to 20 months of age. Mice treated with hydroxy-PCB 30 (200 μg/day) or 17β-estradiol (5 μg/day) showed similar increased incidences of cervicovaginal tract carcinomas (43% and 47%, respectively). Mice treated with hydroxy-PCBs as a mixture showed a change in the type of cervicovaginal tract tumour, shifting from predominantly squamous cell carcinoma to adenosquamous cell carcinoma. The authors of the study concluded that the individual hydroxylated PCBs tested were estrogenic and tumorigenic in mice exposed during development of the reproductive tract and that the results suggested that mixtures may act differently from individual compounds (Martinez, Stephens & Jones, 2005).

(d) Studies on tumour promotion

The majority of rodent carcinogenicity studies on PCBs have used commercial PCB mixtures, and these have been shown to cause hepatocellular carcinomas in rats and mice and thyroid follicular cell adenomas in rats (ATSDR, 2000).

These studies are indicative that PCB mixtures can be complete carcinogens, where some congeners are acting as initiators and others as promoters (Ruiz et al., 2008). PCBs are considered to show tumour promotion activity in mice and co-carcinogenic effects in rats. Tumour promotion experiments have shown that after initiation with a genotoxic carcinogen, technical PCB mixtures and individual DL- and NDL-PCBs can act as liver tumour promoters in rodents.

Some individual NDL-PCB congeners have been tested in tumour promotion studies after initiation with diethylnitrosamine (DEN). PCB 52 was reported to have (weak) promotor activity in rat liver in four studies, and PCB 153 was reported as having promotor activity in rat liver in two studies (Ahlborg, Hanberg & Kenne, 1992). In a medium-term tumour promotion assay in female rats, in which DEN was given as an initiator followed by partial hepatectomy, PCB 126 (a DL-PCB) alone, PCB 153 alone or a combination of the two PCB congeners was given by oral gavage 3 times per week for 8 weeks. When PCB 153 alone was given at doses of 10–10 000 μg/kg bw per day, it caused small, but statistically significant, increases in GST-positive liver cell foci area at 5000 and 10 000 μg/kg bw per day, doses that also caused significant increases in liver weight. PCB 126 alone caused a greater response than PCB 153 at the highest dose at which it was tested, 10 μg/kg bw per day (Dean et al., 2002).

The promoting activity of PCB 153 in male mice initiated with DEN and the question of whether the deletion of the nuclear factor NF-κB p50 subunit influences liver carcinogenesis have been investigated. Four groups of 14–17 wild-type and transgenic mice were injected intraperitoneally with DEN at 9 weeks of age. After a 2-week recovery period, both wild-type and NF-κB $p50^{-/-}$ mice were injected intraperitoneally with PCB 153 at a dose of 0 (corn oil) or 300 μmol/kg bw every 14 days for a total of 20 injections. Mice were then maintained for an additional 15 weeks before being killed. The incidence of hepatocellular tumours, mainly classified as carcinomas, was higher in wild-type mice treated with PCB 153 than in wild-type mice receiving corn oil only. The deletion of p50 decreased the incidence of hepatocellular tumours in mice treated with PCB 153 or corn oil only (Glauert et al., 2008).

Groups of 4–18 male mice were treated with an initiating intraperitoneal dose of DEN and then given a low or a high oral gavage dose of PCB 126, a DL-PCB, or PCB 153, an NDL-PCB, or a low-dose mixture of the two PCBs between 3 and 24 weeks after initiation (Rignall et al., 2013). The low dose was adjusted to induce approximately 150-fold increases in cytochrome P450 (CYP1A1 for PCB 126 and CYP2B10 for PCB 153); the high dose was twice the low dose. To keep liver PCB levels constant, mice were given initial loading doses (low-dose groups: PCB 126 at 62 μg/kg bw, PCB 153 at 67.5 mg/kg bw; high-dose groups: PCB 126 at 124 μg/kg bw, PCB 153 at 135 mg/kg bw) followed by weekly maintenance doses (low-dose groups: PCB 126 at 9.5 μg/kg bw, PCB 153 at 10.5 mg/kg bw;

high-dose groups: PCB 126 at 19 µg/kg bw, PCB 153 at 21 mg/kg bw), calculated on the basis of the half-lives of the two PCBs. When given individually, the PCBs each produced dose-dependent increases in mRNA, protein and activity for the respective cytochrome P450 enzymes that they induce. Combined treatment caused more than additive effects on CYP1A1 mRNA expression, protein level and EROD activity. Changes in the levels of several proteins were detected by proteome analysis in livers of PCB-treated mice. The individual PCBs caused no significant increase in the number of glucose-6-phosphatase-deficient neoplastic lesions in the liver, whereas a moderate significant effect occurred in the combination group. These results suggested weak, but significant, response-additive effects of the two PCBs when given in combination and that cytochrome P450 biomarkers tend to overestimate the carcinogenic response produced by the PCBs in mouse liver.

A variety of mechanisms have been suggested for the tumour promotion activity of PCBs in the liver (reviewed by ATSDR, 2000; Knerr & Schrenk, 2006; Elabbas et al., 2013; IARC, 2015). One proposed mechanism is induction of oxidative stress, and there is evidence that some PCB metabolites are inducers of oxidative stress.

Suppression of apoptosis in preneoplastic cells has also been proposed as a mechanism for the tumour promotion activity of PCBs in the liver. For example, in vitro studies have shown that six out of 20 NDL-PCB congeners tested lowered basal hepatic levels of the tumour suppressor protein p53 and attenuated the p53 response after treatment with inducers (Al-Anati, Högberg & Stenius, 2009), although one congener, PCB 180, has been shown to increase expression of p53 (Viluksela et al., 2014).

Another proposed mechanism is inhibition of gap junctional intercellular communication (GJIC), which has been shown for NDL-PCBs in vivo and in vitro in rodent and human cells (IARC, 2015). DL-PCBs alter p53 signalling, but they have no acute effect on GJIC (Machala et al., 2003; Elabbas et al., 2013). The monochlorinated to hexachlorinated NDL-PCBs, on the other hand, are acute inhibitors of GJIC in vitro, with trichlorobiphenyls to hexachlorobiphenyls that have chlorine substitutions at the *ortho* position (e.g. PCB 136, PCB 153) being particularly potent inhibitors; heptachlorobiphenyls and octachlorobiphenyls have minimal or no GJIC inhibitory activity (Machala et al., 2003, 2004). The assay for GJIC inhibition showed good predictability for tumour promotion of *ortho*-substituted PCBs. Recently, inhibition of GJIC has been confirmed using single doses of ultrapure NDL-PCB congeners; among the six indicator PCBs, the inhibitory activity of PCB 52 was moderate, whereas that of the other five indicator PCBs was weak (Hamers et al., 2011). IARC (2015) noted that different cell- and connexin-specific mechanisms of action probably account for the inhibitory effects of PCBs on GJIC. PCB 153 decreased the number of gap junction plaques

and decreased levels of connexin 43 (constitutive protein of gap junctions) in liver epithelial cells; it enhanced proteasomal and lysosomal degradation of connexin 43 and inhibited trafficking of connexin 43 to the plasma membrane (Šimečková et al., 2009a).

Additional non-genomic effects of NDL-PCBs on membrane-associated proteins, which are closely related to tumour promotion and progression, have been described by IARC (2015). They include the following observations. Initiation of male mice with DEN followed by exposure to PCB 153 appears to strongly select for *Catnb*-mutated, glutamine synthetase–positive tumours of the liver (Strathmann et al., 2006). In a rat liver progenitor WB-F344 cell line, PCB 153 was found to decrease levels of several proteins at adherens junctions involved in cell–cell communication and intracellular signalling, including E-cadherin, β-catenin and plakoglobin (Šimečková et al., 2009b). Oral administration of PCB 126 (a DL-PCB), mono-*ortho*-substituted PCB 118 (a DL-PCB) or PCB 153 (an NDL-PCB) differentially altered expression of the tight junction proteins claudin 5, occludin and ZO-1 in brain capillaries in C57/B16 mice and increased the permeability of the blood–brain barrier. In addition, the rates of formation and progression of brain metastases by luciferase-tagged melanoma cells were enhanced by a single oral gavage dose of PCB 118 or PCB 126 at 150 μmol/kg bw, with a lesser but still significant enhancement by PCB 153 (Seelbach et al., 2010). PCB 104 (an NDL-PCB) induced endothelial hyperpermeability of human microvascular endothelial cells, HMEC-1, and transendothelial migration of human breast cancer cells, MDA-MB-231. These effects were associated with overexpression of vascular endothelial growth factor (Eum et al., 2004). PCB 104 and PCB 153 induced expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1) in the liver, lung and brain of male mice, and PCB 104 also increased levels of matrix metalloproteinase-7 (MMP-7) mRNA in the liver and brain; these are proinflammatory mediators that can contribute to metastasis (Sipka et al., 2008). A mixture of seven NDL-PCBs (PCBs 28, 52, 101, 138, 153, 180 and 209) increased cell motility of human non-metastatic MCF-7 cells and human metastatic breast cancer MDA-MB-231 cells in vitro via production of reactive oxygen species and activation of the Rho-associated kinase (ROCK); in an in vivo study in mice, PCBs significantly promoted disease progression, leading to enhanced capability of metastatic breast cancer cells to metastasize to bone, lung and liver (Liu, Li & Du, 2010). Human skin keratinocytes were exposed to a synthetic mixture of volatile PCBs or to PCB 28 or PCB 52, both prominent airborne NDL-PCB congeners, for up to 48 days. Compared with untreated control cells, the PCB mixture and the two congeners significantly inhibited telomerase activity from day 18, whereas telomere length was reduced by PCB 52 from day 18 and by PCB 28 and by the mixture from day 30 onwards

(Senthilkumar et al., 2011). In a similar study on PCB 153, telomerase activity, telomere length and cell growth were significantly reduced, whereas intracellular superoxide levels were increased, compared with controls, from day 6 to day 48, suggesting that superoxide may be one of the factors regulating telomerase activity, telomere length and cell growth (Senthilkumar, Robertson & Ludewig, 2012).

2.2.4 Genotoxicity

Genotoxicity studies on commercial PCB mixtures and on individual PCB congeners have been summarized by ATSDR (2000) and IARC (2015).

(a) Commercial mixtures of PCBs

For commercial mixtures, the experimental in vitro test systems used have included gene mutation in bacterial and yeast cells, gene mutation, chromosomal aberration and micronucleus formation in animal and human cells, DNA strand breaks in animal and human cells, unscheduled DNA synthesis (UDS) in mammalian cells and DNA adduct formation in mammalian and human cells. The majority of such studies on commercial mixtures showed no genotoxicity, with only a few giving positive results. In vivo studies on commercial mixtures have included investigation of UDS and DNA adducts in rat, mouse and monkey hepatocytes, chromosomal aberrations in rat and mouse bone marrow and spermatogonia, micronucleus formation in mouse bone marrow, dominant lethal mutations in rats, gene mutations in transgenic mice and DNA strand breaks (comet assay) in various mouse tissues. As with the in vitro studies, the majority of in vivo studies on commercial mixtures showed no genotoxicity, with only a few tests giving positive or weakly positive results (IARC, 2015).

Other reviews have concluded that as commercial PCB mixtures exhibit no or minimal mutagenic activity in most assay systems, this suggests that PCBs are not potent genotoxicants (ATSDR, 2000) and that those exhibiting carcinogenicity are probably acting as indirect, non-genotoxic carcinogens (Safe, 1989; Knerr & Schrenk, 2006).

(b) General considerations on PCB metabolites

Some PCB metabolites, particularly those from lower chlorinated congeners, may be more reactive towards DNA than their parent PCB congeners. Robertson & Gupta (2000), for example, showed that metabolism of PCBs can generate electrophilic metabolites and reactive oxygen species that could damage DNA. Srinivasan et al. (2001) showed that dihydroxylated PCBs and PCB quinones, after reaction with glutathione, produced reactive oxygen species in a human cell line and oxidative DNA damage in the form of DNA strand breaks in bacteria

(*Escherichia coli*). Pereg et al. (2001) pointed out that the issue of covalent binding of PCB metabolites to macromolecules was unclear; in vitro studies showed macromolecular binding, including binding to DNA, but conflicting results were obtained in vivo from studies that used different animal models and techniques of differing sensitivity for detection of binding and adduct formation. Formation of a guanine adduct has been reported after incubation of calf thymus DNA with quinones of lower chlorinated PCBs (Zhao et al., 2004). Wangpradit et al. (2009) showed that an enzyme produced in human ovary, breast and prostate tissue, prostaglandin H synthase, which has both cyclooxygenase and peroxidase activities, oxidizes three dihydroxy metabolites of PCB 3 to the corresponding quinones, which are reactive electrophilic species with a potential for protein and DNA damage. Cu^{2+}-mediated activation of PCB catechol and hydroquinone metabolites induces oxidative damage and polar DNA adducts (Spencer et al., 2009). Overall, these studies show that liver enzymes metabolize lower chlorinated PCB congeners to reactive intermediates, such as epoxides, quinones and reactive oxygen species, that have the potential to modify nucleotides and DNA, hence causing mutations, and that oxidative damage may be involved in the production of liver tumours after exposure to PCBs (Ludewig & Robertson, 2013). Recently, lower chlorinated PCB 3 metabolites have been shown to induce gene mutations, chromosome breaks, chromosome loss and polyploidy in cells in culture, providing the first evidence of their potential for mutagenicity (Robertson & Ludewig, 2011). The mutagenicity in vitro of PCB 3 metabolites indicates the need for further studies to assess the risks associated with human exposure to lower chlorinated hydroxy-PCBs.

Ruiz et al. (2008) used a quantitative structure–activity relationship (QSAR) approach to assess the potential for mutagenesis and carcinogenesis of all 209 individual PCB congeners (both DL- and NDL-PCBs) and their possible hydroquinone and benzoquinone metabolites. Their analysis concluded that monochlorinated and dichlorinated PCBs and their metabolites are predicted to have a high probability of being mutagenic. The probability of mutagenicity decreased with increasing numbers of chlorine atoms, and higher chlorinated PCBs were predicted to be non-mutagenic. The predictions were in agreement with experimental data on DNA adduct formation. The higher chlorinated PCBs were, however, predicted to be carcinogenic, particularly in the female mouse model. The benzoquinone metabolites of PCBs could be carcinogenic (but the weight of evidence is poor), and hydroquinone metabolites were less likely than benzoquinone metabolites to be carcinogenic.

(c) Studies on individual NDL-PCBs and their metabolites

The results of in vitro and in vivo studies in which individual NDL-PCBs and/or their metabolites from the indicator group have been tested are shown in Table 7.

Table 7
Genotoxicity studies on individual NDL-PCB congeners and their metabolites

PCB congener no. / metabolite	Test system	Results		Effective dose	Reference
		Without metabolic activation	With metabolic activation		
In vitro studies					
PCB 3	Chinese hamster V79 cells – gene mutation	–	NT		Zettner et al. (2007)
2′-OH-PCB 3		–	NT		
3′-OH-PCB 3		–	NT		
4′-OH-PCB 3		–	NT		
PCB 3-3′,4′ hydroquinone		–	NT		
PCB 3-3′,4′ quinone		+	NT	0.6 µmol/L	
PCB 3-2′,5′ hydroquinone		–	NT		
PCB 3-2′,5′ quinone		+	NT	0.5 µmol/L	
PCB 3	Chinese hamster V79 cells – micronucleus formation	–	NT		Zettner et al. (2007)
2′-OH-PCB 3		+	NT	50 µmol/L	
3′-OH-PCB 3		+	NT	100 µmol/L	
4′-OH-PCB 3		+	NT	75 µmol/L	
PCB 3-3′,4′ hydroquinone		+	NT	15 µmol/L	
PCB 3-3′,4′ quinone		+	NT	5 µmol/L	
PCB 3-2′,5′ hydroquinone		+	NT	2.5 µmol/L	
PCB 3-2′,5′ quinone		+	NT	1 µmol/L	
PCB 3	Chinese hamster V79 cells – sister chromatid exchange or polyploidy	–	NT		Flor & Ludewig (2010)
PCB 3-3′,4′ hydroquinone		+	NT	2.5 µmol/L	
PCB 3-3′,4′ quinone		–	NT		
PCB 3-2′,5′ hydroquinone		+	NT	5 µmol/L	
PCB 3-2′,5′ quinone		–	NT		
PCB 3	Comet assay	NT	NT		
PCB 3-2,5 hydroquinone	– HL-60 cells	+	NT	10 µmol/L	
	– Jurkat cells	–	NT		
PCB 3-2,5 quinone	– HL-60 cells	+	NT	5 µmol/L	
	– Jurkat cells	+	NT	5 µmol/L	
PCB 52	*Salmonella typhimurium* TA1538 – reverse mutation	–	–		Wyndham, Devenish & Safe (1976)
PCB 52	*S. typhimurium* TA98, TA100, TA1535, TA1537 – reverse mutation	NT	–		Hsia, Lin & Allen (1978)
4-OH-PCB 52		NT	–		
3,4-epoxy-PCB 52		NT	–		

Table 7 (continued)

PCB congener no. / metabolite	Test system	Results		Effective dose	Reference
		Without metabolic activation	With metabolic activation		
PCB 52	Mouse fibroblast L-929 cells – DNA strand breaks (alkaline sedimentation)	+	NT	20 µg/mL	Stadnicki & Allen (1979)
4-OH-/3-OH-2,2′,5,5′-tetrachlorobiphenyl (4:1)		+	NT	20 µg/mL	
3,4-epoxy-PCB 52		+	NT	10 µg/mL	
PCB 52	Human lymphocytes (6 donors) – DNA strand breaks (comet assay)	(+)	NT	0.3 µg/mL	Sandal, Yilmaz & Carpenter (2008)
PCB 52	Human lymphocytes (4 donors) – sister chromatid exchange	–	NT		Sargent, Rollof & Meisner (1989)
	Human lymphocytes (5–9 donors) – chromosomal aberrations	–	NT		
PCB 101	Fish fibroblast RTG-2 cells – DNA strand breaks (comet assay)	+	NT	16 µg/mL	Marabini, Calò & Fucile (2011)
PCB 101	Fish fibroblast RTG-2 cells – micronucleus formation	+	NT	16 µg/mL	
3′-$MeSO_2$-2,2′,4′,5,5′-pentachlorobiphenyl (metabolite of PCB 101)	Human lymphocytes – sister chromatid exchange	–	NT		
	Human lymphocytes – micronucleus formation	–	NT		
PCB 138	Fish fibroblast RTG-2 cells – DNA strand breaks (comet assay)	+	NT	25 µg/mL	Marabini, Calò & Fucile (2011)
PCB 138	Fish fibroblast RTG-2 cells – micronucleus formation	–	NT		
PCB 153	Human lymphocytes (5–9 donors) – chromosomal aberrations (structural)	+	NT	1 µg/mL	Sargent, Rollof & Meisner (1989)

PCB congener no. / metabolite	Test system	Results: Without metabolic activation	Results: With metabolic activation	Effective dose	Reference
PCB 153	Human breast epithelial MCF-10A cells – micronucleus formation	+	NT	0.4 µg/mL	Venkatesha et al. (2008)
PCB 153	Human hepatoma HepG2 cells – micronucleus formation	+	NT	36 µg/mL	Wei et al. (2009)
PCB 153	Fish fibroblast RTG-2 cells – DNA strand breaks (comet assay)	+	NT	11 µg/mL	Marabini, Calò & Fucile (2011)
PCB 153	Fish fibroblast RTG-2 cells – micronucleus formation	+	NT	11 µg/mL	
PCB congener no.	**Test system**	**Results**		**Dose**	**Reference**
In vivo studies					
PCB 52	Female Sprague-Dawley rat, 70% hepatectomy, bone marrow cells – chromosomal aberrations (numerical and structural)	–		10 mg/kg in feed, 1 year	Meisner et al. (1992)
PCB 52	Female Sprague-Dawley rat, liver cells after 70% hepatectomy – chromosomal aberrations (numerical)	–		10 mg/kg in feed for 7 or 10 months	Sargent et al. (1992)
PCB 153	Female Sprague-Dawley rat, liver or brain – DNA adducts, M1dG secondary oxidative DNA lesion	–		1 mg/kg bw orally × 5 per week for 53 weeks	Jeong et al. (2008)

diOH: dihydroxy; $MeSO_2$: methyl sulfone; NT: not tested; OH: hydroxy; +: considered to be positive; (+): considered to be weakly positive in an inadequate study; –: considered to be negative

Source: Adapted from IARC (2015)

No studies on PCB 28 or PCB 180 have been found.

PCB 52 and its two major metabolites showed no activity in tests for gene mutation in five strains of *Salmonella typhimurium*. PCB 52 was negative in a test for chromosomal aberrations in human lymphocytes. PCB 52 and its major metabolites were positive or weakly positive in tests for DNA strand breaks in mouse fibroblasts and human lymphocytes, but negative for sister chromatid exchange in human lymphocytes. PCB 52 was negative in two in vivo studies on chromosomal aberrations in bone marrow and liver.

PCB 101 has not been tested in any definitive genotoxicity studies in vitro or in vivo; in other tests, PCB 101 was positive for DNA strand breaks and micronucleus formation in fish cells. Its major methyl sulfone metabolite was negative in a test for micronucleus formation in human lymphocytes and negative in an indicator test for sister chromatid exchange. There are no in vivo tests on the parent congener or its metabolites.

PCB 138 has been tested in fish cells only. It was positive for strand breaks but negative for micronucleus formation.

PCB 153 was positive in three separate tests for chromosomal aberrations and for micronucleus formation in human cells. It was also positive in tests for DNA strand breaks and micronucleus formation in fish cells. In an in vivo study, PCB 153 did not form DNA adducts in rat liver or brain.

2.2.5 Reproductive and developmental toxicity

(a) Reproductive studies on commercial mixtures of PCBs

Early reproductive studies were conducted mainly on commercial mixtures. In male rodents, oral exposure to PCB mixtures caused reductions in spermatozoa, male fertility, and ventral prostate and seminal vesicle weights. In female rodents, adverse effects on the estrous cycle and ovulation and reduction in weights of female reproductive organs were reported (Ahlborg, Hanberg & Kenne, 1992). The ATSDR (2000) review concluded that there was evidence for adverse effects on weights of male reproductive organs and spermatozoa in rodents and monkeys, but the evidence was limited. For female animals, the review concluded that reproductive toxicity had been established in a number of oral studies with commercial PCB mixtures. The effects observed included prolonged estrus, decreased sexual receptivity and reduced implantation rate in adult rats and/or their offspring exposed during gestation and lactation, decreased conception rate in mice, partial or total reproductive inhibition in mink, and prolonged menstruation and decreased fertility in monkeys. Mink and monkeys were considered to be particularly sensitive, with effects occurring at doses in the range of 0.1–1 mg/kg bw per day in intermediate-duration studies and as low as 0.02 mg/kg bw per day in monkeys following chronic exposure (ATSDR, 2000; EFSA, 2005).

(b) Reproductive studies on individual NDL-PCBs and their metabolites

(i) PCB 28

The direct effects of two NDL-PCBs, PCB 28 and PCB 30, on fresh spermatozoa of bulls aged 2–4 years were evaluated in vitro. Median inhibitory concentrations (IC_{50} values) for cytotoxicity of 8.45 and 5.45 ng/mL were measured for PCB 28 and PCB 30, respectively, and divisions or multiples of the IC_{50} were used as the doses to assess effects on sperm motility and viability. Total motility, progressive motility and viability decreased in a dose- and duration-dependent manner. Total motility, at the IC_{50} dose following 2 hours of exposure, decreased by 72% for PCB 28 and by 61% for PCB 30. Motility results were in accordance with the viability and morphology data showing that total abnormalities (especially acrosome reaction rate) were increased (Yurdakok et al., 2015).

(ii) PCB 132

Groups of 12 pregnant rats were given PCB 132 at a dose of 0 (corn oil), 1 or 10 mg/kg bw as a single intraperitoneal injection on gestation day (GD) 15 to investigate effects on reproductive parameters of male offspring. The male offspring were killed, and the epididymal sperm counts, motility, velocity, reactive oxygen species generation, sperm–oocyte penetration rate, testicular histopathology, apoptosis-related gene expression and caspase activation were assessed on postnatal day (PND) 84. Cauda epididymal weight was reduced at both doses, but the reduction was not dose related and was significant only at 1 mg/kg bw. There was no effect on testis histopathology. Epididymal sperm count and motile epididymal sperm count were significantly reduced at both doses in a dose-related manner. Dose-related increases in reactive oxygen species and reductions in sperm–oocyte penetration rate were observed in spermatozoa, reaching statistical significance at the higher dose. In the low-dose group, p53 was significantly induced and caspase-3 was inhibited. In the high-dose group, activation of caspase-3 and caspase-9 was significantly increased, whereas the expressions of the apoptosis-related genes *Fas*, *Bax*, *bcl-2* and *p53* were significantly decreased. The authors commented that these intraperitoneal doses would give rise to levels of PCB 132 in tissues that are several orders of magnitude higher than any present in human tissues (Hsu et al., 2007).

(iii) PCB 153

PCB 153 has been shown to affect bovine oocytes cultured in vitro. Concentrations of 0.84, 8.4 and 84 ng/mL had no effect on oocyte maturation, but resulted in a reduced proportion of oocytes undergoing cleavage at the highest concentration. There were no differences in blastocyst development (Krogenaes et al., 1998).

The effect of three different mixtures of PCB 153 and PCB 118, a DL-PCB, on fetal testis development in sheep has been investigated. Pregnant ewes 2–7 years of age were treated by oral gavage 3 times a week, from mating until euthanasia (day 134). Originally, two exposure groups were planned to receive either 98 µg/kg bw per day of PCB 153 or 49 µg/kg bw per day of PCB 118, with a third group receiving corn oil only. However, there were two episodes of cross-contamination, resulting in a mixed exposure to PCBs in all three groups. This produced three groups of fetuses with distinct PCB levels in adipose tissue: high PCB 153/low PCB 118 (n = 13), low PCB 153/high PCB 118 (n = 14) and low PCB 153/low PCB 118 (n = 14). The corresponding levels of PCB 153 and PCB 118 in adipose tissue (in ng/g lipid) were 47 607/460 for the high PCB 153/low PCB 118 group, 2545/6118 for the low PCB 153/high PCB 118 group, and 1565/1969 for the low PCB 153/low PCB 118 group. Fetal body weight was significantly lower in the high/low and low/high PCB groups compared with the low/low PCB group, but there were no significant differences in testis weight corrected for body weight. Circulating testosterone level and testis morphology showed no differences between the three groups. Proteomic investigations showed 26 statistically significant spot alterations in proteins involved in 15 functional pathways and 10 structural pathways in the testes of fetuses exposed to high PCB 153/low PCB 118 or low PCB 153/high PCB 118, relative to low PCB 153/low PCB 118, the pathways involved indicating effects on stress response, protein synthesis or cytoskeleton regulation (Krogenaes et al., 2014).

(c) Developmental toxicity studies on commercial mixtures of PCBs

The majority of developmental toxicity studies on NDL-PCBs have focused on outcomes related to developmental neurotoxicity, and these are summarized below in section 2.2.5(f). Below, only toxicity studies investigating multiple developmental outcomes other than neurotoxicity are summarized.

Early developmental toxicity studies were conducted mainly on commercial mixtures and have been summarized elsewhere (Ahlborg, Hanberg & Kenne, 1992; ATSDR, 2000; Ulbrich & Stahlmann, 2004). Studies on mice, rats, rabbits, guinea-pigs, mink and monkeys showed one or more of reduced implantations, increased resorptions, increased abortions, reduced fetal growth and delayed development, increased length of gestation, reduced litter size, reduced birth weight, reduced perinatal survival, reduced growth of offspring and delayed developmental landmarks. Postnatal effects on learning and behaviour were seen in rat, mouse and monkey. In the mouse, commercial mixtures caused teratogenicity (hydronephrosis and cleft palate), which was considered to be attributable to the DL-PCB congeners (interaction with AhR). Doses causing developmental toxicity were as low as 0.1 mg/kg bw per day, with

some behavioural effects in monkeys reported at lower doses, down to 0.006 mg/kg bw per day. Developmental toxicity in rodents can occur in the absence of maternal toxicity, but maternal toxicity was also evident in monkeys, even at low doses.

(d) Developmental toxicity studies on individual NDL-PCBs and their metabolites

(i) PCB 28

PCB 28 was given orally by gavage to groups of 6–9 pregnant rats on GDs 10–16 at a dose of 0, 8 or 32 mg/kg bw per day. In the offspring from the high-dose group, there was reduced birth weight and increased liver weight at weaning. High-dose female offspring also showed slower learning in a T-maze (see section 2.2.5(f)). There was no effect on plasma T_4 concentrations (Ness et al., 1993; Schantz, Moshtaghian & Ness, 1995).

(ii) PCB 52

In a study conducted under the ATHON project (Elabbas et al., 2013), PCB 52 was given orally by gavage to groups of 5–6 pregnant rats between GD 7 and PND 10. PCB 52 was dissolved in corn oil, and the total dose levels were 0, 30, 100, 300, 1000 and 3000 mg/kg bw. Controls received only the vehicle. The total dose was divided into 10 equal subdoses given on GDs 7, 9, 11, 14 and 16 and PNDs 1 and 10. Litter size was adjusted to five males and five females on PND 1, pups were weaned on PND 28, and samples were taken from one male and one female offspring on PNDs 7, 35 and 84. Parameters monitored were "development of the reproductive system, bone and teeth, sex steroidogenesis, limited histopathology, biochemistry and molecular biology". Body weight development, mortality and developmental milestones (eye opening, tooth eruption) of the offspring after perinatal exposure were not affected by treatment. An increase in liver weight in offspring was observed (no further details were provided). The developmental neurotoxicity findings from this study are described in section 2.2.5(f). Other findings from this study have not yet been published.

(iii) PCB 153

PCB 153 was given orally by gavage to groups of 6–9 pregnant rats daily from GD 10 to GD 16 at a dose of 0, 16 or 64 mg/kg bw per day. Postnatally, offspring showed reduced body weight during the preweaning period and increased liver weight at weaning in the high-dose group. High-dose males showed decreased response latency in a radial arm maze, and high-dose female offspring showed slower learning in a T-maze (see section 2.2.5(f). Plasma T_4 but not T_3 concentrations were reduced at both doses (Ness et al., 1993; Schantz, Moshtaghian & Ness, 1995).

Groups of 10 pregnant rats were exposed to PCB 153 daily at a dose of 0, 16 or 64 mg/kg bw per day orally by gavage from GD 10 to GD 16. The dams were allowed to litter out and raise their offspring. At 1 or 3 weeks of age, the offspring were examined for changes in developmental parameters. There were no treatment-related effects on body weight, body length, tail length, anogenital distance or weights of kidneys, testes, ovaries or uterus. Liver weight was significantly increased in the high-dose male offspring at 1 and 3 weeks of age, but not in female offspring. There was a dose-dependent decrease in concentrations of T_4 in plasma in males and females combined at 1 and 3 weeks of age, which was statistically significant in the high-dose group. Concentrations of T_3 in plasma were reduced in females in a dose-related manner at 3 weeks of age, and the reduction was statistically significant in the high-dose group. TSH level was not affected. There were no changes in concentrations of growth hormone or insulin-like growth factor-1 (IGF-1) in plasma in any dose group (Kobayashi et al., 2008). In a subsequent study using 10 pregnant rats per dose group but lower doses of 0, 1 and 4 mg/kg bw per day, the same parameters were assessed in the offspring at 1, 3 or 9 weeks of age. There were no effects on any parameter, apart from a dose-related increase in T_3 concentration in plasma in males at 1 week of age; at 3 and 9 weeks of age, there were no effects of treatment on T_3 concentration in males. There were no effects on T_3 concentration in female offspring at any age, nor were T_4 or TSH levels affected in any group (Kobayashi et al., 2009).

Lyche et al. (2004a) investigated the possible effects of gestational exposure to environmental levels of PCB 153, an NDL-PCB, or PCB 126, a DL-PCB, on the hypothalamic–pituitary–gonadal axis in goat kids. Groups of 10 pregnant does were given corn oil vehicle only, PCB 153 (estimated dose 98 µg/kg bw per day) or PCB 126 (estimated dose 49 ng/kg bw per day) orally, 3 times per week, from GD 60 until delivery. Pre-pubertal and post-pubertal concentrations of LH, FSH, prolactin and progesterone in plasma were analysed. LH, FSH, prolactin and progesterone concentrations were also measured during an induced estrous cycle. There were no effects on body weight of the kids. In female offspring exposed to PCB 153, pre-pubertal LH concentration was significantly lower than in controls, there was a significant delay in onset of puberty (by an average of about 8 days) and there was a significant increase in progesterone level during the luteal phase of an induced estrous cycle at 9 months of age. There was no effect on prolactin or FSH level. PCB 126 did not produce any effects on the hypothalamic–pituitary–gonadal axis. The mean concentrations of PCBs in adipose tissue in the goat offspring at 9 months of age were 5.8 µg/g (lipid weight) and 0.49 ng/g (lipid weight) for PCB 153 and PCB 126, respectively.

In a further study by the same research group (Zimmer et al., 2009), groups of 10 pregnant goats were treated with corn oil only, PCB 153 or PCB 126, as described above. In male offspring exposed to PCB 153, mean basal cortisol

concentrations were significantly lower around the onset of puberty and during their first breeding season, compared with controls. Male goat kids exposed to either PCB congener showed a greater and more prolonged rise in plasma cortisol levels compared with controls when animals were subjected to mild stress at 9 months of age. Neither the basal maternal cortisol level in plasma nor adrenal masses in goat kids were affected by PCB exposure.

Lundberg et al. (2006) studied the effects of perinatal exposure to PCB 153 and PCB 126 in female goat offspring. The pregnant goats were exposed to 98 µg/kg bw per day of PCB 153 or 49 ng/kg bw per day of PCB 126 in corn oil from GD 60 until delivery. The offspring were also exposed to the PCBs during the lactation period of 6 weeks. The diaphyseal bone was analysed at a distance of 18% and 50% of the total bone length, and the metaphyseal bone at a distance of 9%. Also, biomechanical three-point bending of the bones was conducted, with the load being applied to the mid-diaphyseal peripheral quantitative computed tomography measure point (50%). Compared with non-exposed goats, PCB 153 exposure significantly decreased the total cross-sectional area, decreased the cross-sectional area of the marrow cavity, decreased the moment of resistance at the diaphyseal 18% measure point and increased the trabecular bone mineral density at the metaphyseal measure point. PCB 126 exposure did not produce any observable changes in bone tissue. The biomechanical testing showed no significant differences between the exposed and control groups for either congener.

(iv) PCB 180

In a study conducted under the ATHON project (Elabbas et al., 2013), PCB 180 was given orally by gavage to groups of 5–6 pregnant rats between GD 7 and GD 10. PCB 180 was dissolved in corn oil, and the total dose levels were 0, 10, 30, 100, 300 and 1000 mg/kg bw. Controls received only the vehicle. The total dose was divided into four equal subdoses given on GDs 7–10. Litter size was adjusted to four males and four females on PND 1, pups were weaned on PND 28, and samples were taken from one male and one female offspring on PNDs 7, 35 and 84. Parameters monitored were "development of the reproductive system, bone and teeth, sex steroidogenesis, limited histopathology, biochemistry and molecular biology". Maternal body weight development was slightly decreased at the highest dose level. Offspring body weight was decreased during the first weeks of life after high-dose exposure, but recovered thereafter. Neonatal mortality was slightly and dose-dependently increased at the two highest dose levels. Analysis of developmental milestones revealed slight delays in balano-preputial separation and vaginal opening. Tooth eruption, eye opening and anogenital distance were not affected. Offspring liver weights were dose-dependently increased on PNDs

7, 35 and 84, but not on PND 1. The developmental neurotoxicity findings from this study are described in section 2.2.5(f). Other findings from this study have not yet been published.

(v) Mixture of PCBs 138, 153, 180 and 126

The effects of a single dose of a reconstituted mixture of NDL- and DL-PCBs were studied in rat dams and offspring after maternal exposure (Cocchi et al., 2009; Colciago et al., 2009). The mixture contained equal concentrations by weight of three NDL-PCBs (PCB 138, PCB 153 and PCB 180), together with a DL-PCB (PCB 126), which was added at a ratio of 1:10 000 of the total mixture. Groups of animals were given 10 mg/kg bw per day of the mixture by subcutaneous injection, daily on GDs 15–19 and twice a week during lactation until PND 21. The dose averaged over the treatment period was estimated to be 3.7 mg/kg bw per day. Offspring were sacrificed on PND 21 and PND 60. Maternal body weight, litter size, sex ratio of the offspring and postnatal mortality were not affected by the treatment. Offspring body weight after weaning was significantly decreased in both males and females. The relative (to body weight) weights of ovary, testis and prostate were not affected. Plasma testosterone concentrations in females in diestrus or in males were not affected on PND 60. No treatment-related effects were observed in free T_3 or T_4 concentrations in plasma on PND 21 or PND 60. Concentrations of IGF-1 in plasma were significantly higher in mixture-treated males and females than in controls on PND 21, but the difference diminished by PND 60.

Alterations observed in the hypothalamic–pituitary growth hormone axis included increased somatostatin expression in the hypothalamic periventricular nucleus in both sexes and in the lateral arcuate nucleus in males only. Expression of growth hormone in the anterior pituitary was decreased in males only. These changes were observed on PND 60.

Treatment-related changes were observed in structure, geometry and mineral content of long bones in the offspring examined on PND 60. The width of uncalcified epiphyseal cartilage in the tibia was significantly increased in both sexes. There was decreased whole bone planar area in both sexes and decreased bone mineral content in males. Using peripheral quantitative computed tomography, changes were observed only in the mid-diaphysis of tibiae of male offspring. These included decreased total bone and trabecular bone area, decreased bone mineral content and decreased periosteal and endosteal diameter and bone thickness. The bone strength index was also decreased in males (Cocchi et al., 2009).

Treatment with the mixture resulted in several alterations in the normal dimorphic expression pattern of the androgen activating enzymes, aromatase

and 5α-reductases 1 and 2, in the hypothalamus. Expression of aromatase was significantly increased in males and slightly decreased in females on PND 21. Hypothalamic expression of 5α-reductase 1 was decreased in females on PND 21, and the decrease persisted until PND 60. In males, expression of 5α-reductase 1 was decreased only on PND 60. In contrast, expression of 5α-reductase 2 was significantly increased in females, but slightly decreased in males, on PND 60. In spite of reduced body weight, the onset of puberty was shown to occur earlier in mixture-treated females than in controls, as indicated by the age and body weight at vaginal opening. In contrast, testicular descent in males was delayed. Studies on copulatory behaviour of adult male rats revealed slight but significant delays in normal male sexual behaviour; female sexual behaviour was not affected. Learning and memory tests showed no changes in the spatial memory test in either sex, but there was a significantly prolonged latency in the passive avoidance test in males. No changes were observed in spontaneous locomotor activity or in depression and anxiety behaviour (Colciago et al., 2009).

(vi) 4-Hydroxy-PCB 107

Exposure of pregnant rats to ^{14}C-labelled 4-hydroxy-PCB 107, given orally by gavage from GD 10 to GD 16, resulted in accumulation of 4-hydroxy-PCB 107 in fetal livers, brain and plasma measured at GD 17 and GD 20 (Meerts et al., 2002).

Thyroid hormone status and metabolism were studied in groups of pregnant rats given 4-hydroxy-PCB 107 (^{14}C-labelled or unlabelled) orally by gavage at 5 mg/kg bw on GDs 10–16. Fetuses were studied at GD 17 and GD 20. The test compound accumulated in the fetal compartment, with fetal/maternal ratios of 11.0, 2.6 and 1.2 in liver, cerebellum and plasma, respectively, at GD 20. Radiolabel was bound to plasma transthyretin in dams and fetuses. Concentrations of total T_4 and free T_4 in fetal plasma were significantly decreased at GD 17 and GD 20 (89% and 41%, respectively, at GD 20), whereas concentrations of TSH in fetal plasma were increased more than 2-fold at GD 20. No effects were seen on T_3 concentrations in fetal brain (Meerts et al., 2002).

The same group investigated the effects of exposure of rats to 4-hydroxy-PCB 107 given orally by gavage on GDs 10–16 at a dose of 0 (corn oil), 0.5 or 5 mg/kg bw per day on postnatal development, sex steroid hormone levels in offspring and reproduction of the F_1 females. F_0 group sizes were 8–11 dams. There were no effects on F_0 maternal toxicity or reproductive parameters. After birth, F_1 litters were culled to four of each sex per litter, weaned at PND 21 and allowed to mature until 11 months of age. Body weights, organ weights and developmental landmarks, including sexual maturation (vaginal opening and preputial separation), were unaffected by treatment. Half the cohort of offspring was mated at approximately 260 days of age, and the pregnant females were

killed on GD 20; there was no effect on reproduction in this F_1 generation. In the unmated cohort, there was a statistically significant and dose-related prolongation of the estrous cycle in female offspring from both treated groups when monitored between PND 210 and PND 231. The mean plasma estradiol concentration in 11-month-old female offspring was significantly increased by 230% in the group given 4-hydroxy-PCB 107 at 5 mg/kg bw per day, and the estradiol:progesterone ratio was also increased in this group (both only at the pro-estrous stage). No effects on male or female reproductive organ weights or on testosterone levels at PNDs 310–325 could be detected (Meerts et al., 2004).

(e) Developmental neurotoxicity: mechanistic aspects

Multiple studies with NDL-PCBs and rodents have shown that these compounds cause neurobehavioural effects, especially after prenatal and/or postnatal exposure. Common end-points that are affected by NDL-PCBs include locomotor activity, spontaneous behaviour, habituation capability, spatial learning and anxiety. Studies with mice and rats maternally exposed to NDL-PCBs before or after birth showed an increase, as well as a decrease, in spontaneous activity (Holene et al., 1998; Gralewicz et al., 2009; Boix, Cauli & Felipo, 2010; Boix et al., 2011). Additionally, exposure to NDL-PCBs can cause impairment of spatial learning and memory abilities in rodents (Piedrafita et al., 2008a,b; Boix, Cauli & Felipo, 2010). It should be noted that these neurodevelopmental studies usually involved a limited number of dose levels. This makes it impossible to determine relative effect potencies and QSARs for the NDL-PCBs. In vivo studies on neurobehavioural or developmental effects using hydroxylated metabolites of NDL-PCBs are lacking. This is despite the fact that in vitro studies point towards a potentially important role for hydroxylated metabolites in neurotoxic mechanisms. Only one perinatal study used a hydroxylated PCB (4-hydroxy-PCB 106) in rats, which indicated hyperactivity in the male offspring (Lesmana et al., 2014). Although the number of studies is limited, the results of neurobehavioural studies with NDL-PCBs in rodents indicate comparable patterns of effects, albeit with congener-specific differences.

Based on the limited number of in vivo studies, a distinct mechanism of action for the neurodevelopmental effects of NDL-PCBs cannot be established. However, results from in vitro or ex vivo studies point towards some possible mechanistic pathways that can involve disruption of, for example, (developing) neuronal cells by effects on either calcium or thyroid hormone homeostasis. The in vitro studies provide useful information with respect to the potential SARs for the in vivo situation. A SAR study with trichlorinated, tetrachlorinated and some pentachlorinated NDL-PCB congeners identified *ortho*-substituted congeners as the most potent for disturbing calcium homeostasis, whereas *para* substitution

was associated with lower activity. However, the more highly chlorinated NDL-PCBs showed no or only subtle effects on calcium homeostasis (Langeveld, Meijer & Westerink, 2012). Another SAR study on the effects of NDL-PCBs on calcium sequestration within brain microsomes and mitochondria identified similar relationships, with congeners having chlorine substitutions at the *ortho* or *ortho*-lateral (*meta*, *para*) positions again being the most potent (Kodavanti et al., 1996). Both studies are also in line with earlier SAR results obtained for the effects of NDL-PCBs on dopamine content in PC12 cells or activation of RyR1 (Shain, Bush & Seegal, 1991; Pessah et al., 2006). Moreover, metabolic hydroxylation of PCBs appears to yield structures with higher activity towards this RyR (Pessah et al., 2006).

With respect to risk assessment of NDL-PCBs, it is interesting to note that a preliminary "neurotoxic equivalency scheme" for PCBs was developed based on in vitro neurotoxicity SAR data, including phorbol ester binding, dopamine release, inhibition of calcium uptake and RyR binding (Simon, Britt & James, 2007). It would be very useful to include in this concept newly available (structure–activity) data on neurotoxicity end-points. For example, a recent SAR study on dopamine transporter interactions of NDL-PCBs showed that most NDL-PCBs (including all NDL-PCBs highlighted in this review) interact with the dopamine transporter with different potencies (Wigestrand et al., 2013).

Thyroid hormones, including T_3 and T_4, are also essential for the development of the prenatal and postnatal nervous system (Murk et al., 2013), and disturbance of thyroid hormone homeostasis in early life stages may affect the central nervous system and express itself, for example, as lower cognitive function (Schroeder & Privalsky, 2014). Thyroid hormones bind to thyroid hormone receptors and regulate, among other things, neurogenesis (Preau et al., 2015) and neuronal differentiation (Ibhazehiebo et al., 2011). Thyroid hormones with *ortho* iodine atoms clearly bear a structural resemblance to NDL-PCBs, whereas the hydroxy group at the *para* position of thyroid hormones resembles some of the more common 4-hydroxylated metabolites of PCBs and PBDEs. This structural resemblance is a mechanistic reason for interference of NDL-PCBs or their hydroxylated metabolites with the functioning of thyroid hormones. A wide range of in vivo studies has shown effects of NDL-PCBs on thyroid hormone homeostasis. Although results are not unequivocal, most studies showed a decrease in total and free T_4 concentrations following exposure to NDL-PCBs (Craft, DeVito & Crofton, 2002; Khan et al., 2002; Kato et al., 2004, 2007, 2010, 2012). In addition, hydroxylated metabolites of NDL-PCBs can also competitively inhibit the binding of T_4 to the transport proteins transthyretin and thyroxine-binding globulin, which offers another possibility for interference with thyroid hormone homeostasis and subsequent effects on the neuronal system (Meerts et al., 2002, 2004). Again, the position of the hydroxy group plays an important role

here, with hydroxy groups present at the *para* and *ortho* positions being more active than those in the *meta* position (Chauhan, Kodavanti & McKinney, 2000; Meerts et al., 2002).

(f) Developmental neurotoxicity studies

Multiple rodent studies have shown that both prenatal and postnatal exposures to NDL-PCBs cause effects on neurobehaviour. Behavioural end-points that were affected by NDL-PCBs include spontaneous (locomotor) activity, habituation capability, spatial learning and anxiety-like behaviour in rodents. Both increases and decreases in spontaneous activity have been observed in studies with developmentally exposed mice and rats. Despite the fact that in vitro studies indicate a role for NDL-PCBs in neurodevelopmental toxicity mechanisms, in vivo studies on the effects of exposure to hydroxylated metabolites of NDL-PCBs on neurobehavioural or developmental end-points are very scarce. Several studies consist of, or include, specific investigations on the effects of NDL-PCBs on one or several neurotransmitter systems in vivo, which are discussed below.

(i) Behavioural studies

The effects of single doses of each of PCB 28 and PCB 52 (NDL-PCBs) and PCB 118 and PCB 156 (DL-PCBs) given orally on PND 10 were studied in male mice. Mice were given the following doses: PCB 28 – 0.18, 0.36 or 3.6 mg/kg bw; PCB 52 – 0.20, 0.41 or 4.1 mg/kg bw; PCB 118 – 0.23, 0.46 or 4.6 mg/kg bw; and PCB 156 – 0.25, 0.51 or 5.1 mg/kg bw. Spontaneous motor activity (locomotion, rearing and total activity) was measured at the age of 4 months over three 20-minute periods in an automated system resembling home cages. Learning and memory functions at the age of 5 months were assessed by performance in the Morris swim maze and radial arm maze. Acute toxicity and effects on body weight were not observed. A significant dose-related change in motor activity was observed in mice exposed to PCB 28 and PCB 52, showing hypoactivity at the lowest dose levels. At the highest dose levels, the pattern of activity was reversed (activity decreased with each 20-minute recording in control animals, whereas the activity was low in exposed animals compared with controls in the first recording and high in the third recording). No effects were observed on these variables in mice exposed to the DL-PCBs, PCB 118 or PCB 156. Effects on water maze performance were observed in mice exposed to PCB 52 at 4.1 mg/kg bw. No effects were observed with the other NDL-PCBs or at lower dose levels of PCB 52. Similarly, impaired radial arm maze performance was observed in mice exposed to PCB 52 at 4.1 mg/kg bw (no effects of PCB 28 or at lower doses of PCB 52). An increase in binding to nicotinic binding sites was observed, which indicates an increased expression of cholinergic nicotinic receptors in mice exposed to the highest dose

of PCB 28 (no effects of PCB 52). No effects on muscarinic acetylcholine receptor expression or neurotransmitter levels were observed after exposure to PCB 28 or PCB 52. The authors concluded that postnatal (neonatal) oral exposure to lower chlorinated NDL-PCBs results in persistent neurotoxic effects in the adult animal (Eriksson & Fredriksson, 1996).

Effects of lactational exposure to a mixture of the six indicator PCBs (PCBs 28, 52, 101, 138, 153 and 180) on neurobehavioural end-points were assessed in mice. Lactating dams received oral gavage doses of 1, 10 or 100 ng/kg bw per day of the mixture on PNDs 0–21. The six PCBs in each mixture were in the proportion 37%, 32%, 11%, 12%, 6% and 2% for PCBs 153, 138, 180, 101, 52 and 28, respectively, reflecting their relative proportions in marine contaminated fish. Offspring (10 of each sex per group) were assessed between PND 0 and PND 275. No effects on body weight of dams or pups or on maternal behaviour were found. Neonatal female offspring exposed to the PCB mixture at 100 ng/kg bw per day exhibited significantly longer turning reflexes on PNDs 7 and 9, whereas a reduction in general locomotor activity was seen at 1 and 10 ng/kg bw per day in male offspring only. These effects disappeared with age. Changes in visuomotor integration (water escape pole climbing test) were observed on PND 32 in the males at 1 and 100 ng/kg bw per day. Anxious behaviour was detected at PND 40 (elevated plus maze) and PND 160 (light/dark choice test) in both sexes of offspring. The authors proposed that the effects may be related to the observed overexpression of RyR3 in the cerebellum. No other effects were detected in an applied battery of developmental, behavioural and cognitive tests or gene expression of neurotransmitter receptors. The authors concluded that exposure to this mixture of NDL-PCBs results in sex-specific neurodevelopmental effects (Elnar et al., 2012).

Male rat offspring were lactationally exposed to PCB 153. Dams were orally dosed with PCB 153 at 5 mg/kg bw every second day from day 3 to day 13 after delivery. No effects were observed on body weight of the dams or physical development of the pups. Effects of exposure to PCB 153 on operant conditioning were studied using a two-component schedule of reinforcement. Exposed offspring demonstrated increased activity ("burst" of lever presses) and attention deficits. In addition to the behavioural testing, xenobiotic metabolizing enzymes (EROD, aldrin epoxidase, GST) and residues of PCB 153 were also determined in the offspring at PNDs 14, 28 and 112 in brain, stomach and liver. The authors concluded that lactational exposure to PCB 153 results in neurotoxic effects (Holene et al., 1998).

The effects of perinatal exposure to PCB 153 on synaptic plasticity in rat offspring from dams given PCB 153 orally from GD 3 to PND 21 at a dose of 1.25, 5 or 20 mg/kg bw per day were studied using long-term potentiation in hippocampal slices taken from the offspring at PND 30. There were no effects

of PCB 153 exposure on body weight of the dams, fertility, birth number or postnatal growth. Reduced long-term potentiation was observed in slices from PCB-exposed rats at all dose levels. The authors concluded that developmental exposure to PCB 153 impairs synaptic plasticity in the hippocampus, which is correlated with learning ability (Hussain et al., 2000). However, it should be noted that chemical analysis revealed contamination of this PCB with very low levels of PCDFs (possibly affecting the outcome of this study).

Female rats were exposed during pregnancy and lactation to PCB 153, given orally at 1 mg/kg bw per day from GD 7 to PND 21. Effects of performance in a Y-maze conditional discrimination task were studied at 3 and 7 months of age. Impaired learning ability was observed in 3-month-old rats (both males and females) exposed to PCB 153, but no effect was observed in 7-month-old rats. The function of the glutamate–nitric oxide–cyclic guanosine monophosphate (cGMP) pathway in the brain (assessed in the same rats by brain microdialysis) was impaired in 3-month-old males and females after exposure to PCB 153. No effects on this pathway were observed after 8 months. The authors concluded that perinatal exposure to PCB 153 affects learning ability in young rats, at least through impairment of the glutamate–nitric oxide–cGMP pathway function (Piedrafita et al., 2008a,b). Other mechanisms may also play a role.

Effects of prenatal and postnatal exposure to PCB 153 were studied in rat offspring from dams given PCB 153 at 1 or 5 mg/kg bw per day by oral gavage from GD 7 to PND 21. No effects were observed on general appearance, home cage behaviour or body weight of the rats. A wide range of neurobehavioural endpoints was studied in the offspring as adults, including spontaneous locomotor activity (open-field test), spatial short-term memory (radial maze), long-term memory (passive avoidance), sensitivity to pain and vulnerability to stress (hot plate test), efficiency of the sensorimotor response (startle response test) and motor coordination (rotarod). Increased locomotor activity was observed in female offspring at both dose levels of PCB 153. Furthermore, increased habituation of the startle reflex was observed in males and females, but only in the low-dose group. In addition, impairment of motor coordination was observed in males exposed to the high dose of PCB 153 (Gralewicz et al., 2009).

Effects of prenatal and postnatal exposure to highly purified PCB 52, PCB 138 or PCB 180 on cognitive function or motor coordination were investigated in rat offspring (3–4 months of age) from dams that were exposed to these PCBs at 1 mg/kg bw per day via feed from GD 7 to PND 21. Cognitive function was assessed as the ability to learn a Y-maze conditional discrimination task. Impaired performance was observed in both male and female rats exposed to PCB 138 and PCB 180. No effects were observed in rats exposed to PCB 52. The authors proposed that this effect on cognition is associated with reduced function of the glutamate–nitric oxide–cGMP pathway and reduced expression

of the NR1 subunit of *N*-methyl-D-aspartate (NMDA) receptors. In addition, motor coordination was assessed using the rotarod, which demonstrated that only PCB 52 impaired motor coordination. The authors concluded that this effect is associated with an extracellular increase of the neurotransmitter gamma-aminobutyric acid in the cerebellum. Overall, the authors concluded that exposure to NDL-PCBs during pregnancy and lactation induces long-lasting effects on cognitive function or motor coordination, with different effects for different NDL-PCBs (Boix, Cauli & Felipo, 2010).

In a second study with these PCBs (PCB 52, PCB 138 and PCB 180), the effects of prenatal and postnatal exposure on motor activity were studied in adult rat offspring (4 months of age) from dams exposed to each PCB at 1 mg/kg bw per day via feed from GD 7 to PND 21. Motor activity was studied in an open-field activity chamber. No effects were observed after exposure to PCB 52, but exposure to PCB 180 resulted in reduced motor activity in males. PCB 138 reduced motor activity in both males and females. Effects on the extracellular neurotransmitters dopamine (by PCB 180 in males and females) and glutamate (by all three PCBs in males and females) and modulation of these through metabotropic glutamate receptors (by PCB 138 or PCB 180 in males and females) were observed in the nucleus accumbens of the exposed rats. Brain (striatum) and perirenal PCB levels were determined at 4 months of age. The authors concluded that different NDL-PCBs have different effects on motor activity and that these effects are also sex dependent (Boix et al., 2011).

Effects of prenatal exposure to PCBs on spatial learning and memory were investigated in rats. Dams were exposed via oral gavage to PCB 28, an NDL-PCB, at 8 or 32 mg/kg bw per day, PCB 118, a DL-PCB, at 4 or 16 mg/kg bw per day or PCB 153, an NDL-PCB, at 16 or 64 mg/kg bw per day, from GD 10 to GD 16. Overt toxicity was not observed in the dams. Birth weight was reduced in offspring exposed to PCB 28 (females) and PCB 118 (males and females), but no effects were seen in other dose or PCB groups. Mildly decreased weight gain during nursing was observed in offspring exposed to PCB 28 (high dose only) or PCB 118 (both dose levels). No effects were observed for PCB 153. Working memory and reference memory in 3-month-old rats were investigated using an eight-arm radial maze. In general, no effects of these dose levels on the number of errors were observed, although a smaller latency (to enter a radial arm) was observed only in males at the high dose of PCB 153. Spatial learning was investigated in a T-maze, delayed spatial alternation task. Impaired performance in this learning task was observed in female rats exposed to high doses of PCB 28, PCB 118 and PCB 153, but not in males. The effect pattern in the learning tasks suggests the occurrence of learning or attentional deficits, rather than a memory deficit. The authors concluded that perinatal exposure to NDL-PCBs results in persistent effects on learning and that these effects may be sex specific (Schantz, Moshtaghian & Ness, 1995).

In a study on exposure to individual PCBs, male rat offspring were directly exposed on three occasions at "around" PND 8, PND 14 and PND 18 (exact time of birth was not observed) to PCB 52, PCB 153 or PCB 180 given by oral gavage at 0 or 10 mg/kg bw. Activity level and stimulus control were measured using an operant visual discrimination task (time of testing not stated). PCB exposure did not produce behavioural changes during training when responding was frequently reinforced using a variable-interval 3-second schedule. When correct responses were reinforced on a variable-interval 180-second schedule, animals exposed to PCB 153 or PCB 180 were less active than controls or those exposed to PCB 52. Stimulus control was better in animals exposed to PCB 180 than in controls and in the PCB 52 group. The PCB 153 and PCB 180 groups also had fewer responses with short inter-response times compared with the PCB 52 group. No effects of exposure to PCB 52 were found when compared with controls (Johansen et al., 2011).

In a further study by the same group on PCB 153, male and female offspring from two different strains of rat – spontaneously hypertensive rats (SHR/NCrl), an animal model of attention deficit hyperactivity disorder (ADHD), and Wistar Kyoto (WKY/NHsd) controls – were directly exposed on three occasions at "around" PND 8, PND 14 and PND 18 to PCB 153 given by oral gavage at 0, 1, 3 or 6 mg/kg bw. The rats were tested between PND 37 and PND 64 in the same operant procedure as in the study described above. Exposure to PCB 153 was associated with pronounced and long-lasting behavioural changes in SHR/NCrl rats; 1 mg/kg bw tended to reduce ADHD-like behaviours and produced opposite behavioural effects compared with 3 and 6 mg/kg bw, especially in the females. In the WKY/NHsd controls and for the three doses tested, PCB 153 exposure produced a few specific behavioural changes only in males. The authors concluded that the data suggest that PCB 153 exposure interacts with strain and sex and also indicate a non-linear dose–response relationship for the behaviours observed (Johansen et al., 2014).

The effects of prenatal exposure to PCB 95 on neurobehavioural functions and binding to RyR in different brain regions were studied in rats. Dams were given PCB 95 (8 or 32 mg/kg bw per day) on GDs 10–16 via oral gavage. At these dose levels, reproductive and developmental parameters were not affected. Locomotor activity was evaluated in the open field at 35 and 100 days of age, and hypoactivity was observed, but only at 100 days of age. Spatial learning and memory were assessed using a working memory task in an eight-arm radial maze at 60 days of age and a T-maze task at 140 days of age. Exposure to PCB 95 was associated with improved performance in the radial maze task for both sexes, but no effects were observed in the T-maze task. After the neurobehavioural testing, [^{3}H]ryanodine binding was assayed in homogenates of the cerebral cortex, hippocampus and cerebellum (PND 181). Region-specific changes were

observed in ryanodine binding, with a decrease in hippocampus, an increase in cerebral cortex and an increase in cerebellum at the lowest dose only. The authors concluded that these changes may be related to the observed neurobehavioural effects of PCB 95 (Schantz et al., 1997). Other mechanisms may also play a role.

The effects of prenatal and postnatal exposure to PCB 52 or PCB 180 on the dopamine neurotransmitter system were indirectly studied in rats. The purity of the PCBs was determined to be less than 0.5 ng TEQ/g for PCB 52 and 2.7 ng TEQ/g for PCB 180. The study utilized catalepsy induced by the dopamine receptor blocker, haloperidol. Dams were given PCB 52 or PCB 180 by oral gavage. PCB 52 was given to groups of seven rats per dose at total dose levels between 30 and 3000 mg/kg bw, divided over 10 different administrations between GD 7 and PND 10 (i.e. individual doses of 0, 3, 10, 30, 100 and 300 mg/kg bw). PCB 180 was given at total dose levels between 10 and 3000 mg/kg bw, given as four daily administrations between GD 7 and GD 10 (i.e. individual doses of 0, 2.5, 7.5, 25, 75 and 250 mg/kg bw). These PCBs were extensively charcoal cleaned to remove dioxin-like impurities. Maternal body weight and developmental milestones in the offspring were not affected by PCB 52. Mild reduction in maternal body weight and delayed sexual development in the offspring were observed in the PCB 180–exposed rats at the highest dose. At the age of 80 days, the offspring were transported to the neurobehavioural testing facility and allowed a 4-week adaptation period. Injecting the adult offspring at 180 days of age with haloperidol resulted in mildly increased latencies to movement onset in females after exposure to PCB 52, but no dose-dependent effects were observed in males. In contrast, exposure to PCB 180 resulted in effects in both sexes, showing in particular a reduced latency to movement that was most pronounced in the male offspring. The authors concluded that the observed changes can be related to PCB-induced changes in the dopaminergic system, showing relatively weak effects of PCB 52 in the females, whereas effects of PCB 180 were more dominant in males. Regarding the cause of these sex-dependent differences, the hypothesis was posed that this may be related to (lack of) interaction with estrogenic processes (Lilienthal et al., 2014).

In an earlier report on the same study, the effects of prenatal and postnatal exposure to PCB 52 or PCB 180 on sexually dimorphic sweet preference were studied in Sprague-Dawley rats. Sweet preference can be studied by measuring saccharin consumption, and female rats typically consume more saccharin solution than males. In parallel, Long-Evans rats received a daily oral dose of PCB 74 (total 229 mg/kg bw) or PCB 95 (total 248 mg/kg bw) from GD 10 to PND 7 (no dosing at PND 0). No effects on sweet preference were observed for PCB 52 in 100- to 120-day-old male or female offspring. Increased saccharin consumption (interpreted by the authors to be supernormal behaviour) was observed in 100- to 120-day-old female offspring exposed to PCB 180 (no effects in males).

Decreased sweet preference was observed in 80-day-old female offspring exposed to PCB 74 (no effects in males). Increased saccharin consumption was observed in 80-day-old males exposed to PCB 95 (no effects in females); this is the only clear indication of reduction in sexually dimorphic behaviour (feminization of males). The authors concluded that different NDL-PCBs exhibit different effects on sexually dimorphic behaviour (Lilienthal et al., 2013).

The effects of prenatal and postnatal exposure to PCB 74 or PCB 95 on the dopamine neurotransmitter system were studied in rats using catalepsy induced by the dopamine receptor blocker, haloperidol. Brainstem auditory evoked potentials (BAEPs) were also studied (see section 2.2.5(f)(iii)). Dams were given the PCBs by oral gavage at dose levels of 12 mg/kg bw per day (PCB 74) or 13 mg/kg bw per day (PCB 95), from GD 10 to PND 7. In both PCB-treated groups, free T_4 concentrations in serum were significantly reduced in male offspring. There was a slight, but statistically significant, reduction in latency to movement onset in female offspring exposed to PCB 74; male offspring exposed to PCB 74 and offspring exposed to PCB 95 were not affected in this test (Lilienthal et al., 2015).

The effects of lactational exposure to a hydroxylated metabolite of PCB 106 were studied in rats. Lactating dams were orally exposed to 4-hydroxy-PCB 106 at 0.5, 5 or 50 mg/kg bw every second day from PND 3 to PND 13. No effects were observed on body weight of the dams, lactation or physical development of the offspring. Motor activity was assessed at PND 28 in an open-field activity chamber in 5-minute sessions. Circadian locomotor activity was recorded at PNDs 28–31 in standard cages for 72 hours. Brain (striatum) samples were collected at PND 31 to determine dopamine levels and dopamine receptor expression. Exposure to this hydroxy-PCB metabolite resulted in hyperactivity (increased locomotor activity) in males only at 0.5 and 5 mg/kg bw, with no effects seen at 50 mg/kg bw. Again in males only, a spontaneous hyperlocomotion was observed during circadian locomotor activity recordings. Furthermore, effects on dopamine levels and/or expression of dopamine receptors in the brain (striatum) were observed at all dose levels. The authors concluded that postnatal exposure to 4-hydroxy-PCB 106 results in neurobehavioural effects that relate to changes in dopamine levels and receptor expression (Lesmana et al., 2014). Other mechanisms may also play a role.

(ii) Neurochemical studies

The effects of prenatal exposure to PCB 47 on dopamine function were investigated in rats. Dams were exposed to 1, 10 or 20 mg/kg bw per day from GD 6 through weaning by incorporation of the PCB congener into cookies. No effects were detected on reproduction or on body weight of the offspring. The concentrations of dopamine and its metabolites were measured in different brain regions (frontal

cortex, caudate nucleus and substantia nigra) on PND 35, PND 60 and PND 90. Decreased concentrations of dopamine were observed in the frontal cortex and caudate nucleus. Based on these results, the authors posed the hypothesis that these reductions are a consequence of inhibition of dopamine synthesis by PCB 47 during brain development (Seegal, Brosch & Okoniewski, 1997).

The effects of prenatal and postnatal exposure to PCB 153 on the expression and affinity of dopamine receptors were investigated in rats. Dams were orally exposed to PCB 153 (at 5 mg/kg bw) every other day from GD 7 to PND 21. No adverse effects were detected in the dams, and this exposure had no influence on reproduction or on development of the offspring. In addition, D1-like and D2-like dopamine receptor densities and affinities in offspring were measured on PND 21 and PND 36 using saturation binding studies. In male offspring, the density of D1 receptors was decreased in the cortex and striatum on PND 21, but this was not detected in females or on PND 36 in both sexes. Density of D2 receptors was increased with reduced affinity in the cortex of male offspring at PND 21 and PND 36. In female offspring, the D2 receptor density was increased at PND 36, whereas D2 receptor affinity was reduced on PND 21 and PND 36. No effects were observed in the striatum in either sex. Chemical analysis revealed measurable and similar levels of PCB 153 in the cortex and striatum, indicating that it is transferred across the blood–brain barrier. The authors concluded that perinatal exposure to PCB 153 affects both D1 and D2 receptor expression and affinity and that some of these effects are specific for sex, age and brain areas (Coccini et al., 2011).

In a similar study from the same group, the effects of prenatal exposure to PCB 153 at 20 mg/kg bw per day from GD 10 to GD 16 were investigated in rats. Dams were dosed by oral gavage. Effects on cholinergic muscarinic receptor (MR) density in the cerebral cortex, cerebellum, hippocampus and striatum were investigated at PND 21. Overt toxicity was not observed in dams or offspring, but PCB 153 decreased MR density in the cerebellum, while increasing MR density in the cortex. No effects on MR density were detected in the striatum or hippocampus. These results show that PCB 153 can affect MR expression in different brain regions (Coccini et al., 2006).

Coccini et al. (2007) also showed that perinatal exposure to PCB 153 given at 5 mg/kg bw per day, via incorporation in sweet jelly placed underneath the normal chow, from GD 7 to PND 21 decreased MR density in the cerebellum of males and in the cerebral cortex in both sexes at PND 36, but MR affinity was not affected. In the cerebral cortex, a decrease in the MR subtypes ACh M1 and ACh M3 immunopositive neurons was also observed. Again, no overt toxicity was observed in the dams or offspring. It should be noted that some neurochemical effects persisted from PND 21 to PND 36, whereas others were not observed before PND 36, although at this time point the brain levels of PCB

153 had already declined significantly. Based on these observations, the authors concluded that PCB 153 can induce delayed neurotoxicity after prenatal and postnatal exposure (Coccini et al., 2007).

The effects of prenatal exposure to PCB 153 on monoamine oxidase B activity and content of dopamine, serotonin, 5-hydroxyindoleacetic acid and homovanillic acid in different brain regions (striatum, hippocampus, cerebellum and cerebral cortex) were investigated in PND 21 offspring. PCB 153 was given at a dose of 20 mg/kg bw to rats via daily oral gavage of dams from GD 10 to GD 16. No effects on monoamine oxidase B activity were detected in females, but reduced monoamine oxidase B activity was detected in the cerebellum of the males. PCB 153 also decreased serotonin levels in the cerebral cortex in both sexes. Additionally, dopamine, 5-hydroxyindoleacetic acid and homovanillic acid contents were reduced in the striatum of exposed males and females. The authors concluded that prenatal exposure to PCB 153 results in sex-specific changes in dopaminergic and serotonergic systems (Castoldi et al., 2006).

The effects of prenatal exposure to PCB 153 on brain neurotransmitter levels were investigated in female rats. Groups of 10 dams were given PCB 153 by oral gavage from GD 10 to GD 16 at 0, 16 or 64 mg/kg bw per day. Brain neurotransmitters and metabolites were measured in different brain regions or whole brain in groups of 5–9 female offspring at 1, 3, 6 and 9 weeks of age and after 1 year. At 1–3 weeks of age, brain levels of dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, serotonin and 5-hydroxyindoleacetic acid were increased in the offspring. At 9 weeks of age, dopamine turnover was reduced in forebrain and hindbrain, whereas 5-hydroxyindoleacetic acid levels were increased in all brain areas. At 1 year of age, reductions in the levels of dopamine, 3,4-dihydroxyphenylacetic acid and homovanillic acid could still be observed in the hippocampus, hypothalamus and medulla oblongata. The turnover of serotonin was increased at 1–9 weeks of age, and the turnover of dopaminergic neurons was reduced at 9 weeks and 1 year of age. Decreases in dopamine, 3,4-dihydroxyphenylacetic acid and homovanillic acid levels were also observed in PCB-exposed dams at 15 weeks of age (3 weeks after parturition). In addition, reduced levels of dopamine and related metabolites were observed in the brain of the dams. The authors concluded that prenatal exposure to PCB 153 results in long-term changes in neurotransmitters and metabolites in the brain, which are dependent on developmental stage (Honma et al., 2009).

In summary, the results of neurodevelopmental studies with NDL-PCBs in rodents indicate comparable patterns of effects, albeit with congener-specific differences. It should also be noted that such studies have usually involved a limited number of dose levels. This aspect hampers the determination of relative effect potencies and QSARs for the NDL-PCBs. Based on in vivo studies, a distinct mechanism of action for the neurodevelopmental effects of NDL-PCBs cannot be

established. However, results from in vitro or ex vivo studies using neuronal cells indicate a number of mechanistic pathways that involve disruption of intracellular calcium or thyroid hormone homeostasis; these have been discussed previously in section 2.2.5(e).

In the majority of neurodevelopmental studies, total dose levels above 1 mg/kg bw or even much higher were tested. In these studies, the maternal dose levels of NDL-PCBs were at least 1–2 orders of magnitude higher than estimated adult human daily exposure levels (Duarte-Davidson & Jones, 1994). There is one study in which effects were detected at doses relevant to humans (Elnar et al., 2012). Although PCB levels in human milk are known, it is complicated to derive margins of exposure (MOEs) in comparison with the results of available neurodevelopmental toxicological studies, as the exposure of the offspring is commonly not measured. However, the lowest effect concentrations in studies in which mouse pups were individually exposed postnatally to a single oral dose (Eriksson & Fredriksson, 1996) are very comparable to, or even up to 1 order of magnitude lower than, those present in human milk (Fürst, 2006).

(iii) Effects on the auditory system

Exposure to Aroclors during the prenatal and preweaning developmental period in rats has been shown to cause delayed development and reduced amplitude of the auditory startle reflex, increased susceptibility to audiogenic seizures as adults and permanent auditory deficits in the low-frequency range attributable to loss of outer hair cells in the cochlear organ of Corti (Overmann et al., 1987; Goldey et al., 1995; Crofton et al., 2000; Powers et al., 2006; Poon et al., 2015). These effects can be attenuated by postnatal administration of T_4 (Goldey & Crofton, 1998). These effects may be partially attributable to the DL-PCBs, such as PCB 126, present in such mixtures (Crofton & Rice, 1999). The study of Meerts et al. (2004) showed that whereas developmental exposure to Aroclor 1254 raised auditory thresholds, exposure to 4-hydroxy-PCB 107 did not. However, the studies described below show that individual NDL-PCB congeners can have effects on the development of the auditory system.

Female rats were exposed to PCB 95 at 0 or 6 mg/kg bw per day from GD 5 to PND 21 by applying the PCB in corn oil to a cornflake, which was rapidly consumed. Control pups were from a minimum of two separate litters, and PCB-exposed pups were sampled from three litters. Postnatally, offspring were divided into three groups; one group was raised in a normal auditory environment, a second group was exposed continuously from PND 9 to PND 35 or from PND 9 to PND 40 to a tone (25-millisecond tone, 5-millisecond ramps) and the third group was exposed continuously from PND 9 to PND 35 or from PND 9 to PND 40 to noise (50-millisecond noise pulses, 5-millisecond ramps) at a sound pressure

of 65–70 dB. Six control or PCB-exposed rats in the normal auditory exposure group, five from each of the tone-reared groups and five from each of the noise-reared groups were mapped. Developmental exposure to PCB 95 did not produce any effect on litter size, sex ratio or weight gain compared with the control group. Hearing sensitivity and brainstem auditory responses of the pups were normal. However, there was abnormal development of the primary auditory cortex in PCB-exposed pups, which was irregularly shaped and marked by internal non-responsive zones. Its topographic organization was grossly abnormal or reversed in about half of the exposed pups, the balance of neuronal inhibition to excitation for A1 neurons was disturbed, and development was significantly altered in pups also exposed to tonal stimuli or noise stimuli from PND 9 to PNDs 35–40, the critical period of plasticity that underlies the normal postnatal auditory system (Zhang, Bao & Merzenich, 2002; Kenet et al., 2007).

Auditory function in Sprague-Dawley rats was assessed following developmental exposure to PCB 52 or PCB 180 (Lilienthal et al., 2011). Pregnant rats received repeated oral doses of PCB 52 (total doses of 0, 30, 100, 300, 1000 or 3000 mg/kg bw) or PCB 180 (total doses of 0, 10, 30, 100, 300 or 1000 mg/kg bw). The purity of the PCBs was determined to be less than 0.5 ng TEQ/g for PCB 52 and 2.7 ng TEQ/g for PCB 180. BAEPs were recorded in adult male and female offspring after stimulation with clicks or pure tones in the frequency range from 0.5 to 16 kHz. Significant elevation of BAEP thresholds was detected in the low-frequency range after developmental exposure to PCB 52. Calculation of BMDs revealed lowest values in the frequency range of 0.5–2 kHz. Effects were more pronounced in male offspring than in female offspring. Latencies of waves II and IV over a range of frequencies were prolonged in exposed males, whereas only wave IV was affected in females. PCB 180 increased BAEP thresholds only at 0.5 and 4 kHz in female offspring, and wave IV latency was prolonged only at 0.5 kHz in female offspring.

In a follow-up study from the same laboratory, further experiments were performed with PCB 74 and PCB 95 using Long-Evans rats (Lilienthal et al., 2015). Rat dams were given equimolar doses of either congener (40 µmol/kg bw, i.e. 11.68 mg/kg bw of PCB 74 or 13.06 mg/kg bw of PCB 95) in corn oil by oral gavage from GD 10 to PND 7. Control dams were given vehicle only. Adult offspring were tested for cataleptic behaviour after induction with haloperidol (see section 2.2.5(f)(i)) and BAEPs. Pronounced changes were observed in BAEPs at low frequencies in PCB 74–exposed offspring, with elevated thresholds in both sexes. PCB 95 increased thresholds in males, but not females. Small effects on latency of the late wave IV were detected in both sexes after developmental exposure to PCB 74 or PCB 95.

In summary, the results confirm that developmental exposure to individual NDL-PCB congeners can affect auditory function and that different

congeners exhibit different potencies. PCB 74 was the most potent congener of the NDL-PCBs tested in terms of inducing threshold increases. The effects of PCB 95 and PCB 52 were similar but were less than those of PCB 74. In contrast, increases by PCB 180 were smaller. Effects of PCB 74 and PCB 52 were more expressed in male offspring than in female offspring, and PCB 95 elevated thresholds only in males. The modest effects of PCB 180 on BAEP thresholds were found only in females. As all congeners resulted in similar reductions in circulating thyroid hormone levels, other factors involved in the development of cochlear and neural structures of the auditory system are likely to contribute to the observed effects; the authors of the studies discussed the potential role of retinoids or the RyR (Lilienthal et al., 2011, 2015).

2.2.6 Special studies

(a) Adult neurotoxicity

This section covers only those studies in which PCB treatments have been given to adult animals; studies in which animals have been exposed during gestation, the perinatal period or postnatally as juveniles are discussed in section 2.2.5(f) above.

Early studies on neurobehavioural effects of PCBs in adult animals exposed for various durations to commercial mixtures, defined experimental mixtures or single congeners have been reviewed by ATSDR (2000). Neurochemical effects of PCBs have also been investigated in rats, mice and monkeys exposed to commercial PCB mixtures or to individual PCB congeners. Some studies have assessed both neurochemical and neurobehavioural effects of PCBs in an attempt to link a biochemical alteration to a particular neurobehavioural deficit. The ATSDR (2000) review considers the studies in terms of effects on motor activity and effects on higher functions, such as learning and memory. In these early studies, effects on higher functions were reported only for exposures occurring during the prenatal, perinatal or postnatal juvenile period. Later in vitro studies illustrate the potential for effects of NDL-PCBs on functions such as learning and memory in adult animals.

Single or repeated administration of relatively high doses of Aroclor 1254 to adult mice or rats generally decreased spontaneous motor activity (ATDSR, 2000). This may be attributable to reductions in brain dopamine levels in adult animals (Seegal, Bush & Brosch, 1991a). The uptake and release of dopamine or other neurotransmitters are dependent on, among other things, the maintenance of intracellular calcium homeostasis, and this has been investigated in a number of SAR studies by the research group of P.R. Kodavanti and H.A. Tilson. They used rat cerebellar granule cells cultured in vitro or microsomal or mitochondrial organelles isolated from brain tissue and treated with various individual PCB

congeners or Aroclor mixtures. Perturbed signal transduction mechanisms involving alterations in several aspects of cellular calcium homeostasis were observed. This has been shown to have consequences for inositol phosphate signalling by inhibiting agonist-stimulated inositol phosphate accumulation. The research group also observed perturbations in protein kinase C (PKC) translocation, which has been confirmed in vivo in rats treated with an Aroclor 1254 mixture of PCBs. PKC signalling plays a significant role in motor behaviour, learning and memory. The effects in vitro on calcium homeostasis and PKC translocation were seen at relatively low concentrations (5–50 μmol/L), whereas higher concentrations (>200 μmol/L) were required to produce cytotoxicity. The SARs for these perturbations of signal transduction and second messenger systems for the 24 PCB congeners tested were consistent with a chlorination pattern that favoured non-coplanarity (NDL-PCBs), whereas the PCB congeners with a chlorination pattern that favoured coplanarity (DL-PCBs) were less active. The studies indicated that the effects of most PCB congeners in vitro may be related to an interaction at specific sites having preference for low lateral substitution or lateral content (*meta* or *para*) in the presence of *ortho* substitution (Kodavanti et al., 1993, 1995, 1996, 1998a; Shafer et al., 1996; Kodavanti & Tilson, 1997; Tilson & Kodavanti, 1998; Tilson et al., 1998).

Other mechanisms that may be responsible for reductions in brain dopamine levels have been investigated. In vitro studies have shown that reductions in brain dopamine levels may be related to inhibition of tyrosine hydroxylase activity, the rate-limiting enzyme for catecholamine synthesis in the brain, although this was not seen in the rat in vivo (Choksi et al., 1997). A later study investigated whether dopamine reductions may involve inhibition of the dopamine transporter (DAT) and/or the vesicular monoamine transporter (VMAT), which are responsible for the uptake of extracellular dopamine and the packaging of nerve terminal cytosolic dopamine into synaptic vesicles, respectively. The results suggested that elevations in 3,4-dihydroxyphenylacetic acid, reflective of increases in nerve terminal cytosolic dopamine due to VMAT inhibition, rather than elevations in media dopamine due to DAT inhibition, were largely responsible for the observed decreases in tissue dopamine content (Bemis & Seegal, 2004).

To investigate whether the chirality of PCB congeners implicated in neurotoxic effects is important, the effects of racemic PCB 84 and two of its enantiomers on PKC translocation in cerebellar granule cells and calcium sequestration in microsomes isolated from adult rat cerebellum were studied. Both (+)- and (−)-PCB 84 enantiomers affected PKC translocation in a concentration-dependent manner, with (−)-PCB 84 being slightly more potent; racemic PCB 84 was significantly more potent and efficacious than either of the pure enantiomers alone. Microsomal calcium uptake was inhibited by both (−)-

and (+)-PCB 84 enantiomers to a similar extent, whereas racemic PCB 84 was more potent (Lehmler et al., 2005).

The same research group has investigated nitric oxide synthases (NOS), which play a key role in motor activity in the cerebellum, hormonal regulation in the hypothalamus and long-term potentiation, learning and memory processes in the hippocampus. In in vitro studies on tissue taken from the cerebellum, hippocampus and hypothalamus of rats aged 90–120 days, two specific dichloro-PCB congeners, some pentachloro- and hexachloro-PCB congeners, and some hydroxy metabolites of tetrachloro-, pentachloro- and hexachloro-PCBs were tested. Only dichloro-*ortho*-PCB (PCB 4) inhibited both neuronal and membrane NOS, whereas the non-*ortho*, *para*-substituted PCB 15 and pentachloro- or hexachloro-PCB congeners did not. Hydroxy substitution of one or more chlorine molecules significantly increased the potency of both *ortho*- and non-*ortho*-hexachlorobiphenyls. The authors concluded that selective sensitivity of NOS to dichloro-*ortho*-PCB and hydroxy metabolites suggests that the inhibition of NOS could play a role in the neuroendocrine effects as well as learning and memory deficits caused by exposure to PCBs (Sharma & Kodavanti, 2002).

Investigation of the distribution of individual PCB congeners following once daily gavage treatment of adult rats with Aroclor 1254 at 0 or 30 mg/kg bw per day, 5 days/week, for 4 weeks showed that in all the tissues, the lower chlorinated (tetra- and penta-) congeners accumulated less than their respective proportions in the parent Aroclor 1254 mixture. Higher chlorinated (hexa- to nona-) congeners accumulated more than the proportion of these congeners found in the Aroclor 1254 mixture. This shift towards accumulation of higher chlorinated congeners was more pronounced in the brain than in liver and fat. Predominant congeners (5–32% of total PCBs) detected in different brain regions, blood, liver and fat were as follows: PCB 163 + PCB 138 (coeluted), PCB 153 + PCB 132 (coeluted), PCB 156 + PCB 171 (coeluted), PCB 118, PCB 99 and PCB 105. These congeners together accounted for about two thirds of the total PCB load in the brain. Of these, all but PCBs 156, 118 and 105 are NDL-PCBs. The total PCB concentrations accumulated in the brain were as high as 50 µmol/L (based on average relative molecular weight of 326.4 for Aroclor 1254), and it is at these concentrations that intracellular second messengers were significantly affected in neuronal cultures and brain homogenate preparations in vitro. These results indicated that concentrations that altered calcium disposition and second messenger systems in vitro are achievable in brain in vivo following repeated exposure (Kodavanti et al., 1998b).

The effects of a commercial mixture (Aroclor 1254), a DL-PCB (PCB 126) and an NDL-PCB (PCB 99) on the expression of NMDA receptors and the subsequent toxic effects have been studied in vitro using a human SHS5-SY neuroblastoma cell line. NMDA receptors are ionotropic receptors gated by the

neurotransmitter glutamate, which allow calcium flux into the cell, and they play an important role in the physiology and pathophysiology of the central nervous system (Waxman & Lynch, 2005). All three PCB treatments increased caspase-3, which plays a central role in cell apoptosis, and induced apoptosis and cell death in a dose-related manner at concentrations of 10–50 μmol/L. The mechanisms involved in cell death were mainly mediated through the NMDA receptors. The authors speculated that this may be induced by a rapid increase in intracellular calcium concentrations, followed by a series of events eventually leading to apoptosis and necrosis. NMDA receptor antagonists and an intracellular calcium chelator gave partial protection to cells against the effects of the PCBs, indicating that there are likely to be other parallel mechanisms leading to cell death. In this study, the NDL-PCB, PCB 99, was found to be more neurotoxic than the DL-PCB or the PCB mixture (Ndountse & Chan, 2009).

Early neurochemical studies showed the potential for commercial PCB mixtures to selectively alter dopamine, noradrenaline and serotonin concentrations in some regions of the adult rat brain following a single high dose given by gavage and in primate brain following 20 weeks of exposure. The concentrations of specific congeners in the affected brain regions indicated that it was non-coplanar NDL-PCBs that may be responsible (Seegal, Bush & Brosch, 1985, 1991a,b; Seegal, Brosch & Bush, 1986). The same group investigated SARs for the effects of individual PCB congeners on dopamine in vitro in PC12 cells, a clonal cell line derived from a phaeochromocytoma of the rat adrenal medulla, which, when cultured in the presence of nerve growth factor or other compounds, differentiate to resemble sympathetic neurons morphologically and functionally. The study showed that (1) congeners with *ortho*- or *ortho*,*para*-chlorine substitutions were most potent; (2) chlorination in a *meta* position decreased cell dopamine content in *ortho*-substituted congeners, but had little effect in *ortho*,*para*-substituted congeners; and (3) increasing congener chlorination did not correlate with a decrease in potency, although total chlorination of a ring appeared to reduce potency. An experiment with PCB 4 indicated that it was the congener and not its metabolites that was the toxicant. Thus, PCB congeners decrease cell dopamine content by interaction at specific sites that have preference for *ortho*- or *ortho*,*para*-substituted congeners (Shain, Bush & Seegal, 1991).

In in vivo studies with individual NDL-PCBs, a reduction in dopamine concentration in the substantia nigra region was observed in female but not male rats after 13 weeks of treatment with PCB 28 at dietary exposure levels of 0.5, 5 and 50 mg/kg feed, giving a lowest-observed-adverse-effect level (LOAEL) of 36 μg/kg bw per day (Chu et al., 1996a). Similarly, reductions in dopamine and serotonin concentrations in the frontal cortex of the rat brain, mainly in females, were observed after treatment for 13 weeks with PCB 153 in the diet at 5 and 50

mg/kg feed, but not at 0.5 mg/kg feed, giving a NOAEL of 34 μg/kg bw per day (Chu et al., 1996b).

The effect of oral exposure to a commercial mixture, Aroclor 1254, on central and systemic vasopressin release following the stimulus of acute dehydration in the rat has been investigated by Coburn and co-workers (Coburn, Gillard & Currás-Collazo, 2005; Coburn, Currás-Collazo & Kodavanti, 2007). Vasopressin has multiple functions, including maintenance of body fluid homeostasis, cardiovascular control, learning and memory, and nervous system development. Central vasopressin release from magnocellular neuroendocrine cells (MNCs) in the supraoptic nucleus (SON) of the hypothalamus occurs within several hours after acute dehydration and is an important autoregulatory mechanism. Male rats were fed daily for 15 days with a cheese puff injected with corn oil vehicle or Aroclor 1254 to give an exposure of 0 or 30 mg/kg bw per day. On the 15th day, acute dehydration was produced by intraperitoneal injection of sodium chloride in half the animals, whereas the other half received physiological saline as normosmotic controls. Water was withheld until sacrifice 4.5–6 hours later. Intranuclear vasopressin release from SON tissue in vitro and systemic vasopressin release were measured. The SON from dehydrated rats not receiving PCBs released significantly more vasopressin than did the SON from normosmotic control rats. In contrast, whereas PCB exposure had no effect on baseline water intake, weight gain or plasma osmolality responses to dehydration, the SON did not respond with increased vasopressin release during dehydration. Dehydrated PCB-fed rats showed a significantly higher increase in plasma vasopressin. The study indicated subtle disruption of the MNC system (Coburn, Gillard & Currás-Collazo, 2005). In subsequent work on the release of vasopressin from SON tissue in vitro in response to specific PCB congeners, it was shown that PCB 47 (an NDL-PCB) but not PCB 77 (a DL-PCB) reduced vasopressin release (Coburn, Currás-Collazo & Kodavanti, 2007). More recently, Coburn et al. (2015) studied NOS activity in the SON of hyperosmotic rats as a potential target of PCB-induced disruption of neuroendocrine processes necessary for osmoregulation. Vasopressin responses to hyperosmotic stimulation are regulated by nitric oxide signalling. Male rats were exposed to Aroclor 1254 (30 mg/kg bw per day) in utero, and NADPH-diaphorase (also known as NOS) activity was assessed, under normosmotic and hyperosmotic conditions, in SON sections at three ages: PND 10, early adult (3–5 months) and late adult (14–16 months). The study showed that developmental but not adult exposure to PCBs significantly reduced NOS responses to hyperosmolality in neuroendocrine cells, compared with controls. The reduced NOS activity produced by in utero exposure persisted in stimulated late adult rats concomitant with reduced osmoregulatory capacity. Rats receiving PCB exposure as early adults orally for 14 days displayed normal responses. These findings suggested that developmental exposure to PCBs permanently

compromises NOS signalling in the activated neuroendocrine hypothalamus, with potential osmoregulatory consequences (Coburn et al., 2015).

A 28-day study in which rats, aged 6 weeks at the start of treatment, were given loading and maintenance doses of PCB 180 (total doses of 0–1700 mg/kg bw) by oral gavage is described in section 2.2.2(b). It showed that the most sensitive end-point was altered open-field behaviour in females (Viluksela et al., 2014).

(b) Immunological effects

(i) Mice

C57BL/6J mice (3–4 weeks old, minimum four animals per dose group) were treated with a single intraperitoneal injection of corn oil alone, TCDD alone (0.0037 μmol/kg bw), PCB 153 alone (100, 400 or 1000 μmol/kg bw) or TCDD plus PCB 153 (0.0037 μmol/kg bw of TCDD plus 100, 400 or 1000 μmol/kg bw of PCB 153) (Biegel et al., 1989). TCDD and PCB 153 were synthesized to greater than 99% purity, as determined by gas chromatography (GC). Five days after treatment, each mouse was injected with sheep red blood cells (SRBCs; 4×10^8 cells), and 5 days later, splenic plaque-forming cell (PFC) responses to SRBCs were assessed. TCDD alone significantly inhibited PFC responses by 75% relative to controls, whereas PCB 153 alone had no significant effect at any dose. Co-administration of TCDD and PCB 153 (100 μmol/kg bw) had the same effect on PFC responses as for TCDD alone. PCB 153 (400 or 1000 μmol/kg bw) in combination with TCDD antagonized the inhibitory effects of TCDD on PFCs. Hepatic EROD was induced by TCDD alone, but not PCB 153. In combination with TCDD, PCB 153 (400 or 1000 μmol/kg bw) partially antagonized EROD induction relative to TCDD alone. Radiolabelled PCB 153 partially displaced TCDD from AhR. The results indicate that PCB 153 antagonizes AhR-mediated TCDD-induced inhibition of T cell–dependent PFC responses without substantively interacting with AhR.

Female B6C3F1 mice (8 weeks old, eight mice per group) were administered a single oral gavage dose of corn oil, PCB 153 (3.58, 35.8 or 358 mg/kg bw), TCDD (0.1, 1.0 or 10 μg/kg bw) or all dose combinations of PCB 153 and TCDD (Smialowicz et al., 1997). TCDD and PCB 153 were more than 98% pure. TCDD alone (1.0 or 10 μg/kg bw) significantly reduced spleen and thymus weights and significantly increased liver weight; PCB 153 alone had no comparable effects at any dose, with the exception of the high-dose group, in which an increase in liver weight was observed. Neither TCDD nor PCB 153 had a significant effect on body weight. When co-administered, PCB 153 and TCDD (10 μg/kg bw) significantly reduced spleen and thymus weights, irrespective of PCB 153 dose. Liver weights were elevated by TCDD (10 μg/kg bw), irrespective

of PCB 153 dose, and by the high dose of PCB 153, irrespective of TCDD dose. To assess PFC responses, mice were immunized 7 days after TCDD and/or PCB 153 exposure with a single intravenous injection of SRBCs (0.2 mL, 2×10^8 cells). Splenocyte primary PFC responses were assessed 4 days after immunization. TCDD (1.0 or 10 μg/kg bw) significantly suppressed PFC responses, whereas PCB 153 (358 mg/kg bw) significantly enhanced PFC responses. When co-administered with TCDD, PCB 153 (358 mg/kg bw) antagonized suppression of PFC responses by TCDD (0.1 or 1.0 μg/kg bw), whereas PCB 153 (358 mg/kg bw) and TCDD (10 μg/kg bw) suppressed splenocyte PFC responses. Taken together, the results indicate that PCB 153 acted as a functional antagonist by inducing a counterbalancing effect on immune responses in the opposite direction to that of TCDD and not via competition for AhR.

Male C57BL/6 and DBA/2 mice (6–8 weeks old, five mice per group) were treated with a single intraperitoneal dose of corn oil or one of the following *ortho*-substituted NDL-PCBs: PCB 206, PCB 207, PCB 208 or PCB 209 (10, 20 or 100 μmol/kg bw in C57BL/6 mice; 25, 100 or 400 μmol/kg bw in DBA/2 mice) (Harper et al., 1993). PCB purity was greater than 99%, as determined by gas–liquid chromatography. Four days after treatment, mice were immunized with SRBCs (4×10^8 cells in 200 μL) or trinitrophenyl-lipopolysaccharide (50 μg in 200 μL). Splenocyte PFC responses were assessed 4 days after immunization. Inhibition of SRBC PFC responses was significant in mice exposed to PCB 207 and PCB 208 (all doses; both strains), PCB 206 (20 and 100 μmol/kg bw, C57BL/6 mice; 100 and 400 μmol/kg bw, DBA/2 mice) and PCB 209 (100 μmol/kg bw, C57BL/6 mice; 400 μmol/kg bw, DBA/2 mice). In C57BL/6 mice exposed to PCBs at 100 μmol/kg bw, PFC responses were inhibited by an average of 72–81% relative to controls. Inhibition of SRBC PFC responses was less pronounced in DBA/2 mice. Minimal to no PFC response inhibition was observed in mice exposed to the T cell–independent antigen trinitrophenyl-lipopolysaccharide. Significant hepatic EROD induction was observed in C57BL/6 mice exposed to PCB 206 (25 and 100 μmol/kg bw). No significant induction of hepatic EROD was observed in C57BL/6 mice for any other PCB or in DBA/2 mice, suggesting an AhR-independent mechanism of action for inhibition of PFC response for higher chlorinated NDL-PCB congeners.

A single gavage dose of PCB 104 or PCB 153 (150 μmol/kg bw) in male C57BL/6 mice increased mRNA expression for the proinflammatory mediators ICAM-1, VCAM-1 and MCP-1 in liver, lungs and/or brain (Sipka et al., 2008).

A 28-day repeated-dose toxicity study compared the effects of polyhalogenated seafood contaminants on female BALB/c mice (Maranghi et al., 2013). Groups of 10 mice were fed diets containing one of the following: PCB 153, 1.3 μg/g; TCDD, 0.6 ng/g; hexabromocyclododecane [HBCD], 1.3 mg/g; or 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47), 3.0 μg/g. Mice were 22 days old at

the beginning of the study. Test substances (purity not indicated) were dissolved in 100% dimethylsulfoxide (DMSO; final concentration 0.4 mL/kg feed) and added to AIN-93G rodent diet that also contained freeze-dried Atlantic salmon. Control mice (n = 15) received diet also containing freeze-dried salmon; the presence of DMSO was not specified. Feed intake was restricted during the study, beginning with 2.25 g feed per day and increasing biweekly with body weight. This allowed for reasonably accurate achievement of the following exposure levels based on feed intake: PCB 153, 195 µg/kg bw per day; TCDD, 90 ng/kg bw per day; HBCD, 199 mg/kg bw per day; and BDE-47, 450 µg/kg bw per day. No significant changes in spleen, thymus or liver weight were observed in mice exposed to PCB 153. Histopathological evidence of immune effects in mice due to PCB 153 exposure included inflammatory infiltration in liver and spleen and thymic changes suggestive of accelerated involution. Increased hepatocyte vacuolation, pyknotic nuclei and periportal lymphocytic infiltration were observed in livers from mice exposed to PCB 153 compared with controls.

(ii) Rats

Female SD rats (starting body weight 150 g; nine rats per group) were fed control diet or diets containing PCB 153 (10, 30 or 100 mg/kg diet), TCDD (0.5 or 5 µg/kg diet) or combinations of PCB 153 and TCDD for 13 weeks (van der Kolk et al., 1992). No PCDDs or PCDFs were detected in PCB 153 using high-resolution gas chromatography with mass spectrometry (HRGC-MS; LOD 0.5 ng TEQ/g). There was no significant effect of PCB 153 alone on body weight at any dose; TCDD (5 µg/kg diet) significantly reduced body weight gain. PCB 153 alone (100 mg/kg diet) and TCDD alone (5 µg/kg diet) significantly increased relative liver weight. Whereas TCDD (5 µg/kg diet) significantly reduced thymus weight, no significant changes in thymus weight due to PCB 153 were observed at any dose. When PCB 153 and TCDD were co-administered, no interactive effects on thymus were evident, although changes in liver weight were additive. PCB 153 alone induced PROD but not EROD activity, whereas TCDD alone induced both PROD and EROD activities. Together, TCDD antagonized PCB 153–induced PROD activity. No interactive effects of PCB 153 on TCDD-induced EROD activity were observed. Thus, exposure to TCDD but not PCB 153 led to thymic atrophy associated with AhR induction. Induction of PROD activity was not associated with thymic atrophy in rats exposed to PCB 153.

Exposure to PCB 153 in the 2-year NTP chronic toxicity study caused inflammation in female rats (NTP, 2006a). Inflammatory lesions in female reproductive organs were observed in Harlan Sprague-Dawley rats exposed to PCB 153 by gavage at 10, 100, 300, 1000 or 3000 µg/kg bw per day, 5 days/week, for 14, 31 or 53 weeks or 2 years (NTP, 2006a; Strauss & Heiger-Bernays, 2012).

Dose-dependent increases in the incidence of chronic active inflammation were observed in the ovary and oviduct of female rats in the 1000 and 3000 μg/kg bw per day dose groups. The incidence of suppurative uterine inflammation and chronic active uterine inflammation increased relative to controls in the 1000 and 3000 μg/kg bw per day dose groups, respectively (NTP, 2006a). Bone marrow hyperplasia, also indicative of chronic inflammation, was seen in female rats in the 3000 μg/kg bw per day dose group (NTP, 2006a; Strauss & Heiger-Bernays, 2012).

(iii) Non-rodent species

The effects of perinatal exposure to PCB 153, an NDL-PCB, or PCB 126, a DL-PCB, on females and their offspring were examined in goats (Lyche et al., 2004b, 2006). Adult female goats (Norwegian breed) were exposed to PCB 153 or PCB 126 at an estimated dose of 98 μg/kg bw per day or 49 ng/kg bw per day, respectively, for 3 days/week from GD 60 to parturition (approximately 90 days, assuming a 150-day gestation period). Their offspring were exposed indirectly during gestation and lactation. Significant changes in immune parameters were observed in does and kids exposed to PCB 153. Two weeks after parturition, increased white blood cell, neutrophil and lymphocyte numbers were detected in blood from kids exposed perinatally to PCB 153. Decreased blood lymphocyte proliferation stimulated by the mitogens concanavalin A and phytohaemagglutinin were also observed. There were no effects on these parameters in PCB-exposed kids at 4 or 8 weeks after parturition (Lyche et al., 2004b). PCB 153 significantly affected maternal humoral responses to vaccination, resulting in reduced transfer of specific antibodies to kids. Perinatal PCB 153 exposure also disrupted antibody responses to vaccination in kids (Lyche et al., 2006). In kids exposed perinatally to PCB 126, blood monocyte numbers were significantly lower at 2, 4 and 8 weeks after parturition, but no further effects were observed (Lyche et al., 2004b). Maternal and juvenile responses to vaccination were also disrupted by PCB 126 (Lyche et al., 2006), but the pattern of disruption differed from that of PCB 153, suggesting that the immunomodulatory effects of PCBs are due to AhR- and non-AhR-mediated events.

(v) In vitro studies

Non-coplanar, *ortho*-substituted PCBs (NDL-PCBs) inhibit mitogen-stimulated murine splenocyte (mixed spleen cell) proliferation more effectively than coplanar PCBs (DL-PCBs) in vitro (Stack et al., 1999; Smithwick et al., 2003; Mori et al., 2006, 2008). Proliferation stimulated by lipopolysaccharides and concanavalin A was inhibited in mouse splenocytes by NDL-PCBs (Smithwick et al., 2003; Mori et al., 2006, 2008), suggesting that pathways common to multiple

immune cell types were affected. Anti-proliferative effects of NDL-PCBs were AhR independent (Stack et al., 1999; Smithwick et al., 2003).

Thymocyte viability was reduced by ex vivo exposure to the *ortho*-substituted, non-coplanar NDL-PCB, PCB 52, at micromole per litre concentrations, but not by the coplanar DL-PCB, PCB 77 (Yilmaz et al., 2006). Thymocyte death was associated with disrupted calcium homeostasis and increased membrane fluidity, indicating that *ortho*-substituted PCBs disrupt cellular membranes. PCB 52 and PCB 77, at micromole per litre concentrations, significantly stimulated interferon gamma and inhibited interleukin-10 (IL-10) production in concanavalin A–stimulated murine thymocytes; PCB 52 was approximately 10-fold more potent (Sandal et al., 2005). However, exposure to PCB 153, an NDL-PCB, did not alter the percentages of human lymphocytes producing interferon gamma or IL-4 in culture (Gaspar-Ramírez et al., 2012).

Lymphocyte proliferation was significantly modulated in vitro in marine mammal lymphocyte cultures (Mori et al., 2006, 2008). Concanavalin A– and lipopolysaccharide-stimulated mouse lymphocytes were consistently inhibited by TCDD, PCB 169 (a DL-PCB) and PCB 138, PCB 153 and PCB 180 (NDL-PCBs); however, B-cell proliferation and T-cell proliferation were unchanged or stimulated in lymphocyte cultures from most of the marine mammals tested.

Non-coplanar NDL-PCB congeners with low affinity for AhR have more pronounced effects in vitro on human and rodent granulocytes than do coplanar DL-PCBs, including activation of quiescent neutrophils and enhancement or inhibition of activated neutrophils (Ganey et al., 1993; Brown & Ganey, 1995; Olivero-Verbel & Ganey, 1998; Voie, Wiik & Fonnum, 1998; Bezdecny, Roth & Ganey, 2005). However, non-coplanarity alone does not fully account for the effects of PCBs on granulocyte functions. For example, chlorine substitutions in the *ortho* or *meta* position are required to stimulate superoxide production in neutrophils in vitro (Brown et al., 1998). Numbers of substitutions at the *ortho* position, congener size and absolute hardness have also been correlated with changes in respiratory burst activity in human granulocytes in vitro (Voie et al., 2000).

In marine mammals, the effects of TCDD, PCB 169 (a DL-PCB) and PCB 138, PCB 153 and PCB 180 (NDL-PCBs) on leukocyte function were congener and species specific (Levin et al., 2004, 2005; Levin, Morsey & DeGuise, 2006). Bottlenose dolphin (*Tursiops truncatus*) monocytes and neutrophils were more sensitive to PCBs than monocytes and neutrophils from beluga whales (*Delphinapterus leucas*). In dolphins and belugas, PCB 169 (a DL-PCB) and TCDD alone were not inhibitory, whereas the individual NDL-PCBs, PCB 138, PCB 153 and PCB 180, and mixtures containing these congeners were inhibitory (Levin et al., 2004). In a larger cross-section of marine mammals, modulation of leukocyte phagocytosis by the same group of test substances was dependent on the presence of at least one NDL-PCB in all species but one (harbour seal, *Phoca*

vitulina); mouse leukocytes were unaffected (Levin et al., 2005). Both NDL- and DL-PCBs modulated respiratory burst in leukocytes from marine mammals, mice and humans (Levin, Morsey & DeGuise, 2006). The results highlight species-specific differences in granulocyte responses to PCBs in vitro.

2.3 Observations in humans

2.3.1 Biomonitoring

(a) Biomarkers for NDL-PCBs

The most commonly used biomarkers of PCB exposure in humans are PCB concentrations in adipose tissue, serum, plasma and milk. The presence of PCBs in human tissues and fluids may reflect exposure from one or more sources, including air, water, food, soil and dust, with food being the major contributor. Exposures from all sources are nearly always to mixtures of PCBs rather than to individual congeners.

There is a strong correlation between concentrations of PCBs in serum and adipose tissue, when expressed on a lipid basis. For example, in non-occupationally exposed subjects, a strong correlation was found between concentrations of nine NDL-PCBs (PCBs 74, 99, 138, 146, 153, 170, 180, 183 and 187) in serum and adipose tissue (Stellman et al., 1998). Similarly, a strong correlation was also found between concentrations of PCB 153 and PCB 180 in serum lipid and breast or gluteal adipose tissue in another study in women undergoing surgery for breast cancer (Rusiecki et al., 2005). Concentrations of PCBs in both serum and adipose tissue are widely regarded as useful biomarkers of PCB body burden.

The concentrations of PCBs in serum or plasma can be significantly influenced by serum lipid content, owing to partitioning of PCBs between adipose tissue and serum lipids. Thus, PCB concentrations in serum lipid or plasma lipid are regarded as better indicators of body burden than PCB concentrations that have not been corrected for lipid content (Brown & Lawton, 1984). In general, concentrations in blood lipids reflect more recent exposures, as well as the full spectrum of PCB congeners to which a person is exposed, whereas the pattern of PCB congeners in adipose tissue reflects long-term exposures. PCB concentrations in human milk largely reflect the pattern and amounts of the congeners present in maternal adipose tissue (ATSDR, 2000; EFSA, 2005).

PCB residue data in humans suggest that assessment of tissue or body burdens of PCBs should be based on individual congeners or groups of congeners, rather than on profiles of commercial PCB formulations. Numerous publications have reported that PCB 138, PCB 153 and PCB 180, all NDL-PCBs, are the most consistently detected and quantitatively dominant congeners found in human tissues. If only one congener is to be used as a marker of total PCB exposure,

then PCB 153 is a good candidate, because it is very stable and often it is the most abundant congener. PCB 153 has been shown to have a high correlation with the total amount of PCBs in human breast milk, human plasma and human serum. However, it has also been noted that the correlations are lower if a more complete profile of congeners is considered and that either total PCBs or PCB 153 as a marker of the total could be misleading indicators of the differential exposure to other individual or groups of congeners of toxicological significance (ATSDR, 2000; Glynn et al., 2000).

In the summary of biomonitoring data that follows, the focus is on the most abundant NDL-PCB congeners, PCB 138, PCB 153 and PCB 180. These three PCBs are the most frequently detected PCBs in population biomonitoring studies (Glynn et al., 2000) and generally account for 65–80% of the measured total sum of PCBs (Needham et al., 2005).

(b) Concentrations of NDL-PCBs in blood, plasma and serum

The most comprehensive, ongoing survey of NDL-PCB levels in human serum is the United States National Health and Nutrition Examination Survey (NHANES). From 1999, the NHANES became a continuous, rolling survey, and blood samples were taken randomly from the population in the USA for measurement of a large number of environmental chemicals, including PCBs. Data on NDL-PCBs are currently available for survey cycles carried out in 1999–2000, 2001–2002, 2003–2004, 2005–2006 and 2007–2008 (CDC, 2015). Over time, the concentrations of 31 individual NDL-PCB congeners have been measured (Table 8), although not every congener has been measured in every survey cycle or in every population subgroup within each survey cycle.

In each survey cycle, blood samples for measurement of environmental chemicals were taken from approximately one third of the participants – that is, from over 1800 children and adults, ranging from children aged 12 years or older up to adults aged 74 years. In the survey cycles between 1999 and 2004, PCBs were measured in individual samples, and the geometric means and selected percentiles were estimated. Such measurements in individuals tend to have a log-normal distribution, with central tendency best estimated using a geometric mean. From 2005 onwards, a weighted pooled sample design was used because of the need to increase sensitivity by using larger volumes and to reduce costs. The measured value for a pooled sample is comparable to an arithmetic average of measurements in individuals. Consequently, a pooled sample result using an arithmetic mean is expected to be higher than the geometric mean of multiple individual results. Within each survey cycle, data are stratified according to sex, race/ethnicity (non-Hispanic, Hispanic, Mexican American) and age group (12–19, 20–39, 40–59, 60+ years).

Table 8
NDL-PCB congeners measured in pooled serum samples in the United States NHANES surveys in 1999–2008

PCB chemical name	PCB congener no.
2,4,4′-Trichlorobiphenyl	28
2,2′,3,5′-Tetrachlorobiphenyl	44
2,2′,4,5′-Tetrachlorobiphenyl	49
2,2′,5,5′-Tetrachlorobiphenyl	52
2,3′,4,4′-Tetrachlorobiphenyl	66
2,4,4′,5-Tetrachlorobiphenyl	74
2,2′,3,4,5′-Pentachlorobiphenyl	87
2,2′,4,4′,5-Pentachlorobiphenyl	99
2,2′,4,5,5′-Pentachlorobiphenyl	101
2,3,3′,4′,6-Pentachlorobiphenyl	110
2,2′,3,3′,4,4′-Hexachlorobiphenyl	128
2,2′,3,4,4′,5′-Hexachlorobiphenyl and 2,3,3′,4,4′,6-hexachlorobiphenyl	138 & 158
2,2′,3,4′,5,5′-Hexachlorobiphenyl	146
2,2′,3,4′,5′,6-Hexachlorobiphenyl	149
2,2′,3,5,5′,6-Hexachlorobiphenyl	151
2,2′,4,4′,5,5′-Hexachlorobiphenyl	153
2,2′,3,3′,4,4′,5-Heptachlorobiphenyl	170
2,2′,3,3′,4,5,5′-Heptachlorobiphenyl	172
2,2′,3,3′,4,5′,6′-Heptachlorobiphenyl	177
2,2′,3,3′,5,5′,6-Heptachlorobiphenyl	178
2,2′,3,4,4′,5,5′-Heptachlorobiphenyl	180
2,2′,3,4,4′,5′,6-Heptachlorobiphenyl	183
2,2′,3,4′,5,5′,6-Heptachlorobiphenyl	187
2,2′,3,3′,4,4′,5,5′-Octachlorobiphenyl	194
2,2′,3,3′,4,4′,5,6-Octachlorobiphenyl	195
2,2′,3,3′,4,4′,5,6′-Octachlorobiphenyl and 2,2′,3,4,4′,5,5′,6-octachlorobiphenyl	196 & 203
2,2′,3,3′,4,5,5′,6-Octachlorobiphenyl	199
2,2′,3,3′,4,4′,5,5′,6-Nonachlorobiphenyl	206
2,2′,3,3′,4,4′,5,5′,6,6′-Decachlorobiphenyl	209

The results have been summarized by the United States Centers for Disease Control and Prevention (CDC, 2009, 2013, 2015). Comparison of results from the earlier years of the survey up to 2004 with those from later years is not possible because of the switch from geometric means of individual results to arithmetic means from pooled samples. In the years up to and including 2004, serum levels of NDL-PCBs were roughly similar over the three surveys (CDC, 2009). The results for the six indicator PCBs (PCBs 28, 52, 101, 138 (+158), 153, 180) are shown in Table 9.

Table 9
Mean concentrations of the six indicator PCBs in serum in the NHANES survey

PCB congener no.	NHANES survey year	Concentration (ng/g of lipid, lipid adjusted)		Concentration (ng/g of serum, whole weight)	
		Mean	95th percentile	Mean	95th percentile
28		*WGM*			
	1999–2000	–[a]	<LOD	<LOD	<LOD
	2003–2004[b]	4.90	11.3	0.030	0.067
		WAM			
	2005–2006[c]	2.74–3.81	–	0.016–0.025	–
	2007–2008[c]	0.715–5.42	–	0.004–0.018	–
52		*WGM*			
	1999–2000	–[a]	<LOD	–[a]	<LOD
	2001–2002	–[a]	16.5	–[a]	0.090
	2003–2004	2.66	7.60	0.016	0.043
		WAM			
	2005–2006[c]	0.348–0.807	–	0.003–0.005	–
	2007–2008[c]	–[a]	–	–[a]	–
101		*WGM*			
	1999–2000	–[a]	<LOD	–[a]	<LOD
	2001–2002	–[a]	<LOD	–[a]	<LOD
	2003–2004	1.65	5.83	0.010	0.033
		WAM			
	2005–2006[c]	0.632[d]	–	0.005	–
	2007–2008[c]	0.608–0.954	–	–[a]	–
138 + 158		*WGM*			
	1999–2000	–[a]	71.2	–[a]	0.460
	2001–2002	19.9	94.6	0.122	0.650
	2003–2004	15.1	75.3	0.092	0.477
		WAM			
	2005–2006[c]	1.92–81.1	–	0.014–0.541	–
	2007–2008[c]	1.84–79.9	–	0.014–0.477	–
153		*WGM*			
	1999–2000	–[a]	114	–[a]	0.750
	2001–2002	27.2	126	0.176	0.860
	2003–2004	19.8	97.1	0.121	0.624
		WAM			
	2005–2006[c]	2.83–130	–	0.015–0.865	–
	2007–2008[c]	2.88–102	–	0.018–0.614	–
180		*WGM*			
	1999–2000	–[a]	79.3	–[a]	0.540
	2001–2002	19.2	87.3	0.118	0.610
	2003–2004	15.1	81.5	0.092	0.534

PCB congener no.	NHANES survey year	Concentration (ng/g of lipid, lipid adjusted)		Concentration (ng/g of serum, whole weight)	
		Mean	95th percentile	Mean	95th percentile
		WAM			
	2005–2006[c]	1.78–88.6	–	0.010–0.589	–
	2007–2008[c]	2.02–82.5	–	0.010–0.501	–

LOD: limit of detection; WAM: weighted arithmetic mean; WGM: weighted geometric mean
[a] Mean not calculated, as proportion of results below LOD was too high.
[b] Values are the WGM for the whole sample.
[c] The range gives the lowest and highest values from the various sex/race/ethnicity/age subgroups of the population in which the PCB congener was measured. Values tended to increase with age.
[d] Only one subgroup included in the survey.
Source: CDC (2015)

CDC (2009, 2013) compared the NHANES results with those of earlier surveys in other countries. The NHANES results confirm earlier reports that PCB 138, PCB 153 and PCB 180 are the most frequently detected PCBs, accounting for 65–80% of total PCBs in human serum, and that concentrations of the di-*ortho*-substituted PCBs are usually higher than those of the mono-*ortho*-substituted PCBs, which in turn are higher than those of the coplanar PCBs (Patterson et al., 1994, 2009; Glynn et al., 2000; Longnecker et al., 2000; Heudorf, Angerer & Drexler, 2002; Bates et al., 2004; Apostoli et al., 2005; Needham et al., 2005; Turyk et al., 2006; CDC, 2013). The NHANES 2001–2002 results also illustrate declines over time, being generally lower than lipid-adjusted serum concentrations measured in selected populations during the 1980s–1990s (Patterson et al., 1994; Glynn et al., 2000; Longnecker et al., 2000; Link et al., 2005; Hagmar et al., 2006; CDC, 2013).

CDC (2013) noted that surveys in other countries have reported higher or lower concentrations of PCBs in serum than those found in the NHANES surveys. For example, in a 1998 study of 624 urban Germans aged 0–65 years (Heudorf, Angerer & Drexler, 2002), 95th percentile levels for PCB 138, PCB 153 and PCB 180 were similar to or up to 2 times higher than 95th percentile levels in the NHANES 1999–2000 subsample. In two separate Italian studies of a regional reference population and a convenience sample in 2001–2003, median levels of PCB 138, PCB 153 and PCB 180 in serum were about 5 times higher than those from NHANES 1999–2000 (Apostoli et al., 2005; Needham et al., 2005; Turci et al., 2006; CDC, 2013). In some other countries, PCB concentrations in serum from comparable populations were 10 or more times higher than in NHANES subsamples from 1999–2000 and 2001–2002 (Jursa et al., 2006; Petrik et al., 2006). In contrast, PCB concentrations in serum from a representative population of New Zealand residents in 1996–1997 (Bates et al., 2004) were slightly lower than those from NHANES 1999–2000.

Biomonitoring results for the six indicator PCBs in human blood, serum and plasma from other studies around the world published since 2004 are summarized in Table 10.

Table 10

Summary of studies on mean blood, serum and plasma concentrations of the six indicator PCBs[a]

Study	Country	No. of subjects	Age range (years)	Type of blood sample analysed	Mean concentration *(variation or range shown in italics)*					
					PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
					in ng/g lipid					
Turci et al. (2004)	Italy	162 M + F	<30–>50 43 (mean)	Individual serum	2.22	0.713	0.622	71.4	105	80.0
Variation not stated										
Rusiecki et al. (2005)	India	29 F	24–65	Individual serum	–	–	–	–	16.08	5.81
Variation as SD									*11.90*	*3.99*
Jaraczewska et al. (2006)	Poland	22 F	22–38	Individual maternal serum	–	–	–	13.7	20.7	17.2
Variation as SD								*6.2*	*10.6*	*9.0*
Jaraczewska et al. (2006)	Poland	22 F	0	Individual cord blood serum	–	–	–	3.6	11.3	13.6
Variation as SD								*2.8*	*6.8*	*10.4*
Petrik et al. (2006)	Slovakia	402 M 636 F	>18	Individual serum	–	–	–	165	267	246
Variation as total range								*8.5–3 500*	*38.8–5 193*	*42.4–4 809*
Petrik et al. (2006)	Slovakia	112 M 106 F	8–10	Individual serum	–	–	–	65.6	109	90.0
Variation as total range								*<8.9–343*	*<13.7–627*	*<8.6–584*
Porpora et al. (2006)	Italy	40 F	20–40	Individual whole blood	5.6	3.0	3.1	53	95	45
Variation as SD					*8.3*	*5.5*	*3.2*	*26*	*55*	*28*
Thomas et al. (2006)	United Kingdom	41 M + F	22–80	Individual serum	2.1[d]	<0.25[d]	<1.3[d]	27[d]	41[d]	33[d]
Variation as total range					*<1.0–14*	*<0.25–4.7*	*<1.3–9*	*<7.1–110*	*<9.3–200*	*<4.7–200*
Turci et al. (2006)	Italy	175 M 151 F	37–43 (means)	Individual serum	11.3	26.1	–	128	170	121
Variation as 95th percentile					*48.5*	*85.1*		*277*	*387*	*298*
Weiss et al. (2006)	Sweden	53 F	52–81	Individual serum	–	–	–	–	260	–
Variation as total range									*70–620*	
Park et al. (2007)	Republic of Korea	47 M 40 F	21–>50	Individual serum	2.46	1.06	1.45	34.00	54.90	28.42
Variation as SD					*2.40*	*1.94*	*2.32*	*27.09*	*54.06*	*27.83*

Study	Country	No. of subjects	Age range (years)	Type of blood sample analysed	Mean concentration *(variation or range shown in italics)*					
					PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
Sandanger et al. (2007)	Canada	109 F	48–76	Individual plasma	–	–	–	25.9	47.1	40.4
Variation as total range								*5.45–101*	*14.4–177*	*1.39–206*
Zhao et al. (2007)	China, Pingqiao District	60 F	0	Individual whole cord blood, lipid extraction	–	1.56	3.13	34.42	12.22	22.66
Variation as total range						*0.05–5.27*	*0.05–38.48*	*5.65–231.21*	*0.10–67.11*	*0.99–102.59*
Cerná et al. (2008)	Czech Republic	124 M 78 F	33 (mean)	Individual serum	14	5	–	186[b]	423[b]	374[b]
Variation as total range					*3–126*	*1–115*		*13–965*	*64–2 280*	*43–2 210*
Kang et al. (2008)	Republic of Korea	20 M 20 F	27–58	Individual serum	6.0	6.6	5.2	16.4	26.6	18.1
Variation as total range					*<0.6–24.6*	*<1.0–25.6*	*0.9–19.2*	*<7.3–67.8*	*6.6–106*	*4.2–82.0*
Todaka et al. (2008)	Japan	51 M	60–79	Individual whole blood, lipid extraction	2.6	1.3	2.0	43	97	68
Variation as SD					*1.5*	*0.8*	*1.2*	*19*	*40*	*34*
Todaka et al. (2008)	Japan	76 F	60–66	Individual whole blood, lipid extraction	2.6	1.3	1.8	39	85	53
Variation as SD					*1.8*	*0.9*	*1.3*	*20*	*41*	*26*
Turrio-Baldassarri et al. (2008)	Italy, general population of Brescia	52 M 42 F	51 (mean)	Pooled serum	<0.3	<0.4	<0.4	108	242	303
Variation not stated										
Axelrad, Goodman & Woodruff (2009)	USA	496 F	16–39	Individual serum	–	–	–	–	14[d]	–
Variation as 95th percentile									*41*	
Koppen et al. (2009)	Belgium	1 054 – 1 071 F	0	Individual cord blood serum	–	–	–	21.3	37.7	26.0
Variation as total range								*2.3–156.7*	*2.3–230.2*	*2.1–153.1*
Porpora et al. (2009)	Italy	78 F	18–45	Individual serum	3.4	1.6	1.6	33.8	61.8	34.4
Variation as 95% CI					*2.5–4.5*	*1.3–1.9*	*1.3–1.9*	*29.0–39.3*	*51.8–73.8*	*29.0–40.8*
Röllin et al. (2009)	South Africa	96 F	Not provided	Individual plasma	–	–	–	3.6	3.2	–
Todaka et al. (2010)	Japan	119 F Primiparous	21–40	Individual whole blood, lipid extraction	1.3	0.8	0.8	14.8	26.8	17.3
Variation as SD					*0.7*	*0.6*	*0.6*	*8.0*	*15.4*	*11.6*
Windham et al. (2010)	USA	611 F	6–10	Individual serum	–	–	–	10.0[c]	14.3	9.3
Variation as SD								*13.1*	*18.4*	*13.4*

Table 10 (continued)

Study	Country	No. of subjects	Age range (years)	Type of blood sample analysed	Mean concentration *(variation or range shown in italics)*					
					PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
Bachelet et al. (2011)	France	1 055 F	<30–49	Individual serum	–	–	–	–	88.4[d]	–
Variation as 90th percentile									*217.6*	
Henríquez-Hernández et al. (2011)	Spain	284 M 323 F	6–75	Individual serum	0.0[d]	0.0[d]	0.0[d]	0.0[d]	21.8[d]	6.7[d]
Variation as 5th–95th percentile					*0.0–1.1*	*0.0–0.0*	*0.0–7.1*	*0.0–132.6*	*0.0–111.1*	*0.0–36.3*
Ibarluzea et al. (2011)	Spain	1 259 F Pregnant	31 (mean)	Individual serum	–	–	–	21.83	38.92	26.99
Variation as 95th percentile								*20.99–22.70*	*37.48–40.42*	*25.92–8.12*
Kalantzi et al. (2011)	Greece	34 M 27 F	20–65	Individual serum	–	–	0.13	24.9	43.2	31.4
Variation as SD							*0.38*	*15.1*	*27.1*	*22.1*
Todaka et al. (2011)	Japan	97 F Secundi-parous	22–41	Individual whole blood, lipid extraction	1.1	0.7	0.7	12.8	24.0	15.3
Variation as SD					*0.6*	*0.5*	*0.4*	*6.4*	*12.5*	*9.7*
Amodio et al. (2012)	Italy (Sicily)	50 M 51 F	<30–>69	Individual serum	4.41[d]	4.23[d]	4.15[d]	22.04[d]	33.52[d]	23.97[d]
Variation as interquartile range					*1.76*	*1.59*	*1.51*	*14.13*	*22.22*	*22.97*
Arrebola et al. (2012)	Plurina-tional State of Bolivia	22 M 90 F	18–70	Individual serum	–	–	–	33.7	59.0	26.7
Variation as SD								*11.3*	*36.5*	*10.2*
Bergkvist et al. (2012)	Sweden	201 F	58–78	Individual serum	–	–	–	62	124	83
Variation as 5th–95th percentile of median								*26–111 (median value 56)*	*63–195 (median value 114)*	*46–130 (median value 79)*
Eguchi et al. (2012)	India	20 (sex information only available in supplementary table)	(age information only available in supplementary table)	Individual serum	4.8	1.2	1.6	28	26	14
Variation as SD					*6.6*	*2.5*	*2.6*	*20*	*22*	*9.2*
Fréry et al. (2012)	France	386	18–74	Individual serum	2.2	1	1.1	70	110	90
Variation as 95% CI					*1.9–2.5*	*0.2–3.1*	*0.9–1.3*	*60–80*	*100–130*	*80–110*
Porta et al. (2012)	Spain	94 M 137 F	18–>65	Individual serum	–	–	–	44.0	63.4	54.4
Variation as 95% CI								*40.0–48.4*	*57.5–70.0*	*82.4–103.5*

Study	Country	No. of subjects	Age range (years)	Type of blood sample analysed	Mean concentration *(variation or range shown in italics)*					
					PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
Rylander et al. (2012)	Norway	273 F	48–62	Individual plasma	–	–	–	66	87	70
Variation as total range								*<LOD–164*	*<LOD–211*	*<LOD–182*
Nøst et al. (2013)	Norway	53 M	29–82	Individual serum	–	–	–	–	120–240	–
Variation not stated										
Aylward et al. (2014)	USA	43 M	55–80	Individual serum	–	–	–	54.0	69.7	63.1
Variation as SD								*33.2*	*39.9*	*38.2*
Ben Hassine et al. (2014)	Tunisia	32 M 81 F	20–81	Individual serum	–	–	0.44	26.1	51.9	34.6
Variation as SD							*3.3*	*10.7*	*19.7*	*11.3*
Chovancová et al. (2014)	Slovakia	20 M 20 F	24–62	Pooled serum	–	–	–	–	236	–
Variation as total range									*16.2–628*	
Esposito et al. (2014)	Italy	32 M 26 F	18–64 24–64	Individual serum	4.4	1.0	3.2	37	56	73
Variation as total range					*0.8–14.9*	*0.2–7.3*	*0.6–4.9*	*6.7–117.7*	*10.1–195.3*	*5.6–1 138*
Huetos et al. (2014)	Spain	963 M	18–>50	Individual serum	–	–	–	45.77	62.49	83.47
Variation as 95% CI								*41.07–50.47*	*54.88–70.10*	*72.23–94.72*
Huetos et al. (2014)	Spain	917 F	18–>50	Individual serum	–	–	–	47.14	60.33	74.63
Variation as 95% CI								*37.69–56.59*	*50.09–70.56*	*61.07–88.19*
Artacho-Cordón et al. (2015)	Tunisia	54 F	38–50	Individual serum	–	–	–	28.59	119.07	31.74
Variation as SD								*16.64*	*35.96*	*11.00*
Ulutaş et al. (2015)	Turkey	57 F	20–41	Individual whole blood, lipid extraction	0.17	0.06	0.10	0.59	0.64	0.39
Variation as SD					*0.34*	*0.28*	*0.34*	*0.78*	*0.75*	*0.47*
Whitehead et al. (2015)	USA	48 F	<34–>41	Individual serum	4.1[g]	–	1.7[g]	6.8[g]	11[g]	10[g]
Variation as 25th–90th percentile					*3.1–6.8*		*<1.6–2.9*	*4.8–14*	*6.5–28*	*6.1–25*
Zubero et al. (2015)	Spain	60 M 102 F	20–69	Individual serum	–	–	–	64.8	92.4	92.4
Variation as 95% CI								*8.7–71.6*	*83.2–102.7*	*84.0–101.7*
					(in pmol/g serum lipid)					
Mrema et al. (2014)	Italy	182 M 185 F	19–70	Individual serum	–	–	–	174–532[d]	265–668[d]	189–403[d]
Variation as total range								*13–1 612[d]*	*13–2 205[d]*	*10–1 616[d]*

Table 10 (continued)

Study	Country	No. of subjects	Age range (years)	Type of blood sample analysed	Mean concentration *(variation or range shown in italics)*					
					PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
					(in µg/L of whole blood)					
Link et al. (2012)	Germany	803 M + F	9–11	Individual whole blood	–	–	–	0.05	0.10	0.06
Variation as SD								*0.04*	*0.09*	*0.06*
Fromme et al. (2015)	Germany	33 M 37 F	4–76	Individual whole blood, lipid extraction	0.003	0.001	0.001	0.150	0.277	0.260
Variation as 95th percentile					*0.008*	*0.002*	*0.003*	*0.552*	*0.995*	*1.022*
					(in ng/g whole blood)					
Hirai et al. (2005)	Japan	12 M 12 F	25–46	Individual whole blood, lipid extraction	0.006 3	0.002 8	0.005 7	0.064 7	0.171 0	0.089 7
Variation as SD					*0.003 4*	*0.003 2*	*0.004 9*	*0.032 4*	*0.088 5*	*0.049 1*
					(in µg/L)					
Apostoli et al. (2005)	Italy[f]	165 M 146 F	20–79	Individual serum	–	–	–	0.83	1.43	1.64
Variation as SD								*0.70*	*1.25*	*1.69*
Redding et al. (2008)	Summary of studies from various countries, 2002–2008			Plasma, serum & whole blood	–	–	–	–	0.1–1.7	–
Variation not stated										
Dirtu et al. (2010)	Belgium	16 M 4 F	Not stated	Individual serum	–	–	–	0.73[d]	1.12[d]	0.71[d]
Variation as total range								*0.19–1.59[d]*	*0.240–2.41[d]*	*0.15–1.71[d]*
Dirtu et al. (2010)	Romania	31 M 22 F	Not stated	Individual serum	–	–	–	0.57[d]	0.68[d]	0.88[d]
Variation as total range								*0.09–4.71[d]*	*0.09–3.83[d]*	*0.07–7.72[d]*
Grimalt et al. (2010)	Spain	410 F	0	Individual cord blood serum	0.014	0.021	0.032	0.17	0.21	0.20
Variation as SD					*0.070*	*0.076*	*0.097*	*0.13*	*0.24*	*0.36*
Grimalt et al. (2010)	Spain	285 M + F	4	Individual serum	0.024	0.036	0.088	0.24	0.35	0.20
Variation as SD					*0.33*	*0.30*	*0.14*	*0.53*	*0.67*	*0.47*
Turci et al. (2010)	Italy (Novafeltria)	19 M 17 F	42 (mean)	Individual serum	–	0.038[d]	0.040[d]	0.220[d]	0.560[d]	0.305[d]
Variation as total range					*<LOD–0.550[d]*	*<LOD–0.500[d]*	*<LOD–0.96[d]*	*0.11–1.64[d]*	*0.50–3.42[d]*	*0.05–0.95[d]*
Turci et al. (2010)	Italy (Pavia)	36 M 23 F	42 (mean)	Individual serum	–	0.105	–	0.400	0.560	0.470
Variation as total range					*<LOD–0.220*	*<LOD–1.10*	*<LOD–0.11*	*<LOD–1.10*	*<LOD–2.10*	*<LOD–1.55*
Cao et al. (2011)	China	1210 F	28 (mean)	Individual cord blood serum	0.25	0.39	0.20	0.09	0.20	–
Variation as maximum					*6.68*	*17.67*	*6.40*	*2.15*	*3.75*	

Study	Country	No. of subjects	Age range (years)	Type of blood sample analysed	Mean concentration *(variation or range shown in italics)*					
					PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
Schettgen et al. (2011)	Germany	105 M + F	5–84	Individual plasma, 7 age groups	0.011–0.016[d]	<0.01[d]	<0.01–0.011[d]	0.117–0.874[d]	0.149–1.338[d]	0.098–1.292[d]
Variation as 95th percentile					*0.025–0.037[d]*	*<0.01–0.017[d]*	*<0.01–0.021[d]*	*0.379–1.655[d]*	*0.536–2.223[d]*	*0.350–1.876[d]*
Lind et al. (2012)	Sweden	506 M 520 F	70	Individual serum	–	–	–	0.819[d]	1.428[d]	1.165[d]
Variation as 25th–75th percentile								*0.619–1.116[d]*	*1.114–1.848[d]*	*0.918–1.488[d]*
Pandelova & Schramm (2012)	Germany	53 M 53 F	20–29	Individual plasma	–	–	–	0.34	0.22	0.12
Variation not stated										
Lopes et al. (2014)	Portugal	68 F Maternal serum	17–41	Individual maternal serum	–	–	–	0.16	1.01	0.46
Variation as SD								*0.08*	*0.24*	*0.24*
Lopes et al. (2014)	Portugal	68 F	0	Individual cord blood serum	–	–	–	0.11	0.97	0.36
Variation as SD								0.05	0.18	0.13

CI: confidence interval; F: females; LOD: limit of detection; M: males; SD: standard deviation
[a] In time-series studies, the values given are for the most recent year.
[b] From a polluted area formerly manufacturing PCBs.
[c] PCB 138/158, when co-eluted.
[d] Median values.

(c) Concentrations of NDL-PCBs in adipose tissue

Adipose tissue concentrations have been measured in the general population and in case–control studies on particular diseases. For details on the latter, see sections 2.3.4–2.3.15.

The results of studies on NDL-PCB concentrations in adipose tissue are summarized in Tables 11 and 12. Table 11 gives the concentrations of the six indicator PCBs in adipose tissue. Table 12 summarizes some studies in which both DL- and NDL-PCBs have been measured, giving overall values for the sum of all PCBs measured together with the sum of the three indicator PCB congeners that make the highest contribution to total PCB levels in food and in adipose tissue – that is, PCBs 138, 153 and 180. The majority of studies found a positive correlation of adipose tissue levels with age, but no significant difference between males and females.

Table 11
Summary of studies on concentrations of the six indicator PCBs in adipose tissue

Study	Country	No. of subjects	Age range (years)	Mean concentration[a] (ng/g lipid) *(variation or range shown in italics)*					
				PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
Covaci et al. (2002)	Belgium	11 M 9 F	19–77 30–65	1.3[b]	0.3[b]	0.8[b]	105.1[b]	211.1[b]	148.3[b]
Variation as total range				*nd–11.8[b] (LOD 0.2–0.5)*	*nd–2.2[b] (LOD 0.2–0.5)*	*nd–8.8[b] (LOD 0.2–0.5)*	*29.0–227.5[b]*	*67.8–399.2[b]*	*50.1–342.6[b]*
Costabeber & Emanuelli (2003)	Spain	123 F	15–87 51 (mean)	39	11	2	102	121	134
Variation as SD				*50*	*14*	*4*	*57*	*66*	*83*
De Saeger et al. (2005)	Belgium	57 M 47 F	2–90 17–91	<LOQ (LOQ 10)	<LOQ (LOQ 10)	<LOQ (LOQ 10)	140	271	213
Variation as total range				*<LOQ–16*	*<LOQ–17*	*<LOQ*	*<LOQ–348*	*10–665*	*<LOQ–570*
Kiviranta et al. (2005)	Finland	214 M 206 F	13–81	4.61	0.784	1.40	74.7	135	106
Variation as SD				*6.92*	*0.779*	*2.02*	*52.9*	*94.9*	*74.8*
Rusiecki et al. (2005)	India	34 F	24–65	–	–	–	–	11.54	4.58
Variation as SD								*19.14*	*4.87*
Li et al. (2006)	Singapore	36 F	22–40	–	–	–	9.36	13.09	6.12
Variation as SD							*5.49*	*8.13*	*6.01*
Naert et al. (2006)	Belgium	31 M 22 F	19–83 22–84	–	–	–	181	310	232
Variation as total range							*19–543*	*55–848*	*11–931*
Vaclavik et al. (2006)	Denmark	402 F	50–65	–	–	–	140	278	201
Variation as total range							*7–629*	*18–1 294*	*13–1 084*
Covaci et al. (2008)	Belgium	18 M 7 F	9–70	nd (LOD 1–4)	nd (LOD 1–4)	–	83.0	131	98.1
Variation as SD							*58.5*	*92*	*74.4*
Fernandez et al. (2008)	Spain	20 F	24–81	5.71	nd (LOQ 0.002–0.2)	0.242	88.3	178	185
Variation as SD						*0.239*	*46.8*	*89.9*	*89.1*
Shen et al. (2008)	China	20 M 4 F	26–73 33–62	12.9	0.6	1.34	50.7	52.5	36.3
Variation as total range				*1.0–189*	*0.15–3.46*	*0.16–4.48*	*3.14–251*	*3.13–247*	*1.17–230*
Tan et al. (2008)	Singapore	88 F	18–40	0.66[c]	–	–	10.3[c]	15.4[c]	9.87
Variation as SD				*1.13[c]*			*12.4[c]*	*20.2[c]*	*14.3*
Kalantzi et al. (2009)	Brazil	25 F	40–71	–	–	–	29.3	20.8	24.2
Variation as SD							*26.5*	*20.1*	*23.3*
Pulkrabová et al. (2009)	Czech Republic	5 M 93 F	17–60	2.0	1.6	4.2	121.6	233.6	245.0

Study	Country	No. of subjects	Age range (years)	Mean concentration[a] (ng/g lipid) *(variation or range shown in italics)*					
				PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
Variation as 5th–95th percentile				*0.9–4.0*	*0.6–3.6*	*0.8–14.0*	*46.7–240.8*	*82.8–492.4*	*61.6–483.8*
Arrebola et al. (2010)	Spain (urban)	105 M	16–81	–	–	–	42.24[d]	206.2[d]	156.28[d]
Variation as SD							*8.13*	*3.26*	*4.85*
Arrebola et al. (2010)	Spain (urban)	81 F	16–85	–	–	–	33.81[d]	174.20[d]	106.22[d]
Variation as SD							*9.08*	*2.97*	*5.66*
Arrebola et al. (2010)	Spain (semirural)	92 M	16–81	–	–	–	23.41[d]	97.89[d]	67.00[d]
Variation as SD							*12.51*	*6.54*	*9.06*
Arrebola et al. (2010)	Spain (semirural)	109 F	16–85	–	–	–	46.26[d]	166.80[d]	112.89[d]
Variation as SD							*7.55*	*4.86*	*6.24*
Çok et al. (2010)	Turkey	25 M (infertile)	21–46	16.5	72.1	57.9	64.6	55.2	94.1
Variation as SD				*47.9*	*93.4*	*59.4*	*78.8*	*33.9*	*131.6*
Çok et al. (2010)	Turkey	21 M (fertile)	21–46	25.1	24.2	49.1	68.3	58.2	48.2
Variation as SD				*67.9*	*36.2*	*55.3*	*81.2*	*66.2*	*23.5*
Bräuner et al. (2011)	Denmark	126 M 119 F	50–64 50–64	–	–	–	140[b]	310[b]	220[b]
Variation as 5th–95th percentile							*77–280*	*200–540*	*150–340*
Arrebola et al. (2012)	Plurinational State of Bolivia	22 M 90 F	18–70	–	–	–	3.6[d]	0.9[d]	1.7[d]
Variation as SD							*15.7*	*7.4*	*19.5*

F: females; M: males; LOD: limit of detection; LOQ: limit of quantification; nd: not detected; SD: standard deviation; –: not measured

[a] Except where otherwise indicated.

[b] Median value.

[c] PCBs 28 + 31; PCBs 138 + 158; PCBs 153 + 132.

[d] Geometric mean.

Table 12
Summary of studies on DL- and NDL-PCB concentrations in adipose tissue

Study	Country	No. of subjects	Age range (years)	No. of PCBs analysed	∑PCBs (ng/g)	Range PCBs 138, 153 + 180 (ng/g lipid)
Smeds & Saukko (2001)	Finland	17 M 10 F	19–88 19–95	7 groups	504[a]	–
Covaci et al. (2002)	Belgium	11 M 9 F	19–77 30–65	35	334[b]	105–211[b]
Costabeber & Emanuelli (2003)	Spain	123 F	15–87	11	560[a]	102–134[a]
De Saeger et al. (2005)	Belgium	57 M 47 F	2–90 17–91	7	658[a]	140–271[a]

Table 12 (continued)

Study	Country	No. of subjects	Age range (years)	No. of PCBs analysed	∑PCBs (ng/g)	Range PCBs 138, 153 + 180 (ng/g lipid)
Johnson-Restrepo et al. (2005)	USA	40 M 12 F	18–51	37	144	–
Kiviranta et al. (2005)	Finland	214 M 206 F	13–81	37	437[b]	63–116[b]
Rusiecki et al. (2005)	India	34 F	24–65	2[c]	–	5–12[a]
Li et al. (2006)	Singapore	36 F	22–40	7	57[a]	6–13[a]
Naert et al. (2006)	Belgium	31 M 22 F	19–83 22–84	7	605[b]	181–310
Vaclavik et al. (2006)	Denmark	402 F	50–65	10	872[b]	130–266[b]
Kunisue et al. (2007)	Japan	18 M 10 F	25–81 53–109	62	1 300 850	–
Covaci et al. (2008)	Belgium	18 M 7 F	9–70	7	334[a]	83–131[a]
Fernandez et al. (2008)	Spain	20 F	24–81	37	687[b]	81–168[b]
Shen et al. (2008)	China	20 M 4 F	26–73 33–62	10	154[a]	36–52[a]
Tan et al. (2008)	Singapore	83 F	18–40	41	45[b]	6–11[b]
Kalantzi et al. (2009)	Brazil	25 F	40–71	4	79.6[a]	30–339[a]
Pulkrabová et al. (2009)	Czech Republic	5 M 93 F	17–60	7	595[b]	110–230[b]
Arrebola et al. (2010)	Spain	179 M 178 F	16–81 16–85	3	323[a] 370[a]	34–150 43–173
Çok et al. (2010)	Turkey	46 M	21–46	7	382[a,d] 351[a,e]	55–94[a]
Bräuner et al. (2011)	Denmark	126 M 119 F	50–64 50–64	10	–	140–310[b] 130–280[b]
Arrebola et al. (2012)	Plurinational State of Bolivia	22 M 90 F	18–70	3		41–105

F: females; M: males
[a] Mean value or range of means.
[b] Median value.
[c] PCB 138 not measured.
[d] Mean for infertile men.
[e] Mean for fertile men.
Source: Expanded and adapted from Arrebola et al. (2010)

(d) Concentrations of NDL-PCBs in breast milk

Human milk is an important source of exposure to PCBs for breastfed infants. Owing to its high fat content, human milk can accumulate large amounts of PCBs, which is easier for detection, making it an ideal matrix for the determination of PCBs. Unlike human blood, human milk can be sampled using non-invasive techniques. It can also be used as a good indicator of the body burden of lipophilic non-metabolized PCBs, as fat is mobilized for the production of milk during lactation. Animal studies have revealed that large amounts of PCBs can

be eliminated through lactation (Lindell, 2012). However, it is less clear that this is the case in humans (see below).

WHO introduced worldwide measurement campaigns to determine the exposure of infants to the 12 DL-PCBs and the six indicator PCBs over time. To date, there have been five rounds of the UNEP/WHO (2013) survey from 2000 up to 2012. For the sum of the six indicator PCBs, the median concentrations over the 12 years of the survey are between 10.8 and 30.7 ng/g lipid, and maxima are between 37.1 and 65.8 ng/g lipid (UNEP/WHO, 2013).

The results of studies on PCB concentrations in human milk are summarized in Table 13. Investigations have included the measurement of both DL- and NDL-PCB congeners. In Table 13, only results relating to the six indicator PCBs are presented, including the congeners that make the highest contribution to total PCB levels in food and in human milk – that is, PCBs 138, 153 and 180.

The study of Link et al. (2012) showed that higher amounts of NDL-PCBs were found in whole blood of children aged 9–11 years if they had been breastfed, compared with children who had not been breastfed. The differences between the two groups were 4-fold, 2-fold and 2-fold for PCBs 138, 153 and 180, respectively. PCB 128, although not one of the routinely reported NDL-PCB congeners, has been measured in human milk at mean concentrations ranging from 0.2 to 4.0 ng/g lipid (Koopman-Esseboom et al., 1994; Todaka et al., 2010; Ryan & Rawn, 2014).

Table 13
Summary of studies on concentrations of the six indicator PCBs in human milk

Study	Country	No. of subjects	Mean concentration (ng/g lipid)[a]					
			PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
EFSA (2005)	Summary of studies from 18 European countries	58 pooled samples	4.6	0.51	0.86	64.0	81.7	58.5
Redding et al. (2008)	Summary of studies from various countries, 1998–2007[b]	–	–	–	–	–	100–10 100 (ng/mL whole milk)	–
Glynn et al. (2001)	Sweden	27	3.5	0.45	0.58	37	74	35
Jaraczewska et al. (2006)	Poland	22	–	–	0.8	26	40	30
Ingelido et al. (2007)	Italy	39	2.1–6.2	0.20–0.33	0.54–1.1	58–98	77–130	48–96
Çok et al. (2009, 2011, 2012)	Turkey	198	1.2–3.0	0.2–0.7	0.3–0.8	1.6–5.8	3.4–11.4	1.6–6.7

Table 13 (continued)

Study	Country	No. of subjects	Mean concentration (ng/g lipid)[a]					
			PCB 28	PCB 52	PCB 101	PCB 138	PCB 153	PCB 180
Lignell et al. (2009)	Sweden	325	2.8	–	–	29	58	28
Cerná et al. (2010)	Czech Republic	90	2.1–19.2	0.32–2.87	0.78–2.80	125–597[c]	93–903[c]	80–539[c]
Glynn et al. (2011)	Sweden	203	<0.6–1.8[d]	–	–	18–24[d]	31–48[d]	15–23[d]
Croes et al. (2012)	Belgium	84	0.88	0.23	0.39	18.7	32.8	17.2
Shen et al. (2012)	China	23 (urban)	2.68	0.34	0.23	14.21	11.2	2.40
		51 (rural)	2.69	0.41	0.17	7.73	6.59	1.48
Focant et al. (2013)	France	44	7.8	15.8	8.3	40.0	83.0	48.3
Malarvannan et al. (2013)	Philippines	30	1.4	0.74	2.0	15	22	4.9
Vigh et al. (2013)	Hungary	22 (days 5, 12 and 84 postpartum)	1.0–1.4	0.8–1.4	2.2–2.8	7.2–8.8	10.5–12.8	3.5–4.3

[a] Except where otherwise indicated.
[b] Excludes results from Inuit populations.
[c] The highest levels for PCBs 138, 153 and 180 were found in residents in an industrial area in the vicinity of a former plant that produced PCB-based paints in the 1970s and 1980s.
[d] Median values.

Early reviews suggested that infant exposure to PCBs may be reduced with duration of lactation and with successive pregnancies. However, whereas time-series data indicate that body burdens of PCBs are lowered by lactation, a study has shown that this occurs slowly, averaging only 1% per month over longer lactation periods (Hooper et al., 2007). The authors concluded that 6 months of breastfeeding would decrease PCB 153 levels in mothers by approximately 4% and that decreases are not higher earlier in lactation, although they may be lower later. Thus, 6–12 months of breastfeeding would not greatly reduce a mother's body burden of these chemicals, and prenatal and lactational exposures for a second child would not be markedly lower than those for the first child.

Redding et al. (2008) developed a model for predicting the concentrations of the most prevalent congener, PCB 153, in human milk. They first transformed an earlier physiologically based pharmacokinetic (PBPK) model for lactational transfer of PCB 153 in mice into a PBPK model for a non-pregnant human female at an average childbearing age of 25 years. They then predicted the body burden buildup of PCB 153 from birth over a 25-year period based on realistic exposure levels found in foods, as reported for the Japanese population, incorporating age-related physiological changes during the first 25 years of life. The PBPK model was then transformed to a lactating 25-year-old woman by incorporating the

physiological changes related to pregnancy and childbirth. Using this model, the authors predicted levels of PCB 153 in milk using three sets of values (minimal, median, maximal) for the most sensitive parameters based on actual data reported in the literature. They found that the range and spread of the model predictions of PCB 153 concentrations in breast milk agreed well with the human biomonitoring data found worldwide. The mean predicted value was 3 μg/L whole milk.

(e) Age trends for body burden of NDL-PCBs

Owing to the accumulation of poorly metabolized PCBs, the total body burden of PCBs, including NDL-PCBs, and their metabolites generally increases with age, and this is reflected in blood and adipose tissue biomarker concentrations (Glynn et al., 2003, 2007; EFSA, 2005; Turci et al., 2006; Park et al., 2007; Sandanger et al., 2007; Arrebola et al., 2010; Ibarluzea et al., 2011; Rylander et al., 2011; Quinn & Wania, 2012; Nøst et al., 2013; Mrema et al., 2014; Quinete et al., 2014; Fromme et al., 2015; Zubero et al., 2015). Apostoli et al. (2005), for example, found an increase of 1.7 ng/mL in concentrations of PCBs (total 24 congeners) in whole blood for every 10-year increase in age.

Increases in cross-sectional body burden trends with age have been variously attributed to bioaccumulation with longer exposure (Naert et al., 2006; Fernandez et al., 2008), age-dependent changes in metabolism (Ahlborg et al., 1995; Fangstrom et al., 2005) or older individuals having lived during periods of greater environmental exposure (Quinn & Wania, 2012).

(f) Time trends for body burden of NDL-PCBs

Since the widespread bans on PCB manufacture and use in the 1970s and 1980s, levels in environmental media have been declining. In smaller studies of various populations in the USA that were not occupationally exposed to PCBs or consuming fish from PCB-contaminated waters, the concentrations of PCBs in adipose tissue and in human milk mostly decreased over time between 1973 and 1996 (ATSDR, 2000).

In the last two decades, a clear decrease in concentrations of PCBs in blood has been observed in Europe. Overall, mean concentrations of PCB 138, PCB 153 and PCB 180 in whole blood appear to have decreased by approximately 80% in 20 years (Link et al., 2005; Hagmar et al., 2006; Agudo et al., 2009; AMAP, 2009). However, compared with North America (CDC, 2005, 2009), concentrations of PCB 138, PCB 153 and PCB 180 in serum were higher by 2- to 5-fold in Germany in 1998 (Heudorf, Angerer & Drexler, 2002) or Italy in 2001–2003 (Turci et al., 2004; Apostoli et al., 2005; Needham et al., 2005). Some examples of the decline in PCB concentrations over time are given below.

A marked decline in PCB levels in blood was shown in the German Environmental Surveys carried out in 1998 (Becker et al., 2002) and 2003–2006

(Becker et al., 2008). Mean concentrations for the sum of PCBs in blood were 1.3–1.7 μg/L in 1998 and 0.3 μg/L in the later survey, with a large difference (a factor of 5.6) between age groups 18–25 and 66–69 years.

A study of 803 German children aged 9–11 years in Baden-Württemberg, in which PCBs 138, 153 and 180 were measured in whole blood in the years 1996–1997, 1998–1999, 2000–2001, 2002–2003, 2004–2005 and 2008–2009, showed that the median concentration of the sum of the three congeners decreased over this time period from 470 to 180 ng/L. For the individual PCBs, median concentrations decreased from 150 to 40 ng/L for PCB 138, from 180 to 70 ng/L for PCB 153 and from 150 to 30 ng/L for PCB 180 (Link et al., 2012).

In a series of 14 annual surveys conducted between 1995 and 2008 in Germany, declines in mean concentrations of three indicator PCBs in plasma (uncorrected for lipid content) were observed in male and female students; the concentrations declined from 0.62 to 0.34 μg/L for PCB 138, from 0.53 to 0.22 μg/L for PCB 153 and from 0.32 to 0.12 μg/L for PCB 180 (Pandelova & Schramm, 2012).

In a study in 53 Norwegian men who were repeatedly sampled over time, mean PCB 153 concentrations in serum steadily declined over the five survey periods, from a range of 280–440 ng/g lipid (mean depended on the age cohort) in 1979 to 120–240 ng/g lipid in 2007 (Nøst et al., 2013).

An Australian study also reported more recent reductions in NDL-PCB exposures over time using pooled serum biomonitoring data from 2003 and 2009, PBPK modelling and reconstruction of historical intake and elimination rates for eight NDL-PCB congeners (PCBs 74, 99, 138, 146, 153, 170, 180 and 197), although PCB 74 and PCB 99 exposures declined more slowly than the others (Bu et al., 2015). A study from the Czech Republic also confirmed a downward trend in NDL-PCB concentrations (PCBs 28, 52, 101, 138, 153 and 180) measured in human milk in biomonitoring conducted between 1994 and 2009 (Cerná et al., 2012).

In the WHO surveys on human milk (UNEP/WHO, 2013), concentrations of the six indicator PCBs were found to be steadily decreasing, with levels mostly in the range of 100–500 ng/g lipid in 2000–2003 and decreasing to around 5–55 ng/g lipid in 2008–2012.

(g) Concentrations of NDL-PCBs in more highly exposed populations

High exposure to PCBs can be due to consumption of foods containing high levels of PCB contamination or living in an area polluted from earlier PCB manufacturing and disposal.

In populations that are exposed to high levels of PCBs through the diet (e.g. from high consumption of fish from PCB-contaminated waters, recreational/sport fish or whale blubber), the concentrations of PCBs in blood, tissue and milk

will be higher than for populations not so exposed (ATSDR, 2000; EFSA, 2005). In a Lake Ontario (USA) population, median PCB concentrations in serum in non-consumers and consumers of sport fish, respectively, were as follows: 42 and 47 ng/g lipid for PCBs 28 + 31; 15 and 17 ng/g lipid for PCB 52; 4.0 and 4.5 ng/g lipid for PCB 101; 52 and 69 ng/g lipid for PCBs 138 + 163; and 51 and 65 ng/g lipid for PCB 180 (Bloom et al., 2005).

In the Faroe Islands population, which includes pilot whale in their diet, arithmetic mean concentrations of PCBs 28, 138 + 158, 153 and 180 in serum were, respectively, 8, 245, 378 and 241 ng/g lipid in 7-year-olds and 8, 81, 250 and 147 ng/kg lipid in 14-year-olds (Barr et al., 2006).

In indigenous populations from three areas of the Russian Arctic, mean serum concentrations of the indicator PCBs 28 (+ 31), 52, 101, 138, 153 and 180 in 72 males and 137 females aged 6–77 years were as follows: 9.7–50 ng/g lipid for PCB 28 (+ PCB 31); 13–56 ng/g lipid for PCB 52; 22–73 ng/g lipid for PCB 101; 32–58 ng/g lipid for PCB 138; 65–123 ng/g lipid for PCB 153; and 23–79 ng/g lipid for PCB 180. Levels were generally higher in older compared with younger people and in men compared with women (Rylander et al., 2011).

In the Inuit population of Greenland, the concentrations of the indicator PCBs 138, 153 and 180 in autopsy samples of adipose tissue from 22 women with mean age 61 years and 19 men with mean age 59 years, collected between 1992 and 1994, were 19-, 21- and 16-fold higher than the concentrations of the respective congeners measured by the same analytical method in Canadians from Quebec City. In the Greenland subjects, the sum of the three most abundant PCB congeners (PCBs 138, 153 and 180) represented 63–68% of the total PCBs in the tissue samples (Dewailly et al., 1999). Similarly, in a review of 30 studies from 15 different countries that measured PCB 153 levels in whole human milk between 1998 and 2007, the mean concentration in milk from Inuit Canadians was 17 µg/L, compared with a range of means from 0.1 to 10.1 µg/L in the other studies. Mean concentrations in milk for non-Inuit Canadians in two of the studies were 3–4 µg/L (Redding et al., 2008).

PCB concentrations have been measured in residents of industrial areas polluted with PCBs due to local manufacturing. In two areas of Slovakia in which commercial PCBs were manufactured between 1959 and 1984, 196 men and 119 women between 20 and 75 years of age, living in the areas in 2001, had mean concentrations in serum of 313, 604 and 630 ng/g lipid for PCBs 138, 153 and 180, respectively (Jursa et al., 2006). In a larger study of one of the two contaminated areas in Slovakia, 434 men and 575 women over 18 years of age, living in the area in 2001, had mean concentrations in serum of 572, 912 and 913 ng/g lipid for PCBs 138, 153 and 180, respectively (Petrik et al., 2006). In children 8–10 years of age from the same contaminated area, mean concentrations of PCBs in serum were lower than those of adults, at 149, 236 and 212 ng/g lipid for PCBs 138, 153

and 180, respectively (Petrik et al., 2006). All levels in adult and child residents of contaminated areas were higher than those in adults and children from non-contaminated areas of Slovakia (see Table 10).

In Italy, only one manufacturing plant in the industrial town of Brescia produced PCBs between 1958 and 1983. The town has about 200 000 residents. Widespread high levels of PCBs in soil, above the legal limit, were found in the area around the plant, with approximately 11 000 residents living in this contaminated area. It included an agricultural area to the south of the plant that contained several small farms, and PCBs from farm produce were known to have entered the local food-chain. In one study, blood samples were collected from 527 male and female Brescia residents in 2003 or 2004. Mean concentrations in serum were 188 ng/g lipid for PCB 138, 332 ng/g lipid for PCB 153 and 424 ng/g lipid for PCB 180 (Zani et al., 2013). In another study, blood samples were collected in 2004 or 2005 from residents in six different pooled sera groups from known contaminated areas and one pooled sera group from the general population of Brescia. The ranges of mean concentrations for the seven areas were as follows: <0.3–5.7 ng/g lipid for PCB 28; 0.2–<7.2 ng/g lipid for PCB 52; 0.2–<9.2 ng/g lipid for PCB 101; 66–925 ng/g lipid for PCBs 138 + 163; 141–2622 ng/g lipid for PCB 153; and 190–4221 ng/g lipid for PCB 180. The highest concentrations were found in former workers at the PCB plant and in consumers of contaminated food from the local farms (Turrio-Baldassarri et al., 2008).

Further examples of PCB concentrations in serum in groups exposed to high levels in the diet are shown in Table 14.

Table 14
PCB concentrations in plasma/serum after consumption of PCB-contaminated fish or marine mammals

Region	Sample	PCB congener no.	Geometric mean concentration (ng/g lipid)[a]	Reference
Nunavik, northern Canada	159 Inuit females	138	58 Range: 10–387	Muckle et al. (2001)
		153	105 Range: 19–709	
		180	44 Range: 8–384	
St Lawrence River, USA	489 male, 264 female Native American adults	28	0.04	DeCaprio et al. (2005)
		52	0.04	
		101	–	
		138 + 163 + 164	0.52	
		153	0.63	
		180	0.47	

Region	Sample	PCB congener no.	Geometric mean concentration (ng/g lipid)[a]	Reference
St Lawrence River, USA	Native American adolescents	52	0.03 (NBF) 0.03 (BF)	Schell et al. (2008)
		101 [+90]	0.05 (NBF) 0.05 (BF)	
		138 [+ 163 + 164]	0.06 (NBF) 0.08 (BF)	
		153	0.07 (NBF) 0.11 (BF)	
		180	0.03 (NBF) 0.05 (BF)	
Great Lakes, USA	Fishing ship male captains	138 + 163	96 µg/L	Knobeloch et al. (2009)
		153 + 132 + 105	97 µg/L	
		180	95 µg/L	
	293 fish consumers	138 + 163	95 µg/L	
		153 + 132 + 105	97 µg/L	
		180	92 µg/L	
	Referents consuming little or no sport fish	138 + 163	77 µg/L	
		153 + 132 + 105	84 µg/L	
		180	84 µg/L	

BF: breastfed as infants; NBF: not breastfed as infants
[a] Unless otherwise indicated.
Source: Adapted from IARC (2015)

(h) Concentrations of NDL-PCB metabolites in blood

Quinete et al. (2014) reviewed the biomonitoring literature from 1950 to 2013 reporting on concentrations of hydroxylated and methyl sulfone PCB metabolites, which are the major metabolites of PCBs, in human blood. The review describes the predominant hydroxy-PCB congeners in human blood as 4-hydroxy-PCB 187 and 4-hydroxy-PCB 107, followed by 4-hydroxy-PCB 146, 3-hydroxy-PCB 153 and 3-hydroxy-PCB 138; 4-hydroxy-PCB 172 and 3-hydroxy-PCB 180 are less frequently detected. Although these congeners have dominated in a number of studies, the one that occurs most commonly varies; this suggests that different PCB sources and metabolism capability may be responsible for the differences in metabolite fingerprints. Median concentrations of total hydroxy-PCBs varied between 0.0002 and 1.6 ng/g wet weight (ww) in serum or plasma.

In comparison, higher concentrations of hydroxy-PCBs have been reported in blood from Canadian Inuit (up to 12 ng/g ww), in pregnant women from the Faroe Islands (median 5 ng/g ww), in women from Slovakia (median 2 ng/g ww) and in men from Latvia (median 5 ng/g ww). These levels are consistent with populations exposed to high levels of PCBs through their diet, which includes high consumption of fish and sea mammals (Canada and Faroe Islands), or living in PCB-polluted areas (Slovakia and Latvia). Overall, the median Σhydroxy-

PCBs/ΣPCBs ratio in human blood from different locations worldwide ranged from 0.06 to 0.51 (Quinete et al., 2014).

The occurrence and levels of lower chlorinated hydroxy-PCBs (1–3 chlorine atoms) in human blood have been much less studied than those of the parent congeners. Quinete et al. (2014) mentioned only two reports on concentrations of lower chlorinated hydroxy-PCBs (trichlorinated and tetrachlorinated hydroxy-PCBs only) in human blood, the first on one male in Japan (Kunisue & Tanabe, 2009) and the other from a study in India (Eguchi et al., 2012). An earlier report from Weiss et al. (2006) studied 3-hydroxy-PCB concentrations in serum of middle-aged and elderly Swedish women who were expected to be relatively highly exposed; the summed median concentration was 1.7 ng/mL.

2.3.2 General considerations on health effects

Based on the available experimental information reviewed above, it seems likely that PCB congeners can cause serious toxicological outcomes, such as carcinogenicity, immunotoxicity, developmental toxicity and neurodevelopmental disorders. In contrast to DL-PCB congeners, for which there are sufficient data to perform a health risk assessment, such information is lacking for NDL-PCB congeners. Humans are always exposed to complex mixtures of individual DL-PCB and NDL-PCB congeners, whose relative contribution to toxicity is unclear, and it has not yet been possible to ascribe the observed effects in epidemiological studies to any individual PCB or subgroup of NDL-PCB congeners.

In 2005, EFSA stated that the available NDL-PCB data were inadequate and that more toxicological data were needed to identify any NDL-PCB hazard and to assess any risk involved with the consumption of NDL-PCBs (EFSA, 2005). The available experimental animal data on carcinogenicity and immunotoxicity were considered unsuitable for risk assessment, as few congeners were tested, the test compounds were not always examined for chemical purity and the mixtures used were not relevant for human exposure situations. The neurobehavioural data, although considered insufficient, were regarded as relevant, as behavioural effects observed in laboratory animals following perinatal PCB exposure had also been observed in humans linked to PCB exposure in epidemiological studies. EFSA (2005) cited BMD calculations made by others based on human studies on developmental neurotoxicity and immunotoxicity after perinatal exposure to total DL- and NDL-PCBs. EFSA (2005) noted that the lower 95% confidence limit (BMDL) of approximately 1 μg PCB per gram lipid is only about 4 times higher than the current median concentration in human milk, but that the existing epidemiological studies do not allow an estimation of the toxicity that may specifically be attributed to the NDL-PCBs. Moreover, EFSA (2005) identified

the developing fetus and the neonate as potential "at risk" populations because of increased susceptibility. Lack of congener-specific exposure and toxicity data has limited the ability to conclude which congeners are responsible for the observed effects. An overall perspective of the toxicology and epidemiology of PCBs was evaluated in the United States ATSDR toxicological profile on PCBs (ATSDR, 2000). Information on the health effects of PCBs is available from studies of people exposed in the workplace, by consumption of contaminated rice oil in Japan (the Yusho incident) and China (the Yucheng incident in the Province of Taiwan), by consumption of contaminated fish and via general environmental exposures, as well as by consumption of food products of animal origin. Health effects that have been associated with exposure to PCBs in humans include liver, thyroid, dermal and ocular effects, immunological alterations, neurodevelopmental changes, reduced birth weight, reproductive toxicity and cancer. Although PCBs may have contributed to adverse health effects in human populations, it cannot be determined with certainty which congeners may have caused the effects.

The following health effects in humans were summarized by the original ATSDR report on PCBs (ATSDR, 2000). Concerning hepatic effects, the findings of human studies are not consistent, but there seems to be an increase in levels of some liver enzymes in the serum of people exposed to PCBs. As for endocrine effects, direct evidence linking PCB exposure to thyroid morbidity in humans is limited, although there is evidence that PCBs can produce both agonistic and antagonistic estrogenic responses. Skin irritation and ocular effects including hypersecretion and abnormal pigmentation have been observed following occupational exposure and accidental ingestion of rice oil contaminated with PCBs (and other halogenated chemicals, such as PCDFs). There seems to be an overall consistency in the data supporting sensitivity of the immune system to PCBs, particularly in infants exposed in utero or via breastfeeding, the most common effect reported being an increased susceptibility to respiratory tract infection. Neurological effects have been studied mainly in newborns and young children; abnormal reflexes, deficits in memory and poorer performance in tests of mental development index have been reported to be associated with PCB exposure. Regarding reproductive effects, miscarriages and shorter length of the menstrual cycle have been reported in occupationally exposed women. The ability of PCBs to cause reproductive effect in males is less clear. Studies on children of environmentally exposed women have produced mixed results for developmental effects such as anthropometric measures at birth and growth during infancy. Finally, carcinogenicity of PCBs in humans has been investigated in retrospective occupational studies in workers exposed during capacitor manufacture and repair and in case–control studies of the general population assessing PCB levels in serum or adipose tissue. Based on indications of PCB-related cancer at several sites, particularly the liver, biliary tract, intestines and

skin (melanoma), the human studies provide suggestive evidence that PCBs are carcinogenic.

An addendum to the ATSDR (2002) report provided further evidence of potential effects of PCBs on human health (ATSDR, 2011). An association has been reported between increased PCB 153 exposure and osteoporotic fractures, but there is no clear association with bone mineral density. An association of PCB exposure and the risk of type 2 diabetes has also been reported. A study of an occupational cohort involving exposed workers indicated that exposure to PCBs likely has an effect on neurodegenerative diseases. Prospective or case–control studies on children indicate that long-term exposure to PCBs can impair dental health and hearing. Increased exposure to PCBs during prenatal and postnatal life could also be associated with risk of cryptorchidism and low testosterone and estradiol levels in male children.

Finally, the International Agency for Research on Cancer (IARC) recently reassessed the carcinogenicity of PCBs (Lauby-Secretan et al., 2013; IARC, 2015); human data included more than 70 independent epidemiological studies with informative data on the carcinogenicity of PCBs. Excess risk for melanoma was reported in several studies, mainly cohort studies of workers in the manufacture of capacitors and transformers and in electric power and equipment maintenance, with a significant linear exposure–response trend. An association between melanoma incidence and PCB exposure was noted consistently in occupational studies in different industries in North America and Europe, in studies of the general population and with cohort and case–control designs. Increased risks for non-Hodgkin lymphoma and breast cancer were also reported, both of which are biologically plausible. However, the associations were not consistent and were considered as providing limited evidence. Data for cancers at other sites were too sparse to allow any conclusions to be drawn. On the basis of sufficient evidence of carcinogenicity in humans and experimental animals, PCBs were classified as carcinogenic to humans (group 1). Additionally, DL-PCBs were also classified in group 1 on the basis of extensive evidence of an AhR-mediated mechanism of carcinogenesis that is identical to that of TCDD and sufficient evidence of carcinogenicity in experimental animals. However, according to the IARC evaluation, the carcinogenicity of PCBs cannot be solely attributed to the carcinogenicity of the DL-PCBs (Lauby-Secretan et al., 2013; IARC, 2015).

As the most recent assessment of the overall health effects of NDL-PCBs was published by EFSA in 2005, we have considered in this review the studies published from 2005 onwards. Given the huge number of studies available and keeping in mind that our primary aim is to assess the health effects of NDL-PCBS, we will only briefly summarize the studies that did not provide specific results for NDL-PCBs, for either individual congeners or groups of NDL-PCBs. Moreover, for studies reporting results for NDL-PCBs, we will provide little detail of cross-

sectional studies, as they do not provide strong evidence of a causal relationship. Within the relevant studies, more attention will be paid to prospective cohorts than to case–control studies. Only studies with specific results for individual NDL-PCB congeners or groups of NDL-PCBs reporting a measurement of the level of exposure will be described in detail.

2.3.3 Mortality

Cooking oil contaminated by Kanechlor has been the source of two accidental mass poisonings, one in western Japan and the other in Taiwan, China. Commercial PCB mixtures were used as heat transfer media in oil tanks; leakage of the pipes caused exposure to the PCB mixture and PCB pyrolytic products, mainly PCDFs and polychlorinated quaterphenyls. In 1968, approximately 1800 people who ingested rice oil contaminated by Kanechlor 400 and its pyrolytic products, mainly in Fukuoka and Nagasaki prefectures in Japan, developed a strange skin disease, including acneform eruption, follicular accentuation and pigmentation, as well as eye discharge and swelling of eyelids. In 1979, about 10 years after the incident in western Japan, a similar food poisoning incident occurred in three counties (Taichung, Changhua and Miaoli) of central Taiwan, China. About 2000 residents from these counties had ingested rice oil contaminated with Kanechlor 500 and its pyrolytic products and showed clinical manifestations similar to those described for Japanese patients. These two accidental mass poisoning diseases were later called "Yusho", oil disease in Japanese, and "Yucheng", oil disease in Chinese (ATSDR, 2000; IARC, 2015). Mortality data among those registered from both groups of patients were identified, and analyses of these cohorts have been published with different follow-up periods. Many of these studies reported data according to different causes of death, mainly cancer, and some of them are referred to in the corresponding sections of this report. Recently updated analyses on overall mortality in the two cohorts have been published. After a 40-year follow-up, Yusho patients showed no significant difference in relative survival compared with the general Japanese population; overall 15-year relative survival was 0.99 (95% confidence interval [CI] 0.98–1.01) (Onozuka, Hirata & Furue, 2011). With the same data, net survival at 15 years was 97.4% (95% CI 94.2–99.6) in males and 100% (95% CI 100.0–100.0) in females (Onozuka, Hirata & Furue, 2014). As for Yucheng patients, after a 38-year follow-up, they had a standardized mortality rate (SMR) of 1.2 (95% CI 1.1–1.3) compared with their neighbourhood referents (Li et al., 2013).

Apart from incidental contamination, chronic exposure to PCBs may occur through a diet rich in foods with a high content of PCBs; such exposure has been observed in northern Europe in populations with a high consumption of fish. No association with overall mortality was reported in studies in Swedish

populations from the east (Baltic) or west coast (Mikoczy & Rylander, 2009), the Baltic coast in Finland (Turunen et al., 2008) or the Great Lakes area of the USA (Wisconsin) (Tomasallo et al., 2010).

Studies have been published on mortality among cohorts of workers exposed to PCBs in several industrial activities and occupations, mostly in North America and Europe, including capacitor manufacture, transformer manufacture and repair, and electric power–related occupations. Most of these studies based the exposure assessment on historical reconstructions of jobs and activities and were mainly designed to assess cancer mortality. Recently, an update on long-term employees of three electrical capacitor manufacturing plants in the USA showed that all-cause mortality was not elevated compared with national mortality rates, with an SMR of 0.99 (95% CI 0.97–1.01) (Ruder et al., 2014). In two Italian capacitor manufacturing plants, the SMR for all-cause mortality was 0.98 (95% CI 0.89–1.08) compared with mortality rates of the Lombardy region (Pesatori et al., 2013).

Overall, there seems to be a small excess mortality of Yusho and Yucheng patients. However, it must be considered that patients from both countries had been exposed to PCDFs in addition to PCBs and that the mean total PCB and PCDF concentrations in the Yusho and Yucheng victims remained several times higher compared with the general population for many years after exposure (IARC, 2015). Compared with cohorts of Yusho or Yucheng patients, who consumed food contaminated with a high level of PCBs for a short period, potential exposure of the general population to PCBs through diet is a long-term, low-level exposure. It should also be borne in mind that fish or local vegetables contaminated by PCBs are often also contaminated by other compounds, such as 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT), PCDFs, PCDDs or heavy metals. In a similar way, workers from cohorts occupationally exposed to PCBs could have been often exposed to other chemicals, and therefore it is difficult to draw definitive conclusions on the causation of possible observed mortality excesses. Finally, in all these studies, PCB exposure involved exposure to complex mixtures of PCB congeners, often unknown, but most likely including both DL- and NDL-PCB congeners.

2.3.4 Developmental toxicity: birth/gestational outcomes

This section covers birth outcomes related to fetal development, mostly determined by means of anthropometric measurements in newborns and infants, including childhood growth in some cases. Effects concerning specific functions, systems or organs are included in other sections. The biggest group of specific developmental effects concerns the nervous system (see section 2.3.5 below), but there are several studies reporting potential effects of PCBs on neonates

and infants regarding thyroid function and thyroid hormones, reproductive effects (mostly in males), including malformations and sex hormone levels, and immunotoxic effects, including response to vaccines, immunoglobulin levels and infections.

(a) Studies on exposure to undefined PCB congeners

PCB concentrations in maternal serum in the Great Lakes sport-caught fish cohort (USA) were not associated with birth weight of newborns; no individual congeners measured were specified (Weisskopf et al., 2005). Serum specimens from pregnant women participating in the Child Health and Development Study in the San Francisco Bay area, California, USA, were collected in the second or third trimesters, and 11 PCB congeners were measured. In male infants, higher PCB exposure (sum of all congeners) was associated with reduced birth weight and head circumference, whereas in female infants, it was associated with shorter gestation (Hertz-Picciotto et al., 2005). In pregnant women enrolled in the United States Collaborative Perinatal Project in 12 centres, 11 PCB congeners were measured in blood collected during pregnancy (third trimester), at delivery and 5 weeks postpartum; higher levels of PCBs (sum of all congeners) were associated with higher (but non-significant) risk of preterm birth, whereas birth weight and length of gestation were unrelated to PCB levels in blood (Longnecker et al., 2005). In a cohort of infants born to mothers residing near a PCB-contaminated harbour in New Bedford, Massachusetts, USA, small negative (non-significant) associations were observed for PCB concentrations in cord blood (sum of PCBs 118, 138, 153 and 180) and birth weight, birth length and head circumference (Sagiv et al., 2007). In breast milk samples from mothers from Melbourne, Australia, no significant association was found between PCB concentration (no individual congeners specified) in breast milk and low birth weight, small for gestational age, and previous miscarriage or stillbirth; there was an elevated but non-significant association with prematurity (Khanjani & Sim, 2007). Among mothers from a multiethnic cohort in New York City, New York, USA, concentrations of PCBs (sum of PCBs 118, 128, 153 and 180) in maternal plasma from blood collected during pregnancy were not associated with lower birth weight, head circumference, birth length or gestational age (Wolff et al., 2007). Within the PCBRISK project in two regions from Slovakia, concentrations of PCBs (17 congeners) were measured in serum from blood collected from mothers at delivery and from children at 8–9 years of age. There was no significant association between PCB levels (sum of six congeners, including two DL-PCBs) and birth weight (Sonneborn et al., 2008); at 8–9 years of age, PCB exposure (no individual congeners specified) was significantly related to developmental enamel defects of permanent teeth, but no association with caries susceptibility, gingival

health or number of teeth was observed (Jan et al., 2007). In a prospective cohort, the Michigan Department of Community Health (USA), PCBs were measured in serum from maternal blood collected at enrolment (before delivery); no significant association was found between estimated PCB levels in maternal serum and gestational age or infant birth weight in adjusted models (Givens et al., 2007). In a selected group of women from the Danish National Birth Cohort, maternal PCB concentrations (seven congeners, including three DL-PCBs) were measured in blood collected during pregnancy; PCB concentrations (sum of seven congeners) in maternal plasma were inversely associated with birth weight and placental weight (Halldorsson et al., 2008). In a prospective birth cohort in a random sample of mother–infant pairs from Flanders, Belgium, PCB levels (PCBs 118, 138, 153, 170 and 180) were measured in cord blood, and children were followed up to 3 years of age; increasing PCB concentrations (sum of all congeners) were associated with lower birth weight, but higher body mass index (BMI) (measured as *z*-score) (Verhulst et al., 2009). In women aged 26–42 years who were resident in the province of Brescia, Italy, and undergoing a planned caesarean section at the University Hospital, concentrations of 30 PCBs were analysed in cord and maternal serum, placenta and maternal subcutaneous adipose tissue; no significant associations were reported between concentrations of PCBs (sum of all congeners) from any origin and preterm birth, small weight for gestational age or small length for gestational age (Bergonzi et al., 2011). Within the Child and Environment (INfancia y Medio Ambiente or INMA) birth cohort in Spain, levels of PCBs (PCBs 118, 138, 153 and 180) in serum were measured in women during pregnancy; rapid growth during the first 6 months was defined as a change in weight-for-age *z*-scores above 0.67, and elevated BMI at 14 months as a *z*-score at or above the 85th percentile. Neither the sum of the PCB congener concentrations nor individual PCB concentrations (data not shown) were associated with rapid growth (Mendez et al., 2011). Finally, the concentrations of all 209 PCB congeners were measured in the maternal and fetal blood of a small cohort of pregnant women in Fukuoka, Japan, as well as several indicators of placental function. Significant associations between PCB exposure (overall) and both placental growth factor and syncytiotrophoblast volume were identified (Tsuji et al., 2013).

In all these studies, exposure was to complex mixtures of PCB congeners, often unknown, but in most instances including both DL- and NDL-PCB congeners. In some studies, it is likely that the highest contribution to the sum of PCB concentrations was from NDL-PCB congeners, but the mixtures also included PCB 118 or another DL-PCB congener. Therefore, they do not provide any relevant information regarding the potential effects of NDL-PCBs on developmental health. It should also be noted that there is remarkable inconsistency across many of these studies.

(b) Studies with specific results for NDL-PCBs

Within the Columbia-Presbyterian cohort of the National Collaborative Perinatal Project, in a subset of mother–child pairs (born 1959–1962) of African American mothers, concentrations of 24 PCB congeners were measured in maternal blood collected during the third trimester. Regression models for repeated measures (at ages 4, 7 and 17 years) were used to investigate associations between PCB concentrations and height and weight through 17 years. After adjusting for maternal pre-pregnancy weight, preterm status, and triglyceride and cholesterol levels in serum, there was a significant negative association between the sum of seven di-*ortho*-substituted congeners (PCBs 99, 101, 138, 146, 153, 170 and 180) and five tri-*ortho*-substituted congeners (PCBs 174, 183, 187, 199 and 203) and weight (not height) through to 17 years of age in girls; no significant associations were found for boys. For girls, for di-*ortho*-substituted PCBs, the β was −10.6 (95% CI −18.2 to −3.0); as PCB concentrations were expressed in natural log scale, this means that for a doubling of maternal di-*ortho*-substituted PCB concentrations, there was an average 7.35% decrease in weight (Lamb et al., 2006).

Umbilical cord blood samples were collected from babies of mothers admitted to the National Hospital of Singapore for caesarean section during 2006; concentrations of 41 PCB congeners were measured and compared with several neonatal variables. Using partial least-squares regression, there was a significant inverse coefficient plot for the relationship between the concentration of PCB 153 in serum and Apgar score at 1 minute; there were also inverse (but non-significant) associations between the concentration of PCB 153 and birth weight, length at birth and head circumference. In this analysis, all the quantitative neonatal variables had significant inverse associations with the DL-PCB, PCB 118 (Tan et al., 2009).

A study involving pregnant women (mean age 26 years) from Greenland (Inuit), Warsaw, Poland, and Kharkiv, Ukraine, was carried out in 2002–2004. The concentration of PCB 153 was analysed in maternal blood collected during pregnancy (at 24 or 33 weeks). There was no significant association between the concentration of PCB 153 and gestational age or risk of preterm birth. An increase in the PCB 153 concentration in the serum of Inuit mothers by one unit on the log scale was associated with a significant decrease in infant birth weight of 72.7 g (95% CI 27–118) and gestational age by 0.2 week (95% CI 0–0.4); decreases observed in the cohorts in Kharkiv and Warsaw were not statistically significant. These associations were adjusted for smoking status (Greenland), age of mother (Kharkiv and Warsaw) and mother's BMI (Warsaw) (Wojtyniak et al., 2010).

In the Child Development Study of the New York State Angler Cohort Study (New York, USA), blood samples were collected from women as they began trying

to become pregnant (preconception), after a positive pregnancy test (prenatal) and at about 6 weeks post-delivery (postnatal) in 1996–1999. Concentrations of 76 PCB congeners were measured in maternal serum. No association was found between birth weight and preconception or prenatal concentrations of a group of coeluting and single estrogenic NDL-PCBs (PCBs 4–10, 5–8, 15–17, 18, 31, 44, 47, 48, 52, 70, 99, 101, 136 and 153). However, a significant reduction in birth weight was observed to be associated with preconception concentrations of anti-estrogenic PCBs, which include the coeluting and single DL-PCBs (PCBs 77–110, 105, 114, 126, 156–171 and 169) (Murphy et al., 2010). Within the same study, concentrations of PCBs were also measured in breast milk and in child serum at age 2 years. A non-significant decrease in weight, length and head circumference at age 2 years was associated with PCB 153 (for both prenatal and breast milk concentrations), whereas increasing concentrations of PCB 77 (a DL-PCB congener) were associated with a significant decrease in length *z*-score at 2 years (Jackson et al., 2010).

Umbilical cord blood samples were collected from Guiyu and the control area of Chaonan, China, and concentrations of 28 PCB congeners were measured. Increased concentrations of PCB 153 were significantly associated with decreases in birth weight, Apgar score and gestational age, with correlation coefficients (*P*-value) of −0.30 (0.02), −0.20 (0.03) and −0.32 (0.01), respectively. There were also significant inverse correlations with concentrations of PCB 138 and PCB 180 (Wu et al., 2011).

Within the Environmental Health Risks in European Birth Cohorts (ENRIECO) project, concentrations of PCB 153 were measured in blood collected during pregnancy, cord serum or plasma, or breast milk from about 7990 women enrolled in 15 study populations from 12 European birth cohorts from 1990 to 2008. To facilitate comparisons, the exposure was expressed as wet weight cord serum levels, which directly reflect fetal exposure at the time of delivery. Linear regression of birth weight on estimates of concentration of PCB 153 in cord serum was performed, adjusted for child's gestational age and sex, mother's region, maternal BMI, height, smoking status during pregnancy, socioeconomic status, mother's age, parity and ethnicity, and time of sampling. Summary estimates were obtained by meta-analysis. Birth weight decreased with increasing concentration of PCB 153 in cord serum from 12 of 15 study populations. The meta-analysis including all cohorts indicated a birth weight decline of 150 g (95% CI 50–250) per 1 μg/L increase in PCB 153 concentration (Govarts et al., 2012). Gestational weight gain, which is associated negatively with PCB levels in maternal and cord blood and positively with birth weight, could substantially confound this association. In a reanalysis of previous data, a modified PCB 153 concentration was obtained by means of a pharmacokinetic model that simulates lifetime exposure and bioaccumulation in the mother and

the fetus. A 118 g decrease in birth weight (95% CI 106–129) for each 1 µg/L increase in simulated PCB 153 level in cord plasma was obtained; after further adjustment for simulated gestational weight gain, the estimated decrease in birth weight was reduced to 6 g (not significant) (Verner et al., 2013). Considering these results, authors of the meta-analysis used data from seven of the 12 cohorts that had actual (not simulated) data on gestational weight gain; moreover, using these data, they estimated change in fat mass. In the reanalysis of these seven cohorts, it was observed that the magnitude of decreased birth weight (per 1 µg/L increase in PCB 153 concentration) was reduced by 48% after including absolute gestational weight gain and by 31% after including change in fat mass, with a marginally significant *P*-value of 0.05 (Govarts et al., 2014).

In a sample of 600 infants born between 1960 and 1963 and randomly selected from the Child Health and Development Study in the San Francisco Bay area, California, USA, concentrations of 11 PCB congeners were measured in serum collected within 3 days of delivery. No significant associations were observed between birth weight or length of gestation and concentrations of PCB 138, 153, 170 or 180 in serum, assessed by means of linear regression adjusted for maternal race, age, employment status, infant sex, laboratory and natural log-transformed triglyceride and cholesterol levels in serum. However, for the sum of the concentrations of di-*ortho*-substituted PCBs (PCBs 99, 138, 153, 170 and 180) in serum, the adjusted means of gestational age for the third and first tertiles were, respectively, 39.8 and 40.2 weeks (P-value < 0.05 for the difference of means). For the group of CYP1A and CYP2B enzyme inhibitors (PCBs 99, 153, 180 and 203), the corresponding adjusted means were 39.8 and 40.3 weeks (P-value < 0.05 for the difference of means) (Kezios et al., 2012).

In the Persistent Organic Pollutants in Uppsala Primiparas (POPUP) study, first-time mothers living in Uppsala County, Sweden, in 1996–2010 agreed to donate breast milk sampled during the third week after delivery; the samples were analysed for PCB 138, PCB 153 and PCB 180 (Lignell et al., 2013). In the multivariate model (adjusted for sum of the concentrations of the polybrominated diphenyl ethers [PBDEs] BDE-47, BDE-99, BDE-100 and BDE-153, age of the mother, pre-pregnancy BMI, weight gain during pregnancy, maternal education, smoking and infant sex), birth weight was significantly increased (P-value = 0.02) by 137 g for each unit increase in the sum of the natural log concentrations of PCBs 138, 153 and 180; when the analysis was stratified by sex, the significant association was restricted to male infants.

The association between dietary exposure to dioxins and PCBs during pregnancy and birth size was studied within the Norwegian Mother and Child Cohort Study, including more than 50 000 women recruited all over Norway from 1999 to 2008. The maternal dietary exposure was estimated using a validated food frequency questionnaire and available data on concentrations of

PCBs in Norwegian foods (Papadopoulou et al., 2013). An inverse dose–response association between dietary exposure to NDL-PCBs and fetal growth was obtained after adjustment for maternal age, energy intake, maternal education, pre-pregnancy BMI, parity, weight gain and smoking during pregnancy, gestational age and child sex. Comparing the highest with the lowest quartile of estimated NDL-PCB dietary exposure during pregnancy, there were significant reductions of 40.9 g (95% CI 30–52) in birth weight, 0.21 cm (95% CI 0.15–0.26) in birth length and 0.06 cm (95% CI 0.02–0.09) in head circumference. In this study, there were similar associations for estimated dietary exposure to dioxins and DL-PCBs. The parameter estimates cannot be directly related to levels of NDL-PCBs in serum (or other body tissues or fluids).

In a cohort of newborns from 14 Inuit communities of Nunavik, Canada, PCB 153 concentration was measured in umbilical cord plasma and child blood. Mothers (1996–2000) were recruited at their first prenatal visit, and children were evaluated at birth and at age 8–14 years; weight, height and head circumference were measured at birth and during childhood. In a cross-sectional analysis, PCB 153 concentrations in cord blood were not associated with anthropometric measurements at birth or school age, but PCB 153 concentrations in child blood were associated with reduced weight, height and head circumference during childhood (mean age of 11 years) (Dallaire et al., 2014).

2.3.5 Neurotoxicity and behaviour

(a) Neurodevelopmental effects (infants and children)

In pregnant women enrolled in the United States Collaborative Perinatal Project in 12 centres, concentrations of 11 PCB congeners (PCBs 28, 52, 74, 105, 118, 138, 153, 170, 180, 194 and 203) were measured in blood collected during pregnancy (third trimester, eighth week), and cognitive test (intelligence quotient [IQ]) scores on the Wechsler Intelligence Scale for Children were assessed at 7 years of age. Overall, there was a non-significant increase in IQ associated with an increase in PCB level (sum of concentrations of all 11 congeners) (Gray et al., 2005). Maternal blood was collected at week 31 of gestation in 1998–2002 from women from the Mount Sinai Children's Environmental Health Center (New York City, New York, USA), and the Brazelton Neonatal Behavioral Assessment Scale was administered before hospital discharge; no adverse associations were found between PCB levels (sum of the concentrations of PCBs 118, 138, 153 and 180) and any behaviour (S.M. Engel et al., 2007). In a cohort of infants born to mothers residing near a PCB-contaminated harbour in New Bedford, Massachusetts, USA, concentrations of 51 PCB congeners were measured in cord serum samples. The sum of the concentrations of PCB congeners (PCBs 118, 138, 153 and 180) showed a significant inverse association with some

Brazelton Neonatal Behavioral Assessment Scale measures, such as the quality of alert responsiveness score (Sagiv et al., 2008). In the same study, the sum of the concentrations of the four PCB congeners (PCBs 118, 138, 153 and 180) in cord serum was associated with a higher risk of atypical behaviour corresponding to ADHD, measured with the Conners' Rating Scale for Teachers (Sagiv et al., 2010). In these studies, PCB exposure involved complex mixtures of PCB congeners. In some studies, it is likely that the highest contribution to the sum of PCBs was from NDL-PCB congeners, but the mixtures included PCB 118 or another DL-PCB congener. Therefore, these studies do not provide any relevant information regarding the potential neurodevelopmental effects of NDL-PCBs.

(i) Case–control studies

The population-based case–control study of the Texas Neural Tube Defect (NTD) Project was carried out among pregnant Mexican American women who resided in the 14 Texas–Mexico border counties during 1995–2000. Cases (infants or fetuses) had diagnoses of anencephalus (ICD-9-CM code 740), spina bifida (ICD-9-CM code 741) or encephalocele (ICD-9-CM code 742.0); controls were randomly selected from study area women delivering normal live births during the same period. Concentrations of 25 PCB congeners were measured in serum samples collected on the first anniversary date of conception (plus or minus 1 month). No significant association was reported for the most common PCB congeners and the risk of NTD; the odds ratio (OR) for PCB 153 was 0.7 (95% CI 0.4–1.2) (Suarez et al., 2005). Several issues must be considered when interpreting the results of this study. First, the concentration of PCB 153 (18 ng/g lipid) was low compared with the range of 30–45 ng/g reported for 10 other study populations. Second, specimens were collected 1 year post-conception, which may or may not mirror the PCB burden during the relevant window of neural tube formation; postpartum events (e.g. breastfeeding) could potentially alter the PCB levels in serum. Of greater concern is the reduced participation in the blood collection, with a slight tendency for women of higher socioeconomic status to participate in the blood collection for PCB analysis compared with those enrolled in the original case–control study.

(ii) Cohort studies

The Oswego, New York, USA, study tracks a cohort of children who were born between 1991 and 1994. Immediately after birth, a sample of umbilical cord blood and placental tissue was obtained. Concentrations of 68 PCB congeners were measured in cord blood, although a sum of the concentrations of the most persistent and higher chlorinated congeners (heptachlorinated, octachlorinated and nonachlorinated homologues: PCBs 170 + 190, 172, 174, 177, 179, 180, 183,

185, 187 + 181, 194, 195, 199, 203 + 196, 206) was used as a measure of prenatal PCB exposure in cord blood; all of them are NDL-PCBs. Moreover, concentrations of PCB 153, PCB 138 and PCB 180 were measured in placental tissue. In this cohort, several tests to assess behavioural processes and cognitive development were performed in children; the Neurobehavioural Evaluation System 2 (NES2) Continuous Performance Test (CPT) was applied at 8 years, and the Extended Continuous Performance Test (E-CPT) at 9.5 years. After taking into account many measured covariables, including maternal IQ, maternal sustained attention and maternal response inhibition, results revealed associations between PCB level in cord blood and impulsive responding at both testing ages. At 8 years of age, there was a dose–response relationship between total commission errors on the NES2 CPT and PCB levels (*P*-value = 0.026). E-CPT testing at 9.5 years clearly indicated that the PCB-related impulsive responding was due to impaired response inhibition (the association with commission errors was significant only at higher levels [70–90%] of probability of targets appearing) (Stewart et al., 2005). To assess inappropriate responding on intermittent reinforcement schedules, the Differential Reinforcement of Low Rates task protocol was used to evaluate the inter-response times. The sum of the concentrations of higher chlorinated PCBs was associated with shorter inter-response times; the covariate-adjusted standardized β was −0.170 (*P*-value = 0.03) (Stewart et al., 2006). These results were significant taking into account multiple potential confounders, including several non-PCB contaminants: prenatal methylmercury, 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene (DDE), hexachlorobenzene (HCB), and prenatal and postnatal lead. In the same study, the IQ score was measured at 9 years by means of the Wechsler Intelligence Scale for Children and was compared with PCB levels in placental tissue. In the analysis using a maximal covariate set, there were inverse (but non-significant) associations between the full-scale IQ and placental concentrations of PCBs 138, 153 and 180. However, a 1 ng/g increase in PCB 153 concentration was associated with a decrease of 0.234 standard units of the verbal IQ (*P*-value = 0.006) and with 0.253 standard units of the freedom from distractibility score (*P*-value = 0.008) (Stewart et al., 2008).

In the Cord Blood Monitoring Program, which took place in Inuit communities of Nunavik in northern Quebec, Canada, concentrations of 14 PCB congeners were measured in umbilical cord plasma of newborns between 1993 and 1996, as well as at the time of the neurological examination at age 4–6 years (mean 5.4). Gross motor functions as well as fine neuromotor performance were assessed using quantitative measures of postural hand tremor, reaction time, sway oscillations, and alternating and pointing movements. Negative effects of PCB concentrations in cord blood on neuromotor development were not clearly observed. However, PCB 153 concentration in blood at testing time (cross-sectional relationship) was associated with transversal sway in balance conditions;

adjusted for several maternal and child covariates, the Pearson correlation coefficient was 0.15, and the standardized β was 0.22 (both with *P*-value < 0.05) for the relationship between the log-transformed concentration of PCB 153 and 1 standard deviation of the transversal sway (in millimetres) (Després et al., 2005). In the same children, pattern reversal visual evoked potentials (VEPs) were also assessed; latency and amplitude of VEPs are useful to detect subclinical effects on visual processing. The following standard VEP components were examined: N75 (negative deflection at 75 milliseconds), P100 (positive deflection at 100 milliseconds) and N150 (negative deflection at 150 milliseconds); for each component, the latency was determined from the stimulus onset to the maximal waveform peak, whereas the amplitude was calculated from peak-to-peak procedure (N75-to-P100 and P100-to-N150). When PCB 153 concentrations in cord blood and at the testing time were included in a multivariate model, there was no association between VEPs and PCB 153 levels in cord blood. After adjustment for maternal alcohol and marijuana consumption, maternal non-verbal reasoning abilities, haemoglobin concentrations at testing time, highest grade completed by the primary caregiver, number of children and adults at home, sex, parity and height at birth, PCB 153 concentration in plasma at testing time was significantly related to longer P100 latency at 95% and 12% contrast and N150 latency at 12% contrast, with βs of 2.5 (*P*-value < 0.01), 3.22 (*P*-value < 0.05) and 5.58 (*P*-value < 0.05), respectively. The amplitudes of the N75-to-P100 and the P100-to-N150 at 95% contrast were significantly reduced as a function of increased PCB 153 concentration in the plasma of the children, with respective βs of −3.74 and −3.17 (both with *P*-value < 0.05) (Saint-Amour et al., 2006).

In a cohort of healthy mother–infant pairs recruited between 1993 and 1995 from the obstetrical wards of three hospitals in Düsseldorf, Germany, concentrations of PCBs 138, 153 and 180 were measured in cord blood, early breast milk (around 2 weeks) and 42-month serum. The Kaufman Assessment Battery for Children (K-ABC) was administered to children at 42 and 72 months (6 years) of age. This test yields a Mental Processing Composite, which is comparable to a conventional IQ (mean 100, standard deviation 15). The effect size on the test was assessed by comparing the scores corresponding to the sum of the concentrations of PCBs 138, 153 and 180 of the 95th and the 5th percentiles. For PCBs in milk, the effect size was −8.5 (*P*-value = 0.028) for test score administered at 42 months; there was a similar effect size (−10.3, *P*-value = 0.025) for the PCBs in serum collected at 42 months. For PCBs in both milk and serum, the effect sizes on the test at 72 months were also negative, but no longer significant. These effects were adjusted for sex, parental education, maternal IQ, birth weight, breastfeeding (duration) and HOME score (an indicator of quality of the home environment) (Winneke et al., 2005). Mental development and motor development were assessed by means of the Bayley Scales of Infant

Development (BSID) at the ages of 12 and 24 months in the same study, as well as among a subset of the Duisburg, Germany, cohort, including healthy mother–infant pairs recruited in Duisburg in which concentrations of 18 PCB congeners were measured in maternal blood during pregnancy and in maternal milk. The test was applied at ages 10 and 30 months (Düsseldorf) or at ages 12 and 24 months (Duisburg). The PCB concentration (sum of PCBs 138, 153 and 180) showed a negative relationship with both mental and motor development; the associations were non-significant. The more significant result was for mental development at 30 months in the Düsseldorf cohort: the per cent change in the BSID score (mental development) was −3.3 (95% CI −9.3 to 0.3) for doubling the PCB concentration, adjusted for parental education and occupation, alcohol and smoking during pregnancy, duration of pregnancy, mother's age at delivery, thyroid disease during pregnancy, medication during pregnancy, Apgar score at 5 minutes, neonatal jaundice, duration of breastfeeding, child's home environment (HOME score) and lead concentrations in mother's blood (Wilhelm et al., 2008).

Mother–infant pairs for a birth cohort were recruited in 2002–2004 from two districts in eastern Slovakia (Michalovce, with high PCB contamination from a chemical manufacturing plant, and Svidnik, with lower levels of PCBs). The concentrations of 15 PCB congeners were determined in the maternal and cord serum samples collected at delivery. The BSID-II was administered to children at 16 months of age. Two scales of the BSID, the mental development index (MDI) and the psychomotor development index (PDI), were used for the constructs of cognitive and motor development, respectively. Higher concentrations of NDL-PCBs (PCBs 138, 153, 170 and 180) in either maternal or cord serum were associated with lower levels of both MDI and PDI scores, and this association was significant for PCB concentrations in cord serum in relation to PDI. In multiple linear regression models adjusting for district, HOME score, sex and Raven score (a non-verbal intelligence test applied to the mothers after delivery), the β (score change in PDI) was −2.14 (P-value < 0.05) for a one-unit change in natural log concentration of PCB 153 and −1.95 (P-value < 0.05) for a one-unit change in natural log sum of the concentrations of PCB congeners 138, 153, 170 and 180. In this study, a strong inverse relationship was found between concentrations of DL-PCBs (in maternal and cord serum) and both PDI and MDI scores (Park et al., 2010). In the same subjects, hydroxylated PCBs were measured; some studies have shown that concentrations in cord plasma are approximately 50% of maternal levels, whereas they are only 30% of the parent PCB congeners, suggesting an active transport of hydroxy-PCBs across the placenta. In the same analysis conducted previously, no significant association was found for 3-hydroxy-PCB 153 in maternal or cord serum and either MDI or PDI. However, the 4-hydroxy-PCB 107 concentration in cord serum was significantly associated with lower MDI (β −2.27, P-value = 0.01) and PDI (β −4.50, P-value = 0.004);

also, the 4-hydroxy-PCB 107 concentration in maternal serum was significantly associated with lower MDI (β −1.76, *P*-value = 0.03) but not PDI (Park et al., 2009).

The Tohoku study of child development included mother–neonate pairs from an urban coastal area of the Tohoku district in Japan that were recruited during 2001–2003. Concentrations of all 209 PCB congeners were measured in cord blood. The Neonatal Behavioral Assessment Scale was administered 3 days after birth, and the K-ABC, composed of four scales used to assess their intelligence and achievement, was applied at the age of 42 months. The motor cluster of the Neonatal Behavioral Assessment Scale was negatively associated with PCB concentration (sum of all congeners) in cord serum; therefore, this result does not provide any relevant information regarding the potential effects of NDL-PCBs (Suzuki et al., 2010). In the same subjects, the K-ABC results were compared with concentrations of PCB congeners in cord blood grouped according to their degree of chlorination. The multiple regression analysis showed that the sum of the log concentrations of nine higher chlorinated PCBs was associated with a decrease of 8.172 (95% CI 1.108–15.24) in the sequential processing score and 6.793 (95% CI 0.771–12.81) in the mental processing score, after adjustment for sex, concentrations of mercury and lead in cord serum, birth order, child age at examination, tester of the K-ABC, analytical institute, drinking and smoking habits during pregnancy, the Raven scores, annual family income and duration of breastfeeding (Tatsuta et al., 2014).

In a population-based birth cohort established in three Spanish regions (INMA study), maternal blood was obtained between the seventh and 26th weeks of pregnancy, and concentrations of PCBs 28, 52, 101, 118, 138, 153 and 180 were measured in serum. Neuropsychological assessment by means of the BSID was carried out at age 14 months (range 11–21 months) (n = 1391). Prenatal exposure to PCBs, particularly to PCBs 138 and 153, tended to show an impairment of psychomotor development, although the results were not significant. After adjustment for region of study, gestational age and paternal social class, decreases in psychomotor test scores of 1 point (*P*-value = 0.059) and 0.99 point (*P*-value = 0.072) were associated with 10-fold increases in concentrations of PCB 138 and PCB 153 in serum, respectively (Forns et al., 2012a). In a reanalysis of these subjects restricted to 1175 children, increasing prenatal PCB 153 concentrations were associated with lower mental and psychomotor scores, although significance was reached only for psychomotor development (β −1.36, 95% CI −2.61 to −0.11), adjusted for region of study, gestational age and paternal social class (Gascon et al., 2013). The exclusions in the second analysis were justified because the authors aimed to estimate postnatal exposure via breast milk by means of a physiologically based kinetic (PBK) model using data on breastfeeding as well as height and weight profiles through the first year of life; children for which this information

was not available (n = 216) were not included. In contrast, the McCarthy Scales of Children's Abilities (MSCA) were applied at age 4 years to the subset of children from the study residents in Menorca with PCB concentrations measured in cord serum and in blood collected at 4 years. PCB 153 concentrations in cord serum were negatively associated with several MSCA scores: the β (change in the score for 1 unit in the log concentration [ng/mL] of PCB 153) for the general cognitive score was −3.23 (P-value = 0.01); and the βs for specific MSCA scores were −2.71 for verbal, −2.75 for quantitative, −3.02 for perceptual, −2.82 for memory and −2.26 for motor – all of them except the last one were significant at a P-value of <0.05. These associations were adjusted for psychologist, child's age, maternal social class, folic acid supplementation during pregnancy, maternal cigarettes during pregnancy, paternal education, child sex and duration of breastfeeding. The association between PCB 153 concentration and general cognitive score remained significant (β −3.45, P-value = 0.017) after further adjustment for concentrations of DDE and HCB. The associations for PCBs 138 and 180 were less precise, whereas no significant associations were reported for the DL-PCB congener, PCB 118 (Forns et al., 2012b).

Pregnant women from the Hokkaido Study on Environment and Children's Health were recruited in 2002–2004 from the Sapporo Toho Hospital in Hokkaido, Japan. Concentrations of a total of 68 PCB congeners were measured in blood collected during pregnancy (third trimester). Mental development and motor development were assessed by means of the BSID-II administered to children at 6 months of age. After adjustment for gestational age (days), smoking during pregnancy, caffeine intake during pregnancy (mg/day) and blood sampling time, there were no significant associations between the BSID-II scores (MDI, PDI) and the two NDL-PCBs (PCBs 170 and 180) or the DL-PCBs, although significant negative associations were reported for some PCDD or PCDF isomers (Nakajima et al., 2006).

In a Faroe Islands birth cohort established in 1994–1995, prenatal exposure was determined from maternal concentrations of PCBs in pregnancy serum (blood obtained at gestational week 34) and milk. At 7 years of age, a new blood sample was taken and used for a new assessment of PCB concentrations as well as to analyse MRs in lymphocytes and the enzyme activity of monoamine oxidase-B in platelets as potential markers of neural cell function. No correlation was found between the two biomarkers and concentrations of PCBs 28, 77, 105, 115 and 153 and 4-hydroxy-PCB 107 or the sum of the concentrations of PCBs 138, 153 and 180 (results not shown) (Coccini et al., 2009).

Within the New York State Angler Cohort Study, a population-based cohort from 16 counties along Lakes Erie and Ontario in New York State, USA, established in 1991, concentrations of 62 single eluting and 12 co-eluting PCB congeners in maternal serum collected during pregnancy (around 8 weeks of

gestation) were measured, and postnatal exposure was assessed by quantifying all 209 PCBs in breast milk. At a 24-month home visit, the child psychologist administered the BSID-II to assess cognitive and psychomotor development. When examining the combined effect of prenatal and postnatal exposure to PCB 153 on BSID-II scores, there was the suggestion of an increase in MDI associated with higher levels of prenatal exposure, although the effect was not statistically significant after adjustment for maternal IQ and maternal prenatal lead level. Regarding PDI, higher levels of postnatal (breast milk) exposure were associated with a decrease in PDI; children in the third tertile of PCB 153 exposure had a decrease of 24.9 points (95% CI −44.3 to −5.5) compared with the PDI score of children in the lowest tertile (Lynch et al., 2012).

Within the first Flemish Environment and Health Study, mothers and their newborns were recruited through 25 maternity hospitals from Flanders, Belgium, in 2002–2003. Concentrations of PCBs 118, 138, 153, 170 and 180 were measured in cord blood. Children were recontacted when they were 7–8 years old, when behavioural problems were assessed using the standardized Strengths and Difficulties Questionnaire, a validated screening questionnaire, which comprises five domains: emotional, conduct, hyperactivity, peer and social problems. No significant associations were found between exposure to NDL-PCBs (sum of concentrations of PCBs 138, 153 and 180 in log scale) and emotional symptoms (score ≥5), conduct problems (score ≥5), hyperactivity (score ≥7) and total difficulties (score ≥16). In the same analysis, no associations were found for dioxin-like compounds (total of PCDDs/PCDFs and DL-PCBs) (Sioen et al., 2013).

Mother–infant pairs from the northern part of the Netherlands were included in an observational study between 1998 and 2000; only women whose pregnancy or delivery had not involved serious illness or complications and only infants born at term who had no congenital anomalies or diseases were included. Umbilical cord blood samples were taken immediately after delivery; concentrations of 10 PCBs and six hydroxy-PCBs were measured. When the infants were 3 months old, their motor development was evaluated by assessing the presence and performance of spontaneous movement patterns from video recordings. The Motor Optimality Score was calculated by means of a Motor Optimality List consisting of five categories; the score could range from low (5) to high (28) optimality. Although the levels of several PCB congeners were positively associated with the Motor Optimality Score or specific motor optimality categories, after adjusting for sex, gestational age and maternal smoking during pregnancy, the only significant associations were for PCB 118 (a DL-PCB congener), with an OR of 1.84 (95% CI 1.02–3.32) for the absence of antigravity movements for a 10 ng/g lipid increase, and for 4′-hydroxy-PCB 172, with an OR of 0.19 (95% CI 0.05–0.79) for more manipulation (Berghuis et al., 2013).

Within the birth cohort Health Outcomes and Measures of the Environment Study, pregnant women from seven prenatal clinics in the Cincinnati area, Ohio, USA, were recruited in 2003–2006. Women provided a serum sample around 16 and 26 weeks of pregnancy and within 24 hours of delivery, in which concentrations of 27 PCB congeners were measured. When children were 4 and 5 years old, mothers completed the Social Responsiveness Scale (SRS), a measure of autistic behaviours. The SRS yields a T-score (mean 50, standard deviation 10); higher scores indicate more autistic behaviours, with T-scores of 60 and higher considered to be indicative of clinically significant deficiencies in reciprocal social behaviour and T-scores of 75 and higher being consistent with a clinical diagnosis of autism spectrum disorders (Braun et al., 2014). After adjustment for demographic factors, as well as depressive symptoms during pregnancy, HOME score, gestational serum cotinine concentration and concentrations of other endocrine-disrupting chemicals in a semi-Bayesian hierarchical regression model, most PCB concentrations were associated with negligible changes in SRS scores, with the absolute change being 1.5 points or less. The largest effects were for PCBs 153, 194 and 178, although only the effect for the last congener was statistically significant. The T-score decreased by 1.5 points (β −1.5, 95% CI −4.1 to 1.2) for an increment of 2 standard deviations in the log concentration of PCB 153, whereas the change in SRS scores among children born to women with detectable versus non-detectable concentrations of PCB 178 was −2.6 (95% CI −4.4 to −0.2).

(b) Neurophysiological and neuropsychological effects in adolescents

In Akwesasne Mohawk adolescents (age 10–16 years, average 13 years) resident along the St Lawrence River near the junction of New York State, USA, and Ontario and Quebec, Canada, overall exposure to PCBs (a sum of the concentrations of the 16 PCB congeners detected as individuals, pairs or triplets in 50% or more of the serum samples) showed a significant negative relationship with two separate measures of long-term memory, as well as with a measure of comprehension and knowledge (Newman et al., 2006). In the same population, no evidence of negative effects of PCB levels in blood of adolescents (a summary measure of 10 PCBs, including PCB 118, a DL-PCB congener) on ADHD-like behaviour was found (Newman et al., 2006). In these studies, PCB exposure involves exposure to mixtures of PCB congeners; even though in the last study it is likely that the highest contribution to the sum of PCBs was from NDL-PCB congeners, the study included one DL-PCB congener, and therefore these studies do not provide relevant information regarding the potential neurotoxicity of NDL-PCBs in adolescents. However, in the same adolescents, cognitive function was found to be associated with a group of NDL-PCBs (PCBs 52, 70, 84, 74, 87,

95, 99, 101 [+ 90], 110, 138 [+ 163 + 164], 153, 180 and 187) in a cross-sectional analysis (Newman et al., 2009). Two measures of long-term memory, Delayed Recall Index and Long Term Retrieval, were inversely associated with NDL-PCB concentrations in multivariate linear regression analysis. The Delayed Recall Index is measured by the Test of Memory and Learning, a measure of general and specific memory functioning, whereas the Long Term Retrieval is one of the domains of cognition measured by the Woodcock-Johnson Revised Tests. The standardized β for the Delayed Recall Index for 1 standard deviation of the sum of serum concentrations of NDL-PCBs was −0.21 (*P*-value < 0.05); for the Long Term Retrieval, it was −0.25 (*P*-value < 0.05). Similar effects were also reported for the group of DL-PCBs.

In 12-year-old children from three districts in eastern Slovakia (Michalovce, Svidnik and Bratislava), concentrations of 15 PCBs (PCBs 28, 52, 101, 105, 114, 118, 123, 138, 153, 156, 157, 167, 170, 180 and 189) were measured in serum. As a marker of cochlear status, transient evoked and distortion product otoacoustic emissions were measured, and their cross-sectional association was analysed in relation to PCB concentrations (Trnovec et al., 2010). In multivariate regression models in which otoacoustic emission measures were modelled as a function of log PCB concentrations, with adjustment for sex, age and site of examination, NDL-PCB concentrations (sum of PCB congeners 138, 153, 170 and 180) were significantly associated with lower transient evoked otoacoustic emissions at 1000 Hz (β −3.47, *P*-value = 0.007) and 1500 Hz (β −2.01, *P*-value = 0.051) and with lower distortion product otoacoustic emissions at 1000 Hz (β −3.31, *P*-value = 0.036) in the left ear only. In this study, similar effects were also reported for the group of DL-PCBs.

(c) Neurophysiological and neuropsychological effects in adults

No overall excess of Parkinson disease, amyotrophic lateral sclerosis or dementia was found among workers exposed to PCBs in three electrical capacitor manufacturing plants in the USA; however, sex-specific analyses revealed that women had an excess of amyotrophic lateral sclerosis and that highly exposed women had an excess of Parkinson disease and dementia (Steenland et al., 2006). In elderly (≥60 years) Yucheng patients (Taiwan, China), exposed women had reduced functioning in attention and digit span, visual memory span and verbal memory recalls, whereas all test results were similar to those of the reference group in exposed men (Lin et al., 2008); furthermore, there was no statistically significant difference in the Mini-Mental State Examination, but attention and digit span forward and total scores showed a significant decline in the exposed subjects (Lin et al., 2010). A neuropsychological evaluation assessed by a battery of 18 tests was carried out in Akwesasne Mohawk adults aged 18–79 years who

were residents along the St Lawrence River near the junction of New York State, USA, and Ontario and Quebec, Canada; overall exposure to PCBs (sum of the concentrations of 101 congeners measured in serum) was significantly related to outcome variables in the domains of executive functioning, motor functioning and memory (Haase et al., 2009). In men and women aged 50–89 years who were former capacitor workers from the General Electric Corporation at either of its two factories in New York, USA, the concentration of PCBs (as a sum of 30 congeners) in serum was not significantly correlated with deficits in neurocognitive function (Seegal et al., 2013). In all these studies, PCB exposure involved complex mixtures, and no results were provided for individual congeners; therefore, these studies do not provide any relevant information regarding the potential neurotoxicity of NDL-PCBs in adults.

Potential neurotoxic effects of NDL-PCBs have been assessed in several cross-sectional studies. The neuropsychological status of older adults (aged 55–74 years) living along contaminated portions of the upper Hudson River (New York, USA) was evaluated by means of a battery of 34 tests capable of detecting subtle deficits in cognition, motor function, affective state and olfactory function. Concentrations of 30 PCB congeners were measured in serum samples. After adjustment for potential confounders, the serum concentrations of PCBs 138, 170 and 180 (but not PCB 153) were significantly associated with a decrease in verbal learning, as measured by a California Verbal Learning Test trial, and the four congeners (i.e. including PCB 153) were associated with an increase in depressive symptoms as measured by the Beck Depression Inventory. The β (change in 1 score of the test for 1 unit log concentration of PCB) for PCB 153 was −0.338 (*P*-value = 0.14) for the California Verbal Learning Test and 0.975 (*P*-value = 0.01) for the Beck Depression Inventory (Fitzgerald et al., 2008).

Cross-sectional analyses have been carried out in older adults (≥60 years) from NHANES 1999–2004 in relation to 11 PCB congeners. Using audiometry measures, hearing impairment was defined as a pure-tone average of the thresholds at 0.5, 1, 2 and 4 kHz of greater than 25 dB hearing level in the better ear, consistent with the WHO definition. There was an increased risk of hearing impairment associated with higher levels of PCB congeners 138, 153, 170 and 180 in serum, but the association was significant only for PCBs 170 and 180. The ORs for the subjects with the highest quintile of exposure to PCBs compared with subjects with PCB values below the detection level were 5.8 (95% CI 1.2–28.2) and 7.8 (95% CI 1.8–33.4) for PCB 170 and PCB 180, respectively, adjusted for age, sex, ethnicity, education, cigarette smoking, occupational/loud/firearm noise exposure, ototoxic medication, history of diabetes/hypertension/thyroid disease, BMI, triglyceride level and total cholesterol level. In the same study, no association was observed for the only DL-PCB congener analysed, PCB 118 (Min, Kim & Min, 2014). In an analysis restricted to older adults (aged 60–

84 years) from the NHANES 1999–2002, the Wechsler Adult Intelligence Scale Digit-Symbol Coding Test, used to detect brain impairment in a clinical setting, was not associated with the concentrations of NDL-PCBs (sum of PCBs 99, 138, 146, 153, 170, 180 and 187) in serum; in the same study, restricted to subjects aged 70–84 years, a significant inverse association was reported for the sum of the concentrations of five DL-PCB congeners in serum (Bouchard et al., 2014).

2.3.6 Cancer

IARC recently assessed the carcinogenicity of PCBs (Lauby-Secretan et al., 2013; IARC, 2015). Although the epidemiological studies included in the review date back more than 20 years, in order to be consistent with other sections of this monograph, we will review here the studies published from 2005 onwards. Only those reporting specific results for NDL-PCBs will be reviewed in detail.

Studies of cancer mortality and incidence have been conducted among workers exposed to PCBs used mainly as dielectric fluids in the manufacture of capacitors (Prince et al., 2006a,b; Ruder et al., 2006; Silver et al., 2009; Hopf et al., 2010; Pesatori et al., 2013) or in transformer manufacture and repair (Caironi et al., 2005). In these studies, significant excess risk of cancer death (SMR) or standardized incidence rate (SIR) has been reported for lymphomas and cancers of the digestive tract (Pesatori et al., 2013), melanoma (Ruder et al., 2006), all cancers and stomach cancer (Prince et al., 2006b; Hopf et al., 2010) and all cancers (Silver et al., 2009).

Mortality data among those exposed to two accidental mass poisonings through ingestion of rice oil contaminated with PCBs and PCDFs in Japan and Taiwan, China (Yusho and Yucheng patients, respectively), have been published, with different follow-up periods. Regarding the Yusho patients, after a 40-year follow-up, there was a significant excess mortality from all cancers and from cancers of the lung and liver (Onozuka et al., 2009; Yoshimura, 2012). In an analysis restricted to the most severely affected area, where SMRs were estimated using regional instead of national death rates, the excess risks for cancer (all, lung, liver) were not significant (Kashima, Yorifuji & Tsuda, 2011). As for Yucheng patients, the analysis follow-up to 2003 revealed that mortality from cancers overall and at several sites was similar to that of the national population (Tsai et al., 2007). However, in a second analysis with extended follow-up (1980–2008), a significantly increased mortality was reported for cancer of the stomach and neoplasms of lymphatic and haematopoietic tissue among men (Li et al., 2013).

Apart from incidental food contamination, chronic exposure to PCBs may occur through a diet rich in foods with a high content of PCBs, mostly in populations with a high consumption of fish. In Swedish populations from the east (Baltic) or west coast, no association with overall mortality was found, but

there was a significant increase in the incidence of skin cancer on the west coast (Mikoczy & Rylander, 2009). No significant associations with cancer mortality were reported in residents on the Baltic coast in Finland (Turunen et al., 2008). Cancer mortality rates did not differ from those of the general population for those consuming fish from the Great Lakes area in the USA (Wisconsin) (Tomasallo et al., 2010).

Another source of exposure to PCBs is environmental exposure. In residents in an industrialized area from Sweden, there was a significant increase in excess mortality from lymphoma following an accidental spill of oil contaminated with PCBs (Helmfrid et al., 2012). Ten years after the release of PCB contamination in the favoured fishing grounds of a village from Guam, an increase in the proportional cancer mortality rate was observed among residents in the contaminated area compared with other villages (Haddock, Badowski & Bordallo, 2011). The mortality in an area near Rome, Italy, heavily polluted over the years by industrial wastes, including high levels of PCBs, was compared with that of the general population in the Lazio region. There was a significant increase in the risk of mortality by cancer (all neoplasm), as well as for cancers of the larynx, lung and pleura, among men, but no significant associations were reported among women (Fantini et al., 2012).

Occupational studies mainly assessed exposure to PCB mixtures through job–exposure matrices and historical measurements, but most did not have data on non-occupational risk factors, which are important for many cancer sites. Moreover, workers from cohorts occupationally exposed to PCBs could have been often exposed to other chemicals. Regarding Yusho and Yucheng patients, it must be taken into account that they were exposed to PCDFs in addition to PCBs; the mean total PCB and PCDF concentrations in the Yusho and Yucheng victims remained several times higher than in the general population many years after exposure. Compared with occupational or accidental exposure, potential exposure to PCBs through diet is a long-term, low-level exposure; however, fish or local vegetables contaminated by PCBs are often also contaminated by other compounds, such as pesticides, furans, dioxins and heavy metals. Overall, the studies reported above may have some value for the assessment of the potential effects of PCBs, but they do not provide any relevant information regarding the carcinogenic effects of NDL-PCBs.

(a) Prospective studies: nested case–control studies of PCBs in blood or adipose tissue

Several cohort studies have analysed the potential relationship between risk of cancer and internal measurements of exposure to PCBs. The most commonly used marker of past PCB exposure is the serum or plasma concentration of a set of PCB congeners, although a few studies have measured PCB concentrations

in adipose tissue. Most studies have used a case–control design nested within a cohort, whereas a few studies have used a case–cohort approach, in which the referent group is formed by a random sample of the whole cohort selected at baseline. PCB 118, PCB 138, PCB 153 and PCB 180 are the congeners most often reported, because they are frequently analysed and prevalent in human biological samples. Usually a summary estimate of the sum of all measured PCB concentrations is used as the main indicator of exposure, but results for individual congeners or groups of congeners are provided in some instances.

(i) Breast cancer

Between 1993 and 1997, 29 875 Danish women aged 50–64 years were enrolled in a prospective study of diet and cancer and followed until 2000 through linkage with the Danish Cancer Registry. During this period, 409 women were diagnosed with postmenopausal breast cancer and matched to one control by age, postmenopausal status and use of hormone replacement therapy. Concentrations of 18 PCB congeners were measured in adipose tissue biopsies. After adjustment for age, use of hormone replacement therapy, benign breast tumour, BMI, alcohol, parity, age at delivery, years of hormone replacement therapy and lactation, no significant association was found with concentrations of PCBs in the whole data set, but an inverse association was observed when the analysis was restricted to the 75 estrogen receptor–negative cases. There was a significant trend of decreased risk across quartiles of serum concentration of PCBs 138, 153, 170, 180, 183 and 187; however, the only significant OR for specific quartiles was for PCB 153 (OR 0.3, 95% CI 0.1–0.9) when comparing the fourth with the first quartile (Raaschou-Nielsen et al., 2005). Within the same study, further analyses were carried out showing no significant associations between breast cancer risk and concentrations of Wolff's groups (Bräuner et al., 2014). Wolff's groups (Wolff et al., 1997) are as follows: Group 1 (estrogenic, including PCBs 187 and 201), Group 2A (DL-PCBs 118 and 156), Group 2B (anti-estrogenic, PCBs 138 and 170) and Group 3 (cytochrome P450 inducers, PCBs 99, 153, 180 and 183). This is the largest nested case–control study on breast cancer and PCBs and the only one with PCB concentrations measured in adipose tissue. The inverse association of concentrations of some PCB congeners among women with estrogen receptor–negative tumours does not have a clear interpretation.

Within the residents of Oakland, California, USA, participating in the Child Health and Development Study, where cases were identified by linkage to the California Cancer Registry and the California Vital Status Records, a nested case–control study compared serum concentrations of 16 PCBs in archived early-postpartum serum samples from 112 cases and age-matched controls (median time from blood draw to diagnosis was 17 years). No associations

were reported between risk of cancer of the breast and sum of total PCBs or Wolff's groups (results not shown). PCB 203 was associated with an increased risk when comparing highest versus lowest quartile (OR 6.3, 95% CI 1.9–21.7). No significant associations were found for common congeners, such as PCB 130, 153, 170 and 180. The OR for a 1 mmol/L increase in the concentration of PCB 153 was 1.11 (*P*-value = 0.91). In this study, there was also a significant decreased risk associated with PCB 167, a DL-PCB congener. These associations were adjusted for total cholesterol, total triglycerides, parity, year of blood draw, BMI and breastfeeding after current pregnancy, in addition to matching by age (Cohn et al., 2012). This is the only nested case–control study to include mostly premenopausal women, but it has limited power.

Besides these studies, the IARC (2015) review included another 12 articles published from 1994 to 2002 with results from seven cohorts. In three studies, no specific results on NDL-PCBs were provided; in three studies, no statistical associations were reported for PCBs 138, 153 and 180 or Wolff's groups including NDL-PCB congeners. One study reported a significant increase for higher concentrations (fourth quartile) of PCB 138, but no significant associations for PCB 138, 180 or 118.

(ii) Non-Hodgkin lymphoma

Among residents of Washington County, Maryland, USA, who had participated in one of two studies conducted in 1974–1989 to obtain blood samples for a serum bank (the CLUE I study), participants were followed up until 1994 by linkage with the Washington County Cancer Registry. Seventy-four cases of non-Hodgkin lymphoma (NHL) (ICD-8 200 or 202) were identified during follow-up, and 147 controls matched by race, sex and age were included in a case–control study. PCB concentrations were measured in serum collected before diagnosis and corrected for lipids. In addition to matching variables, the estimates were adjusted for education and cigarette smoking. There was a significant dose–response relationship between risk of NHL and quartiles of lipid-corrected serum concentrations for the sum of 28 measured congeners. In the analysis focusing on the effect of specific congeners, there was a significant exposure–response relationship between risk of NHL and increasing concentrations of PCB 138 and PCB 153 (*P*-value for trend < 0.05). The ORs for the fourth versus the first quartile were 4.4 (95% CI 1.5–12.6) and 2.2 (95% CI 0.9–5.2) for PCB 138 and PCB 153, respectively. It must be noted that there was also a significant association between risk of NHL and increasing levels of the DL-PCB congener, PCB 118, in serum (L.S. Engel et al., 2007).

The Nurses' Health Study was established in 1976 and included more than 120 000 registered nurses in the USA, who were subsequently followed by

questionnaire every 2 years; 32 826 women from the cohort provided a blood sample between 1989 and 1990. Thirty women with incident NHL diagnosed between the date of blood collection and 1994 (median follow-up, 1 year) were included as cases, and 78 cohort members selected previously as controls for a study of cancer of the breast served as controls. A statistically significant exposure–response relationship was observed between the risk of NHL and increasing concentrations of lipid-corrected PCBs (sum of 21 congeners) adjusted for age, BMI and smoking status. A significant exposure–response relationship was also observed for PCB 138 (*P*-value for trend < 0.05), but not for PCB 153. The OR for the third versus the first tertile of PCB 138 was 3.8 (95% CI 1.1–13.6), whereas the corresponding value for PCB 153 was 3.2 (95% CI 0.9–11.8). In this study, there was also a significant exposure–response relationship (*P*-value for trend < 0.05) between NHL risk and levels of the DL-PCB congener, PCB 118, in serum (L.S. Engel et al., 2007).

An extended follow-up of the Nurses' Health Study cohort (median time to diagnosis, 5.8 years) included 145 cases of NHL identified by annual follow-up questionnaires and confirmed by review of medical records and pathology reports; two controls were selected for each case (n = 290), matched by age, race, month of blood draw and fasting status. No association was observed between risk of NHL and total concentrations of PCBs (sum of 51 congeners measured as lipid-corrected concentrations) or concentrations of specific congeners (PCB 118, PCB 138, PCB 153, PCB 180) in serum after adjustment for race, age, date of blood draw, fasting status at blood draw (matching), region, BMI, smoking, height, parity and breastfeeding. The OR for the third versus the first quartile for PCB 153 was 0.82 (95% CI 0.43–1.56). The same pattern of no association was observed in the subgroup analysis by the main subtypes of NHL: diffuse large B-cell lymphoma, follicular lymphoma and chronic lymphocytic leukaemia/small lymphocytic lymphoma (Laden et al., 2010). It must be noted that this is a well-designed study and that the positive association observed in the initial study was not confirmed in the second, larger study, after adjustment for additional relevant confounders. Moreover, in the second study, the time since blood draw to diagnosis of cases was prolonged (5.8 years compared with 1 year), and PCB measurements were carried out at different laboratories.

Within the Physicians' Health Study, started in 1982 in the USA as a randomized trial for the primary prevention of cardiovascular disease and cancer, 14 916 participants (male physicians aged 40–84 years at enrolment) provided a blood sample in 1982–1984 (before randomization). Newly diagnosed cases of NHL until 2003, identified by means of annual questionnaires, were confirmed by review of medical records. After excluding those diagnosed within 6 months after blood collection, with a prior diagnosis of cancer, with NHL of uncommon subtypes (e.g. mantle cell lymphoma) or lacking sufficient information for subtype

classification, 205 cases with available blood samples were included. For each case, two controls per case were randomly selected among subjects at risk of NHL when the case occurred, matched by race, age and date of blood collection. Lipid-corrected concentrations of 51 PCB congeners in serum were determined for cases and controls. A significant association was observed between NHL risk and log of lipid-corrected concentrations of PCBs (sum of all congeners), adjusted (in addition to matching variables) for region, BMI, smoking status, alcohol intake and height. The association was also significant for the log concentrations of PCB 138, PCB 153 and PCB 180, but not for PCB 118, a DL-PCB congener. The ORs for the fifth versus the first quintile were 2.1 (95% CI 1.1–3.8) for PCB 153 and 2.4 (95% CI 1.3–45) for PCB 180 (Bertrand et al., 2010). This is a well-designed study with reasonable sample size, although it was restricted to men.

The JANUS Serum Bank contains serum samples collected between 1973 and 1991 from almost 300 000 individuals undergoing routine health examinations in Norway. Through linkage with the Norwegian Cancer Registry up to 1999 (median time to diagnosis, 16.6 years), 194 histologically confirmed cases of NHL were ascertained. Information, including lipid-corrected concentrations of 36 PCB congeners, was available for 190 case–control pairs matched by age, sex, county and date of examination. In the analysis, further adjustments were made for BMI and smoking status. No significant association was observed between NHL risk and the concentration of PCBs (sum of all congeners) when comparing higher quartiles with the first quartile, although there was a significant upward dose–response trend (P-value for trend < 0.05). A statistically significant increase in risk was reported for the highest to the lowest quartile of PCB 153 concentrations (OR 2.0, 95% CI 1.0–3.9), with a significant dose–response trend (P-value for trend < 0.05). Significant trends were also reported for PCB 118 and PCB 138 (L.S. Engel et al., 2007). It is not clear why significant associations were found for three common congeners (PCBs 118, 138 and 153), but not for all PCBs combined.

Among participants in the Danish diet and cancer study described above (Raaschou-Nielsen et al., 2005), 278 initially cancer-free cohort members were diagnosed with NHL up to July 2008 (mean follow-up, 9.6 years); a subcohort of 256 participants was randomly selected for analysis using a case–cohort approach. Valid measurements of concentrations of 10 PCB congeners in adipose tissue were available for 239 cases and 245 subcohort members. No association was observed between lipid-corrected concentrations of total PCBs in adipose tissue and risk of NHL, adjusted for age, sex and BMI. There was also no consistent association and no significant trend with several congeners analysed individually, including PCB 153, PCB 138 and PCB 180, as well as some DL-PCB congeners, such as PCBs 118 and 156 (Bräuner et al., 2012). It must be noted that this is the

largest nested case–control study on NHL and PCB concentrations measured in adipose tissue, but estimates were adjusted only for age, sex and BMI.

(iii) Cancers of the male genital tract

A nested case–control study on the risk of testicular germ cell tumours was carried out within the Norwegian JANUS cohort described above (L.S. Engel et al., 2007). Male cases and controls were matched by region, age group (2 years) and year of blood draw. Lipid-corrected measurements of the concentrations of 34 PCBs were available for 49 cases (34 seminomas, eight non-seminomas, five of mixed histology and two of unknown histology) and 51 controls. There was no statistically significant association (adjusted for matching variables) between risk of testicular germ cell tumours and total PCB concentration or concentrations of common NDL-PCB congeners, such as PCB 153 or PCB 138. When the analysis was restricted to seminomas, the OR for the highest versus the lowest tertile of PCB 99 concentration was 4.4 (95% CI 1.0–19.8). In this study, the strongest (and most significant) association was the increased risk observed for the DL-PCB congener PCB 167, for both all testicular germ cell tumours and seminomas (Purdue et al., 2009). It must be noted that this is a well-designed study, but with a small sample size and very limited power.

In a cohort of men in the United States military, concentrations of 15 PCBs were analysed in pre-diagnostic serum samples of 736 incident cases of testicular germ cell tumours and 913 controls matched to the cases on age, race and serum draw date. Of the 15 PCB congeners analysed, four (PCB 28, PCB 52, PCB 105 and PCB 128) were excluded from data analysis, as fewer than 35% of the study samples had values above the LOD. The sum of the concentrations of the 11 remaining PCBs was significantly associated with decreased risk of all testicular germ cell tumours, as well as with seminoma and non-seminoma, adjusted for age, race/ethnicity, date of serum sample collection (matching), serum DDE level, age at serum draw, BMI and height. Results were also analysed in terms of individual congeners and by Wolff's groups. Statistically significantly decreased risks of all testicular germ cell tumours were associated with increasing concentrations (P-value for trend < 0.05) of eight specific PCBs (PCB 118, PCB 138, PCB 153, PCB 156, PCB 163, PCB 170, PCB 180 and PCB 187), but not with three other specific PCBs (PCB 99, PCB 101 and PCB 183). Statistically significantly decreased risks of all testicular germ cell tumours were also associated with all Wolff's groups. Similar decreases in risk were observed for both seminomas and non-seminoma tumours. However, no significant ORs were observed when comparing tertiles of PCB concentrations (McGlynn et al., 2009a). In an analysis restricted to 568 cases and 698 controls that examined associations between testicular germ cell tumours and concentrations of 11 PCBs in relation to polymorphisms in genes encoding

hormone metabolizing enzymes, a statistically significantly reduced risk (*P*-value for trend < 0.01) for PCB 138 (and PCB 118) was found only among subjects with the major homozygous allele for HSD17B4 (Chia et al., 2010). It must be noted that this appears to be a large, well-designed and well-implemented study, but the consistent inverse associations of cancer risk with exposure to PCBs is difficult to explain biologically.

The cohort of the Japan Public Health Center–based Prospective Study consisted of 65 657 men, 14 203 of whom donated blood between 1990 and 1995. In total, 201 newly diagnosed cases of cancer of the prostate (97% pathologically confirmed) were identified up to 2005. For each case, two controls were selected, matched by age (within 3 years), public health centre area, residence, date and time of day of blood collection, and duration of fasting. Lipid-corrected concentrations of 41 PCB congeners were measured in plasma. Apart from matching variables, comparisons were further adjusted for BMI, smoking, alcohol, marital status, and intakes of green tea and miso soup. No statistically significant association with all cancers of the prostate was seen for total PCBs, individual PCBs or Wolff's groups. For individual congeners, ORs were not presented, but no significant differences were found between cases and controls in median concentrations of PCB 153 (*P*-value = 0.33), PCB 138 (*P*-value = 0.20), PCB 180 (*P*-value = 0.62) or PCB 170 (*P*-value = 0.48) in plasma. No statistically significant differences were found for concentration of total PCBs according to stage (localized or advanced) at diagnosis of cancer of the prostate (Sawada et al., 2010). This was a well-designed and well-conducted study showing null results; although the sample size is limited, power is reasonable for the main analysis, although limited for subgroup analyses.

(b) Case–control studies

(i) Non-Hodgkin lymphoma

In a case–control study in Australia including 694 histologically confirmed cases of NHL and 694 controls, exposure to PCBs was coded by an expert industrial hygienist based on questionnaire information. After adjusting for age, sex, residence and ethnicity, ever exposure to PCBs was not related to increased risk of NHL (Fritschi et al., 2005). A case–control study including 495 NHL cases and 495 controls was conducted in an area of northern Italy where environmental exposure had resulted from soil contamination; PCB concentration in the soil was used to define four areas with increasing levels of exposure. Risk of NHL was elevated for subjects having resided 10 or more years in any of the three most polluted areas, and particularly in the most polluted area (Maifredi et al., 2011). These studies do not provide any relevant information regarding the carcinogenic effects of NDL-PCBs.

A population-based case–control study in Sweden included 99 cases of NHL and 99 controls matched by age, sex and health service region (Hardell et al., 2009). After adjusting for age, sex and BMI, risk of NHL was elevated for subjects with PCB concentrations above the median concentration of the sum of 35 PCBs in plasma of controls, although this difference was statistically significant only for follicular lymphoma. PCBs were grouped according to the degree of chlorination, as lower chlorinated (PCBs 52, 66 and 74), moderately chlorinated (PCBs 99 + 113, 101, 105, 110, 118, 138, 153, 156, 170 + 190, 172 + 192, 178, 180 + 193, 182 + 187 and 189) and higher chlorinated PCBs (PCBs 194 and 206); whereas lower and higher chlorinated PCBs included NDL-PCBs only, the broader group of moderately chlorinated PCBs included a mixture of DL- and NDL-PCB congeners. No significant associations were reported by subgroups in the whole data set, but when the analysis was restricted to follicular lymphoma, the OR for the above versus below median concentration of higher chlorinated PCBs in serum was 9.6 (95% CI 1.9–49). The risks of NHL associated with both lower and higher chlorinated PCBs were higher among Epstein Barr virus early antigen IgG–positive subjects, especially among cases with diffuse large B-cell lymphoma. It must be noted that in this study, no adjustment for multiple comparisons was considered, in spite of the huge number of estimates and tests carried out.

A large population case–control study was conducted in Canada. Lipid-adjusted concentrations of 14 PCB congeners were measured in pretreatment samples of plasma from 422 cases of NHL and 460 controls frequency-matched to cases by 5-year age groups, sex and residence. ORs were adjusted for age, sex, education, BMI, ethnicity, farming and family history of NHL. There was a significantly increased risk of NHL for the sum of the concentrations of all PCBs. Risk of NHL was found to be highest in the highest quartile of the sum of the concentrations of seven NDL-PCBs (OR 2.18, 95% CI 1.41–3.38), with a significant trend. There were also significant associations for the concentrations of PCBs 138 and 153; for the latter, the OR for the highest versus the lowest quartile was 1.79 (95% CI 1.17–2.72). A similar pattern was observed for follicular lymphoma, with significant increased risk associated with the sum of the concentrations of NDL-PCB congeners and with the concentration of PCB 153, whereas no significant associations were reported for the diffuse large B-cell lymphoma. It must be noted that there was also an increased risk associated with the sum of the concentrations of the three DL-PCB congeners analysed, for both all lymphoma and the follicular subtype (Spinelli et al., 2007). This is a high-quality study and was one of the largest studies of NHL and PCBs. It accounts for relevant confounders and provides results for individual congeners and lymphoma subtypes. The participation rate for controls was less than 50%, but this is typical of most of the available population-based case–control studies, and

potential confounding factors (e.g. education) were comparable between cases and controls, despite differences in participation.

A multicentre study included 174 NHL cases and 203 controls from France, Germany and Spain. Patients admitted to the same hospital as the cases for non-cancer diseases were selected as controls in France and Spain, whereas German controls were selected from the general population. Concentrations of nine PCB congeners were measured in plasma, and individual results were provided for PCBs 28, 118, 138, 153, 170 and 180. Moreover, PCBs were grouped in functional groups as follows: pseudo-estrogenic (PCBs 28, 52 and 153), higher chlorinated anti-estrogenic (PCBs 170, 180 and 194), phenobarbital inducers (PCBs 101, 153, 180 and 194), 3-methyl cholanthrene inducers (PCBs 118, 138 and 170), immunotoxic (PCBs 138, 153 and 180) and BRCA1 inhibitors (PCBs 101 and 138). Risk estimates were adjusted for age, sex, education and centre. Risk of NHL did not increase by quartile of PCB concentration in plasma overall, for specific congeners or for the functional PCB congener groups. When exploring risk by lymphoma subtype, no significant associations were found for diffuse large B-cell lymphoma or chronic lymphocytic leukaemia/small lymphocytic lymphoma in the whole data set. However, in the German and French groups, but not in the Spanish group, combined risk of diffuse large B-cell lymphoma associated with concentrations of immunotoxic PCBs in plasma above the median concentration showed a 3-fold increase (OR 3.2, 95% CI 0.9–11.5), increasing to 6-fold (OR 6.1, 95% CI 1.0–37.8) in the upper quartile (*P*-value for trend = 0.04) (Cocco et al., 2008). This study is of good quality, with a meticulous classification of lymphoma. The association of the concentration of immunotoxic PCBs with diffuse large B-cell lymphoma in two centres is noteworthy. The heterogeneity between countries may have been a result of differences in PCB exposure or distribution of confounding factors. No adjustment for multiple comparisons was considered, in spite of the huge number of estimates and tests carried out.

A case–control study conducted in 1998–2000 by the United States National Cancer Institute in four areas with population-based cancer registries included 1321 NHL cases and 1057 general population controls. Pretreatment plasma samples were available in a subset of 100 cases with a histologically confirmed diagnosis and 100 controls, for which concentrations of 40 PCB congeners in plasma were measured. In this analysis, only 28 congeners detected in at least 30% of samples were included. ORs were adjusted for the matching factors, age, sex, study site and date of blood draw; other potential confounders were tested (education, race, BMI and family history of NHL), but no confounding was observed. The results showed significant upward trends in risk of NHL with increasing quartiles of concentration of the subgroup of higher chlorinated PCB congeners (*P*-value for trend = 0.04) (this group includes PCBs 156, 180 and 194) in plasma. Regarding individual congeners, significant increases in

risk were reported only for PCB 180 (*P*-value for trend = 0.01) and PCB 194 (*P*-value for trend = 0.04). For PCB 180, there was also a significantly increased risk for the highest versus the lowest tertile (OR 3.5, 95% CI 1.53–9.15). Some associations were stronger among the cases of diffuse large B-cell lymphoma than among the cases of follicular lymphoma (De Roos et al., 2005). Further analysis of these data explored the interaction between PCB 180 and common variants (61 single nucleotide polymorphisms) in 36 genes implicated in the immune and inflammatory response; significant increases in risk of NHL were observed for PCB 180 in plasma for *IFNG (C-1615T) TT*, *IL16 (3′-UTR, Ex22871A > G) AA*, *IL8 (T-251A) TT* and *IL10 (A-1082G) AG/GG* genotypes (Colt et al., 2009). Further analyses explored the interaction with status of HLA-DRB1*01:01 class II leukocyte surface antigen and of the extended ancestral haplotype (AH) 8.1 (*HLA-A*01-B*08-DR*03-TNF-308A*); risk of NHL was elevated among study subjects with concentrations of PCB 180 in blood above the median concentration and lacking the *HLA-DRB1*01:01* allele or the *AH 8.1* allele (Wang et al., 2011). These related studies were well conducted, and an extensive and detailed analysis was carried out; however, this is a relatively small study, particularly for subgroup analyses, with wide confidence intervals for the estimates.

In a study among residents in an area of Besançon, France, close to a municipal solid waste incinerator, cases were subjects with newly diagnosed NHL during 2003–2005 at the Department of Hematology of the University Hospital (the only tertiary referral hospital in the region). Thirty-four cases (out of 53 eligible) were included; 34 controls were randomly selected from the donor registry of the regional blood bank living in the study area, matched by sex, age and date (year) of blood draw. Concentrations of a total of 18 PCB congeners were measured in serum. The OR associated with serum concentrations of NDL-PCBs (sum of PCBs 28, 52, 101, 138, 153 and 209) was 1.02 (95% CI 1.01–1.05) per 10 ng/g lipid. The OR for NDL-PCBs did not substantially change when adjusting (in addition to matching variables) for BMI or pesticides (β-hexachlorocyclohexane, *p,p′*-DDT). Significant associations were also observed for the individual congeners PCB 130, PCB 180 and PCB 153; for PCB 153, the OR (per 10 ng/g lipid) was 1.04 (95% CI 1.00–1.09). It must be noted that in this study, the strongest (and most significant) positive associations were observed for DL-PCBs, both when analysed as the sum of 12 congeners and in the analysis for individual congeners (Viel et al., 2011).

Besides the studies discussed above, IARC (2015) reviewed another three case–control studies, but in all of them the results referred to a mixture of PCBs, including both NDL- and DL-PCB congeners, and therefore they do not provide any relevant information regarding the potential effects of NDL-PCBs on the risk of NHL.

(ii) Breast cancer

PCB exposure (28 congeners) was measured in banked serum collected in 1981–1987 from 63 Alaskan native women who subsequently developed breast cancer and 63 age-matched controls; no association with PCB exposure (sum of all congeners) was found after adjusting for ethnicity, family history of cancer of the breast and parity (Rubin et al., 2006). In a study in Greenland among subjects of Inuit descent, higher concentrations of PCBs in serum were found for 31 cases of breast cancer compared with 115 controls; however, the OR for total PCBs (sum of 12 congeners) did not demonstrate any significant association (Bonefeld-Jorgensen et al., 2011). In a population-based study in North Carolina, USA, including 612 breast cancer cases and 599 controls, in which a significantly increased risk of breast cancer had previously been found for higher concentrations of PCBs (sum of 35 congeners) among African women after adjusting for age, menopausal status, BMI, parity/lactation, hormone replacement therapy and income, statistically significant multiplicative interactions were observed between CYP1A1 M2-containing genotypes and total PCBs among white women and between CYP1A1 M3-containing genotypes and total PCBs among African American women (Li et al., 2005). In a population-based case–control study of African American women including 355 cases and 327 controls, risk of breast cancer was not associated with PCB concentrations (measured using Aroclors 1242 and 1260 and reported as total PCBs) in serum adjusted by age, BMI and breastfeeding; moreover, PCB concentrations in serum were not associated with an increase in the risk of any subtype of cancer defined by tumour receptor status (progesterone receptor, estrogen receptor, p53 or HER-2/neu) (Gatto et al., 2007). In these studies, the results refer to a mixture of PCBs (in some instances of unknown composition), and therefore they do not provide relevant information regarding the potential effects of NDL-PCBs on breast cancer risk.

In a hospital-based case–control study on breast cancer in Nagano, Japan, PCB concentrations (sum of 41 congeners) were measured in serum samples from 403 matched pairs collected from 2001 to 2005. After adjustment for total lipid concentration in serum, BMI, reproductive risk factors, smoking, diet and medical history, serum concentrations of total PCBs were associated with significantly decreased risk of cancer of the breast. For the specific congeners PCB 153 and PCB 180, the ORs comparing the highest to the lowest concentration quartiles were 0.40 (95% CI 0.18–0.91) and 0.29 (95% CI 0.13–0.66), respectively. The trend in the inverse relationship persisted when results were stratified by hormone receptor and menopausal status (Itoh et al., 2009). It is not clear how the inverse associations reported in this study may be explained.

In a hospital-based case–control study in Mexico, blood samples were used to measure serum concentrations of 20 PCBs for 70 breast cancer cases

and 70 controls. Age, age at menarche, lactation, menopausal status, BMI and family history of breast cancer were adjusted for in the analysis. A significantly increased risk was apparent for the sum of the concentrations of all PCBs. When PCBs were grouped according to the Wolff's groups, significantly increased risks were reported for group 2B (di-*ortho*-substituted, PCBs 128, 138 and 170), with OR 1.90 (95% CI 1.25–2.88); group 3 (cytochrome P450 inducers, PCBs 153 and 180), with OR 1.81 (95% CI 1.08–3.04); and group 4 (PCBs 8, 195, 206 and 209), with OR 1.57 (95% CI 1.20–2.07). Elevated ORs were reported for several PCB congeners (PCBs 128, 138, 170, 180, 187, 195, 206 and 209), but not for PCB 153 (OR 1.36, 95% CI 0.67–2.73). The ORs were generally higher in postmenopausal women. No significant association was reported for group 2A, which includes several DL-PCBs, but a significantly increased risk was observed for PCB 118, the most common DL-PCB congener (Recio-Vega et al., 2011). Although this was a small study, several increased risks were reported; however, no attempt was made to correct for multiple comparisons. It must be noted that the age distribution was different in cases and controls, suggesting potential for residual confounding by age. Furthermore, the analytical approach is unclear; actually, it is impossible to clarify, from the information provided in the paper, to what level of PCB exposure the ORs reported correspond.

Besides these studies, IARC (2005) reviewed 12 more case–control studies (articles published between 1998 and 2004) on the risk of breast cancer and PCBs. No specific results on NDL-PCBs were reported in half of these studies. In four studies, statistical associations were observed for either individual congeners or groups of NDL-PCBs, and no significant association of NDL-PCBs with breast cancer risk was observed in the remaining two studies.

Occupational risk factors for cancer of the male breast were investigated in a multicentre study of 104 cases and 1901 controls in eight European countries. Lifetime work history was obtained by in-person interviews, and potential occupational exposures, including to PCBs, were assessed using expert judgement. No significant association was observed for PCBs and dioxins combined (Villeneuve et al., 2010). Results from this study do not provide any relevant information regarding the effects of NDL-PCBs on cancer of the male breast.

(iii) Cancer of the prostate

A hospital-based case–control study was conducted in Iowa, USA, in which 30 PCBs were measured in serum samples from 58 patients with cancer of the prostate and 99 age-matched controls. Different approaches for the grouping of PCBs were used, but specific results were shown for three groups: the moderately chlorinated PCBs included 18 congeners, among which were some DL-PCBs;

the phenobarbital inducers included PCBs 99, 101, 153, 180, 183 and 194 (all of them NDL-PCBs); and the phenobarbital inducers and persistent PCBs included PCBs 99, 153, 180, 183 and 203. It should be noted that there is an important degree of overlapping between the two phenobarbital inducer groups. The estimates were adjusted for age, BMI and history of prostatitis; in a second model, further adjustment was carried out for total lipids. For the group phenobarbital inducers, there was a marginally significant, increasing risk of prostate cancer across tertiles of PCB concentrations (ng/mL) (*P*-value for trend = 0.048), which was no longer significant (*P*-value for trend = 0.10) after further adjustment for total lipids. The same pattern was observed for the phenobarbital inducers and persistent PCBs group, with *P*-values for trend of 0.043 (not lipid adjusted) and 0.09 (lipid adjusted). In this group, the OR for the highest versus the lowest tertile (not lipid adjusted) was 2.44 (95% CI 1.01–5.90) (Ritchie et al., 2005). It should be noted that this study was small, with multiple comparisons.

In a population-based case–control study in Sweden, concentrations of 37 PCBs in samples of fat tissue from 58 cases of cancer of the prostate were compared with 20 controls with benign prostate hyperplasia. The association with the sum of PCBs was not significant. The concentration of PCB 153 in fat tissue (above versus below median concentration) was associated with a significantly increased risk of cancer of the prostate (OR 3.15, 95% CI 1.04–9.54), adjusted for age and BMI. In the stratified analysis by prostate-specific antigen levels, the increased risk was significant only for men with prostate-specific antigen concentration above 10 ng/mL (OR 7.91, 95% CI 2.0–31.2) (Hardell et al., 2006a). It should be noted that this study was small, with multiple comparisons.

In a case–control study among urology patients in Ontario, Canada, concentrations of 14 PCB congeners were measured in serum of 79 men with incident cancer of the prostate and 329 age-matched controls. No association was observed between the sum of the concentrations of all PCBs or concentrations of individual PCBs, including common NDL-PCB congeners (PCBs 138, 153, 170 and 180) as well as DL-PCB congeners (PCBs 118 and 156), adjusted for age, physical activity, alcohol consumption and tobacco smoking (Aronson et al., 2010). As both cases and controls underwent the same diagnostic procedures and were screened by prostate-specific antigen level and digital rectal examination, selection bias was unlikely in this study.

(iv) Malignant melanoma

In a multicentre case–control study in nine European countries, 293 men and women with uveal melanoma were compared with 3198 population and hospital controls frequency-matched by country, age and sex. Exposure to transformer oils was assessed by questionnaire, based upon the subject's reported exposure to

a named brand of oil with known PCB content. There was a strong, significantly increased risk of uveal melanoma for confirmed exposure, especially for exposure to Pyralène, among men (Behrens et al., 2010). However, the exposure to PCBs refers to a mixture of (unknown) congeners, and therefore this study does not provide any relevant information regarding the effects of NDL-PCBs on uveal melanoma.

Within a large study originally set up to evaluate the effect of exposure to ultraviolet light and gene variants on risk of melanoma, with controls recruited using population-based registries, a case–control study was conducted including 80 patients with malignant melanoma of the skin and 310 controls. Lipid-adjusted concentrations of 14 PCB congeners in plasma were determined. Results were adjusted for age, sex, education, skin reaction to repeated sun exposure and total recreational sun exposure. Statistically significant associations with malignant melanoma were observed for the sum of the concentrations of all 14 PCB congeners, as well as for the 11 NDL-PCB congeners; for the latter, the OR for the highest compared with the lowest quartile was 7.02 (95% CI 2.30–21.4), with a significant trend across quartiles (*P*-value for trend < 0.001). Concerning specific congeners, significantly increased risks were also found for PCBs 138, 153, 170 and 187. The OR for the highest compared with the lowest quartile of PCB 153 concentration was 4.86 (95% CI 1.68–14.1). In this study, significantly increased risks were also observed for the sum of the concentrations of DL-PCBs, as well as for some specific DL-PCB congeners, such as PCBs 118 and 156 (Gallagher et al., 2011). It should be noted that in light of its appropriate design and control of relevant potential confounders, this is a high-quality study, despite the relatively small sample size. It cannot be discounted that the positive associations for all the individual PCB congeners may have been a result of correlations among congeners. In contrast, multiple comparisons were not formally addressed, but it is likely that this would not change the interpretation of the results.

(v) Other cancers

In a European multicentre case–control study of 183 men with histologically confirmed carcinoma of the extrahepatic biliary tract and 1938 matched controls, self-reported job descriptions were used as indicators of occupational exposure to suspected endocrine-disrupting compounds, including PCBs. After adjustment for age, country and history of gallstones, a significantly increased risk of extrahepatic biliary tract cancer was reported for ever-exposure to PCBs. These results were based on a small number of exposed cases, and trends were inconsistent (Ahrens et al., 2007). Results from this study do not provide any relevant information regarding the effects of NDL-PCBs on cancer of the extrahepatic biliary tract.

In a case–control study in Sweden, concentrations of 37 PCBs were measured in serum from blood collected from 61 cases of cancer of the testis and 58 age-matched controls from the Swedish population registry, as well as from 44 mothers of cases and 45 mothers of controls. No association between cancer of the testis and the sum of PCB concentrations in serum in cases and controls was observed. However, there was a significant association between the concentration of PCBs analysed in serum from mothers of cases and increased risk of testicular cancer in the sons, both for the sum of all congeners and for the group of enzyme inducers (sum of PCBs 99, 153, 180, 183, 199 and 201, all of them NDL-PCBs); for the latter, the OR for above versus below the median concentration was 2.6 (95% CI 1.1–6.5). The increased risk was also significant for the non-seminoma cases, but not for the seminomas (Hardell et al., 2006b). The timing of blood collection of the mother, which was decades after the births of the cases, makes interpretation of these results difficult.

In a case–control study in northern Mexico including 43 cases of lung cancer and 86 controls recruited from two hospitals, information on history of exposure to PCBs was collected through in-person interview, and concentrations of 20 PCB congeners were measured in serum. After adjustment for age, agricultural occupation and tobacco smoking, the association between PCB 18 concentration and cancer of the lung (OR 1.13, 95% CI 1.04–1.38) was the only significant result out of the 20 individual congeners analysed. No significant associations were found for concentrations of the sum of all PCBs or of any of the seven groups of PCBs tested (Recio-Vega et al., 2013). It should be noted that this study provides information about lower chlorinated PCBs, which are rarely measured; however, the etiological relevance of such measurements of PCBs of short half-life is questionable. In addition, methods used for subject recruitment and statistical analysis were not clearly described, and the possibility of residual confounding by age or other factors cannot be ruled out. For instance, cases were older than controls (mean age 66 versus 55 years), with a higher proportion of males (77% versus 66%); moreover, the increase in risk for history of smoking was relatively low (OR 2.72). Regarding the analysis, it is impossible to clarify, from the information provided in the paper, to what levels of PCB exposure the ORs reported correspond.

A population-based case–control study in California, USA, included 184 children aged 0–7 years with acute lymphocytic leukaemia and 212 controls matched by birth date, sex, race and ethnicity. Concentrations of six PCB congeners (PCBs 105, 118, 138, 153, 170 and 180) in residential carpet dust were used as an exposure indicator. In addition to matching variables, the estimates were adjusted for age of home and breastfeeding duration. There was a significant association between the risk of acute lymphocytic leukaemia in children and PCB concentration in dust for PCB 138 and PCB 153. The OR

comparing concentrations of PCB 153 above versus below the LOD of 1 ng/g was 1.67 (95% CI 1.06–2.63); moreover, there was a significantly increased risk of acute lymphocytic leukaemia across tertiles of PCB 153 concentration (*P*-value for trend = 0.018). Risk estimates for the PCB congeners were not changed by adjustment for concentrations of the organochlorine pesticides DDT, DDE, α-chlordane, methoxychlor and pentachlorophenol. In this study, a significantly increased risk was also reported for the common DL-PCB congener, PCB 118 (Ward et al., 2009). This is a well-designed study, using a good method of exposure assessment; moreover, potential confounding was ruled out.

2.3.7 Endocrine and metabolic effects

(a) Thyroid function and thyroid diseases

Associations of total T_4 and TSH levels with PCB concentrations (22 congeners) were assessed in adults without thyroid disease who participated in the 1999–2002 NHANES, a sample representative of the United States population. There were significant inverse associations of total PCB concentrations with T_4 and TSH levels in women over 60 years of age (Turyk, Anderson & Persky, 2007). The concentrations of 15 PCBs in serum and indicators of thyroid structure and function were analysed in adults from two areas from eastern Slovakia. The sum of the concentrations of all PCBs was significantly associated with higher thyroid volume and higher concentration of thyroperoxidase antibodies (Langer et al., 2007a), higher levels of T_4 and lower levels of T_3 (Langer et al., 2007b), and a higher prevalence of antinuclear antibodies (Cebecauer et al., 2009), indicators of autoimmune or possible immunotoxic effects. In a cohort of women from Michigan, USA, no association was found between the cumulative incidence of thyroid disease during the 25-year follow-up and PCB levels in serum collected at baseline, measured by means of the PCB–Aroclor 1254 detection method (Yard et al., 2011). In a case–control study in the area of Fukuoka, Japan, a strong association was reported between congenital hypothyroidism (cretinism) in neonates and total PCB concentrations (congeners not specified) in breast milk of mothers (Nagayama et al., 2007). In all these studies, the PCB exposure refers to a complex mixture of PCBs, and results for individual congeners are not reported. Therefore, thse studies do not provide any relevant results regarding the potential effects of NDL-PCBs on the thyroid.

(i) Cross-sectional analyses

In a cohort of 118 pregnant women 25–34 years of age and 118 newborns from the general population in central Taiwan, China, concentrations of 27 PCBs (including the six indicator congeners) were measured in placental blood, and thyroid hormone levels were measured in cord blood. A significant positive

correlation was observed between the sum of the concentrations of PCB 138, PCB 153 and PCB 180 and levels of total and free T_4 only in female neonates. No association was found for T_3, TSH or thyroxine-binding globulin (Wang et al., 2005).

In a study on adults resident in three areas in eastern Slovakia, concentrations of nine PCBs (including the six indicator congeners) in serum and thyroid volume, TSH level and thyroid peroxidase antibodies were measured. A significantly increased thyroid volume was observed for subjects with the highest concentration of PCB 101 (P-value < 0.02); a non-significantly increased thyroid volume (P-value > 0.06) was also observed for higher concentrations of PCBs 153 and 180. No association was reported with TSH level or thyroid peroxidase antibodies (Langer et al., 2005).

In south-western Quebec, Canada, maternal blood was collected during the first or second trimester from pregnant women, and cord blood was also collected at delivery. Concentrations of 14 PCB congeners and TSH, total T_3 and free T_4 were measured in serum from both blood samples. In maternal blood during pregnancy, there was a significant negative correlation between total T_3 level and concentrations of PCB 138, PCB 153 and PCB 180 in serum. No associations were observed for TSH or free T_4 level. No associations were observed between PCB concentrations and levels of thyroid hormones measured in cord blood (Takser et al., 2005). It should be noted that although prenatal and postnatal measurements were carried out in this study, only cross-sectional analyses were reported.

Lipid-adjusted concentrations of PCB 153 and TSH levels in serum were measured in middle-aged and elderly men from the east (Baltic) coast of Sweden. No association was observed between PCB concentrations and the concentration of TSH (Rylander et al., 2006).

Concentrations of PCBs 118, 138, 153, 170 and 180 and thyroid hormones were measured in the cord blood of neonates from Antwerp, Belgium. Significant inverse correlations were observed between PCBs 138, 170 and 180 and both free T_3 and free T_4 levels and between PCB 153 and the level of free T_4. No association was observed between any of the PCB congeners measured and TSH level (Maervoet et al., 2007).

Concentrations of 57 PCB congeners in serum, as well as free T_4, total T_3 and TSH, were measured in adult men recruited from an infertility clinic from 2000 to 2003 in Boston, Massachusetts, USA. In multivariate linear regression, significant associations were found between increasing concentrations of PCB 138 and PCB 153 and lower levels of total T_3 and higher levels of TSH; no significant association was reported between PCB concentrations and the level of free T_4 (Meeker, Altshul & Hauser, 2007).

Maternal concentrations of thyroid hormones and PCBs (34 congeners) were measured in blood collected at around 26 weeks of gestation (n = 320) or before delivery (n = 14) from a birth cohort study (CHAMACOS) in pregnant women and children in the Salinas Valley, California, USA. Multiple linear regression analysis showed a significant inverse association between free T_4 level and concentrations of PCB 28, PCB 52 and PCB 105; there was an inverse association as well with concentrations of PCBs 138, 183 and 180, but it was not statistically significant. No significant associations were reported between concentrations of NDL-PCBs and total T_4 or TSH level (Chevrier et al., 2008).

The cross-sectional relationship between concentrations of thyroid hormones and seven PCB congeners was analysed in children from a general population birth cohort in Menorca, Spain, with blood samples collected at age 4 years. Concentrations of PCB 138 and PCB 153 in blood were significantly related to lower total T_3 levels, whereas no relationship was found between any of the measured NDL-PCBs and free T_4 or TSH level (Álvarez-Pedrerol et al., 2008).

Concentrations of thyroid hormones and 18 PCBs were measured in serum from youth members, aged 13 years, of the Akwesasne Mohawk Nation who were resident in the proximity of the St Lawrence River in New York State, USA, and in Ontario and Quebec, Canada. In multiple regression analysis, a significant association was observed between increased levels of TSH and higher concentrations of PCB 138 (measured as the sum of PCB congeners 138 + 163 + 164) and PCB 153, whereas free T_4 level was significantly associated with lower concentrations of PCB 52, PCB 138 (+ 163 + 164), PCB 101 (+ 90) and PCB 153. No significant associations were reported between any of the measured NDL-PCB congeners and total T_3 or total T_4 level (Schell et al., 2008).

Concentrations of 16 PCB congeners and thyroid hormones were measured in serum from adult freshwater fish consumers, aged 18–74 years, from two lakeside regions in Quebec, Canada. The following significant associations were found: increased concentrations of PCB 138 were related to lower levels of T_3 in women and T_4 in men; increased concentrations of PCB 153 were related to lower levels of T_4 in women; and increased concentrations of PCB 138 and PCB 180 were related to higher levels of TSH (Abdelouahab et al., 2008).

Between 2004 and 2005, umbilical cord blood from women delivering at the Johns Hopkins Hospital, Baltimore, Maryland, USA, was collected for the measurement of the concentrations of six PCBs (PCBs 74, 99, 118, 138 [co-eluted with 158], 153 and 180) and thyroid hormones in serum. In the full study population, none of the PCBs was associated with a change in average levels of thyroid hormones. For infants born by spontaneous, vaginal, unassisted deliveries, concentrations of PCBs 138 (+ 158), 153 and 180 in serum were associated with lower levels of total T_4 and free T_4, but no association was observed with TSH level (Herbstman et al., 2008).

A cross-sectional study was conducted in 2004 among the adult (≥18 years of age) Inuit population of Quebec, Canada, in which concentrations of thyroid hormones, thyroxine-binding globulin and 14 PCBs were measured in serum. In multiple linear regression models, increased concentrations of PCBs 138, 153 and 180 were significantly associated with lower levels of free T_4 and total T_3; and increased concentrations of PCBs 138 and 180 were significantly associated with higher levels of TSH. No significant associations were found for any of these three congeners and thyroxine-binding globulin (Dallaire et al., 2009).

(ii) Prospective studies

In the CHAMACOS cohort described above, concentrations of 34 PCB congeners measured in blood collected at around 26 weeks of gestation in Mexican American women from the Salinas Valley, California, USA, were compared with TSH levels in their children's blood collected shortly after birth. Linear regression models, adjusted for neonatal age at time of heel stick for TSH measurement, gestational age at birth, infant birth weight, sex and mother's pre-pregnancy BMI, were used to assess the relationship between the concentrations of TSH and the 19 PCB congeners with a detection frequency of 75% and above, both expressed on the log scale. A significant positive association with TSH level was found with PCBs 101, 138, 153 and 180. Each 10-fold increase in the concentration of PCB 101 was associated with an increase of 23% in TSH concentration (95% CI 7–45%); the corresponding figures for other indicator congeners were 23% (2–51%) for PCB 138, 20% (0–48%) for PCB 153 and 23% (2–48%) for PCB 180. There were positive associations with PCBs 28 and 52, but they were not statistically significant. In this analysis, PCB congeners were grouped according to previously proposed structure-based and mechanism-based groupings; in addition, another group was based on the congeners' ability to induce a group of enzymes (UGT, CYP1A/EROD, CYP2B/PROD). This group showed a positive association with TSH level, but it includes two DL-PCB congeners. Among the mechanism-based groups, only group 3 of the Wolff classification (phenobarbital, CYP1A and CYP2B inducers), including PCBs 99, 153, 180 and 183, was significantly associated with TSH level. Among the 19 congeners analysed individually, two DL-PCB congeners were included (PCB 118 and PCB 166); none of them showed a significant association with TSH level (Chevrier et al., 2007).

In the cohort from the Johns Hopkins Hospital 2004–2005 study described above, in addition to umbilical cord blood, blood for a second T_4 test was collected during a routine paediatric visit, on average at 18 days of age (range 5–117 days), for a subset of 139 infants. In the analysis, restricted to 92 infants born by spontaneous, vaginal, unassisted deliveries, concentrations of

the four measured PCBs were inversely associated with T_4 level, although the association was not statistically significant for PCB 180. Using multiple logistic regression, the ORs for each increase in one unit of ln PCB concentration (ng/g lipid), comparing the lowest 20% with the highest 80% of T_4 level, adjusted for baby's sex, gestational age, maternal age, maternal race, maternal pregnancy BMI, smoking status and time (days) since birth, were as follows: PCB 138: 5.30 (95% CI 1.73–16.21); PCB 153: 3.40 (95% CI 1.31–8.83); and PCB 180: 1.89 (95% CI 0.83–4.30). The only DL-PCB congener measured in this study, PCB 118, was also inversely associated with T_4 level, with OR 4.53 (95% CI 1.53–13.4).

Primiparous women in the Uppsala region of Sweden who were recruited between 1996 and 1999 (POPUP cohort) agreed to donate a serum sample in late pregnancy (32–34 weeks), and breast milk was obtained from the women 3 weeks after delivery. Newborns were sampled for blood at 3 weeks and 3 months after birth. Thyroid hormones were measured in serum, and concentrations of 10 PCB congeners were measured in serum and milk. The analysis was carried out by means of linear regression using log-transformed concentrations of TSH (mU/L), total T_3 (nmol/L) or free T_4 (pmol/L) with log-transformed concentrations (ng/g lipid) of three groups of PCBs: lower chlorinated PCBs (PCBs 28, 52 and 101), di-*ortho*-substituted PCBs (PCBs 138, 153 and 180) and DL-PCBs (PCBs 105, 118, 156 and 167); concentrations of the DL-PCBs were expressed in TEQs. In simple regression models, only two significant associations were observed. The inverse association between prenatal exposure to lower chlorinated PCBs and total T_3 levels at 3 weeks of age became non-significant (*P*-value = 0.057) after adjustment for the covariate with the strongest influence on the association (birth weight), but further adjustment of the association with alcohol consumption, age of the mother and sex of the infant made the association significant again (*P*-value = 0.048) (adjusted coefficients with 95% CI not provided). In contrast, the positive association between TSH levels at 3 months of age and prenatal di-*ortho*-substituted PCB exposure became non-significant (*P*-value = 0.093) after adjustment of the association for sex of the infant, which was the potential confounder with the strongest influence on the association (adjusted coefficients with 95% CI not provided) (Darnerud et al., 2010). In this study, no association was reported between thyroid hormone levels and the sum of the concentrations of the four DL-PCB congeners analysed.

(b) Diabetes

In the polybrominated biphenyls (PBBs) cohort in Michigan, USA, who were exposed to PBBs via their food due to accidental contamination of cattle feed in the 1970s, the incidence of diabetes assessed during a 25-year follow-up of more than 1000 participants was associated with concentrations of PCBs measured as

Aroclor 1016, 1254 or 1260 in serum collected at baseline (Vasiliu et al., 2006). In a cohort of Great Lakes sport fish consumers (Wisconsin, USA) formed in 1990, in a cross-sectional analysis of data from 2004 to 2005, the concentration of total PCBs (the sum of the concentrations of 19 congeners, including the DL-PCB, PCB 118) in serum was not associated with the prevalence of self-reported diagnosis of diabetes (Turyk et al., 2009a). In the same cohort, concentrations of PCBs were assessed prospectively in patients free of diabetes in 1994–1995 and followed through 2005. The incidence of diabetes was not associated with the baseline concentrations of a sum of 18 PCB congeners (including PCB 118) in serum (Turyk et al., 2009b). In adult subjects from three regions from eastern Slovakia, the prevalence of diabetes (from level of fasting plasma glucose, oral glucose tolerance test or diabetes diagnosed and treated by a physician) was significantly associated with increasing concentrations of the sum of 17 PCB congeners (Ukropec et al., 2010). In these studies, PCB exposure referred to a mixture of PCBs, including some DL-PCB congeners, and results for individual congeners were not reported. Therefore, these studies do not provide any relevant information on the potential association between diabetes and exposure to NDL-PCBs.

(i) Cross-sectional analyses

In a cohort of professional fishermen and their wives (aged 49–77 years) from the Swedish east coast, the participants were asked if they had diabetes and, if so, since which year; moreover, they were asked if they were taking oral antidiabetic drugs or insulin or were on a diet. In a cross-sectional analysis, the prevalence of diabetes, adjusted for potential confounders, was significantly associated with increased concentration of PCB 153 in serum (Rylander, Rignell-Hydbom & Hagmar, 2005). In an analysis of the previous cohort, there was also a significant association between higher concentrations of PCB 153 in serum and prevalence of type 2 diabetes among women (Rignell-Hydbom, Rylander & Hagmar, 2007).

In the adult population of the USA from the NHANES 1999–2002, the participants were considered to have diabetes if their fasting plasma glucose was ≥126 mg/dL, their non-fasting plasma glucose was ≥200 mg/dL or they reported a history of physician-diagnosed diabetes. Compared with subjects with concentrations of PCB 153 in serum below the LOD, after adjustment for age, sex, race and ethnicity, poverty income ratio, BMI and waist circumference, diabetes prevalence was strongly positively associated with lipid-adjusted concentrations of PCB 153 in serum (Lee et al., 2006). In the NHANES 2002–2004, a positive finding of diabetes (type 2 diabetes) for a participant was determined if glycosylated haemoglobin was ≥6.5% or if the participant answered "yes" to the question, "Have you ever been told by a doctor or health professional that you

have diabetes or sugar diabetes?". A positive association of prevalence of diabetes with concentration of PCB 153, as well as with concentrations of the DL-PCBs, PCB 118 and PCB 126, was observed (Hofe et al., 2014).

In a cross-sectional study of an adult (≥30 years) Native American (Mohawk) population (New York, USA), fasting serum samples were analysed for 101 PCB congeners. Participants who had fasting glucose values above 125 mg/dL or who were taking antidiabetic medication were defined as persons with diabetes. The prevalence of diabetes was associated with higher concentrations of PCB 153 and PCB 74 in serum; however, this association became non-significant after adjustment for concentrations of other analytes (DDE, HCB and mirex) in serum (Codru et al., 2007).

From 1999 to 2002, the Greenland population study was carried out among adult Inuit living in Greenland. Thirteen PCB congeners were measured in the serum of participants. Participants were asked whether a physician had ever told them that they had diabetes, in which case a fasting venous plasma glucose measurement was taken. All other participants had an oral glucose tolerance test. No significant associations were observed between the prevalence of diabetes or impaired glucose tolerance and concentrations of NDL-PCBs (sum of PCBs 28, 52, 99, 101, 128, 138, 153, 163, 170 and 180) in serum (Jørgensen, Borch-Johnsen & Bjerregaard, 2008).

Concentrations of eight PCB congeners were measured in serum from adults (≥15 years) from a First Nations community in northern Ontario, Canada. A significant association was observed between the prevalence of self-reported diabetes and concentrations of PCB 153 and PCB 74 (Philibert, Schwartz & Mergler, 2009).

In a study performed among the participants, aged 40–64 years, in a Control Obesity Program in Saku, Japan, concentrations of 13 PCB congeners were measured in blood. Subjects with a fasting plasma glucose concentration of ≥126 mg/dL, a glycated haemoglobin (HbA1c) level of ≥6.5%, a prescription for hypoglycaemic medicine or a history of physician-diagnosed diabetes were defined as having diabetes. A significant association with prevalence of diabetes was observed for higher concentrations of PCB 180, but no association was found for other NDL-PCB congeners (PCB 138, 153 or 180) (Tanaka et al., 2011).

In a study of previous employees in a capacitor manufacturing plant in Illinois, USA, a cross-sectional analysis was carried out with data collected in 1996 on postmenopausal women. Concentrations of 38 PCB congeners were measured in blood, and diabetes was defined as an affirmative answer to the question, "Have you ever been diagnosed by a doctor as having diabetes mellitus or high blood sugar?". A significant increase in prevalence of diabetes was associated with higher concentrations of NDL-PCBs (sum of 31 congeners) and

estrogenic PCBs (sum of PCBs 52, 99, 101, 110 and 153) in serum (Persky et al., 2011).

A cross-sectional study was carried out in elderly participants (aged 57–70 years) from the Helsinki Birth Cohort Study in Finland, which represents a general adult urban Finnish population. The diagnosis of diabetes was based on an oral glucose tolerance test and the WHO (1999) criteria for glucose intolerance. A positive but non-significant association was observed between the prevalence of diabetes and higher concentrations of PCB 153 (Airaksinen et al., 2011).

Volunteers from a cross-sectional study of randomly selected adults (≥18 years) from the Anniston community in Alabama, USA, completed a health survey and underwent measurements of fasting glucose and 35 PCB congeners in serum. Diabetes was defined as self-report of physician-diagnosed diabetes or a fasting glucose level above 125 mg/dL. No significant association was found between the prevalence of diabetes and the concentrations of two groups of NDL-PCBs in serum: estrogenic congeners (PCBs 44, 49, 66, 74, 99, 110 and 128) and di-*ortho*-substituted, tri-*ortho*-substituted and tetra-*ortho*-substituted PCBs (20 congeners, including PCBs 52, 101, 138, 153 and 180) (Silverstone et al., 2012).

In a representative sample of the general adult population of Catalonia, Spain, aged 18–74 years, concentrations of PCBs 28, 52, 101, 118, 128, 153 and 180 were analysed in serum from blood samples obtained during the health examination of the Catalan Health Survey. Participants were considered to have diabetes if their fasting plasma glucose level was ≥126 mg/dL, they answered affirmatively to the question, "Do you have or did a doctor tell you that you have diabetes?" or they reported a current use of insulin or antidiabetic medication. The prevalence of diabetes increased in a dose-dependent manner across concentration quartiles of PCBs 138, 153 and 180, as well as the DL-PCB, PCB 118 (Gasull et al., 2012).

In a hospital-based cross-sectional study among adults (>16 years) from Granada, Spain, concentrations of PCBs 138, 153 and 180 were measured in serum and adipose tissue samples. The prevalence of diabetes was assessed using both self-reported information and clinical records. In multiple logistic models adjusted for age, sex, BMI and adipose tissue of origin, no significant associations were found between the prevalence of diabetes and the concentrations of PCB 138, PCB 153 or PCB 180 in adipose tissue (Arrebola et al., 2013).

(ii) Prospective studies

A case–control study was performed within a well-defined cohort of women aged 50–59 years (the Women's Health In the Lund Area cohort) from the southern part of Sweden. Several biomarkers, including PCB 153 concentration, were analysed in stored serum samples from blood collected at the baseline

examination (1995–2000). Women with previously confirmed diabetes or with prevalent diabetes according to plasma glucose level or oral glucose tolerance test assessed at recruitment were excluded from this study. By linkage with the Swedish inpatient and outpatient registers, 410 women from the cohort who had developed type 2 diabetes before 31 December 2006 were identified (cases). One control per case was randomly selected from the cohort and matched for age, calendar year, BMI and the presence or absence of any features of metabolic syndrome. No association was found for the risk of diabetes in relation to PCB 153 exposure; the OR estimated by means of conditional logistic regression (adjusted for the matching variables) was 0.99 (95% CI 0.71–1.40), comparing women with PCB 153 concentrations in serum above 1790 μg/mL (the 75th percentile) with women with PCB 153 concentrations in serum at or below 1790 μg/mL. However, this association tended to increase with the time of follow-up; for instance, when only cases (and their matched controls) diagnosed more than 7 years after the baseline examination were included, the OR was 1.6 (95% CI 0.61–4.0) (Rignell-Hydbom et al., 2009).

The risk of type 2 diabetes was investigated within the Coronary Artery Risk Development in Young Adults (CARDIA) cohort, with participants at baseline (1985–1986) in four centres from the USA (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California); follow-up examinations were completed at years 2, 5, 7, 10, 15 and 20 (2005–2006). Individuals were eligible for the current study if they had had no diagnosis of diabetes at years 0 and 2 and if they had been diagnosed with type 2 diabetes at any subsequent examination. Diabetes was defined as ever having taken antidiabetic medications or ever having had a fasting glucose level of ≥126 mg/dL at two or more examinations during the 18 years of follow-up. Concentrations of a total of 35 PCB congeners were measured in blood samples collected at baseline. No significant ORs (adjusted for age, sex, race, BMI, and triglyceride and total cholesterol levels at year 2) were observed across quartiles of any of the 12 congeners analysed individually (including PCB 153) or different groups of PCBs (Lee et al., 2010).

In the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study in elderly subjects (70 years of age) from Uppsala, Sweden, concentrations of 14 PCBs were measured in plasma collected at baseline (2000–2004). During 2006–2009, when the subjects turned 75 years of age, reinvestigation of the cohort was performed; using this information, type 2 diabetes was defined as a fasting blood glucose level above 6.2 mmol/L or the use of insulin or oral hypoglycaemic agents. After adjustment for sex, BMI, cigarette smoking, exercise, alcohol consumption, triglyceride level and total cholesterol level, there was a significant trend of increasing risk of type 2 diabetes across quintiles of concentration of PCBs 74, 99, 194 and 206. In contrast, significant

ORs were found when comparing the risk of diabetes in subjects in the fifth quintile with those in the first quintile of PCB 174 and PCB 180 concentrations, as well as for the fourth concentration quartile for PCB 153 (OR 3.4, 95% CI 1.1–10.2), PCB 138 (OR 5.9, 95% CI 1.6–21.7) and PCB 170 (OR 5.0, 95% CI 1.2–20.5); in these cases, non-significantly increased risks were also found in the fifth quintile. No significant ORs were reported for the four DL-PCBs analysed (PCBs 105, 118, 156 and 157) (Lee et al., 2011a).

Concentrations of the four most abundant PCB congeners (PCBs 118, 138, 153 and 180) were measured in plasma from blood drawn in 1989–1990 from 1095 women who were free of diabetes and participated in two nested case–control studies in the Nurses' Health Study, with cases identified through June 2008. Diagnosis of diabetes was based upon self-reported information on symptoms, diagnostic tests and treatment, using criteria of the American Diabetes Association (1997) to confirm the cases. No significant increase in risk of type 2 diabetes was observed across tertiles of any of the congeners analysed. The OR for the third versus the first tertile of lipid-standardized plasma concentration of PCB 153, adjusted for age, smoking status, alcohol intake, physical activity, family history of diabetes and baseline BMI, was 1.36 (95% CI 0.59–3.10). Furthermore, no significant association for any of the four congeners was observed after pooling the results of these two case–control studies with those of six published prospective studies including 842 diabetes cases in total (Wu et al., 2013).

(iii) Type 1 diabetes

All the studies reviewed so far (either cross-sectional or prospective studies) dealt with adult or type 2 diabetes. Only one study was identified on the relationship between PCB concentrations and type 1 diabetes. The study was performed as a case–control study within a biobank in Malmö, southern Sweden, and included 150 cases (children who had their diagnosis mostly before 18 years of age) and 150 controls, matched for sex and day of birth. The concentration of PCB 153 was measured in venous blood samples from mothers and umbilical cord blood samples obtained routinely at the hospital maternity unit. Cases were children born from 1970 to 1990 who developed type 1 diabetes before the year 2002. The vast majority (88%) were diagnosed before the age of 18 years and were diagnosed and treated at the Department of Paediatrics at Malmö University Hospital. Patients who developed type 1 diabetes between 18 and 27 years of age were identified through the Diabetes Incidence Study in Sweden registry. When comparing the quartile with the highest concentrations of PCB 153 in maternal serum with the lowest quartile, an OR of 0.64 (95% CI 0.32–1.29) was obtained (Rignell-Hydbom et al., 2010).

(c) Obesity and metabolic-related conditions

(i) Obesity in adults: prospective studies

A two-generation study was carried out in 11 communities of Lake Michigan, USA; prenatal exposure to PCBs was estimated from maternal blood collected at delivery, and anthropometric measurements were taken in the female offspring aged 20–50 years. Prenatal PCB concentrations were not associated with height, weight or BMI in female offspring. However, no details about individual congeners were provided, and therefore no relevant information can be derived on the relationship between NDL-PCBs and BMI (Karmaus et al., 2009).

In the CARDIA cohort in four centres from the USA described above, measurements of 22 PCBs in blood samples taken at baseline were compared with BMI and other factors related to insulin resistance after 20 years of follow-up in subjects free of diabetes. There was a significant (or marginally significant) trend to a decrease in BMI across quartiles of concentration of PCB 194, PCBs 196 + 203 and PCB 209, adjusted for age, sex, race, triglyceride level and total cholesterol level. No associations were observed for PCB 153 or PCB 180 (Lee et al., 2011b).

In the population-based PIVUS study in Uppsala, Sweden, described above, concentrations of 14 PCBs measured in plasma collected at baseline from elderly subjects (70 years of age) were compared with waist circumference after a 5-year follow-up. There was a non-significant trend to a decreased waist circumference across quintiles of individual PCB concentrations in men, but there were significant associations in women for PCBs 170, 180, 194 and 106, as well as for two DL-PCB congeners, PCBs 156 and 189. For PCB 153, the OR for the fifth versus the first quintile, adjusted for calorie intake, exercise, cigarette smoking, alcohol consumption, triglyceride level and total cholesterol level, was 0.3 (95% CI 0.1–1.1) (Lee et al., 2012).

(ii) Obesity in children: prospective studies

In a population-based birth cohort study (Asthma Multicentre Infants Cohort Study [AMICS]–INMA) from Menorca, Spain, the concentrations of seven PCB congeners (PCBs 28, 52, 101, 118, 138, 153 and 180) in cord blood were compared for those overweight at 6.5 years, defined as a BMI *z*-score at or above the 85th percentile of the WHO reference values. There was a significant increase in relative risk (RR) of overweight for the third compared with the first tertile of the sum of the concentrations of the seven PCB congeners, adjusted for birth weight, previous parity, maternal pre-pregnancy BMI, maternal education and social class at pregnancy, maternal smoking in pregnancy, maternal age at delivery and breastfeeding. This RR became non-significant when additionally adjusted for concentrations of HCB and DDT/DDE in cord blood. No results for individual

congeners were provided (Valvi et al., 2012). Although it is likely that the highest contribution to the sum of PCBs in this study comes from NDL-PCB congeners, the group includes PCB 118, a DL-PCB congener. Therefore, these results cannot be linked to NDL-PCB exposure.

A birth cohort formed in the Faroe Islands was established in 1997–2000. Prenatal exposure to PCBs was determined from maternal concentrations of PCBs in pregnancy serum (blood obtained at gestational week 34) and milk. Total NDL-PCBs was defined as the sum of the concentrations of PCB 138, PCB 153 and PCB 180. Subsequent BMI was measured in children at 5 and 7 years of age. No associations were observed between PCB concentrations and BMI in boys, 5-year-old girls or 7-year-old girls with normal weight mothers. For 7-year-old girls who had overweight mothers, PCB concentrations were associated with increased BMI (β 2.07, *P*-value = 0.007) and with an increase in BMI from 5 to 7 years of age (β 1.23, *P*-value = 0.003). PCB concentration was associated with increased waist circumference in girls with overweight mothers (β 2.48, *P*-value = 0.001) and normal weight mothers (β 1.25, *P*-value = 0.04) (Tang-Péronard et al., 2014).

(d) Insulin resistance and metabolic syndrome

Cross-sectional analyses were carried out in non-diabetic participants from the NHANES to assess the relationship between metabolic syndrome (Lee et al., 2007a) and insulin resistance (Lee et al., 2007b) and concentrations of five NDL-PCBs (PCBs 138, 153, 170, 180 and 187) and four DL-PCBs in serum. Metabolic syndrome was diagnosed if a subject satisfied at least three of the following criteria: waist circumference >102 cm (men) or >88 cm (women), triglyceride level ≥1.7 mmol/L, high-density lipoprotein (HDL)–cholesterol level <1.1 nmol/L (men) or <1.4 mmol/L (women), average blood pressure ≥130/85 or currently taking hypertension medication, and fasting serum glucose level ≥5.6 mmol/L. The NDL-PCBs showed a significant, inverse, U-shaped association, with adjusted quartile ORs of 1.0, 1.3, 1.8 and 1.0, with a significant quadratic term. Insulin resistance was estimated using the homeostasis model assessment method, calculated as fasting insulin [mU/L] × fasting glucose [mmol/L]/22.5). Adjusted prevalence (homeostasis model assessment insulin resistance above its 90th percentile) was significantly associated with higher concentrations of PCB 170 and PCB 187 in serum; no associations were observed with the concentrations of other PCB congeners (PCBs 138, 153 and 180).

In the CARDIA cohort study described above for BMI, the relationship between the concentrations of 22 PCBs at baseline and insulin resistance after 20 years of follow-up was also analysed prospectively in subjects free of diabetes. No significant associations were observed for increased homeostasis model

assessment insulin resistance across quartiles of concentration of any of the NDL-PCBs measured, including PCBs 138, 153 and 180 (Lee et al., 2011b).

2.3.8 Reproductive and sexual function

In female Yucheng (see section 2.3.2) adolescents aged 13–19 years, there was a higher rate of irregular menstrual cycle, shorter mean duration of bleeding and higher levels of estradiol compared with controls (Yang et al., 2005). However, no significant differences in menstrual cycle characteristics or age at menarche were reported between adult Yucheng women (mean age 39 years) and age-matched controls (Yang et al., 2011). In boys born to exposed Yucheng women, the estradiol levels in serum at puberty (>12 years) were higher than in controls, and testosterone levels and FSH activities were lower than in controls (Hsu et al., 2005). In Yucheng women, a significant increase in time to pregnancy and a significantly higher infertility ratio compared with controls were observed (Yang et al., 2008). For Yusho patients (see section 2.3.2) during the first 10-year follow-up, there were higher rates of induced and spontaneous abortions and preterm delivery compared with controls (Tsukimori et al., 2008), and a low sex ratio (proportion of male births) was reported in the second generation of Yusho women (Tsukimori et al., 2012). Levels of free testosterone, FSH, LH and sex hormone binding globulin (SHBG) were not significantly associated with the sum of the concentrations of all PCBs in serum from male Great Lakes fish consumers (Turyk et al., 2006). In 9-year-old girls from New York, USA, breast development was reduced among those with a higher sum of the concentrations of four PCB congeners (PCBs 118, 138, 153 and 180) and low (below median) BMI (Wolff et al., 2008). In offspring of a female cohort in Michigan, USA, there was an increased but non-significant OR for a male birth for higher parental exposure to PCBs (measured as Aroclor 1254) (Terrell et al., 2009). However, secondary sex ratio was not associated with occupational exposure to PCBs in female workers in three electrical capacitor manufacturing plants in the USA (Rocheleau et al., 2011). In a Russian study, higher PCB concentration (sum of 41 congeners) in maternal serum was associated with earlier pubertal onset in 8- to 9-year-old boys followed for 4 years (Humblet et al., 2011). In middle-aged (41–55 years) males from three regions in Slovakia, no significant correlation was observed between concentrations of testosterone and total PCBs (sum of 15 congeners) in serum (Langer et al., 2012). In a birth cohort in Duisburg, Germany, the association between maternal exposure to PCBs (sum of 18 congeners) and behavioural sexual dimorphism was examined using Pre-school Activities Inventory (PSAI), consisting of 24 items grouped into three categories: preferred toys (e.g. guns, dolls), preferred activities (e.g. playing house, fighting) and behavioural characteristics (e.g. enjoys rough and tumble play, likes pretty

things). Exposure to dioxins and PCBs in boys was associated with more feminine behaviour, whereas exposure in girls was associated with less feminine behaviour (Winneke et al., 2014).

In all these studies, exposure to PCBs involved complex mixtures of PCB congeners, often unknown, but in most instances including both DL- and NDL-PCB congeners; moreover, results for individual congeners were not reported. Therefore, these studies do not provide any relevant information regarding the potential health effects of NDL-PCBs.

(a) Male reproductive function

(i) Cross-sectional studies

Fishermen aged 27–67 years from the west and east coasts of Sweden provided semen and blood for the analysis of hormones and PCB 153. The proportion of Y and X chromosome–bearing sperm in semen samples was determined by fluorescence in situ hybridization (FISH) analysis. The log-transformed lipid-adjusted PCB 153 concentration was significantly (*P*-value = 0.05) associated with the Y chromosome fraction (β 0.42, 95% CI 0.01–0.83) (Tiido et al., 2005).

In a cross-sectional study of men seeking infertility evaluation from the Massachusetts General Hospital, Boston, Massachusetts, USA, FISH for chromosomes X and Y was used to assess sex chromosome disomy in sperm nuclei, and serum was analysed for concentrations of 57 PCB congeners. Significant increases in the rate of XY and total sex chromosome disomy and a decrease in XX disomy were observed across quartiles for the sum of estrogenic PCBs (PCBs 44, 49, 52, 101, 187, 174, 177 and 157 + 201) (McAuliffe et al., 2012).

Semen samples from Faroese men were obtained from three cohorts. The UM cohort consisted of young volunteers from the general population who had been born in 1981–1984; the K1S cohort was generated from consecutive births at the three Faroese hospitals in 1986–1987; and the K5P cohort consisted of men whose pregnant partner participated in a study focusing on fertility and environmental factors. Concentrations of PCBs 138, 153 and 180 were measured in the serum from blood collected from 499 male subjects. The Y:X ratio (measured in semen by FISH) was not significantly associated with the concentration of PCBs (sum of log-transformed concentrations of three congeners multiplied by 2) in serum in the total cohort. However, a statistically significant negative association was found in the K5P subcohort (*P*-value = 0.030) (Kvist et al., 2014).

A cross-sectional study involving Inuit from Greenland, Swedish fishermen and men from Warsaw, Poland, and Kharkiv, Ukraine, with a total of 707 adult males aged 18–67 years, was carried out. Semen and blood samples were collected between 2002 and 2004 for the measurement of concentrations of PCB 153 in serum and several indicators or markers of male reproductive function.

A sperm chromatin structure assay was used to assess sperm DNA/chromatin integrity, and a strong and monotonically increasing DNA fragmentation index was observed with increasing concentrations of PCB 153 in serum among European but not Inuit men, reaching a 60% higher average level in the highest-exposure group (Spanò et al., 2005). No significant association was found with sex hormones, but there were differential results across centres: in Kharkiv, statistically significant positive associations were found between concentration of PCB 153 and SHBG and LH levels; in Greenland, there was a positive association with LH level (Giwercman et al., 2006). As for the relationship between PCB 153 concentration in serum and indicators of epididymal and accessory gland function (measured in seminal plasma), a negative association with the activity of neutral α-glucosidase was found in the aggregated cohort, a positive association was observed between PCB 153 and prostate-specific antigen as well as zinc level among Kharkiv men, and a negative association was found between PCB 153 and fructose level in the Swedish cohort (Elzanaty et al., 2006). In relation to sperm quality, sperm motility decreased across all four regions, on average by 3.6% (95% CI 1.7–5.6%) per one unit increase in the log of PCB 153 concentration in blood (ng/g lipid). No associations were found for sperm concentration or the proportion of morphologically normal sperm (Toft et al., 2006). In the Swedish cohort, log-transformed PCB 153 concentration was significantly positively associated with Y chromosome fractions (P-value = 0.04), whereas in the Polish cohort, PCB 153 concentration correlated negatively with the proportion of Y-bearing fraction of spermatozoa (P-value = 0.008) (Tiido et al., 2006). Finally, an article summarizing the main results from several publications on these four populations concluded that (1) an association between high PCB 153 concentrations in serum and low sperm counts was detected within a subgroup of men with short androgen receptor CAG repeat length; (2) a relationship between increased PCB 153 concentrations in serum and decreased sperm motility was seen in all four studied regions, and indications of reduced neutral α-glucosidase activity in seminal plasma point to a post-testicular effect; and (3) in Greenlandic Inuit, impairment of sperm chromatin integrity was related to PCB 153 concentration. Despite these effects, fertility in terms of time taken to conceive was not related to PCB 153 concentration in serum, except in Inuit (Bonde et al., 2008).

(ii) Prospective and case–control studies

All men aged 50–80 years who visited a group of five urologists for various conditions from 1997 to 1999 in Kingston, Ontario, Canada, were potentially eligible for this study. Cases were 101 men with a clinical diagnosis of erectile dysfunction at the time of study enrolment; controls comprised all

other participants who were not suspected on a clinical basis to have erectile dysfunction (234 men) and who had been diagnosed with a variety of benign urological conditions. Concentrations of a total of 14 PCB congeners (PCBs 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183 and 187) were measured. No associations were found between erectile dysfunction and concentrations of any of the congeners analysed (Polsky et al., 2007).

In a birth cohort formed in 1986–1987 in the Faroe Islands, prenatal exposure was determined from maternal concentrations of PCBs in pregnancy serum (blood obtained at gestational week 34) and milk; total NDL-PCB concentration was defined as the sum of the concentrations of PCB 138, PCB 153 and PCB 180. At age 14 years, a total of 438 boys participated in a clinical examination to assess Tanner stage for puberty development (based upon pubic hair and genital development), and a venous blood sample was obtained to measure the concentrations of sex hormones and binding proteins in serum. Regression analysis was carried out with LH, testosterone and SHBG as dependent variables, with adjustment for age, BMI, history of cryptorchidism and time of blood sampling. The free fraction of testosterone, as expressed by the testosterone/SHBG ratio, and LH were inversely related to the concentration of PCB 153 (*P*-values = 0.016 and 0.023, respectively), whereas SHBG level was positively associated with the concentration of PCB 153 (*P*-value = 0.003). After additional adjustment for Tanner stage, only the result for SHBG remained statistically significant (β 0.08, *P*-value = 0.03). As both variables were log transformed, this value corresponds to an increase in SHBG level (nmol/mL) by about 6% for each doubling in the concurrent PCB exposure (Grandjean et al., 2012).

A case–control study was carried out within a screening study during 2002–2004 in two hospitals from Nice, France. Diagnosis of cryptorchidism was accepted after at least two concordant examinations by a senior paediatrician before discharge; babies were followed at 3 and 12 months to confirm the diagnosis. In a total of 78 cases and 86 controls, concentrations of seven PCB congeners (the six indicator PCBs and PCB 118) were measured in cord blood and maternal milk. No significant differences were observed between median concentrations (in cord blood or milk) of any of the measured PCBs in cases and controls. In the analysis using logistic regression after adjustment for gestational age, birth weight, maternal BMI before pregnancy, maternal age, parity, season of birth, paternal history of cryptorchidism and city of delivery, the OR for cryptorchidism at birth, comparing above with below sum of the median concentrations of all measured PCBs in maternal milk, was 2.74 (95% CI 1.15–6.53); however, the OR became non-significant for cryptorchidism at 3 months. Moreover, it should be taken into account that total PCBs included six NDL-PCBs plus the DL-PCB congener, PCB 118 (Brucker-Davis et al., 2008).

The Collaborative Perinatal Project enrolled pregnant women in 12 United States medical centres during 1959–1965. For the present study, third-trimester blood samples from mothers and 230 sons with cryptorchidism, 201 with hypospadias and 593 with neither condition were analysed to measure concentrations of 11 PCB congeners in serum (McGlynn et al., 2009b). In the analysis by logistic regression, adjusting for study centre and DDE concentration in serum, no significant ORs were observed between either cryptorchidism or hypospadias and higher concentrations of any of the PCBs measured. A significant increase of 69% in risk of hypospadias was associated with the highest versus the lowest quartile of the concentration of all PCBs. However, it must be kept in mind that the group of 11 measured PCBs included two DL-PCBs (PCBs 15 and 118).

A study was carried out on 80 children with hypospadias and 80 healthy controls, recruited during 2005–2007 in two hospitals in Rome, Italy, where children with hypospadias are surgically treated. Cases were defined as children aged 0–24 months who were suffering from any form of hypospadias that required surgical treatment, and controls were defined as healthy male children aged 0–24 months without any congenital defect who were attending the Outpatient Vaccination Service of the same hospital. Data on occupational and dietary exposures to polychlorinated compounds (without further specification) in the perinatal period were collected; maternal exposure to four PCB congeners (PCBs 118, 130, 153 and 180) was also ascertained in blood samples taken 8–12 months after delivery from a subset of cases and controls. No association was observed with any of the measured PCBs (Giordano et al., 2010). It should be noted that exposure was measured several months after the outcome; although concentrations of persistent compounds in serum can be an indicator of past exposure, this study cannot be strictly seen as a prospective study.

(b) Female reproductive function

A cross-sectional analysis was carried out among Akwesasne Mohawk Nation girls, 10–16 years of age, resident in the proximity of the St Lawrence River in New York State, USA, and in Ontario and Quebec, Canada. Blood samples and sociodemographic data were collected, and attainment of menses (menarche) was assessed as present or absent at the time of the interview. The 16 PCBs detected in more than 50% of the samples were grouped (Wolff's groups). The OR for attainment of menarche was 8.39 (P-value = 0.04) for an increase in one unit in the log scale of the sum of the concentrations of four PCBs in the Wolff's group of estrogenic PCBs (PCBs 52, 70, 101 and 187) (Denham et al., 2005).

A study was carried out among women born between 1960 and 1963 in the Oakland area, California, USA; these women and their mothers were among

participants in the Child Health and Development Study. PCBs were measured in mothers' preserved serum samples collected 1–3 days after their daughters' birth, and time to pregnancy in daughters 28–31 years later was recorded. The fecundability ratio (ratio of probability of pregnancy in each cycle for daughters exposed to higher versus lower PCB concentrations in utero) was estimated by Cox regression; a fecundability ratio above 1 indicates a greater probability of pregnancy per cycle and therefore a shorter time to pregnancy. Increasing concentrations of PCB 99 and PCB 187 were significantly associated with higher infertility (ORs of 0.75 and 0.44, respectively, for 1 standard deviation of concentration in serum), whereas higher concentrations of PCB 138 were associated with higher probability of pregnancy (OR of 1.99 [95% CI 1.45–2.75] for 1 standard deviation of concentration in serum). Significant associations were also found for the DL-PCB congeners, PCBs 105 and 156 (Cohn et al., 2011). Analysis of mixtures of PCBs may be problematic, as components have a complex correlation structure, and, along with limited sample sizes, standard regression strategies are problematic. A novel weighted quantile sum approach indicated that the dominant functionality groups associated with longer time to pregnancy were the dioxin-like, anti-estrogenic group (average weight, 22%). In contrast, in the association with shorter time to pregnancy, the anti-estrogenic group and the phenobarbital inducers group (phenobarbital, CYP1A and CYP2B inducers) played a more important role (60% and 23%, respectively) (Gennings et al., 2013).

(c) Effects on reproductive and sexual function assessed in both males and females

A cross-sectional study was carried out in Akwesasne Mohawk adults, aged 18–95 years, resident along the St Lawrence River near the junction of New York State, USA, and Ontario and Quebec, Canada, for at least 5 years. Fasting serum samples were analysed for 101 PCB congeners, as well as testosterone, cholesterol and triglycerides. Testosterone levels in males were significantly and inversely related to concentrations of PCBs 74, 99 and 153, whereas testosterone levels were much lower in females than in males and not significantly related to concentrations of PCBs in serum. A significant inverse association was also found between testosterone level and the sum of the concentrations of DL-PCB congeners (Goncharov et al., 2009).

In a birth cohort study initiated in the year 2000, healthy mother–infant pairs were recruited in Duisburg, Germany. Concentrations of PCBs (the six indicator PCBs, PCBs 28, 52, 101, 138, 153 and 180, and 12 DL-PCB congeners) were measured in maternal blood during pregnancy (32 weeks) and in maternal milk. Testosterone and estradiol levels were measured in maternal and cord serum of a subsample of mother–infant pairs. Linear regression analysis was used to describe the association of PCB concentrations in maternal blood or milk

with sex steroid concentrations after adjustment for age of mother, nationality of mother, BMI of mother before pregnancy, length of gestation, birth weight, alcohol consumption during pregnancy and smoking during pregnancy. There was a significant reduction in testosterone level in cord serum of girls related to the sum of the concentrations of the six indicator PCBs in maternal blood, but not in boys; among girls, the change in geometric mean of hormone concentrations with a doubling of the sum of the concentrations of the six indicator PCBs, expressed as a mean ratio, was 0.76 (95% CI 0.61–0.96) (Cao et al., 2008).

In the Child Health and Development Study described above, serum specimens were collected from pregnant women from the San Francisco Bay area, California, USA. Concentrations of a total of 11 PCBs were determined in specimens collected during the second or third trimester of gestation, and the secondary sex ratio, or sex ratio at birth, was evaluated as a function of maternal serum concentrations. There were inverse associations between the risk of a male birth and concentrations of most NDL-PCBs measured, although none of them was significant. The RRs for a male birth for a given increase in PCB concentration from the 10th to the 90th percentile, adjusted for specimen characteristics and an indicator of a prescription for sex steroids, oral contraceptives or corticosteroids, were 0.82, 0.82 and 0.85 for PCB congeners 138, 153 and 180, respectively. There was a significantly decreased risk for a male birth associated with the sum of the concentrations of all measured PCBs (PCB congeners 105, 110, 118, 137, 138, 153, 170, 180 and 187), which includes both NDL- and DL-PCB congeners (Hertz-Picciotto et al., 2008).

In a cohort of pregnant women 25–34 years of age and newborns from a general population in central Taiwan, China, concentrations of 27 PCBs were measured in placental tissue. Children were examined at 8 years of age, and bone age, sex hormone concentrations and indicators of reproductive development, including Tanner, breast, genital and armpit stages, were assessed. No significant association was observed between the concentration of indicator NDL-PCBs (sum of PCBs 138, 153 and 180) and any indicators of reproductive development, except for a significant association with lower fundus length of the uterus for in utero exposure to increased concentrations of indicator PCBs in girls; the OR for high versus low (according to the median) PCB concentrations and fundus length above versus below the median was 0.08 (95% CI 0.01–0.83). In the same study, no significant associations were found for dioxin compounds (Su et al., 2012).

2.3.9 Immune function and related outcomes

This section includes a diversity of outcomes, including thymus size, levels of immunoglobulins (Igs) in blood, blood leukocyte counts and other outcomes.

Infections would be included in this section as well, but as all the studies dealing with infections and PCB exposure addressed respiratory infections, they have been reported in section 2.3.11 below, together with other respiratory effects.

Second-grade schoolchildren, aged 7–10 years, were recruited in the state of Hesse, Germany. Several immune function biomarkers were measured in blood, together with concentrations of eight PCBs (PCBs 110, 118, 138, 153, 170, 180, 183 and 187) in serum. In a cross-sectional analysis, the sum of PCB concentrations was significantly associated with increased IgM levels (Karmaus et al., 2005). No results for individual congeners were provided. Although it is likely that the highest contribution to the sum of PCB concentrations comes from NDL-PCB congeners, the group includes PCB 118, a DL-PCB congener. Therefore, these results cannot be linked to NDL-PCB exposure.

In mothers recruited in 2002–2004, at the time of delivery, from two districts in eastern Slovakia (Michalovce and Svidnik), blood samples were collected at delivery for measurement of the concentrations of 15 PCBs (PCBs 28, 52, 101, 105, 114, 118, 123, 138, 153, 156, 157, 167, 170, 180 and 189). Thymus volume was measured in infants shortly after birth and at ages 6 and 16 months using ultrasonography. Prenatal PCB exposure was associated with a smaller thymic index at birth (Park et al., 2008), whereas PCB concentration was not predictive of 6- or 16-month thymus volume (Jusko et al., 2012). The exposure refers to a mixture of PCBs, including DL- and NDL-PCBs, and therefore these results cannot be linked to NDL-PCB exposure.

In this same cohort from Slovakia, in addition to maternal blood, cord blood and blood from infants at 6 months were collected. IgG, IgA and IgM levels were measured in the blood collected at 6 months. PCB concentrations in maternal, cord or 6-month infant blood were not associated with total immunoglobulin levels in serum at 6 months, regardless of the timing of PCB exposure, PCB congener or specific immunoglobulin. Congener-specific results were not reported (Jusko et al., 2011). Concentrations of IgG-specific anti-*Haemophilus influenzae* type b, tetanus toxoid and diphtheria toxoid were assayed in 6-month infant sera using enzyme-linked immunosorbent assay (ELISA) methods. Overall, there was no evidence of an association between infant antibody concentrations and PCB measures during the prenatal and early postnatal period. Specific results were reported for PCB 138, PCB 153, PCB 170 and PCB 180, with no significant results for any of them (Jusko et al., 2010).

Two birth cohorts were formed in the Faroe Islands: in 1994–1995, a cohort of births was established from consecutive spontaneous singleton births at term; and during 1999–2001, an additional birth cohort was formed using similar criteria. Prenatal exposure was determined from concentrations of PCBs in pregnancy serum (blood obtained at gestational week 34) and maternal milk; total NDL-PCB concentration was defined as the sum of the concentrations

of PCB 138, PCB 153 and PCB 180. Following routine childhood vaccinations against tetanus and diphtheria, 119 children were examined at 18 months and 7 years of age, and their serum samples were analysed for tetanus and diphtheria toxoid antibodies. The antibody response to diphtheria toxoid decreased at 18 months by 24.4% (95% CI 1.63–41.9) for each doubling of the cumulative PCB exposure, but there was no association at age 7 years. The tetanus toxoid antibody response was affected mainly at age 7 years, decreasing by 16.5% (95% CI 1.51–29.3) for each doubling of the prenatal exposure, whereas no association was observed at 18 months (Heilmann et al., 2006). In the subcohort 1999–2001, further assessment of antibodies was performed at age 5 years. The risk for an anti-diphtheria antibody concentration below a clinically protective level (0.1 IU/L) increased by about 3% for a doubling of the concentration of NDL-PCBs in milk or 18-month serum; the ORs were 1.34 (95% CI 1.11–1.61) and 1.30 (95% CI 1.08–1.57), respectively. No significant associations were found for anti-tetanus toxoid (Heilmann et al., 2010). Moreover, no association was reported between prenatal concentrations of NDL-PCBs and IgE level, allergy or atopic dermatitis at age 7 years (Grandjean et al., 2010).

The potential relationship between PCB exposure and immune function markers has also been assessed in adults. A cross-sectional analysis was carried out in a cohort of individuals aged 70 years from Uppsala, Sweden. Levels of protein complement 3 (C3), 3a (C3a), 4 (C4) and C3a/C3 ratio and 16 PCBs were measured in serum from blood samples collected at recruitment. No association was observed between any of the protein complements and the NDL-PCB congeners analysed individually, including PCBs 138, 153, 170 and 180 (Kumar et al., 2014). Plasma PCB concentrations (36 congeners) and immune function natural killer cell cytotoxicity and phytohaemagglutinin-induced T-lymphocyte proliferation were measured at baseline and 1 year later in postmenopausal, overweight women in the Seattle area, Washington, USA. Higher concentrations of moderately and highly chlorinated PCBs (all of them NDL-PCBs) were associated with higher phytohaemagglutinin-induced T-lymphocyte proliferation cross-sectionally, but not longitudinally. No association was observed with natural killer cell cytotoxicity (Spector et al., 2014).

2.3.10 Cardiovascular outcomes

Blood pressure, or specifically hypertension, is the cardiovascular outcome or condition most often assessed in relation to PCB exposure. Other cardiovascular-related risk factors or outcomes analysed are carotid atherosclerosis, left ventricular systolic and diastolic function, and serum lipids. Unfortunately, the potential relationship with PCB exposure is always evaluated by means of a cross-sectional approach (the exposure is related to the *prevalence*, not to the *incidence*

of the disease). In this design, both the exposure (PCB level) and the outcome (i.e. hypertension) are evaluated at the same time, so there is not a clear time sequence of events; it could be the case that the disease onset took place before the exposure. These studies at most can suggest an association, but they provide only weak support for a potential causal relationship.

(a) Blood pressure or prevalence of hypertension

Cross-sectional association between the concentrations of 11 PCB congeners (including six NDL-PCBs) in serum and the prevalence of hypertension was investigated in subjects from the NHANES 1999–2002; hypertension was defined as having systolic blood pressure (SBP) of 140 mmHg (18.7 kPa) and above or diastolic blood pressure (DBP) of 90 mmHg (12.0 kPa) and above (subjects with hypertension treatment were excluded). NDL-PCBs tended towards a positive association among men, with a significant trend across quartiles for the sum of the concentrations of the six PCB congeners (PCBs 99, 138, 153, 170, 180 and 197) and for the concentration of PCB 170; however, none of the ORs for the highest versus the lowest quartile was significant. No association was observed among women (Ha et al., 2009). In the NHANES 1999–2004, serum measurements included 22 PCB congeners, including the six indicator PCBs. In addition to the blood pressure measurement (SBP ≥140 mmHg or DBP ≥90 mmHg), the definition of prevalent hypertension included a previous diagnosis of hypertension by a doctor or being under treatment for hypertension. In a cross-sectional analysis for individual congeners, a positive association was found for PCB 52, PCB 101 and PCB 153, but not for PCB 138, PCB 170 or PCB 180. Correlation and multicollinearity among PCB congeners were evaluated, clustering analyses were performed to determine groups of related congeners and a weighted sum was constructed to represent the relative importance of each congener. Using this approach to equalize different ranges and potencies, PCBs 66, 101, 118, 128 and 187 were significantly associated with hypertension (Yorita Christensen & White, 2011).

In Aniston, Alabama, USA, the site of a PCB production plant until 1971, concentrations of 37 PCBs were measured in serum in 2005–2007 in a sample of individuals over 18 years of age, together with other lifestyle and health-related data, including the presence of hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg, or being on antihypertensive treatment). Hypertension prevalence was found to be positively associated with the sum of the concentrations of all measured PCBs. No details for individual congeners were reported, and therefore this result cannot be linked to NDL-PCB exposure (Goncharov et al., 2010). However, an analysis of the subsample of these subjects who were not taking antihypertensive medication provided results on specific congeners. Multiple

linear regression analysis of log-transformed SBP and DBP was used to compare means of blood pressure across tertiles of individual congeners; a significant increase of the mean SBP and DBP was observed across tertiles for PCB 138, PCB 153 and PCB 180 (Goncharov et al., 2011).

Concentrations of 15 PCB congeners were measured in plasma of adults (≥18 years) living in 13 Inuit villages in Greenland, together with other health-related data gathered by interview and anthropometric and blood pressure measurements. Hypertension was defined as having SBP of 140 mmHg and above or DBP of 90 mmHg and above. No association was found between the prevalence of hypertension and the sum of the concentrations of the 12 NDL-PCB congeners analysed or the concentration of any of the individual congeners, including the six indicator congeners. It must be noted that this is a highly exposed population: for PCB 153, the geometric mean concentration in plasma was 504 ng/g lipid (range 478–530 ng/g lipid) (Valera et al., 2013a). In Inuit from Nunavik, Quebec, Canada, concentrations of 14 PCBs were measured in plasma samples from adults (≥18 years); hypertension was defined as having SBP of 140 mmHg or above, having DBP of 90 mmHg or above or being on antihypertensive medication. The prevalence of hypertension was significantly associated with higher sum of the concentrations of nine NDL-PCBs as well as with higher concentrations of PCBs 101, 138 and 187 (but not PCB 153, 170 or 180) in plasma; in this population, the level of exposure was lower than for the previous one, with a geometric mean concentration of 283.6 ng/g lipid for PCB 153 in serum (Valera et al., 2013b).

Blood pressure and several factors related to hypertension were recorded for a representative sample of the adult population, aged ≥18 years, in the Canary Islands, Spain, together with concentrations of 18 PCB congeners in serum samples. In a cross-sectional analysis, the association of hypertension (SBP ≥140 mmHg, DBP ≥90 mmHg or use of antihypertensive medication) in relation to groups of PCBs or individual congeners, adjusted for potential risk factors for hypertension, was investigated. No association was observed between the prevalence of hypertension and the sum of the concentrations of the NDL-PCBs or the concentration of PCB 153 or 180 in serum (Henríquez-Hernández et al., 2014).

In the study from Aniston, Alabama, USA, described above, in addition to blood pressure, concentrations of lipids in serum were measured as well. In a cross-sectional analysis, a significant positive association was found between concentrations of PCBs 28, 138, 153, 170 and 180 and concentrations of total lipids, triglycerides and total cholesterol in serum, but not concentrations of HDL- or low-density lipoprotein (LDL)–cholesterol (Aminov et al., 2013).

(b) Other cardiovascular outcomes

In the population-based PIVUS study in seniors 70 years of age from Uppsala, Sweden, the prevalence of carotid artery plaques was determined by ultrasound, and the intima-media thickness (IMT) and grey-scale median of the intima-media complex (IM-GSM) were measured; concentrations of 16 PCBs in serum were also measured. In a cross-sectional analysis, concentrations of PCB 138, PCB 153, PCB 170 and PCB 180 were significantly associated with higher prevalence of carotid artery plaques, but no association was observed with IMT or IM-GSM. PCB 206 and PCB 209 had significant positive associations with higher prevalence of carotid artery plaques, higher values of IMT and lower values of IM-GSM (Lind et al., 2012). In the same study, cross-sectional analysis was carried out to assess the potential association between PCB concentrations and left ventricular dysfunction. Concentrations of PCBs 138, 153, 170 and 180 were significantly associated with lower ventricular ejection function, whereas no association was found between any of these congeners and the ratio between the Doppler transmitral amplitude of waves E and A (E/A ratio) and the isovolumetric relaxation time (Lind et al., 2012).

The only vascular outcome assessed in a prospective study was stroke. Incident ischaemic or haemorrhagic strokes were diagnosed during a 12-year follow-up in the Swedish Mammography Cohort, a population-based prospective cohort of women established in 1987–1990. Estimates of dietary PCB exposure were obtained via a food frequency questionnaire administered at baseline that had been validated against PCB concentrations in serum from women from the cohort. A significant increase in risk for all kinds of stroke was observed with increased dietary PCB exposure (Bergkvist et al., 2014). Unfortunately, in this study, no results for individual congeners or groups of PCBs were provided, and therefore these results cannot be linked to specific NDL-PCB exposures.

2.3.11 Respiratory outcomes

Prenatal exposure to PCBs (PCBs 28, 52, 101, 118, 153, 138 and 180) was assessed in cord serum of 405 children from Menorca, Spain, and asthma (current wheezing, persistent wheezing or doctor-diagnosed asthma) was assessed at 4 years of age. No association was found between overall exposure to PCBs and asthma (Sunyer et al., 2005). In a subset of these children, prenatal exposure to PCBs was not associated with inflammatory cytokines (Gascon et al., 2014a). No results for individual congeners were provided. Although it is likely that the highest contribution to the sum of PCBs in this study comes from NDL-PCB congeners, the group includes PCB 118, a DL-PCB congener. Therefore, these results cannot be linked to NDL-PCB exposure.

In the birth cohort from the Faroe Islands (1994–1995) described above, prenatal exposure was determined from concentrations of NDL-PCBs in maternal serum in gestational week 34 and in maternal milk (sum of PCB 138, PCB 153 and PCB 180). No significant association was reported between prenatal concentrations of NDL-PCBs and asthma at age 7 years (Grandjean et al., 2010).

Children from the BraMat, a subcohort of the Norwegian Mother and Child Cohort Study, were followed during the first 3 years of life using annual questionnaires, and blood parameters were examined at 3 years of age. The questionnaire included the occurrence of respiratory disorders, infections, allergy and immune-related outcomes. The maternal dietary exposure to PCBs was estimated using a validated food frequency questionnaire and available data on concentrations of PCBs in Norwegian foods. The occurrence of wheeze during the first year of life was significantly associated with maternal exposure to NDL-PCBs; the adjusted OR for a dietary exposure at or above the 80th percentile was 2.79 (95% CI 1.20–6.49) (Stølevik et al., 2011). In the extended follow-up up to 3 years of age, the association between maternal NDL-PCB exposure and wheeze remained (adjusted OR for dietary exposure at or above the 80th percentile was 4.03, 95% CI 1.59–10.2), but there was no association with asthma (Stølevik et al., 2013).

Concentrations of PCBs (PCBs 118, 138, 153, 156, 170 and 180) were measured in maternal serum collected at the 30th gestational week in a birth cohort formed in 1988–1989 in Aarhus, Denmark. Risk of asthma in offspring after 20 years of follow-up was obtained from a national registry. Weak (non-significant) associations were found between incidence of offspring asthma and maternal exposure to NDL-PCBs (sum of concentrations of PCBs 138, 153, 170 and 180 in serum). The hazard ratio (HR) for the highest (compared with the lowest) tertile of NDL-PCB concentration was 1.30 (95% CI 0.78–2.17) (Hansen et al., 2014).

A meta-analysis was carried out in 4422 mothers and children enrolled in nine birth cohort studies from six European countries with available data on PCB 153 concentration in cord serum, as well as parent-reported bronchitis or wheeze during the first 4 years of life. Overall, there was no association between PCB 153 exposure and occurrence of bronchitis or wheeze; the RR for the highest versus the lowest PCB 153 concentrations was 0.95 (95% CI 0.75–1.21). Within the nine studies included in the meta-analysis, there was a significant increase in risk for two cohorts, a significant decrease in risk for one cohort and no significant association for the remaining six cohorts. In contrast, a significant association was observed for the occurrence of bronchitis before age 18 months with PCB 153 concentration measured on a continuous scale; the RR for doubling the concentration of PCB 153 was 1.06 (95% CI 1.01–1.12). However, the association was not significant when comparing the third with the first tertile (RR 1.17, 95%

CI 0.97–1.14). The occurrence of wheeze (either before or after age 18 months) was not associated with PCB 153 concentration in serum (Gascon et al., 2014b).

A general population-based birth cohort was established in three Spanish regions (INMA study). Maternal blood was obtained between the seventh and 26th weeks of pregnancy, and concentrations of PCB congeners 28, 118, 138, 153 and 180 in serum were obtained; parental reports on lower respiratory tract infection were obtained when children were 12–14 months old. No association was observed between the concentration of PCBs (sum of the five congeners) and the occurrence of lower respiratory tract infection (Sunyer et al., 2010; Gascon et al., 2012). No results for individual congeners were provided. Although it is likely that the highest contribution to the sum of PCBs comes from NDL-PCB congeners, the group includes PCB 118, a DL-PCB congener. Therefore, these results cannot be linked to NDL-PCB exposure.

In the Norwegian cohort BraMat described above, maternal dietary exposure to NDL-PCBs was associated with infections of the upper respiratory tract. The OR for the number of upper respiratory tract infections diagnosed between ages 0 and 3 years was 1.04 (95% CI 1.01–1.08) for each nanogram per kilogram of body weight of daily exposure (Stølevik et al., 2013).

In a cohort of newborns from 14 Inuit communities of Nunavik, Quebec, Canada, PCB 153 concentration was measured in umbilical cord plasma; occurrence of respiratory infections from 0 to 5 years of age was assessed by a review of medical history. Exposure to PCB 153 was significantly associated with acute otitis media and upper respiratory tract infection, but not with lower respiratory tract infection. The RRs for fourth quartile PCB 153 concentrations (compared with the first quartile) and acute otitis media and upper respiratory tract infection were, respectively, 1.37 (95% CI 1.20–1.55) and 1.44 (95% CI 1.20–1.72), whereas for lower respiratory tract infection, the RR was 1.09 (95% CI 0.97–1.24) (Dallaire et al., 2006).

Maternal serum during pregnancy (weeks 32–34) and mothers' milk during the third week after pregnancy from primiparous women from Uppsala, Sweden, were used to assess perinatal exposure to 10 PCB congeners (four DL-PCBs and six NDL-PCBs); when the infant was 3 months old, respiratory infections and other health outcomes were assessed by interview with the mother. No significantly increased risk of respiratory infections was observed in relation to postnatal exposure to NDL-PCBs. Regarding prenatal exposure, there was no association with PCB 153 concentration, but the third tertile of the sum of the concentrations of PCBs 28, 52 and 101, compared with the first tertile, had an adjusted RR of 3.4 (95% CI 1.4–7.8) (Glynn et al., 2008).

2.3.12 Hepatic effects

In an analysis of a 24-year follow-up among Yucheng patients, mortality from liver cancer disease and cirrhosis was increased for men, but not for women (Tsai et al., 2007). As mentioned in section 2.3.2, these subjects were exposed to PCDFs and to a complex mixture of PCBs, and therefore these effects cannot be specifically linked to NDL-PCBs.

Alanine aminotransferase function, an indicator of non-alcoholic fatty liver disease, and concentrations of PCBs in serum were assessed in adults from the NHANES 2003–2004. In a cross-sectional analysis, a significant association was found between increased levels of alanine aminotransferase and higher concentrations of NDL-PCBs (sum of 27 congeners), as well as with concentrations of PCB 138 and PCB 153 (Cave et al., 2010).

2.3.13 Musculoskeletal effects

Among Yucheng patients followed for 24 years, there was a significant increase in risk of dying from diseases of the musculoskeletal system and systemic lupus erythematosus in women, but not in men (Tsai et al., 2007). As already mentioned, these effects cannot be specifically linked to NDL-PCBs.

Cross-sectional analyses have addressed the potential relationship between concentrations of some NDL-PCBs and bone mineral density and bone metabolism markers in adult or elderly populations in Sweden and the USA. Forearm bone mineral density and serum markers of osteoblastic (osteocalcin) and osteoclastic (CrossLaps) functions were measured in men and women, median age 59 and 62 years, respectively, from the east (Baltic) coast of Sweden. After correction for age and BMI, no association was observed between serum concentrations of PCB 153 and bone mineral density, osteocalcin or CrossLaps (Wallin et al., 2005). In a subset of women from this population, concentrations of hydroxylated PCB metabolites in serum were measured for some PCB congeners (4-hydroxy-PCB 107, 4-hydroxy-PCB 146, 4-hydroxy-PCB 187); no association was observed between bone mineral density and any of the hydroxy-PCB metabolites (Weiss et al., 2006). Bone mineral density was measured in a population 60–81 years of age living near the Baltic coast of Sweden, close to a river contaminated by PCBs and heavy metals (nickel, cadmium). The sum of the concentrations of the three most abundant NDL-PCBs (PCBs 138, 153 and 180) in serum was not associated with low bone mineral density (Hodgson et al., 2008). In adults (≥20 years old) from the NHANES 1999–2004, bone mineral density was not found to be associated with concentrations of PCB 153 or PCB 138 in serum, but PCB concentrations modified the association between bone mineral density and fat mass or lean mass (Cho et al., 2011).

Cross-sectional association of concentrations of five NDL-PCBs (PCBs 138, 153, 170, 180 and 187) in serum with the prevalence of self-reported arthritis was assessed in adults (≥20 years old) from the NHANES 1999–2002. There was a significant association between the sum of the concentrations of the five NDL-PCBs and prevalence of arthritis in women, but no clear association was observed in men. The association among females was stronger for rheumatoid arthritis; compared with the lowest quartile of PCB concentrations in serum, the ORs for the third and fourth quartiles were, respectively, 4.4 and 5.4, both statistically significant, with a significant trend (*P*-value for trend < 0.01) (Lee, Steffes & Jacobs, 2007).

2.3.14 Endometriosis

Concentrations of 40 PCB congeners were measured in serum from infertile Japanese women examined by laparoscopy and diagnosed as either cases with endometriosis or controls. No association was observed with concentrations of total PCBs in serum (Tsukino et al., 2005). Similarly, concentrations of 62 PCB congeners were measured in serum in women undergoing laparoscopy in Buffalo, New York, USA. No association was observed with concentrations of total PCBs or subgroups of congeners (estrogenic or anti-estrogenic) in serum (Louis et al., 2005). Serum samples from a female cohort in Michigan, USA, were collected at baseline, and PCBs were quantified as Aroclor 1254. The incidence of endometriosis was higher in women with higher concentrations of PCBs in serum, but the association was not significant (Hoffman et al., 2007). In these studies, the exposure referred to a mixture of PCBs, including DL- and NDL-PCB congeners, without specific information on individual congeners; therefore, no relevant conclusions concerning the effect of NDL-PCBs can be drawn.

Several case–control studies on the relationship between endometriosis and NDL-PCB exposure have been published in India, Italy and the USA. Detectable concentrations of four NDL-PCBs (PCBs 1, 5, 29 and 98) were measured in serum collected from infertile women from southern India who underwent transvaginal ultrasound scan screening followed by laparoscopy; 85 were classified as cases with endometriosis, whereas 135 were classified as controls. The mean concentration of the four PCBs was significantly higher in cases than in controls; ORs were not reported (Reddy et al., 2006).

Women living in the Rome, Italy, area and undergoing laparoscopy for suspected endometriosis or other benign gynaecological conditions provided a blood sample before laparoscopy, and concentrations of 11 PCB congeners were measured in serum. Cases were 40 women with histologically confirmed endometriosis; controls were 40 women with benign gynaecological conditions with no evidence of endometriosis. The adjusted OR for women in the third

tertile of PCB 153 concentration compared with the first tertile was 9.1 (95% CI 1.9–43). An increased risk of endometriosis was also reported for increasing concentrations of PCBs 138 and 180 (Porpora et al., 2006). The period of recruitment was extended up to the inclusion of 80 cases of endometriosis and 78 controls. In this analysis, the adjusted ORs for women in the third tertile of PCB 138, PCB 153 and PCB 180 concentration were, respectively, 3.78 (95% CI 1.60–8.94), 4.88 (95% CI 2.01–11.0) and 3.05 (95% CI 1.25–7.42) (Porpora et al., 2009). In a subset of these patients, a gene–environment interaction was observed for GSTP1 Ile/Ile and GSTM1 null genotypes, modulating the effect of PCB 153 and PCB 180 (Vichi et al., 2012).

Among women 20–45 years of age seeking reproductive assistance in Atlanta, Georgia, USA, 60 women with recently diagnosed endometriosis by biopsy and laparoscopy were defined as cases and were compared with 60 controls; in all of them, concentrations of 13 PCB congeners were measured in serum. No significant differences in median concentrations of PCB 138, PCB 153 or PCB 180 were observed; ORs for NDL-PCB congeners were not reported (Niskar et al., 2009). In a case–control study in Washington State, USA, concentrations of 20 PCB congeners were measured in serum from 251 surgically confirmed endometriosis cases that were newly diagnosed in 1996–2001 and from 538 controls matched for age and reference year. None of the six indicator PCBs (PCBs 28, 52, 138, 153, 170 and 180) was associated with an increased risk of endometriosis. The adjusted OR for a unit increase in the natural log–transformed concentration of PCB 153 was 1.1 (95% CI 0.8–1.8) (Trabert et al., 2010).

2.3.15 Other health effects

The cross-sectional relationship between concentrations of 14 PCB congeners in serum and some molecules sensitive to oxidative stress was assessed in Inuit adults. The PCB concentration in serum was associated with the LDL oxidation (Bélanger et al., 2006). This result refers to the whole group of PCBs; no specific results for NDL-PCBs were reported.

Concentrations of 20 PCB congeners and inflammatory markers were assessed in Japanese children 0–4 years of age. In cross-sectional analysis, IL-8 was significantly correlated with PCB congeners 163 + 162, 177 and 180 + 193, whereas COX-2 correlations with individual congener levels were recognized only among control subjects, not among asthmatic subjects. No significant results were reported for PCB 153 (Tsuji et al., 2012).

2.3.16 Summary of epidemiological studies

A number of potential health effects associated with exposure to NDL-PCBs have been identified, including changes in thyroid hormone homeostasis,

neurodevelopmental effects, immunological effects and some types of cancer. Some of the results offer support for the toxicological findings. The results of prospective (Chevrier et al., 2007; Herbtsman et al., 2008; Darnerud et al., 2010) and cross-sectional studies in newborns (Takser et al., 2005; Wang et al., 2005; Herbstman et al., 2008) and children (Álvarez-Pedrerol et al., 2008; Schell et al., 2008) suggest that increasing concentrations of NDL-PCBs are correlated with lower levels of T_4 and higher levels of TSH in blood, although there are some inconsistencies between results across studies. The key human studies are summarized in Tables 15 and 16.

Maternal and early postnatal exposure to NDL-PCBs in some birth cohorts was also associated with impaired behavioural, cognitive and psychomotor development (Stewart et al., 2005; Park et al., 2010; Forns et al., 2012b; Lynch et al., 2012; Gascon et al., 2013; Tatsuta et al., 2014) and with alteration of VEPs (Saint-Amour et al., 2006).

Perinatal exposure to NDL-PCBs in birth cohorts was found to be associated with increased incidence of acute respiratory infections in children (Dallaire et al., 2006; Glynn et al., 2008; Stølevik et al., 2013).

Regarding cancer, the recent evaluation by IARC (2015) reported an association between melanoma and PCB exposure, mainly based upon cohort studies of exposed workers in various industries, for whom exposure would be by multiple routes. IARC (2015) also considered studies in the general population with different study designs. Only one population-based case–control study (Gallagher et al., 2011) reported specific results for NDL-PCBs, showing a significantly increased risk of melanoma for a group of 11 NDL-PCBs, as well as for some individual congeners. In this study, a similar increased risk was also observed for two DL-PCB congeners. The association between NDL-PCBs and NHL has also been assessed in several prospective cohorts (L.S. Engel et al., 2007; Bertrand et al., 2010; Laden et al., 2010; Bräuner et al., 2012), but the results were not consistent.

Table 15

Prospective studies on the association between NDL-PCBs and thyroid hormones in newborns and infants

Reference	Location and period	Subjects	Blood/serum concentration (ng/g lipid)	Outcome	Main results	Comments
Chevrier et al. (2007)	Salinas Valley, California, USA 1999–2000 (CHAMACOS cohort)	Birth cohort: 285 pairs of pregnant Mexican American women and newborns	34 PCBs in maternal serum (26th week) PCB 153: GM (95% CI) 5.6 (5.2–6.0) Range 0.3–85.6	TSH in serum of children taken shortly after birth (mIU/L) GM (95% CI) 5.7 (5.3–6.1)	% increase in TSH (95% CI) For 10-fold increase in PCB PCB 101: 23% (7–45%) PCB 138: 23% (2–51%) PCB 153: 20% (0–48%) PCB 180: 23% (2–48%) Inducers of CYP2B: 29% (2–58%) (PCBs 99, 153, 180, 183)	Adjusted for neonatal age at blood collection, gestational age at birth, birth weight and mother's pre-pregnancy BMI PCBs 118 and 156 (DL-PCBs): no significant association
Herbstman et al. (2008)	Johns Hopkins Hospital, Baltimore, Maryland, USA 2004–2005	Birth cohort: 92 infants born by spontaneous, unassisted delivery	Umbilical cord blood PCBs measured: 74, 99, 118, 138 + 158, 153, 180 PCB 153: Mean (SD) 6.8 (2.1)	Total T_4 in blood of children taken at average of 18 days of age (range 5–117 days) Total T_4: Mean (SD) 15.16 (3.92) (µg/dL)	OR (95% CI) comparing the lowest 20% of total T_4 concentration to the rest, for 1-unit ln PCB concentration: PCB 138: 5.30 (1.73–16.21) PCB 153: 3.40 (1.31–8.83) PCB 180: 1.89 (0.83–4.30) Estimated lowest 20% of total T_4: 11.86 µg/dL	Adjusted for sex, gestational age, maternal age, maternal race, maternal pregnancy BMI, smoking and days since birth PCB 118 (DL-PCB): significantly associated
Darnerud et al. (2010)	Uppsala region, Sweden 1996–1999 (POPUP cohort)	Birth cohort: 160 primiparous women and 150 infants	10 PCBs in maternal blood (32nd–34th weeks) PCB 153: Median (range) 65 (23–158)	TSH, total T_3, free T_4 in children 3 weeks and 3 months after birth	PCBs 138, 153, 180 inversely associated with total T_3 at 3 weeks (P-value = 0.048) Non-significant, positive association with TSH at 3 months (P-value = 0.093)	Adjusted for birth weight, sex, alcohol consumption and age of mother (total T_3); adjusted for sex (TSH) No significant association for free T_4 or for the sum of DL-PCBs

CI: confidence interval; GM: geometric mean; IU: International Units; SD: standard deviation; T_3: triiodothyronine; T_4: thyroxine; TSH: thyroid stimulating hormone

Table 16
Cross-sectional analyses on the association between NDL-PCBs and thyroid hormones in newborns and children

Reference	Location	Subjects	Exposure measurements	Outcome	Main results	Comments
Wang et al. (2005)	Central Taiwan, China	118 newborns	27 PCBs in cord blood	Free T_4, T_3, TSH, TBG	Significant positive correlation of free T_4 with sum of PCBs 138, 153 and 180 only among female neonates	No associations between T_3, TSH or TBG and any of the PCBs measured
Takser et al. (2005)	Quebec, Canada	92 newborns	14 PCBs in cord blood	Free T_4, total T_3, TSH	No associations for any hormone with any PCB	The 14 PCBs included the six indicator PCBs
Maervoet et al. (2007)	Antwerp, Belgium	198 newborns	5 PCBs in cord blood	Free T_4, free T_3, TSH	Significant inverse associations of PCBs 138, 170, 180 with free T_4 and free T_3 and between PCB 153 and free T_4	No associations between TSH and any of the PCBs measured (118, 128, 153, 170 and 180)
Herbstman et al. (2008)	Johns Hopkins Hospital, Baltimore, Maryland, USA	289 newborns	6 PCBs in cord blood	Free T_4, total T_4, TSH	No associations in the whole population. Among infants born by spontaneous unassisted delivery, significant inverse associations between free T_4 and total T_4 and PCBs 138 (+ 158), 153 and 180	No associations between TSH and any of the PCBs measured (74, 99, 118, 138 + 158, 153 and 180)
Álvarez-Pedrerol et al. (2008)	Birth cohort Menorca, Spain	259 children aged 4 years	7 PCBs in serum (28, 52, 101, 138, 153, 180)	Free T_4, total T_3, TSH	Significant inverse associations between total T_3 and PCBs 138 and 153	No associations between free T_4 or TSH and any of the PCBs measured Significant association between total T_3 and PCB 118 (DL-PCB)
Schell et al. (2008)	USA/Canada	232 Akwesasne Mohawk youth, 13 years old	18 PCBs in serum	Free T_4, total T_4, total T_3, TSH	Significant positive associations between TSH and PCB 153 and PCBs 138 + 163 + 164 Significant inverse associations between free T_4 and PCBs 52, 101 + 90, 153 and 138 + 163 + 164	No associations between total T_3 or total T_4 and any of the PCBs measured Significant positive association between TSH and PCB 118 (DL-PCB)

T_3: triiodothyronine; T_4: thyroxine; TBG: thyroxine-binding globulin; TSH: thyroid stimulating hormone

3. Analytical methods

3.1 Chemistry

The general structure of PCBs and the numbering system for individual PCB congeners have been described in section 1.2.

PCBs are anthropogenic compounds that were produced commercially in considerable amounts between the 1930s and 1970s and were used for a wide range of applications. PCBs can also be unintentionally produced and released from many industrial thermal processes, including waste incineration and metallurgical processes (Nie et al., 2012; Liu et al., 2013). They are chemically resistant to hydrolysis and oxidation, but are subject to photolysis under some conditions (Hutzinger, Safe & Zitko, 1974). Owing to their overall chemical stability and their resistance to biological transformation, PCBs were widely used as heat transfer and hydraulic fluids, solvent extenders, flame retardants, organic diluents, paints and dielectric fluids (Hutzinger, Safe & Zitko, 1974; Jones, 1988). Technical/commercial PCB formulations were marketed worldwide under different names: they were sold as Aroclors in North America and the United Kingdom, Clophens in Germany, Chlorofen in Poland, Delors in Slovakia, Kanechlors and Santotherm in Japan, Phenochlor and Pyralène in France, Sovol mainly in Russia and Fenclor in Italy (Hutzinger, Safe & Zitko, 1974; Noma et al., 2006; Burkhard & Lukasewycz, 2008; Mandalakis et al., 2008). The chlorine content varied between different formulations and in some cases differed between lots (e.g. Aroclor 1254 lot A4 versus lot G4) (Hansen, 1999). Although there are 209 possible PCB congeners, only approximately 130 have been reported in commercial mixtures (Fattore et al., 2008; Elabbas et al., 2013).

The physicochemical properties of PCBs vary between individual PCB congeners. PCBs are liquids or solids at room temperature, appear colourless to pale yellow and are odourless (EFSA, 2010). PCBs have relatively low vapour pressures, with volatility decreasing with increasing degrees of chlorination, and have limited solubility in water (Fischer, Wittlinger & Ballschmiter, 1992; Shiu & Ma, 2000). PCBs are thermally stable, persist in the environment and are transported large distances beyond their area of release (Safe, 1994). PCBs are also lipophilic compounds and accumulate in the tissues of living organisms (Safe, 1994; Jankovic et al., 2011; Klincic et al., 2014); they are taken up by humans primarily through the consumption of food, with foods of animal origin being the primary source of human exposure (Henríquez-Hernández et al., 2011).

In general, individual laboratories restrict their analysis to a subset of the 209 PCB congeners. A key challenge associated with the analysis of PCBs originates in the decision associated with which congeners should be considered

to be representative of the NDL-PCBs. The analysis frequently involves the separate determination of both DL- and NDL-PCB congeners. Unfortunately, there is no universal approach to the selection of the NDL-PCB congeners to be measured. As the determination of all 209 individual congeners is not routinely performed, owing to the onerous nature of isolating each congener, laboratories have developed their own suite of congeners to represent total PCBs (DL-PCBs + NDL-PCBs) and more recently total NDL-PCBs (Boumphrey et al., 1993; Behnisch et al., 1997; Atuma et al., 1998; Ayotte et al., 2005). Lack of comparability between laboratories reporting total PCB or total NDL-PCB concentrations can thus be challenging, as well as complicating toxicological assessment (Bordajandi et al., 2003).

Owing to the high degree of effort required to measure the full suite of PCB congeners, some laboratories use technical mixtures or combinations of them (e.g. Aroclor 1254:1260) for quantification of PCB concentrations in unknown samples (Bhavsar et al., 2007), whereas others have established a subset of individual congeners to represent total PCBs (Jones, 1988; Zuccato et al., 1999; Baars et al., 2004; Bloom et al., 2005). One suite of congeners that has been used is composed of seven marker PCBs (i.e. PCBs 28, 52, 101, 118, 138, 153 and 180), selected because they were identified as representing approximately 50% of the total PCBs detected in food (Arnich et al., 2009). In human plasma samples, it was found that the sum of PCB congeners 138, 153 and 180, multiplied by a factor of 2, resulted in a concentration equal to 50% of the total PCBs in the samples (Morck et al., 2014). In another study, the sum of the concentrations of the seven marker PCBs (PCBs 28, 52, 101, 118, 138, 153 and 180) in eel liver and muscle samples represented 22% and 29% of total PCB concentrations, respectively (Oliveira Ribeiro et al., 2008). The use of this suite of the seven marker congeners seemed to result in variability in concentration relative to the total PCBs being reported. Unfortunately, this subset also includes PCB 118, which has dioxin-like activity and therefore cannot be used for reporting NDL-PCB concentrations (Chewe et al., 1997; Baars et al., 2004; Kim et al., 2004; Zuccato et al., 2008; Arnich et al., 2009; Blanchet-Letrouvé et al., 2014). Other congener subsets have been suggested for use as indicator PCBs because these congeners have been observed in technical mixtures and other sources of PCBs, such as municipal solid waste, emission gases and indoor air (Ishikawa et al., 2007). One example is the subset consisting of PCBs 3, 8, 28, 52, 77, 101, 105, 118, 126, 138, 153, 180, 194, 206 and 209. Again, however, this proposed set of congeners includes congeners with dioxin-like activity. A smaller subset (n = 4) of congeners (PCBs 118, 138, 153 and 180) has also been proposed as the suite for use in tracking body burdens (Axelrad, Goodman & Woodruff, 2009). Ultimately, a subset of congeners established to represent exclusively NDL-PCBs has been developed and includes the six indicator PCBs, PCBs 28, 52, 101, 138, 153 and 180 (Cerveny et al., 2014).

Current publications increasingly report this subset in the literature (Traag et al., 2006; Blanchet-Letrouvé et al., 2014). These six indicator PCBs have been selected not because they all have similar toxicological actions, but because they represent approximately 50% of total NDL-PCBs measured in analysed samples (Cimenci et al., 2013).

Although indicator PCBs are used for reporting concentrations in the scientific literature and in some regulations (e.g. European Union: European Commission, 2011; and China: Ministry of Health of the People's Republic of China, 2012, 2014; Shao et al., 2014), there are some national guidelines that continue to be based on total PCB concentrations, including those of Japan, the USA and Canada (currently under review) (Japan External Trade Organization, 2011; Health Canada, 2012; USFDA, 2014).

3.2 Description of analytical methods

3.2.1 Introduction

The methodology for the analysis of PCBs has evolved with advances in the technology since the initial research reported in the early 1970s. Some of the early analysis of PCBs was performed using PCB technical mixtures, prior to the availability of standards of the individual congeners, and this practice has continued over the years in some laboratories (Webb & McCall, 1973; Boonyathumanondh et al., 1995). Separation of PCBs was initially achieved using packed columns (Albro, Corbett & Schroeder, 1981). PCB separation improved as the column type changed: from megabore columns to support-coated open tubular columns, with capillary columns being adopted universally (Sissons & Welti, 1971; Frame, 1997). Although multidimensional gas chromatography (GC × GC) has been applied to PCB analysis, multiple columns with different polarities have been used in the separation of congeners and aid in the identification of co-eluting congeners (Duinker & Hillebrand, 1979; Albro et al., 1981; de Vos et al., 2011). The synthesis of individual congeners and their availability for use as analytical standards, coupled with the capillary column use for separation of individual congeners, have allowed laboratories to determine and report individual PCB congeners and total PCB concentrations as a function of the sum of the individual congeners (Mullin et al., 1984).

Owing to the thermal stability of PCBs, analyses have been performed primarily using GC for the separation of congeners combined with a variety of detection methods. Nuclear magnetic resonance spectroscopy was also employed in the effort to identify congener-specific information (Sissons & Welti, 1971). Webb & McCall (1973) established the relative chlorine content of individual Aroclor mixtures through the application of a gas chromatograph coupled

to a Coulson conductivity detector, in addition to employing electron capture detection (ECD) and mass spectrometry (Webb & McCall, 1973). All 209 PCB congeners were synthesized and confirmed using nuclear magnetic resonance spectroscopy, and relative elution order for each of the congeners was reported in 1984 (Mullin et al., 1984). Although ECD has been used consistently for the detection and quantification of PCBs in technical mixture formulations and extracts of biotic and abiotic matrices, additional PCB analysis has been performed using flame ionization detection (Schulz, Petrick & Duinker, 1989). Mass spectrometry was used in the original identification of PCB congeners and continues to be used in the analysis of these compounds at present, owing to the selectivity and specificity of this technique (Sissons & Welti, 1971; Loutfy et al., 2008; Masci, Orban & Nevigato, 2015).

3.2.2 Screening tests

In some of the early work, PCB confirmation of quantified samples was obtained by using pre-coated thin-layer chromatography plates (Mes & Davies, 1979). Comprehensive two-dimensional GC was also used for rapid PCB analysis of human serum (Patterson et al., 1996; Liem, 1999). The analysis of coplanar PCBs (DL-PCBs) has been performed using rapid methodologies developed for screening, such as the DR CALUX assay (Hoogenboom et al., 2006a,c). There are few screening tests for the DL-PCBs, because they are present at very low concentrations, and purification of extracts and isolation of these compounds are time consuming and expensive. The analysis of NDL-PCBs generally does not require as extensive a cleanup procedure as for the DL-PCBs or PCDDs/PCDFs; thus, routine screening methods are not generally reported in the literature. ELISA-based detection methods have been reported for PCBs, following standard sample preparation techniques for POP analysis, and the results obtained compared well with concentrations determined using traditional detection methods (Galloway et al., 2002).

3.2.3 Quantitative methods

Quantitative methods for the analysis of PCBs were initially developed using solvent extraction coupled to GC separation of peaks and analysis using ECD. The quantification was completed by comparing the results in unknown samples relative to established technical mixtures (e.g. Aroclor, Kanechlor), and this practice has continued in some laboratories (Bhavsar et al., 2007), although the transition to congener-specific analytical standards has been more frequently the approach taken (Boonyathumanondh et al., 1995; Gill, Schwartz & Wheatley, 1995; Polder et al., 1998; Eljarrat et al., 2001; Bordajandi et al., 2003; Fernandes et al., 2004; Kim et al., 2004; Bloom et al., 2005; Gomara et al., 2005; Costopoulou et al.,

2006; Jursa et al., 2006; Storelli et al., 2006; Malisch & Dilara, 2007; Esteve-Turrillas et al., 2008; Loutfy et al., 2008; Arnich et al., 2009; Turrio-Baldassarri et al., 2009; Grassi et al., 2010; Jankovic et al., 2011; Cimenci et al., 2013; Julshamn et al., 2013; Blanchet-Letrouvé et al., 2014; Cerveny et al., 2014). The general steps required for the determination of NDL-PCBs in food and other matrices (e.g. environmentally relevant organisms, human tissues and fluids, environmental compartments) are to extract them from the matrix in which they are to be determined, followed by isolation and purification of the prepared extracts, with the effort culminating in analysis. In some cases, samples have been freeze-dried before initiation of sample extraction, which is frequently done with food samples (Fernandes et al., 2004; Cimenci et al., 2013). Prior to the initiation of an extraction of PCBs from a matrix, PCB analogue analytical standards – whether they are stable isotope (^{13}C) analogues of analytes of interest or native (^{12}C) PCB congeners known to be absent from the matrix under investigation – are added to the sample (Dewailly et al., 1991; Boumphrey et al., 1993; Borgå et al., 2005; Weiss, Papke & Bergman, 2005; Ingelido et al., 2007). Known quantities of these standards are added for use as surrogates to aid in the correction for any losses during the sample preparation. These compounds have properties similar to those of NDL-PCBs because they are structural analogues and they behave similarly to the analytes themselves, and any losses of the analogues that may occur at any stage of the sample preparation can be determined and used to correct for the unknown PCB concentrations.

Extraction of PCBs generally requires organic solvents combined with some mixing procedure to ensure that the sample is exposed to the maximum solvent possible to enhance partitioning into the solvent from the original matrix. The methods employed include solvent extraction using liquid–liquid partitioning (Weistrand & Noren, 1993; Storelli et al., 2012b) or rotation of homogenized samples with solvent (Bhavsar et al., 2007). Food and other samples can be ground with anhydrous sodium sulfate and other adsorbents (e.g. silica gel, Florisil) in advance of the extraction step to dry the samples and bind any analytes and added to columns with or without prior shaking followed by elution from the column using solvent, which is the method known as matrix solid-phase dispersion (Criado et al., 2004; Fernandes et al., 2004; Bordajandi, Abad & Gonzalez, 2008). In the case of samples with very high lipid content (e.g. melted butter, oil) or liquid samples, solvents can be added directly to the sample and allowed to sit to maximize the PCB partitioning into the solvent phase (Criado et al., 2004; Weiss, Papke & Bergman, 2005; Cimenci et al., 2013). Saponification using sodium or potassium hydroxide/ethanol has also been performed for these matrices (Tuinstra, Traag & Keukens, 1980; Chou, Chen & Li, 2004). Similar to matrix solid-phase dispersion, the rationale for homogenization of samples with the solvents is to maximize the ratio of the sample surface area to solvent exposure (Elskus et al., 1994; Rawn et al., 2012). Soxhlet extraction, which uses

repeated cycles of hot solvent, is another effective method for extracting PCBs from samples and is sometimes performed using automated Soxhlet systems (e.g. Soxtec) (Chu, Covaci & Schepens, 2003; Grassi et al., 2010; Carro et al., 2012). Additionally, ultrasonication has been used to extract PCBs from non-food organic material (e.g. graphite, humic material) (Abrha & Raghavan, 2000).

Increasingly, the development of automated methods for sample preparation is being undertaken. These methods may involve grinding samples and drying reagents prior to extraction, which is performed using hot, pressurized solvents in repeated cycles using a pressurized solvent extractor or accelerated solvent extraction systems, for example (Esteve-Turrillas et al., 2008; Cimenci et al., 2013). Although supercritical fluid extraction was investigated in lipid-rich samples (e.g. herring), it is not routinely utilized in PCB analysis (van der Velde et al., 1996). In addition to these automated techniques, the application of microwave-assisted extraction has been used for the extraction of PCBs, particularly from sediments and water, although it has been tested using blubber (Camel, 2000; Sparr Eskilsson & Björklund, 2000; Fujita et al., 2009). Filtration of samples is required following microwave-assisted extraction prior to performance of the needed extensive cleanup, owing to the exhaustive nature of this method (Fidalgo-Used, Blanco-González & Sanz-Medel, 2007). The application of newer technologies allows analysts to use lower solvent volumes and decrease the sample preparation time prior to analysis.

A critical parameter in the successful extraction of PCBs, including NDL-PCBs, is the selection of appropriate solvents. Although PCBs are non-polar, hydrophobic compounds, extraction from food, biological samples and abiotic environmental samples is generally accomplished using a mixture of polar and non-polar solvents in variable ratios. Some of the popular choices include acetone:hexane (Chu, Covaci & Schepens, 2003; Gomara et al., 2005) and dichloromethane:hexane (Guruge et al., 2005; Bjermo et al., 2013), although toluene:acetone (Blanchet-Letrouvé et al., 2014), cold light petroleum:acetone (Cirillo et al., 2008), diethyl ether:petroleum ether (Esposito et al., 2014), chloroform:methanol (Klincic et al., 2014), ethyl ether:hexane (Ingelido et al., 2007) and isopropanol:ethyl acetate (Julshamn et al., 2013) are also used for the extraction of PCBs. Initial extraction from some sample types (e.g. blubber) can be accomplished using hexane alone in a Soxhlet apparatus (Kannan et al., 1993).

Once the samples have been extracted, isolation and purification of the extracts must be performed to ensure that the compounds of interest are retained and free of interfering co-extractives prior to analysis. Given that the PCBs are lipophilic compounds and found at elevated levels in lipid-rich foods, separation of the NDL-PCBs from the lipid is a critical step in the process of isolating the NDL-PCBs from the DL-PCBs and other persistent organic compounds (e.g. PCDDs/PCDFs). Given the chemical stability of PCBs to acid, treatment of extracts with

acid to digest the lipid is frequently performed and aids in the removal of co-extracted compounds more easily degraded through digestion under these harsh conditions. Acid digestion is frequently achieved using acid-treated silica gel or via washing the extract with excess sulfuric acid, treatment with fuming sulfuric acid or some combination of these approaches (Kim et al., 2004; Borgå et al., 2005; Witczak & Ciereszko, 2006b; Julshamn et al., 2015). Although digestion is usually performed with sulfuric acid, formic acid has also been used in the extraction of human serum as part of the sample preparation for NDL-PCB analysis (Koppen et al., 2002; Jursa et al., 2006). Additionally, size exclusion chromatography or gel permeation chromatography is employed early in the cleanup process (Masuda et al., 2005; Malisch & Dilara, 2007). Compounds are eluted from the gel permeation chromatography columns based on molecular size so that separation can be completed without consideration of polarity, allowing for separation of other non-polar compounds from the NDL-PCBs. When working with samples containing cholesterol, the application of gel permeation chromatography in advance of treatment with strong acid may be advantageous, because under harsh acidic conditions, the cholesterol may be converted to cholestadiene (Burke et al., 1974; Schüpfer & Gülaçar, 2000; Xiong, Wilson & Pang, 2007). Cholestadiene is difficult to remove from extracts using the usual routine adsorption chromatography approaches (e.g. Florisil, silica gel), and its presence has an impact on analytical results. Without the use of gel permeation chromatography cleanup in advance of acid digestion, separation of cholestadiene from the NDL-PCBs in the extracts can be achieved using silica that has not been acidified, for samples with high levels of cholesterol (e.g. egg yolks) (Rawn et al., 2012).

Fractionation of the different groups of PCBs (DL- versus NDL-PCBs) can be achieved using stepwise elution from columns prepared with different adsorbents. The columns may be multilayered or prepared in series and generally include acidified silica, neutral silica gel and anhydrous sodium sulfate combined with a silicate (e.g. aluminosilicate, magnesium silicate, potassium silicate) and carbon. Silica treated with potassium hydroxide may be employed as well (Berggrena et al., 1999; Gomara et al., 2005; Costopoulou et al., 2006; Bordajandi, Abad & Gonzalez, 2008; Konuspayeva et al., 2011; Klincic et al., 2014). Separation of the NDL-PCBs, including the six indicator congeners and mono-*ortho*-substituted congeners, can be achieved through the combination of adsorbents and elution solvents, with the ratio between the polar and non-polar solvents being a critical parameter to achieve separation (Košcan et al., 1994). The packing of columns can depend on how the sample is prepared and extracted. For instance, if a sample is freeze-dried or ground with a drying reagent, it may be packed directly into the column above the adsorbents used for the isolation of the NDL-PCBs from other co-extractives (Krokos et al., 1997). The multiple layers of adsorbents, including potassium silicate and silica gel, allow for the removal of

numerous co-extractives, whereas the use of carbon allows the separation of the planar DL-PCBs and PCDDs/PCDFs through an appropriate choice of solvents (Krokos et al., 1997). High-performance liquid chromatography has been used in the separation of different PCB congeners (e.g. *ortho*-substituted versus non-*ortho*-substituted), although this is not routinely reported in the literature (Echols et al., 1997; Pietrogrande et al., 2002).

Automated systems for the cleanup and separation of different fractions (e.g. coplanar PCBs + PCDDs/PCDFs; NDL-PCBs + mono-*ortho*-substituted PCBs) of individual extracts are being used with greater frequency (Eljarrat et al., 2001; Focant, Pirard & De Pauw, 2004; Focant et al., 2006; Uçar et al., 2011). A series of columns containing alumina, Florisil and carbon have been used for cleanup. The NDL-PCBs can be eluted from the alumina column using dichloromethane:hexane (50:50), with elution of the planar molecules (e.g. DL-PCBs) from carbon columns using toluene (Kim et al., 2004). Additionally, the application of multiple layered columns (e.g. acid/basic silica) has been used to destroy the lipid in samples, followed by a partly deactivated alumina column for the separation of the planar PCBs + PCDDs/PCDFs from the non-planar PCBs, including the NDL-PCB congeners (L'Homme et al., 2015).

Owing to the high number of individual compounds being analysed when PCBs are under investigation and all of them having a similar structure, co-elution of some congeners is known to occur using most GC columns available. The choice of column or columns used in GC measurement of PCBs will have an impact on which congeners will co-elute (Fujita et al., 2009). Some researchers have used temperature programming, different film thicknesses and carrier gas flow rates to improve the separation; others have performed sample analysis using more than one column, where each has a different polarity (Frame, 1997; Focant, Sjödin & Patterson, 2004). Employment of chiral columns to separate individual congeners has also been performed (Bordajandi et al., 2005). Additionally, the use of high-performance liquid chromatography with pyrenyl columns coupled to GC for separation of PCB congeners has been reported (Ramos, Hernández & González, 1999). Despite different approaches to overcome the issue of co-eluting congeners, separation of some congeners while performing routine analysis is an ongoing challenge.

Detection of the PCBs has been performed routinely using ^{63}Ni ECDs since the first analyses, and ECDs or micro-ECDs continue to be used for routine PCB analyses in some laboratories (Webb & McCall, 1973; Mullin et al., 1984; Schulz, Petrick & Duinker, 1989; Dewailly et al., 1991; Danielsson et al., 2005; Gomara et al., 2005; Bhavsar et al., 2007; Van Leeuwen et al., 2007; Bordajandi, Abad & Gonzalez, 2008; Oliveira Ribeiro et al., 2008; Storelli et al., 2008; Cirillo et al., 2009; Jankovic et al., 2011). Owing to the presence of the chlorines (n = 1–10) on each PCB congener, the detection of PCBs is sensitive; however, ECDs are not

specific detectors, and the possibility of misidentification of analytes is present. To overcome this issue, ECDs have been used in combination with two GC columns of differing polarity for separation of PCBs, thus providing confirmation of the analyses (Storr-Hansen & Cederberg, 1992; Atuma et al., 1998; Kearney et al., 1999; Danielsson et al., 2005; Polder et al., 2008b; Cerveny et al., 2014). Some laboratories have elected to use both ECD and mass spectrometry for quantification (Criado et al., 2004).

As accessibility to mass spectrometers has increased, so has their use in PCB analysis. They are a popular tool, because they can provide structural information about the analytes being measured, rather than simply a response to certain functional groups. In some cases, the application used is low-resolution mass spectrometry (Tanabe et al., 1997; Pietrogrande et al., 2002; Fernandes et al., 2004; Witczak & Ciereszko, 2006a; Storelli et al., 2012a), which may be coupled with large-volume injections to improve LODs (Traag et al., 2006; Witczak & Ciereszko, 2006a) using selected ion monitoring. Chemical ionization has been used for these analyses (Polder et al., 2008a), although electron ionization is used more frequently (Turrio-Baldassarri et al., 2009). High-resolution mass spectrometry is also used with greater frequency (Arnich et al., 2009), in part because the cost of these instruments has decreased and there is greater accessibility to them. Laboratories analysing PCDDs/PCDFs and DL-PCBs require the use of high-resolution mass spectrometric detection for these compounds because of their ultra-low concentrations in food and other tissues; therefore, some authors are reporting their use in the analysis of NDL-PCBs as well (Tsutsumi et al., 2002; Baars et al., 2004; Wingfors et al., 2005; Focant et al., 2006; Noma et al., 2006; Zuccato et al., 2008; Rawn et al., 2012; Blanchet-Letrouvé et al., 2014; Pavuk et al., 2014). In some publications, authors are adopting the technology of coupling gas chromatographs to tandem mass spectrometers for NDL-PCB analysis and may employ large-volume sample injection volumes (Pirard, Focant & De, 2002; Esteve-Turrillas et al., 2008; Cimenci et al., 2013). The use of GC coupled to ion trap detection capable of tandem mass spectrometry has been applied to PCB analysis in food samples. Some ionization inhibition occurred in the more highly contaminated samples analysed (e.g. cod liver); however, this method proved beneficial, owing to its greater selectivity compared with the more routinely used micro-ECD (Gomara et al., 2006).

LODs and limits of quantification (LOQs) may vary between methods used for NDL-PCB analysis. The LOQ is generally taken to be a concentration 3-fold higher than the LOD. Numerous factors contribute towards the LOD/LOQ values attainable during analysis. The matrix under investigation, the sample size taken for analysis, whether a sample extract was split for additional analyses and the final volume to which the sample extract is taken all have an impact on the LOD. Extraction efficiency may be better in some matrices relative to others, which

will contribute towards improved LODs, whereas other matrices may have co-extracting artefacts leading to elevated LODs. Additionally, the LOD may increase or decrease as a result of the sensitivity of the instrument used for detection. The LODs reported in the data submitted to the Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) database in response to the call for NDL-PCB concentration data in food ranged from 0.03 pg/kg (0.000 03 ng/kg), reported in rice, to 0.02 mg/kg (20 000 ng/kg), reported in fish. Individual PCB congener concentrations reported in the literature for food commodities and human tissues generally are below 1 ng/mL or 1 μg/kg (1000 ng/kg) in manuscripts dating from 2000 forward. Frequently, LODs are reported at levels of ≤0.2 μg/kg or <0.5 ng/mL (Chu, Covaci & Schepens, 2003; Fernandes et al., 2004; Costopoulou et al., 2006; Bordajandi, Abad & Gonzalez, 2008; Esteve-Turrillas et al., 2008; Cirillo et al., 2009; Grassi et al., 2010; Jankovic et al., 2011; Cimenci et al., 2013; Fromme et al., 2015). If LOD values are very high, exposure estimates developed using the LOD for the upper-bound concentrations may result in artificially elevated exposure levels.

3.2.4 Quality assurance considerations

Owing to the ubiquitous nature of the NDL-PCBs, the confirmation and removal of background levels from analytical results must be performed. Within each set of unknown samples to be analysed, NDL-PCBs should be measured in one or two laboratory blank or reagent blank samples. By establishing the background level in the laboratory where the analyses are performed, corrections can be made so that the final reported concentrations in the unknown samples do not include background concentrations resulting from handling in the laboratory.

Additionally, ongoing testing of laboratory quality should be performed through the routine testing of quality assurance samples. These samples may be reference materials with certified concentrations of NDL-PCBs or samples that have been tested over time in the laboratory, so that results may be evaluated on an ongoing basis.

The uncertainty of sample analyses should be determined for the analytical results developed by a laboratory. The uncertainty can be established using more than one approach: (1) cumulative uncertainty developed through examination of each step in the sample preparation and analysis protocol and (2) comparison of the results obtained relative to the reference materials tested (Fernandes et al., 2004; Eppe et al., 2014).

The use of proficiency testing programmes and participation in interlaboratory studies such as the POPs programme organized by the Norwegian Institute of Public Health (Bremnes, Broadwell & Becher, 2013) are encouraged, to aid in validation of analytical results.

3.2.5 Reference methods

The long history with the analysis of PCBs, including both DL- and NDL-PCBs, has allowed different groups to establish methods for use as references for the analysis of these compounds. The United States Environmental Protection Agency (USEPA) has established a method for the analysis of PCBs, as both individual congener concentrations and concentrations based on Aroclor (1016, 1221, 1232, 1242, 1248, 1254, 1260) equivalents. The method is recommended for use with solid and aqueous matrices and is available online (EPA method 8082) (USEPA, 1996). EPA method 8082 was subsequently expanded to include analysis of PCBs in tissue samples (EPA method 8082A) (USEPA, 2000). These methods were developed for use with ECD or electrolytic conductivity detection and include five of the six indicator PCB congeners (PCBs 52, 101, 138, 153, 180); PCB 28 is not listed as one of the target compounds for these analyses (USEPA, 1996, 2000). These methods have been used and adapted by many researchers for successful PCB analysis worldwide. More recently, the USEPA developed EPA method 1668 for the analysis of PCB congeners in water, soil, sediment and biosolids, in addition to tissue. It employs the use of high-resolution mass spectrometry (USEPA, 2008). Additionally, other agencies (e.g. AOAC International and the International Organization for Standardization) have developed validated matrix-specific methods for the analysis of PCBs (AOAC International, 1983; ISO, 2008).

In contrast, the European Union has developed criteria for the analysis of PCBs (NDL- and DL-PCBs), in addition to the PCDDs/PCDFs, in feed and food. The criteria established for NDL-PCB analysis focused on GC methods employing ECD, low-resolution mass spectrometry (e.g. unit mass resolution mass spectrometry), tandem mass spectrometry and high-resolution mass spectrometry (>8000 resolution) (Malisch, Kotz & Wahl, 2009). The criteria included limitations to the deviation in relative retention time of the analyte in unknown samples when compared with analytical standards, the number of ions to be included for each analyte and limitations to mass range, particularly for the low-resolution methods (Malisch, Kotz & Wahl, 2009). The issues of concern identified for consideration include those parameters required for good quality assurance practices (e.g. validation of methods within the range of interest, recoveries of surrogate standards, consistently having high-quality results when examining quality control samples).

The European Union conducted five proficiency tests between 2009 and 2013 using foods of animal origin for testing (Kotz et al., 2014). As part of the discussion on the results, it is noted that the criteria for the methods do not extend to the extraction methods, but rather focus on the extraction efficiency of the methods employed (Kotz et al., 2014).

4. Sampling protocols

Although there are no established protocols set specifically for the collection and storage of samples for NDL-PCB analysis, the best practices established for other POPs present at ultra-trace levels (e.g. PCDDs/PCDFs, DL-PCBs) should be followed. The collection of samples should be performed using containers that are non-reactive (e.g. glass, aluminium) and have been chemically cleaned or certified to be free of contaminants, and the samples should be collected by experienced individuals.

When sampling commercial food products, samples collected must be representative of the lot. Therefore, collection of multiple samples (incremental) from within the lot is recommended, and the multiple samples may be used to form an aggregate sample from which laboratory samples may be analysed. Adoption of a subsampling protocol similar to that identified by the European Union may be beneficial (European Commission, 2014). Prior to the subsampling for laboratory analysis, homogenization of the aggregate sample should be performed.

Sample container lids should be lined with a non-reactive material. In some situations, plastic bags may be used for sample collection. There is concern, however, that the sample may be exposed to phthalates and other plasticizers, so the use of plastic bags for long-term storage and throughout the sample preparation phase is discouraged (De Boer, 1999; Muir & Sverko, 2006). Food samples must be stored in a manner that ensures the integrity of the food during transport to the laboratory and through storage (Melis & Zuccato, 2012). Lyophilization of samples is known to aid in removal of moisture prior to storage, which is beneficial when working with fresh food (Fernandes et al., 2004). The use of freeze-drying, however, can result in the loss of the more volatile, lower chlorinated PCB congeners, owing to their greater volatility and aqueous solubility (Berdié & Grimalt, 1998; Juan et al., 1999; De Voogt, Van Der Wielen & Govers, 2000). PCB losses during the freeze-drying process are influenced by the properties of the food being dried (e.g. fat content) and not strictly the properties of the analytes of interest (Witczak & Ciereszko, 2006b). The drying of samples with high fat content (e.g. meat) may result in cells collapsing and clumping, which could limit the efficacy of the solvent in the extraction of analytes from the matrices (Ridgway, Lalljie & Smith, 2007). The use of drying agents (e.g. anhydrous sodium sulfate) to dry and grind food may be more advantageous in some cases.

Sample storage space is a restriction placed on most laboratories, and ensuring sufficient space to retain subsamples for archival purposes is advantageous (Gunter, 1997; Wells & Hess, 2000; Muir & Sverko, 2006). Samples retained for short periods pending PCB analysis can be stored at a higher

temperature (e.g. −25 °C) than that used for samples being retained for a long period (>2 years), where the suggested temperature is less than −70 °C (De Boer & Smedes, 1997). The storage of multiple aliquots that are relatively small in size may be more beneficial than storage of one large sample, particularly for frozen samples, because this will limit the number of freeze–thaw cycles to which the sample may be subjected when reanalysis is to be performed (Gunter, 1997; Wells & Hess, 2000).

5. Effects of processing

In contrast to other contaminants, NDL-PCBs are thermally stable and resistant to degradation. Studies on the impact of processing on PCB concentrations have been largely focused on the cooking techniques used to prepare foods. Techniques that change the fat content will have an impact on PCB concentrations (e.g. PCB concentrations are lowered in skimmed milk, but increased concentrations are found in foods with higher fat content, such as cheese or cream) (Newsome, Davies & Sun, 1998). Although the studies related to the impact of processing on PCB concentrations include both DL-PCBs and NDL-PCBs, the impact on the concentrations is similar for both groups. Ultimately, processing that results in the removal of lipids will lead to a decrease in PCB concentrations in the final food product.

Food preparation prior to the cooking stage can lead to a reduction in the concentration of PCBs. In studies using salmon and bluefish, the removal of the skin resulted in a reduction of PCB content compared with fish prepared with the skin remaining (Salama et al., 1998; Bayen et al., 2005). However, a review of published studies to determine the impact of processing of fish on contaminant concentrations resulted in a conclusion that losses observed with different cooking methods are not affected by whether the skin was removed (Wilson et al., 1998). Additionally, the location along the fish from which the salmon steaks were taken was observed to have an impact on PCB concentrations, with those taken closer to the head having higher concentrations than those prepared from the region nearer to the tail (Bayen et al., 2005).

The process of cooking food can also have an impact on PCB residue concentrations. Cooking has been reported to lower PCB concentrations in bluefish, although frying and baking resulted in less reduction in the PCB concentrations than observed for other techniques, such as smoking, microwave cooking or charbroiling (Salama et al., 1998). Baking, charbroiling and smoking also resulted in significantly lower PCB residues compared with raw trout samples, although smoking lowered PCB concentrations to a greater extent than the other methods tested (Zabik et al., 1996). The greater losses found in the smoked fish were hypothesized to result from the long, slow smoking process with its higher final temperature, which ultimately leads to greater fat losses (Zabik et al., 1996). In the study focused on salmon steaks, cooking by pan frying, microwave cooking, boiling or baking generally reduced PCB concentrations, although the differences in the PCB content were not significantly lower, regardless of the type of cooking method used (Bayen et al., 2005). A reduction in PCB concentrations was generally observed following cooking of samples of a variety of finfish and non-finfish species, although only relatively small changes in the PCB concentrations were observed, regardless of whether samples were baked,

boiled or fried (Rawn et al., 2013). In a review of the data developed to determine the impact of cooking on contaminant (DDT, PCBs) concentrations, Wilson et al. (1998) found that greater variability in the reduction of the compounds of interest was observed when broiling, frying and boiling, relative to baking or smoking. Additionally, baking was thought to remove more consistent amounts of fat than would occur for other methods (Wilson et al., 1998). Sherer & Price (1993) recommended reporting results of this type based on the mass of PCBs in the final cooked samples relative to the raw products. Although the literature generally is in agreement that a reduction in PCB concentration occurs with cooking, the approaches dealing with the data differ, with some researchers focusing on changes based on whole weight concentrations and others focusing on lipid-adjusted concentrations. Overall, multiple authors have observed PCB losses associated with cooking different fish species (e.g. salmon, bluefish, trout), ranging from approximately 25% to 65% (Salama et al., 1998; Wilson et al., 1998; Bayen et al., 2005).

In a study to examine the effect of the smoking process exclusively, it was determined that cold smoking of mackerel and herring fillets resulted in an elevation in PCB concentrations, whereas hot smoking resulted in an overall lowering of PCB concentrations (Witczak & Ciereszko, 2006b). PCB reductions were observed during the first hour of the hot smoking process, although a small increase in these concentrations was found during the later stages of this process (Witczak & Ciereszko, 2006b). This small increase in PCB concentrations at the later stages of the hot smoking process was postulated to have occurred as a result of the co-distillation of PCBs with water vapour.

Additionally, studies have been performed to determine the impact of the refining process on PCB concentrations in crude fish oils for use as dietary supplements. Among the different steps in the refining process (neutralization, bleaching and deodorization), deodorization resulted in the greatest reduction in PCB concentrations in fish oils, whereas the other steps did not have a significant effect on the concentrations (Hilbert et al., 1998). Fish meal and fish oil are known to be sources of POPs, including both PCBs and PCDDs/PCDFs.

A number of approaches have been investigated to decrease the levels of POPs in fish meal products, including ultraviolet light treatment, enzymatic treatment, pH shift processes and distillation processes (Baron, Børresen & Jacobsen, 2005, 2007; Marmon, Liljelind & Undeland, 2009; Oterhals & Berntssen, 2010). Although ultraviolet A exposure did not lower POP concentrations, ultraviolet B exposure did. Although changes in pH resulted in lower PCDD/PCDF and DL-PCB concentrations, protein losses were observed in the herring mince samples tested (Baron, Børresen & Jacobsen, 2005; Marmon, Liljelind & Undeland, 2009). Only limited reduction occurred, however, when fish meal was exposed to oxidoreductase enzymes (Baron, Børresen & Jacobsen, 2007).

Short-path distillation of fish oil contributed to lower PCDD/PCDF and DL-PCB concentrations; however, losses of vitamins were detected (Oterhals et al., 2007). The impact of temperature, moisture content and leaching time during fish meal production was investigated to establish optimal conditions to reduce PCDD/PCDF and DL-PCB concentrations while maintaining fish meal protein quality. Leaching (solid–liquid) extraction with triglyceride used as the extracting solvent reduced POP concentrations and maintained the quality of the final fish meal products (Oterhals & Kvamme, 2013).

Although the majority of studies to determine the impact of cooking on POP concentrations have been performed using fish, the impact on meat has also been reported. No consistent decrease in PCDD/PCDF or DL-PCB concentrations in beef, pork and fish products was observed following broiling, compared with concentrations in the raw food. No investigation of the NDL-PCB congeners was performed, although it is thought that the broad behaviour of the NDL-PCBs generally can be represented by the DL-PCB congeners in this context (Schecter et al., 1998).

6. Prevention and control

Food consumption is well known to be the primary pathway of exposure to PCBs and other POPs (e.g. PCDDs/PCDFs). Exceptions to this may occur for individuals who have been exposed through occupational activities. Within the broad category of food, foods of animal origin are the most significant contributors to human PCB body burdens, owing to the bioaccumulation of these chemicals through the food-chain to the top-level predators (i.e. humans) (Malisch & Kotz, 2014). Given the major source of PCBs and other POPs, the focus of efforts related to preventing exposure is through limitations to exposure along the food-chain, including exposure of food production animals. With the knowledge that fish, meat and dairy product consumption contributes most greatly to PCB exposure, methods of PCB reduction in animals from which the foods are derived are of primary interest (Jelinek, 1985; Malisch & Kotz, 2014).

Knowledge on the transfer of contaminants from feed to animal food products is essential for food safety risk assessment. Feeding studies have been carried out with both terrestrial and aquatic farmed animals by exposing them to contaminated diets under controlled conditions, which allowed for the determination of the carry-over rate from the feed into food. These data have been summarized in a review article and in a database of the carry-over rates for contaminants, including PCBs, in various terrestrial farmed animals, including cattle, poultry, pigs, sheep, goats, rabbits and birds (Kan & Meijer, 2007; Leeman, Van Den Berg & Houben, 2007). Geometric mean carry-over rates, calculated as the concentration of PCBs in animal products relative to the PCB concentrations in animal feed, differed by commodity: meat (0.14), fat (3.9), edible offal (0.7), eggs (0.92) and whole milk (0.26) (Leeman, Van Den Berg & Houben, 2007). Berntssen et al. (2011) determined the amount of POPs, including the six indicator PCBs, retained in farmed Atlantic salmon fillets relative to the amount consumed via feed and reported that the retention ranged from 42 ± 3% to 50 ± 2% for PCBs 138 and 101, respectively (sum of six indicator PCBs = 46 ± 3%). Additionally, they compared the carry-over rates reported for PCBs in terrestrial farmed animals (median = 0.12, maximum = 0.36) with those determined for DL-PCBs in the fish fillet (0.79) and found that the carry-over rate for salmon fillets was approximately 2–7 times higher than that for terrestrial meat products, depending on whether the median or maximum value was compared (Berntssen et al., 2011). In the above studies, information on carry-over rates specifically for NDL-PCBs, however, was insufficient, as few data sets distinguished NDL-PCBs from the sum of PCBs in these studies.

Transfer of DL- and NDL-PCBs from feed to animal food products has been reported in other studies in the literature. The feed to milk transfer of PCBs has been assessed using lactating goats and cows (Thomas, Sweetman

& Jones, 1999a,b; Kerst et al., 2004; Costera et al., 2006; Ounnas et al., 2010). Carry-over percentages of the NDL-PCBs have been determined in lactating goats fed with contaminated hay and in cows reared with naturally contaminated or background-level pastures. The carry-over rates of the NDL-PCB congeners, reported as a percentage, into milk were similar for goats and cows: PCBs 138, 153 and 180 showed high carry-over percentages, more than 40% for goats and more than 60% for cows, whereas PCBs 28, 52 and 101 were transferred poorly, less than 30% for goats and less than 10% for cows (Thomas, Sweetman & Jones, 1999a; Costera et al., 2006). Similar transfer patterns for indicator PCBs were observed in the eggs and fat of laying hens (Hoogenboom et al., 2006b) and in the fat of broilers and pigs (Hoogenboom et al., 2004). Following removal from exposure to contaminated feed, concentrations of indicator PCBs in milk and egg fat decreased rapidly to about 50% within 10 days, followed by a gradual elimination (Hoogenboom et al., 2006b; Fournier et al., 2013). Owing to the efficiency of the transfer of NDL-PCBs from feed to food products, it has been stated by multiple authors that the international limits for PCBs in feed may be approached and that these limits may be insufficient to guarantee related food safety (Costera et al., 2006; Hoogenboom et al., 2006b; Ounnas et al., 2010; Fournier et al., 2013).

Given the limits established in 2006 for PCDD/PCDF and DL-PCB concentrations in food and feed in the European Union (European Commission, 2006), studies have been undertaken to determine the impact of food production animal environments on PCB and PCDD/PCDF concentrations. PCB and PCDD/PCDF concentrations in beef exceeded maximum guideline levels when animals were raised on floodplains with elevated PCB and PCDD/PCDF concentrations, similar to animals raised on lands near sources of these contaminants and those raised on land treated with sewage sludge in the 1960s/1970s (Weber et al., 2014). The results indicated that for animals to have concentrations of these contaminants below regulated levels, pasturelands having low POP concentrations are necessary. Poultry is another important source of meat for human consumption. An investigation into the use of activated carbon through the feed as a means of reducing PCDDs/PCDFs and DL-PCBs was performed. Although the carbon treatment did reduce POP concentrations in chicken muscle, abdominal fat and eggs, a reduction in important vitamins (α- and γ-tocopherol) was also observed (Guruge et al., 2012). Although these studies have been focusing on the determination of the impact of selected treatment on the levels of PCDDs/PCDFs and DL-PCBs, the extension to the NDL-PCBs is something to consider.

The adherence to good agricultural practices and good animal feeding practices should contribute to the efforts to reduce POPs (e.g. PCBs) in food for human consumption (FAO/WHO, 2006; Mansour, 2011). PCB contamination of animal housing and/or buildings (e.g. silos) near animal pastures contributes to

animal exposure levels, as does the pasturing of animals on lands contaminated with PCBs during periods when these lands were used for other activities (e.g. railway lines) (Weber et al., 2014). Potential PCB exposure of grazing animals necessitates the need to identify contaminated pastures to ensure that they are not used for this purpose. PCB contamination can be further reduced by establishing and adhering to soil guideline values for agricultural purposes, performing diligent monitoring programmes to confirm compliance and establishing critical control points for the feed manufacturing process where PCBs can be reduced (FAO/WHO, 2006). Additionally, farming practices should include plans for isolation, among other procedures, if contamination is detected (Mansour, 2011).

7. Levels and patterns of contamination of food commodities

Thirty countries provided data to the Committee for its review of NDL-PCBs. Among the submissions from countries responding to the call, 23 were from Europe through EFSA. Six other contributing countries were from the western Pacific region, and one was from the Americas (Table 17). Those data that were not in an acceptable format for evaluation by the Committee were removed from the data set. Among the submitted data, the vast majority represented commercial-type food, with only two records of human milk reported (for PCBs 28 and 101).

In general, countries reported the NDL-PCB occurrence data as individual congeners. The majority of countries restricted the submission of data to the six indicator PCB congeners (PCBs 28, 52, 101, 138, 153 and 180) for each food category. The focus on the six indicator PCB congeners is consistent with the regulations pertaining to NDL-PCBs in foodstuffs within the European Union. Maximum European Union limits are established for the sum of the six indicator PCB congeners in meat and meat products (40 ng/g fat), liver of terrestrial animals and derived products (40 ng/g fat), fish liver and derived products (200 ng/g ww), fish and fishery products (75 ng/g ww), wild-caught freshwater fish (125 ng/g ww), wild-caught eel (300 ng/g ww), marine oils (200 ng/g fat), raw milk and dairy products (40 ng/g fat), hen eggs and egg products (40 ng/g fat), fat from bovine animals, sheep, poultry and pigs (40 ng/g fat), mixed animal fats (40 ng/g fat), vegetable oils and fats (40 ng/g fat) and foods for infants and young children (1 ng/g ww) (European Commission, 2011). The European Commission had also recommended that member states monitor concentrations of PCDDs/PCDFs and PCBs in food and feed, and the results of the monitoring activity for the NDL-PCBs have been reported by EFSA (2010, 2012). Recommendations as to the annual minimum number and type of food samples to be analysed for PCDDs/PCDFs, DL-PCBs and, if possible, NDL-PCBs were established for member countries in 2004 (European Commission, 2004).

Some countries reported additional congeners for foods of high interest (e.g. fish), while maintaining the reporting of the six indicator congeners for all other food types reported. Still other countries reported all NDL-PCB congeners measured. One country supplied the majority of their occurrence data as technical mixture (Aroclor 1254, 1260) equivalents, with indicator congeners reported only in fish samples.

Of the 30 reporting countries, only four (Australia, Germany, New Zealand and Slovakia) reported some aggregated results; among them, only New Zealand restricted reporting to aggregated sample results.

Table 17
Summary details of the NDL-PCB data sets submitted to JECFA, by country[a]

Country	No. of records	No. of congeners routinely reported	No. of aggregated results reported	No. of individual results reported	Sample collection years
Australia	356	—[b]	42	314	2005–2008
Austria	978	6 indicators	0	978	2007–2012
Belgium	3 804	6 indicators	0	3 804	2002–2013
Canada	2 120	20[c]	0	2 120	2005–2006
China	10 398	6 indicators	0		
Mainland	8 694			8 694	2005–2014
Hong Kong SAR	1 704			1 704	2010–2011
Cyprus	1 092	6 indicators	0	1 092	2009–2013
Czech Republic	2 688	6 indicators	0	2 688	2005–2013
Estonia	2 388	6 indicators (19 in a subset of samples)	0	2 388	2003–2007
Finland	7 159	6 indicators (25 congeners in fish)	0	7 159	2002–2010
France	8 010	6 indicators	0	8 010	2003–2010
Germany	46 311	6 indicators	39	46 272	1995–2010
Greece	2 700	6 indicators	0	2 700	2000–2010
Iceland	822	6 indicators	0	822	2003–2005
Ireland	2 178	6 indicators	0	2 178	2003–2006
Italy	1 554	6 indicators	0	1 554	2001–2003
Japan	505	5 indicators[d]	0	505	2012
Luxembourg	72	6 indicators	0	72	2002
Netherlands	1 278	6 indicators	0	1 278	1999–2009
New Zealand	2	2 indicators	2	0	1998
Norway	6 540	6 indicators	0	6 540	1999–2013
Poland	2 838	6 indicators	0	2 838	2006–2010
Republic of Korea	5 424	6 indicators	0	5 424	2012–2013
Romania	1 050	6 indicators	0	1 050	2006–2007
Singapore	36	6 indicators	0	36	2013–2014
Slovakia	1 192	6 indicators	724	468	2000–2010
Slovenia	1 314	6 indicators	0	1 314	2004–2012
Spain	206	6 indicators	0	206	2004–2012
Sweden	3 858	6 indicators	0	3 858	2000–2013
United Kingdom	7 856	6 indicators (35 congeners in fish)	0	7 856	2001–2006

SAR: Special Administrative Region
[a] Data from Denmark not included.
[b] Most reported data as Aroclor equivalents (1254, 1260).
[c] Co-elution of PCB 101 with other congeners, removed from submission.
[d] Co-elution of PCB 52 with other congeners, data not submitted

Most countries reported PCB concentrations in fish, milk, meat, eggs, and fats and oils, although some countries reported results for a much wider range of foods, including composite foods (e.g. pizza), fruit, legumes, nuts, snacks, starchy roots and tubers, and vegetables. Because the majority of exposure to PCBs occurs through the consumption of fish, milk, meat, eggs and their products, the summary of the results has focused on these categories. Infant food was considered using food produced exclusive of human milk, as the concentrations of NDL-PCBs were below the LOD in the only human milk results submitted.

Each country submitted data using relevant time frames for their work; some included more historical data sets (i.e. ≤ year 2000), whereas others reported data for recent collections only (≥ year 2010). The collection period differential may have contributed to the difference in maximum concentrations observed. This is consistent with the temporal decrease in POP, including NDL-PCB, concentrations in food reported in the literature. In this data set, foods known to have elevated levels of animal fat had higher indicator PCB concentrations relative to other food types. Maximum concentrations in foods from these categories (fish, meat, eggs, milk) were well in excess of 10 000 ng/kg ww (PCB 101: 1 200 000 ng/kg ww in fish and 240 000 ng/kg ww in meat; PCB 138: 34 820 ng/kg ww in eggs; PCB 153: 16 900 ng/kg ww in milk). The maximum indicator PCB concentration in foods identified for infants and very young children was less than 10 000 ng/kg ww (PCB 153: 5920 ng/kg ww). Although maximum concentrations were elevated, the central tendency of the data was low, with median values generally below 1 μg/kg (1000 ng/kg) for the indicator congeners. This result is consistent with the contributed data sets having had data with concentrations frequently below the LOD (Table 18) and taken to be zero for summary purposes. A more detailed description of minimum and maximum concentrations of the indicator PCBs by country and food category may be found in Appendix 1, with mean concentrations reported in Appendix 2.

The largest number of results submitted for this review was from samples belonging to the fish and fish products category (>7000 records for each indicator congener). The maximum indicator PCB concentration was observed in foods from this category. It was noted that increasing concentrations of the higher chlorinated congeners (PCBs 101, 138, 153 and 180) were observed in the fish products relative to the trichlorinated PCB 28 and tetrachlorinated PCB 52 (Fig. 3), similar to the pattern observed in eggs (Fig. 4). Although there was a large spread in concentrations reported, the median concentrations remained very low for all six congeners for both food groups.

Table 18

Summary of the number of samples and proportion of detected samples by country and food category for the submitted data for the six indicator PCB congeners

Food category (by country)	No. of data submitted	No. of detections[a]	Frequency of detection (%) (six indicator congeners)
Australia			
Fish and other seafood (including amphibians, reptiles, snails and insects)	42	0	0
Austria			
Cereals and cereal-based products	12	12	100
Eggs and egg products	156	156	100
Fish and other seafood (including amphibians, reptiles, snails and insects)	132	132	100
Food for infants and small children	72	72	100
Herbs, spices and condiments	12	12	100
Meat and meat products (including edible offal)	396	396	100
Milk and dairy products	168	168	100
Products for special nutritional use	30	30	100
Belgium			
Eggs and egg products	402	169	42
Fats and oils of animal and vegetable origin (excluding butter)	978	218	22
Fish and other seafood (including amphibians, reptiles, snails and insects)	1 050	488	46
Food for infants and small children	60	0	0
Fruit and fruit products	36	1	3
Legumes and pulses	6	0	0
Meat and meat products (including edible offal)	162	15	9
Milk and dairy products	996	417	42
Other foods	30	1	3
Products for special nutritional use	84	14	17
Canada			
Composite food (including frozen products)	90	90	100
Eggs and egg products	10	10	100
Fats and oils of animal and vegetable origin (excluding butter)	20	20	100
Fish and other seafood (including amphibians, reptiles, snails and insects)	40	40	100
Food for infants and small children	50	50	100
Herbs, spices and condiments	10	10	100
Meat and meat products (including edible offal)	130	130	100
Milk and dairy products	140	140	100
Nuts and oilseeds	10	10	100
Snacks and desserts	10	10	100
Starchy roots and tubers	10	10	100
Sugar and confectionary (including cocoa products)	10	10	100
China, mainland			
Cereals and cereal-based products	252	178	71
Eggs and egg products	288	195	68

Table 18 (continued)

Food category (by country)	No. of data submitted	No. of detections[a]	Frequency of detection (%) (six indicator congeners)
Fish and other seafood (including amphibians, reptiles, snails and insects)	2 082	1 814	87
Food for infants and small children	822	637	77
Legumes and pulses	252	215	85
Meat and meat products (including edible offal)	2 274	1 597	70
Milk and dairy products	2 226	1 753	79
Starchy roots and tubers	252	186	74
Vegetables and vegetable products (including fungi)	246	154	63
China, Hong Kong Special Administrative Region			
Cereals and cereal-based products	312	0	0
Composite foods (including frozen products)	240	0	0
Eggs and egg products	72	0	0
Fats and oils of animal and vegetable origin (excluding butter)	24	0	0
Fish and other seafood (including amphibians, reptiles, snails and insects)	456	205	45
Herbs, spices and condiments	24	0	0
Meat and meat products (including edible offal)	288	6	2
Milk and dairy products	144	10	7
Non-alcoholic beverages (excluding milk, fruit and vegetable juice, water and stimulants)	24	0	0
Snacks and desserts	24	0	0
Starchy roots and tubers	24	0	0
Stimulant beverages, dried and diluted excluding cocoa products	48	0	0
Sugar and confectionary (including cocoa products)	24	2	8
Cyprus			
Eggs and egg products	300	48	16
Fish and other seafood (including amphibians, reptiles, snails and insects)	240	162	68
Food for infants and small children	18	18	100
Meat and meat products (including edible offal)	204	90	44
Milk and dairy products	318	108	34
Other foods	12	12	100
Czech Republic			
Alcoholic beverages	24	3	13
Cereals and cereal-based products	234	90	38
Composite food (including frozen products)	54	25	46
Drinking-water (water without any additives except carbon dioxide; includes water ice for consumption)	12	4	33
Eggs and egg products	36	24	67
Fats and oils of animal and vegetable origin (excluding butter)	84	36	43
Fish and other seafood (including amphibians, reptiles, snails and insects)	276	136	49
Food for infants and small children	54	8	15
Fruit and fruit products	174	14	8
Fruit and vegetable juices	6	0	0

Food category (by country)	No. of data submitted	No. of detections[a]	Frequency of detection (%) (six indicator congeners)
Herbs, spices and condiments	18	4	22
Legumes and pulses	36	1	3
Meat and meat products (including edible offal)	720	287	40
Milk and dairy products	282	112	40
Non-alcoholic beverages (excluding milk, fruit and vegetable juice, water and stimulants)	24	6	25
Nuts and oilseeds	12	6	50
Snacks and desserts	36	8	22
Starchy roots and tubers	102	14	14
Stimulant beverages, dried and diluted excluding cocoa products	12	0	0
Sugar and confectionary (including cocoa products)	216	15	7
Vegetables and vegetable products (including fungi)	276	60	22
Estonia			
Eggs and egg products	144	135	94
Fats and oils of animal and vegetable origin (excluding butter)	6	0	0
Fish and other seafood (including amphibians, reptiles, snails and insects)	708	522	74
Meat and meat products (including edible offal)	78	46	59
Milk and dairy products	90	46	51
Sugar and confectionary (including cocoa products)	72	6	8
Finland			
Composite food (including frozen products)	6	6	100
Eggs and egg products	60	60	100
Fish and other seafood (including amphibians, reptiles, snails and insects)	3 006	2 998	100
Food for infants and small children	48	48	100
Meat and meat products (including edible offal)	168	168	100
Milk and dairy products	90	44	49
France			
Eggs and egg products	690	510	74
Fats and oils of animal and vegetable origin (excluding butter)	66	66	100
Fish and other seafood (including amphibians, reptiles, snails and insects)	5 220	5 030	96
Food for infants and small children	102	102	100
Fruit and fruit products	30	30	100
Legumes and pulses	18	18	100
Meat and meat products (including edible offal)	1 674	579	35
Milk and dairy products	210	180	86
Germany			
Alcoholic beverages	66	0	0
Cereals and cereal-based products	66	60	91
Composite food (including frozen products)	30	6	20
Eggs and egg products	1 704	978	57
Fats and oils of animal and vegetable origin (excluding butter)	102	74	73
Fish and other seafood (including amphibians, reptiles, snails and insects)	8 053	3 326	41

Table 18 (continued)

Food category (by country)	No. of data submitted	No. of detections[a]	Frequency of detection (%) (six indicator congeners)
Food for infants and small children	162	154	95
Fruit and fruit products	128	120	94
Fruit and vegetable juices	126	0	0
Legumes and pulses	60	60	100
Meat and meat products (including edible offal)	3 534	1 371	39
Milk and dairy products	31 788	30 652	96
Products for special nutritional use	42	29	69
Starchy roots and tubers	120	120	100
Stimulant beverages, dried and diluted excluding cocoa products	6	0	0
Sugar and confectionary (including cocoa products)	78	0	0
Vegetables and vegetable products (including fungi)	246	240	98
Greece			
Eggs and egg products	246	144	59
Fats and oils of animal and vegetable origin (excluding butter)	894	136	15
Fish and other seafood (including amphibians, reptiles, snails and insects)	426	189	44
Food for infants and small children	30	30	100
Fruit and fruit products	36	36	100
Meat and meat products (including edible offal)	798	420	53
Milk and dairy products	270	232	86
Iceland			
Cereals and cereal-based products	6	2	33
Eggs and egg products	30	21	70
Fish and other seafood (including amphibians, reptiles, snails and insects)	522	435	83
Meat and meat products (including edible offal)	96	68	71
Milk and dairy products	138	116	84
Products for special nutritional use	24	22	92
Starchy roots and tubers	6	4	67
Ireland			
Cereals and cereal-based products	18	18	100
Composite food (including frozen products)	6	6	100
Eggs and egg products	630	557	88
Fats and oils of animal and vegetable origin (excluding butter)	492	480	98
Fish and other seafood (including amphibians, reptiles, snails and insects)	726	720	99
Fruit and fruit products	18	0	0
Herbs, spices and condiments	6	0	0
Meat and meat products (including edible offal)	186	186	100
Milk and dairy products	312	312	100
Products for special nutritional use	276	210	76
Starchy roots and tubers	12	0	0
Vegetables and vegetable products (including fungi)	36	0	0

Food category (by country)	No. of data submitted	No. of detections[a]	Frequency of detection (%) (six indicator congeners)
Italy			
Eggs and egg products	162	6	4
Fats and oils of animal and vegetable origin (excluding butter)	72	0	0
Fish and other seafood (including amphibians, reptiles, snails and insects)	732	576	79
Meat and meat products (including edible offal)	342	12	4
Milk and dairy products	174	0	0
Sugar and confectionary (including cocoa products)	72	0	0
Japan			
Fish and other seafood (including amphibians, reptiles, snails and insects)	505	499	99
Luxembourg			
Fish and other seafood (including amphibians, reptiles, snails and insects)	72	72	100
Netherlands			
Eggs and egg products	12	12	100
Fats and oils of animal and vegetable origin (excluding butter)	24	19	79
Fish and other seafood (including amphibians, reptiles, snails and insects)	1 158	1 158	100
Meat and meat products (including edible offal)	36	36	100
Milk and dairy products	36	30	83
Snacks and desserts	12	12	100
New Zealand			
Milk and dairy products	2	0	0
Norway			
Cereals and cereal-based products	24	24	100
Eggs and egg products	114	89	78
Fats and oils of animal and vegetable origin (excluding butter)	114	63	55
Fish and other seafood (including amphibians, reptiles, snails and insects)	5 658	5 487	97
Fruit and fruit products	12	11	92
Legumes and pulses	6	0	0
Meat and meat products (including edible offal)	306	208	68
Milk and dairy products	288	245	85
Other foods	6	6	100
Snacks and desserts	6	6	100
Vegetables and vegetable products (including fungi)	6	6	100
Poland			
Composite food (including frozen products)	6	0	0
Eggs and egg products	390	299	77
Fish and other seafood (including amphibians, reptiles, snails and insects)	1 608	1 582	98
Meat and meat products (including edible offal)	444	423	95
Milk and dairy products	360	323	90
Sugar and confectionary (including cocoa products)	30	5	17
Republic of Korea			
Fish and other seafood (including amphibians, reptiles, snails and insects)	5 424	2 930	54

Table 18 (continued)

Food category (by country)	No. of data submitted	No. of detections[a]	Frequency of detection (%) (six indicator congeners)
Romania			
Cereals and cereal-based products	6	0	0
Composite food (including frozen products)	12	0	0
Fats and oils of animal and vegetable origin (excluding butter)	12	0	0
Fish and other seafood (including amphibians, reptiles, snails and insects)	24	0	0
Meat and meat products (including edible offal)	708	0	0
Milk and dairy products	198	0	0
Other foods	18	0	0
Stimulant beverages, dried and diluted excluding cocoa products	6	0	0
Sugar and confectionary (including cocoa products)	66	0	0
Singapore			
Food for infants and small children	36	0	0
Slovakia			
Eggs and egg products	111	70	63
Fats and oils of animal and vegetable origin (excluding butter)	25	6	24
Fish and other seafood (including amphibians, reptiles, snails and insects)	278	78	28
Meat and meat products (including edible offal)	492	161	33
Milk and dairy products	286	127	44
Slovenia			
Eggs and egg products	30	18	60
Fats and oils of animal and vegetable origin (excluding butter)	114	51	45
Fish and other seafood (including amphibians, reptiles, snails and insects)	798	223	28
Food for infants and small children	168	38	23
Fruit and fruit products	12	4	33
Meat and meat products (including edible offal)	30	23	77
Milk and dairy products	42	22	52
Nuts and oilseeds	48	4	8
Products for special nutritional use	30	30	100
Sugar and confectionary (including cocoa products)	30	5	17
Vegetables and vegetable products (including fungi)	12	0	0
Spain			
Eggs and egg products	95	0	0
Fats and oils of animal and vegetable origin (excluding butter)	50	0	0
Fish and other seafood (including amphibians, reptiles, snails and insects)	6	6	100
Milk and dairy products	55	0	0
Sweden			
Cereals and cereal-based products	120	72	60
Composite food (including frozen products)	24	24	100
Eggs and egg products	474	424	89
Fats and oils of animal and vegetable origin (excluding butter)	558	385	69

Food category (by country)	No. of data submitted	No. of detections[a]	Frequency of detection (%) (six indicator congeners)
Fish and other seafood (including amphibians, reptiles, snails and insects)	1 818	1 802	99
Food for infants and small children	144	118	82
Fruit and fruit products	42	42	100
Meat and meat products (including edible offal)	168	125	74
Milk and dairy products	372	308	83
Products for special nutritional use	66	24	36
Starchy roots and tubers	24	24	100
Vegetables and vegetable products (including fungi)	48	48	100
United Kingdom			
Cereals and cereal-based products	30	22	73
Composite food (including frozen products)	978	848	87
Eggs and egg products	360	293	81
Fats and oils of animal and vegetable origin (excluding butter)	114	73	64
Fish and other seafood (including amphibians, reptiles, snails and insects)	1 704	1 615	95
Fruit and fruit products	30	18	60
Meat and meat products (including edible offal)	1 782	1 149	64
Milk and dairy products	396	297	75
Nuts and oilseeds	6	4	67
Products for special nutritional use	30	17	57
Starchy roots and tubers	6	5	83
Sugar and confectionary (including cocoa products)	6	6	100
Vegetables and vegetable products (including fungi)	84	62	74

[a] Detection frequency was impacted by the LODs attained with the methods used by individual countries.

Fig. 3
Indicator PCB congener concentrations in fish and fish products

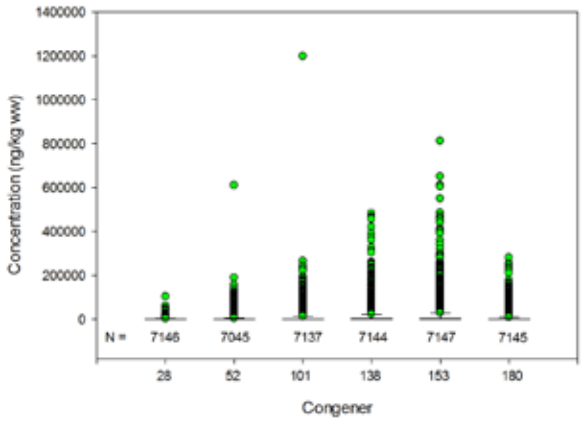
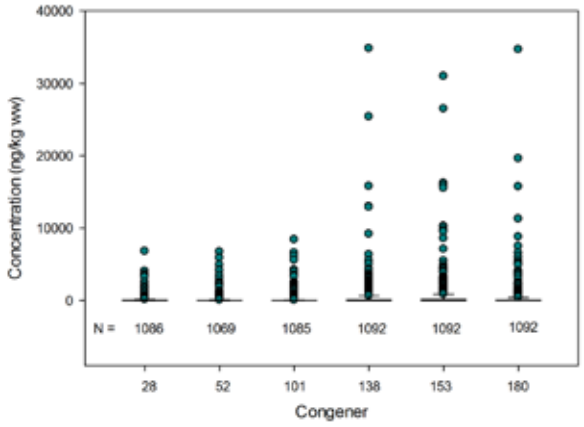


Fig. 4
Indicator PCB congener concentrations in egg and egg products



Indicator congener concentrations were more consistently distributed in meat and meat products, and no clear increase in concentration was associated with degree of chlorination (Fig. 5). Although similar to the fish products, the median values for the indicator congeners in the meat and meat products were very low relative to the maximum concentrations. Variability in the concentration patterns was observed in milk and milk products, and maximum values were more than an order of magnitude lower than those observed in fish and meat products (Fig. 6).

Fig. 5
Indicator PCB congener concentrations in meat and meat products

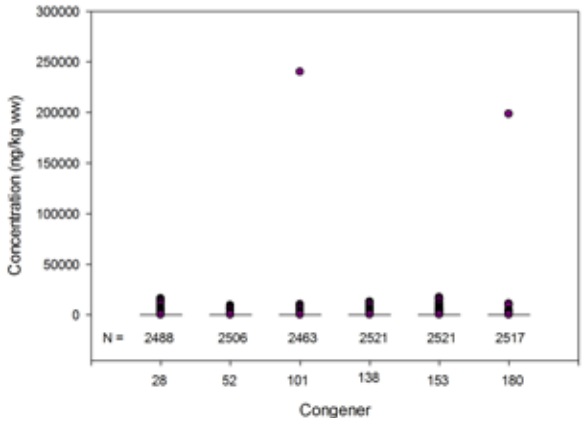
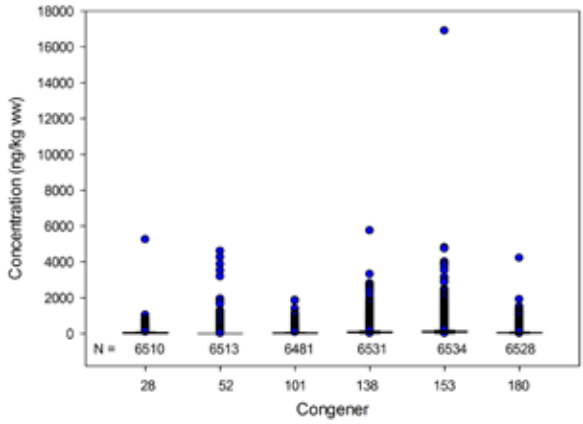


Fig. 6
Indicator PCB congener concentrations in milk and milk products



8. Dietary exposure assessment

8.1 Introduction and background

An evaluation of the dietary exposure to NDL-PCBs was undertaken by the Committee. The focus of this evaluation was the six indicator PCBs – namely, PCBs 28, 52, 101, 138, 153 and 180. PCB 128 was also included where relevant and possible. This selection of PCBs for inclusion in the dietary exposure assessment was based on the availability of toxicological and exposure data.

The six indicator PCBs make up around 50% of total NDL-PCBs in food (EFSA, 2005). For both the occurrence data submitted to the GEMS/Food database and the available estimates of dietary exposure, a range of NDL-PCBs was included; however, the majority of this information was for the six indicator PCBs. This may be as a result of the setting of maximum levels by the European Commission (2011) for the six indicator PCBs, along with required monitoring, as much of the available information was from European countries. The information on the NDL-PCBs other than the six indicator congeners was much less substantial.

As outlined in the section above on occurrence, the predominant foods containing NDL-PCBs are those of animal origin, such as fish and seafood, eggs, milk and dairy products, meat and offal. The lowest concentrations are in foods of plant origin (EFSA, 2010). Owing to their lipophilic nature, the NDL-PCB residues are usually found in the fatty portion of foods. It was therefore important to evaluate estimates of dietary exposure in which these types of foods were included.

8.2 Methods

8.2.1 Overview of the methods for the NDL-PCBs exposure assessment

Both national and international assessments of dietary exposure were reviewed by the Committee. These included those sourced from the literature, information provided to JECFA and estimates calculated by the Committee. Based on the outcomes of the toxicological assessment by the Committee, it was determined that only chronic dietary exposure assessments were required for the evaluation.

For NDL-PCBs, there are no TEFs for use in the assessment of dietary exposure to adjust for varying toxicities of different congeners when the sum of a number of congeners is used for the assessment. This is unlike the process used for DL-PCBs (WHO, 1998; van den Berg et al., 2006).

Estimates of dietary exposure to NDL-PCBs have been reported for whole populations, as well as adults and children separately, and some "lifespan" estimates have been reported. Therefore, a review of all of these groups was

included in the evaluation. PCBs are transferred from mother to child through breastfeeding; therefore infants, both breastfed and formula fed, were also considered, where possible, as a specific subgroup. Populations with potentially higher exposures were also evaluated where information was available.

The occurrence data indicated that animal foods, particularly the lipid portions, have the highest concentrations of NDL-PCBs. Many of the dietary exposure assessments included a focus on animal foods, but often were not limited to these food groups. Where the estimates of dietary exposure were focused just on animal and animal-based foods, the results were still included in this evaluation, as they were considered to include the key contributors to dietary exposure. Less emphasis was placed on estimates of dietary exposure that did not include animal-based foods; however, this was assessed on a case-by-case basis, because for some countries, non-animal foods may make up a larger portion of the diet (e.g. high vegetable consumption in China; Xing, Wu & Wong, 2010), in which case they would be important inclusions in a dietary exposure assessment.

A literature review was undertaken to source published papers with estimates of dietary exposure to NDL-PCBs in any combination. The EFSA (2005) review of NDL-PCBs included dietary exposure estimates from a number of European countries; therefore, the EFSA report was used to obtain key estimates of relevance to this assessment as a starting point. The literature search aimed to source any later published papers from Europe or papers from non-European countries. The countries for which estimates of dietary exposure obtained from the literature included the six indicator PCBs included Austria, Belgium, China (including Hong Kong Special Administrative Region), Egypt, France, Germany, Italy, the Netherlands, Norway, Serbia, Slovakia, Spain and Turkey.

Many of the estimates of dietary exposure reviewed from the literature included different combinations of PCBs. For this evaluation, estimates covering the sum of the six indicator PCBs were included. Also included were estimates based on the sum of seven PCBs (i.e. the six indicator PCBs plus PCB 118, a DL-PCB), with a conversion factor of 0.85 applied to express the exposure in the equivalent form of the six indicator PCBs (EFSA, 2005).

A number of national and international dietary exposure estimates were also calculated specifically for this evaluation. These were conducted using concentration data submitted via the GEMS/Food concentration database. For the national estimates of dietary exposure, concentration data from individual countries were summarized and combined with country-specific consumption data from the FAO/WHO Chronic Individual Food Consumption database – summary statistics (CIFOCOss). More details of how this was done are provided below. For international estimates of dietary exposure, the concentration data were pooled for countries according to the 17 GEMS/Food cluster diets, then summarized and combined with the consumption data for each cluster to estimate

dietary exposure. The specific methods used to summarize the GEMS/Food data and match them with the relevant consumption data are described further below. The aim of the international assessment is to provide information on clusters of countries that may have higher dietary exposures compared with other clusters of countries and to evaluate key contributing foods to dietary exposure in different regions. It also provides useful information about possible levels of dietary exposure for countries for which no national data exist. Calculations of national and international dietary exposures were done deterministically using mean concentrations multiplied by mean food consumption per person. A common approach of multiplying mean exposures by a factor to obtain an approximate high-percentile exposure (WHO, 1985; FAO/WHO, 2009) was used and is outlined further below. The national and international estimates of dietary exposure, although both based on GEMS/Food concentration data, are not directly comparable because of the different bases for the consumption data.

Where national estimates of dietary exposure were calculated by the Committee, this was done both for the sum of the six indicator PCBs as well as for each of these six indicator PCBs individually. The estimates for the individual congeners were used to estimate body burdens of individual congeners. Individual values were needed, given the different ways in which the congeners behave in the body, including their metabolism and differing half-lives.

The main foods contributing to dietary exposures were also determined. These may have been reported in studies in the literature. The majority (around 90%) of total exposure to NDL-PCBs comes from food (EFSA, 2005). Other routes of exposure, such as dermal and inhalation routes, were assessed where information was available.

Assessing the impact of potential maximum levels in foods on dietary exposure was not required for this assessment.

8.2.2 How the GEMS/Food concentration data were used for the dietary exposure assessment

Concentration data for NDL-PCBs from the GEMS/Food database available for use in the dietary exposure assessment were from Australia, Austria, Belgium, Canada, China (including Hong Kong Special Administrative Region), Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Poland, Republic of Korea, Romania, Singapore, Slovakia, Slovenia, Spain, Sweden and the United Kingdom. The national data sets varied widely in the range of congeners reported. Many included only the six indicator PCBs. A range of food groups was included, ranging from only one food for a country to just animal-based foods to a broad range of foods. Some data were derived using analytical methods with a

greater sensitivity than others (i.e. had lower LODs). These data were used by the Committee to calculate estimates of dietary exposure, with edits and exclusions made where required for the assessment as outlined below.

There were over 125 000 data points for NDL-PCBs in the data set; around 90% of these were for the six indicator PCB congeners (with an even proportion for each of the six congeners). The remainder of the data set was made up of results for 36 other congeners and mixtures. For the dietary exposure assessment, data for total PCBs, total NDL-PCBs and PCB mixtures were excluded. Data for individual congeners were retained, allowing them to be combined and summarized as required for the dietary exposure assessment. Individual data for the six indicator PCB congeners and PCB 128 were used for this evaluation. The majority (around 85%) of analytical results were from European countries, and the rest were from the non-European countries noted above.

The majority of data points related to "individual" samples of food. In the majority of cases, it was not specifically stated if these were single purchase units or composite samples. For some data points, it was noted that the result was for a composite (e.g. composite of three samples). Some of the data were provided as aggregates or summaries of many individual results, where only summary statistics from all analytical results were provided (i.e. number of samples, means and percentiles). Aggregated data were not used in the national assessments where those countries had also provided individual (non-aggregated) data or where the data did not relate to a food or PCB congener of relevance. Aggregated data were not used in the international assessments, as they could not be pooled with the individual data points from other countries for deriving summary concentrations for each cluster.

The data needed to be manipulated in order to make them consistent and in a usable format for summarizing and using in the dietary exposure assessment. This is outlined below.

All data points were converted to the same concentration units (ng/kg).

Data were available for the years 1995–2014. No data were excluded because they were gathered at earlier times. This is despite evidence that concentrations have decreased over time. However, data from earlier time periods have still contributed to the body burden of lifetime exposure for older persons and are relevant for lifetime or population-based estimates of dietary exposure.

Analytical results below the LOD (non-detects or left-censored data) made up around 24% of the data points. However, there was considerable variation in the LODs reported by different countries. To enable concentration data to be summarized, a numerical value was required to be assigned to the non-detects. For the dietary exposure calculations, two scenarios were defined, one where non-detects were assigned a zero concentration (lower bound) and one where they were assigned the value of the LOQ (upper bound). The actual

concentration will be somewhere between the lower bound and the upper bound. Some samples had high LOQs (up to around 80 μg/kg). Substituting the value of the LOQ for non-detects could lead to a very conservative estimate of the upper bound of dietary exposure. It was determined by the Committee that analyses with LODs of 1 μg/kg (equivalent to an LOQ of around 3.5 μg/kg) or less represented more reliable results. Therefore, dietary exposures were estimated after eliminating samples with LOQs above this level.

A small number of samples (0.2%) had a numerical concentration provided that was between the LOD and LOQ (i.e. a "trace" result). These concentrations were accepted and used in relevant calculations.

Where estimates of dietary exposure were calculated by the Committee, the lower-bound scenario (where a concentration of zero was assigned to any result below the LOD) was used to determine the major contributors in order to not exaggerate the contribution of food groups that had non-detectable levels of NDL-PCBs.

Where concentrations were expressed on a lipid basis (45% of samples), concentrations were converted to a fresh weight basis to make them consistent with the food consumption data. The conversions used food composition data on the proportion of fat in the food from a range of data sources (e.g. as provided in the GEMS/Food database for the specific food, United States Department of Agriculture, Food Standards Australia New Zealand, European Food Information Resource Network).

Some concentrations were expressed on a dry weight basis (e.g. shrimp, milk powder) and therefore were converted to a fresh weight basis to match the food consumption data. This conversion used a factor derived from the difference in moisture content between the dried and fresh versions of the food. The moisture content was derived from food composition tables.

The majority of results were provided for foods analysed in their raw state (26%) or unknown (72%), with around 2% of results relating to cooked foods. No conversion of concentrations from a cooked to raw state was made in order to make the samples match the form for the majority of samples in the data set, because the small number of data points would have had a very minor impact on the estimated dietary exposures. Concentration data were matched to consumption data for the raw commodity in the majority of cases. Animal foods, such as meat, eggs and seafoods, are usually consumed cooked; therefore, the effect of cooking on NDL-PCB concentrations needs to be taken into account when interpreting the dietary exposure estimates.

Where unique sample identifiers were provided for each data point, the sum of the six indicator congeners for each individual sample was determined before deriving mean concentrations per food group. Therefore, if concentration data for one of the six congeners were missing for a sample, this sample was

excluded from the data used to derive the mean for the food group in question. In addition, where the assessment excluded samples with LOQs above 3.5 μg/kg, the whole sample was excluded if one of the six congeners fell into this category. This method of summing the six indicator PCB concentrations by sample unique identifier was used for 25 of the 31 countries that submitted data. However, some data sets did not provide unique identifiers for samples (Canada, Japan, Republic of Korea and Singapore). In these cases, the mean concentration for each food group for each of the six indicator congeners was determined separately in the first instance, then the means were summed for the six congeners. One limitation of this approach is that there may have been a different number of samples for each food for each of the six congeners.

Concentration data for foods for infants were also included in the data set. There were two rows of data for human milk that were aggregate data from New Zealand for two of the indicator PCBs (PCBs 28 and 101). For infant formula, data were submitted for both powder and liquid formulas. Where the PCBs analysed were mixtures, these data points were excluded (eight data points for Australia). There were 80 data points from Canada for a range of congeners in infant formula; however, there were only data for five of the six indicator congeners. Concentration data on infant formula were available from China (n = 822 data points), Czech Republic (n = 12 data points), France (n = 24 data points), Sweden (n = 30 data points) and Singapore (n = 35 data points). For follow-on formula, there were a small number of data points (n = 12) from France. There were around 900 data points for foods for infants (cereal, vegetable, dairy or meat based, etc.).

Most results in the concentration data set were for the edible portion of the food only (99%), with the remainder relating to the edible plus inedible portion. Based on further analysis of these data, no conversions were made of concentrations given for edible plus inedible to be representative of just the edible portions. This was for a number of reasons, including that "edible plus inedible" was used mostly for seafoods, the data were for foods that included shells, etc., such as oysters, and were unlikely to be analysed with the shell, and the small number of results would have had a very minor impact on the estimated dietary exposures.

A small number of data points (2%) were indicated to be from "targeted" sampling. The remainder were "random" samples or unknown. There could be many different reasons for targeting samples, including investigation of a contamination incident or targeting analysis of specific foods in which the food chemical in question is known to occur. The database does not specify the reason. Results from targeted sampling were not excluded from further analyses. The small number of data points would have had a very minor impact on the estimated dietary exposures.

No weightings were applied to the concentrations, as there was insufficient information about the available data to allow this to be done.

There were some outliers in the concentration data sets. Outliers will have the effect of skewing mean concentrations upwards, and therefore dietary exposure estimates will be inflated. Some outliers were in the data sets for countries for which a dietary exposure could not be calculated and therefore did not influence the evaluation or conclusions. The treatment and effect of the outliers on the dietary exposure are discussed in the text where relevant to the assessment.

8.2.3 National estimates of dietary exposure using the FAO/WHO Chronic Individual Food Consumption database – summary statistics (CIFOCOss)

The CIFOCOss data were used for the national estimates of dietary exposure calculated by the Committee. The diets were for individual countries and are based on national food consumption survey data from individuals with 2 or more days of data (for further details, see http://www.who.int/foodsafety/databases/en/). The consumption data were combined with the GEMS/Food concentration data to estimate national dietary exposure to NDL-PCBs, where both data sets were available for the country. Consumption data were available for 27 countries; however, not all of these countries had submitted concentration data to the GEMS/Food database. National estimates of dietary exposure were derived for Belgium, China (excluding Hong Kong Special Administrative Region), Cyprus, Czech Republic, Finland, France, Germany, Greece, Ireland, Italy, Japan, the Netherlands, Republic of Korea, Spain, Sweden and the United Kingdom.

National estimates were not conducted where either no CIFOCOss data were available (Austria, Canada, Estonia, Iceland, Luxembourg, New Zealand, Norway, Poland, Romania, Singapore, Slovakia and Slovenia) or the concentration data for the country were not suitable, sufficient or in a usable format (e.g. Australia only had NDL-PCB mixture data, New Zealand only had two aggregate data points for human milk, too few samples for Spain).

Food consumption data in the CIFOCOss database have been classified using a combination of raw commodity classification codes and classifications for some processed foods. Each food in the GEMS/Food concentration database was assigned to a food in the most specific level of the CIFOCOss classification structure (Level 3) to enable them to be summarized and mean concentrations to be derived for each classification for use in the dietary exposure calculations. Some foods in the CIFOCOss data set could have more than one classification code, which could include raw commodity codes and/or processed food classifications. For example, the possible classification codes that could be used for consumption data for butter are 2.2.1 as a processed commodity, ML0100 Mammalian fat or

ML0812 Cattle fat. Therefore, all possible codes were evaluated for the relevant country to determine where the consumption data were reported, and then the concentration data were assigned that same code.

The major foods in which NDL-PCBs are detected are foods of animal origin at the raw commodity level. Many of these foods, such as eggs, milk and meat, are used as ingredients in mixed dishes. It was originally requested that food consumption data for mixed dishes be broken down by recipes for the purposes of the CIFOCOss data set so consumption of the individual ingredients would be captured under each raw commodity classification. However, in the consumption data set, some data related to composite dishes were included.

The mean consumption amount for all respondents (consumers and non-consumers) in grams per kilogram of body weight per day for each food was used to allow the exposure to be summed across food groups in order to estimate exposure from the whole diet, or from as much of the diet as captured by the concentration data. By using the consumption data on a gram per kilogram of body weight basis, the relevant body weights from each country were implicitly taken into account. As the high-percentile consumption data provided in the CIFOCOss data set could not be used to sum exposures across food groups, a factor of 2 was applied to the mean exposure estimate to approximate potential high-percentile exposures. This factor approximates the 90th percentile. In some cases, there may have been concentration data available for a food, but no consumption data – for example, for specific types of seafood for toddlers or young children.

Food consumption data for a number of different age groups were represented in the CIFOCOss data set. These included population subgroups such as toddlers, children, adolescents, adults, elderly and very elderly. Some countries provided specific age ranges for their data; others from Europe follow the EFSA-defined age ranges for the population group descriptors (EFSA, 2011). Therefore, dietary exposure was estimated for a range of ages in the population where the data existed for the countries with concentration data available. The data were not split by sex.

8.2.4 International estimates of dietary exposure using the GEMS/Food cluster diets

The GEMS/Food cluster diets were used for the international estimates of dietary exposure calculated by the Committee. GEMS/Food supranational model diets, called cluster diets, are based on food balance sheet data from individual countries and are for mean amounts of food available for consumption per capita. The diets include consumption amounts of raw or minimally processed foods. They do not include consumption data for any population subgroups by either age or sex;

therefore, they do not allow for separate assessments for groups such as children or infants. Further information on the cluster diets can be found at http://www.who.int/foodsafety/databases/en/.

Lower- and upper-bound estimates of international dietary exposure were derived deterministically using lower-bound mean and upper-bound mean concentrations of the six indicator PCBs for relevant foods in each cluster food group, where available.

Consumption data for the clusters were not available on a body weight basis; therefore, estimates of dietary exposure were divided by a standard body weight of 60 kg to enable them to be expressed per kilogram of body weight.

There are 17 GEMS/Food cluster diets. The individual data points from the GEMS/Food concentration data were pooled from the countries that were in the same cluster to determine mean concentrations per food group for each cluster. Concentration data were available for only seven of the 17 clusters from 27 individual countries. The seven clusters (and concentration data sources) were cluster 6 (Greece), cluster 7 (Finland, France, Iceland, Luxembourg, Norway, United Kingdom), cluster 8 (Austria, Germany, Poland, Spain), cluster 9 (China, including Hong Kong Special Administrative Region), cluster 10 (Canada, Cyprus, Estonia, Italy, Japan, Republic of Korea), cluster 11 (Belgium, the Netherlands) and cluster 15 (Czech Republic, Ireland, Romania, Slovakia, Slovenia, Sweden). There were no data from the other clusters, which covered mostly African and South American countries. Data from some countries were excluded from the data set if they were aggregate results, did not contain concentrations for the six indicator PCBs or were not of sufficient quality.

In total, there were over 124 000 data points that could be assigned to relevant clusters and the cluster food groups. There were 2700 data points for cluster 6, 30 459 for cluster 7, 50 294 for cluster 8, 10 392 for cluster 9, 13 083 for cluster 10, 5058 for cluster 11 and 12 096 for cluster 15.

Where all of the countries in the one cluster had data for the six indicator PCBs, as well as sample unique identifiers for each sample, the sum of the six congeners was calculated per sample first, then the mean concentration for the food group for that cluster was derived (clusters 6, 7, 8, 11 and 15). Where all countries in the cluster had data for the six indicator PCBs, but did not have sample unique identifiers for all countries in the cluster, the mean concentration for each individual indicator congener for a food group from all country data for that cluster was derived, then the sum of the six congeners was calculated (clusters 9 and 10).

Where there were no data points for a cluster (clusters 1, 2, 3, 4, 5, 12, 13, 14, 16 and 17), the data from all clusters were pooled to obtain mean concentration data for the dietary exposure calculation for these clusters (n = 124 082 data points). This is based on the assumption that there is a global food

supply with many foods traded between countries, and concentration data from one area of the world are representative of the concentrations in foods consumed in other areas of the world.

8.3 Estimates of dietary exposure

8.3.1 National estimates of dietary exposure

National estimates of dietary exposure to NDL-PCBs were from two sources – firstly, the literature, and secondly, the estimates calculated by the Committee.

EFSA (2005) derived national estimates of dietary exposure to NDL-PCBs for some European countries and concluded that average daily exposures to total NDL-PCBs for general adult populations were in the range of 10–45 ng/kg bw per day, depending on the country, and for children, 27–50 ng/kg bw per day. They also concluded that high meat eaters had an exposure around 20 ng/kg bw per day, and high fish eaters, 35 ng/kg bw per day.

EFSA (2012) more recently estimated dietary exposure to NDL-PCBs across 17 member states for various population groups, based on the most recent monitoring data at that time. The mean dietary exposure to the sum of the six indicator PCBs was estimated to be between 4.3 and 25.7 ng/kg bw per day, depending on the country and population subgroup. This was very similar to the conclusions of the 2005 report, where mean estimates of exposure to the sum of the six indicator PCBs were summarized as 5–23 ng/kg bw per day (50% of the total NDL-PCB exposure of 10–45 ng/kg bw per day). Dietary exposures at the 95th percentile were estimated as 7.8–53.7 ng/kg bw per day for the sum of the six indicator PCBs.

A literature review identified a number of published papers with national estimates of dietary exposure for a range of NDL-PCBs in varying combinations, including individual congeners and the sum of a number of congeners (e.g. three, six, seven or 23 congeners). Some estimates were for usual long-term exposures (based on statistical adjustment methods), most were deterministic calculations, some used individual dietary records and others used duplicate diet approaches. In relation to food consumption data, a range of sources was used, including national consumption surveys, 7-day surveys, market baskets, duplicate diet studies or food balance sheet data. Many of the assessments focused on foods of animal origin; however, some also included a broader range of foods. Some estimates based on the sum of seven PCBs have been included here, with a conversion factor of 0.85 applied to express the exposure to the equivalent amount of the sum of the six indicator congeners (EFSA, 2005).

National dietary exposures were also estimated by the Committee where GEMS/Food concentration data and consumption data from CIFOCOss were

available. Food consumption data were provided according to both the CIFOCOss classification system, which for most food groups is based on the Codex raw commodity classification system, as well as the classification system in the Codex General Standard for Food Additives, for some processed commodities. Not all foods that had consumption data had associated NDL-PCB concentration data, and not all concentration data had corresponding food consumption information (e.g. some seafoods for young children).

Estimates of national dietary exposure focusing on the sum of the six indicator PCBs, either from the literature or calculated by the Committee, were from a range of countries, including Belgium, China, Cyprus, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Republic of Korea, Serbia, Slovakia, Spain, Sweden and the United Kingdom.

A summary of the national estimates of dietary exposure for the sum of the six indicator PCBs can be found in Table 19 for the published dietary exposure estimates and Table 20 for the national estimates calculated by the Committee. Further details can be found in Appendix 3.

Overall, mean national estimates of dietary exposure to the sum of the six indicator PCBs from the literature for adults ranged between 1 and 18 ng/kg bw per day (lower bound to upper bound), with high-percentile exposure ranging between 8 and 45 ng/kg bw per day. For children, the dietary exposure estimates were slightly higher, with a mean exposure of 3–24 ng/kg bw per day and a high-percentile exposure of 12–87 ng/kg bw per day. Lifelong averaged exposures estimated by one country (the Netherlands) were within this range, being 6 ng/kg bw per day at the mean and 10–12 ng/kg bw per day for a high consumer. The estimates of national dietary exposures calculated by the Committee covered a slightly broader range than the literature values. Mean exposures for adults ranged from <1 to 25 ng/kg bw per day, and high exposures ranged from <1 to 51 ng/kg bw per day. For children (also including adolescents), mean exposures ranged from <1 to 82 ng/kg bw per day, and high exposures from 1 to 163 ng/kg bw per day.

Some estimates of dietary exposure made by the Committee were lower than those from other sources. This is due to the different consumption and concentration data sets used, along with the different methodologies used to estimate the exposures. Even where the same concentration data sets were used (e.g. for estimates for some European countries), the concentrations were assigned to different food groups, and the classifications assigned to foods in the data submitted to GEMS/Food may not have had a direct match in the CIFOCOss consumption database, which will lead to different estimates. Better matching between and use of the two input data sets could be done if there were more metadata for both the concentration and consumption data sets and more detail in the data descriptors that would allow better interpretation of the data.

Table 19

Summary of national estimates of dietary exposure to sum of the six indicator PCBs from the literature

Country	Food concentration data used	Consumption data used	Population groups (age range in years)	Estimated dietary exposure (ng/kg bw per day)	Major contributors	Reference
Austria	Range of animal foods (meat, poultry, game, offal, fish and fish products, milk and dairy, eggs and egg products) ($n = 157$ foods). Analysed 2006–2011. No NDs.	National food consumption data. Men and women a 24 h recall. Children a 3-day food record.	Children (6–15) Adult males (19–65) Adult females (19–65)	Mean Children = 3.4 Adult males = 2.6 Adult females = 3.2	Fish and fish products (23–27%), cheese (18–23%), butter (19–22%), meat (15–23%), milk (11% children, 5–6% adults), eggs (4–7%)	Mihats et al. (2015)
Belgium	Game meat, processed meat, liver and products, fish, crustaceans, molluscs, fish salads, fish products, vegetable oil, cakes/pies/pastries. Analysed 2008. LB, MB, UB concentrations.	2004 Belgian food consumption survey, 15+ years, 2 × 24 h recall, $n = 3\,083$. C-SIDE, software for intake distribution estimation, used to determine usual intake.	Adults (15+)	Mean LB = 5.3 MB = 5.7 UB = 6.1 Median LB = 4.9 P99 LB = 16.1	Dairy, then fish (no proportions given)	Cimenci et al. (2013)
China, mainland	Meat, eggs, milk, cereals, legumes, nuts, tubers, vegetables.	Total diet study 2007 and 2011. 3-day household weighed record. Mean consumption 8 foods derived.	Adult males (18–45) 12 provinces	2007: Mean = 1.88 (difference of 7 across provinces) 2011: Mean = 0.67 (difference of 26 across provinces)	2007: cereals 40%, aquatic 19%, vegetables 14%, meat 13% 2011: aquatic 48%, vegetables 17%, meat 13%, cereals 11%	Data submitted to JECFA
China, Hong Kong Special Administrative Region	Range of food groups (pork, ruminant meat, poultry, fish, other seafood, dairy products, eggs and fat/oils). Analysed 2008–2010.	2005–2007 population-based consumption survey.	Adults	Mean 2.83 P95 9.48	Fish 60.3%, other seafood 9.0%, poultry 8.6%, pork 7.5%, eggs 4.7%, ruminants 3.9%, fats and oils (3.8%)	Xu & Cai (2015)
Egypt	Foods of animal origin: meat (beef, chicken), dairy (butter, cream, cheese), seafood (fish, crab, bivalves). Sampled in 2003. LB used (ND = 0).	Food balance sheet data for animal foods. Mean 60 kg body weight.	Whole population	Mean = 4.36	Fish 47%, chicken 40%	Loutfy et al. (2008)

Table 19 (continued)

Country	Food concentration data used	Consumption data used	Population groups (age range in years)	Estimated dietary exposure (ng/kg bw per day)	Major contributors	Reference
France	1 665 samples over 4 years of monitoring and other surveys. Mean concentrations. No NDs in results.	1998–1999. 7 days. 3+ years.	Children 3–14 (n = 1 018) Females 19–44 (n = 389) All other adults 15+ (n = 1 085)	Mean (sum of 6): Children 3–14 years mean 12.9, P95 27.3 Females 19–44 years mean 7.6, P95 16 All other adults 15+ years mean 7.7, P95 16	Fish products (children 38%, females 19–44 years 42%, other adults 47%) Meat products (children 24%, females 19–44 years 22%, other adults 21%) Dairy products (children 21%, females 19–44 years 20%, other adults 18%) Fruit and vegetables (children 9%, females 19–44 years 8%, other adults 7%) Eggs (children 6%, females 19–44 years 5%, other adults 4%) Seafood (children 2%, females 19–44 years 2%, other adults 3%)	Arnich et al. (2009)
France	Range of foods from Total Diet Study, prepared ready for consumption.	National individual food consumption data (INCA2). 7-day food record.	Adults (18–79) Children and teenagers (3–17)	Adults: Mean = 2.71 P95 = 7.90 Children and teenagers: Mean = 3.77 P95 = 11.7	Adults: fish 59%, butter 7%, meat 7%, cheese 6% Children/teenagers: fish 48%, butter 9%, meat 8%, milk 6%, other dairy/yoghurts 6%, cheese 6%	Sirot et al. (2012)
Germany	Range of foods.	Integrated exposure assessment survey (INES). Duplicate diet for 7 days.	Munich adults (19–58) n = 20 (10 females, 10 males)	MB Mean = 5.6 Median = 5.6 P95 = 8.9	Not provided	Fromme et al. (2007, 2009b)

Country	Food concentration data used	Consumption data used	Population groups (age range in years)	Estimated dietary exposure (ng/kg bw per day)	Major contributors	Reference
Germany	From Germany and other sources (if German data were not available). Range of foods. $n = 545$ individual food items.	National Health Survey 2005–2006 (NVZ-II) study of German consumption. Diet histories.	General public (14–80); $n = 20\,000$ persons	Mean = 10.86 High consumer method = 22.61	Fish products 36%, dairy products 30%, vegetable products 7%, meat products 7%	Schwarz et al. (2010, 2014)
Italy	Cereals and products, fruits and vegetables, eggs, fats and oils, fish and seafood, meat and products, offal, milk and dairy. Post-1997 data.	3- to 7-day diary national consumption survey individuals 1994–1996, 0.5–94 years of age, $n = 1940$.	Toddlers and young children (0.5–6) excluding breastfed Children (7–12) Adults (13–94)	Toddlers and young children: mean 24.6, P90 49.3, P95 60.0 Children: mean 16.1, P90 28.7, P95 33.8 Adults: mean 10.9, median 11.0, P90 20.0, P95 23.8	Toddlers: milk 38%, fish 36%, vegetable oil 12% Children: fish 38%, milk 28%, vegetable oil 15%, pork 7% Adults: fish 42%, milk 24%, vegetable oil 16%, pork 6% For P95 exposed: Toddlers: fish 59%, milk 24%, vegetable oil 13% Children: fish 60%, milk 23%, vegetable oil 11% Adults: fish 68%, milk 12%, vegetable oil 12%	Fattore et al. (2008)
Italy	Range of foods, whole diet. Mid-1990s.	Duplicate diet, 3 non-consecutive days, $n = 20$.	Mean age (±SD) 38 ± 13	Mean = 18 P95 = 39	Not provided	Zuccato et al. (1999)
Netherlands	Range of food groups (including meat, seafood, oils, nuts, vegetables) via analysis and recipes. Survey 1998–1999.	3rd Dutch National Food Consumption Survey 1997–1998, $n = 6\,250$, 2-day dietary record. Usual intake via STEM.	2, 10, 40, all	Σ6 congeners (derived by Σ7*0.85) 2 years: mean 11.5, median 10.3, P95 21.8 10 years: mean 7.8, median 5.8, P95 12.5 40 years: mean 4.9, median 4.4, P95 8.1 Lifelong averaged median: 4.8 P95 lifelong: 10.1 (based on LB concentrations)	Meat 27%, fish 26%, industrial oils and fats 18%, dairy products 17%, eggs 5%, vegetable products 7%	Bakker et al. (2003); Baars et al. (2004); EFSA (2005)

Table 19 (continued)

Country	Food concentration data used	Consumption data used	Population groups (age range in years)	Estimated dietary exposure (ng/kg bw per day)	Major contributors	Reference
Norway	Dairy, eggs, meat, vegetable oils, lean fish, oily fish, fish liver, shellfish, fish oils, seagull eggs, other.	Semiquantitative food frequency questionnaire.	21–80; $n = 184$ (73 in representative group, 111 in high consuming group)	Median 5.2 whole group LB mean: representative consumers 4.3, high consumers 6.4	Semi-oily and oily fish For fish and seafood PCB 153, representative consumers 68%, high consumers 63%	Kvalem et al. (2009)
Serbia	Wholegrain wheat flour, wheat bran, sunflower oil, sugar beet, molasses, sugar. 2002 analysis. LB and UB. Nationally analysed foods only (no imports included).	Mean daily per capita consumption of foods analysed, plus proportion of mixed foods where they were ingredients (21% of Serbian market basket). Mean body weight of 60 kg assumed.	Per capita	LB mean sum 6 = 2.9 UB mean sum 6 = 3.4 Note: underestimates, because no animal products included; article shows meat, milk and fish make up 36% of market basket.	Wholegrain wheat flour (79%), but that is of three food groups: flour, oil, sugar	Skrbic & Durisic-Mladenovic (2007)
Slovakia	Animal origin. 48 groups.	National consumption data, food balance sheets.	Average inhabitant Children 4–6, 7–11, 12–15 70 kg adult	Adults: mean 17, P95 45 Children: 4–6 years: mean 30, P95 87 7–11 years: mean 20, P95 56 12–15 years: mean 17, P95 47	Fats (47%), eggs and egg products (28%)	Salgovicová & Pavlovicová (2007)
Spain	Range of foods (meat, fish, milk, dairy, cereals, pulses, vegetables, tubers, fruits, fats and oils, bakery products). 2002–2003 Catalan Nutrition Survey.	2002–2003 Catalan Nutrition Survey (Serra-Majem et al., 2003).	Adults Mean body weight = 70 kg	Mean calculated from raw data in the report: 15	Fish and seafood 91%, milk 2%	Llobet et al. (2008)
Turkey	Milk, dairy products and butter.	Food consumption data from various regions in Turkey. No further details provided.	Turkish population	Butter only: mean 0.059 Milk, dairy and butter: mean 0.183	Not provided	Uçar et al. (2011)

INCA2: Etude individuelle nationale des consommations alimentaires 2; LB: lower bound; MB: middle bound; ND: non-detects; P90: 90th percentile; P95: 95th percentile; P99: 99th percentile; SD: standard deviation; STEM: STatistical Exposure Model; UB: upper bound

Table 20

Summary of the national estimates of dietary exposure for the sum of the six indicator PCBs from the calculations conducted by the Committee at mean and high percentile[a] for various population groups[b]

	Lower bound–upper bound dietary exposure (ng/kg bw per day)															
	Infants		Toddlers		Children		Adolescents		Adults		Elderly		Very elderly		General population	
Country	Mean	High exposure	Mean	High exposure	Mean	High exposure	Mean	High exposure	Mean	High exposure	Mean	High exposure	Mean	High exposure	Mean	High exposure
Belgium	–	–	16–82	33–163	12–63	25–125	11–30	22–60	8–24	15–47	6–23	12–46	7–25	13–51	–	–
China	–	–	–	–	1.0–1.0	1.9–2.0	–	–	–	–	–	–	–	–	0.5–0.5	1.0–1.0
Cyprus	–	–	–	–	–	–	4–17	7–35	–	–	–	–	–	–	–	–
Czech Republic	–	–	–	–	0.7–5.2	1.4–10.4	0.6–3.5	1.1–6.9	0.3–1.8	0.7–3.6	–	–	–	–	–	–
Finland	–	–	11–11	21–21	1.4–1.4 DIPP	2.9–2.9 DIPP	–	–	0.8–0.8	1.6–1.6	1.7–1.7	3.5–3.5	–	–	–	–
					9.5–9.5 STRIP	19–19 STRIP										
France	–	–	–	–	1.3–1.7	2.5–3.3	0.6–0.8	1.2–1.6	0.7–0.9	1.5–1.8	1.0–1.1	1.9–2.3	1.0–1.2	2.0–2.3	–	–
Germany[c]	–	–	9.3–10.8	18.5–21.6	5.9–6.2	11.9–12.4	2.6–2.8	5.2–5.5	3.4–3.6	6.7–7.2	3.8–4.1	7.5–8.2	3.8–4.2	7.6–8.4	–	–
Greece	–	–	–	–	10–14	21–27	–	–	–	–	–	–	–	–	–	–
Ireland	–	–	–	–	–	–	–	–	0.8–1.2	1.6–2.4	–	–	–	–	–	–
Italy	0.003–7.4	0.007–14.8	0.02–3.5	0.04–7.0	0.6–2.7	1.2–5.3	0.3–1.1	0.7–2.2	0.3–1.0	0.6–2.0	0.2–0.9	0.4–1.8	0.1–0.8	0.2–1.5	–	–
Netherlands	–	–	3.7–3.7	7.4–7.5	3.5–3.5	6.9–7.0	–	–	2.6–2.6	5.2–5.2	–	–	–	–	–	–
Republic of Korea	–	–	–	–	0.2–0.2	0.3–0.4	–	–	–	–	–	–	–	–	0.5–0.6	0.9–1.1
Sweden	–	–	–	–	6.7–13.7	13.3–27.4	3.4–7.5	6.7–15.0	5.3–7.1	10.5–14.1	–	–	–	–	–	–
United Kingdom	–	–	–	–	–	–	–	–	1.4–1.5	2.8–2.9	–	–	–	–	–	–

DIPP: Finnish Type I Diabetes Prediction and Prevention Nutrition Study; STRIP: Turku Coronary Risk Factor Intervention Project for Children

[a] Notes: high exposure = mean exposure × 2, which approximates the 90th percentile.

[b] Where specified based on the nutrition survey data, infants are <1 year, toddlers >1 to <3 years, children >3 to <10 years, adolescents >10 to <18 years, adults >18 to <65 years, elderly >65 to <75, very elderly >75 years.

[c] Three surveys used for toddlers and children, all very similar, so only showing results based on the most recent 2008 consumption survey.

Overall, the main contributor to dietary exposure to the sum of the six indicator PCBs was fish and seafood for a large number of the countries assessed. Meat and meat products along with dairy products (mainly cheese, butter and/or milk) were also common contributors, although usually to a lesser degree and for fewer countries, compared with fish and seafood. This was for both the assessments in the literature and those estimated by the Committee. Information on food contributors from the various estimates of dietary exposure was presented in different levels of detail, from specific foods to food groups. Owing to the variable nature of concentrations and consumption patterns within and between countries, the contribution reported from different foods is highly variable. These factors, combined with the different methods used to estimate the dietary exposure and major contributors, make comparison of contributors within and between countries difficult. From both the reports in the literature and the dietary exposures estimated by the Committee, contributions for fish and seafood ranged from 2% to 100%, depending on the country and population group. For meat and meat products, contributions ranged from <1% to 100%, depending on the country and population group. For dairy products, cheese contributed 5–60%, butter contributed 2–54% and milk contributed <1–79%. For children, milk and dairy products made a greater contribution to dietary NDL-PCB exposure, usually double the contribution compared with that for adults where both groups were assessed.

(a) **Austria**

Dietary exposure to the sum of the six indicator PCBs was estimated for Austria from a range of animal-based foods for adults and children (Mihats et al., 2015). The estimated mean exposure was 3.4 ng/kg bw per day for children, 3.2 ng/kg bw per day for women and 2.6 ng/kg bw per day for men. The results for children were only slightly higher than those for adults. Although this is not the usual trend, children usually have higher exposures than adults on a body weight basis; this may be explained by the fact that there were 3 days of consumption data for children and only 1 day of data for adults. The major contributor to exposure was fish and fish products for all three population groups (23–27%). Children had double the contribution from milk (11%) compared with adults (5–6%) due to their higher consumption of this food.

(b) **Belgium**

Estimated dietary exposures to the sum of the six indicator PCBs for Belgian adults (15 years and above) (Cimenci et al., 2013) ranged between 5.3 and 6.1 ng/kg bw per day (lower bound [LB] to upper bound [UB] mean, respectively). High consumers (99th percentile) had a LB exposure of 16.1 ng/kg bw per day. The

main contributors to dietary exposure were dairy (as a whole group) followed by fish.

EFSA (2012) also estimated dietary exposures for Belgium for a range of population subgroups using monitoring data. Mean dietary exposures (LB mean – UB mean) for toddlers were 10.8–11.8 ng/kg bw per day, for children, 9.3–10.2 ng/kg bw per day, for adolescents, 3.7–4.5 ng/kg bw per day, and for adults and the elderly, 4.6–6.6 ng/kg bw per day. Ninety-fifth percentile exposures for toddlers were 20.0–23.5 ng/kg bw per day, for children, 24.4–26.9 ng/kg bw per day, for adolescents, 12.4–13.1 ng/kg bw per day, and for adults and the elderly, 14.7–17.4 ng/kg bw per day. For toddlers, milk contributed 44%, meat 25% and fish 21%. The same foods contributed for children (milk 36%, fish 30%, meat 24%). By adolescence, meat was the main contributor (37%), then fish (31%) and milk (20%). For adults and the elderly, fish contributed 43–54%, meat 21–29% and milk 11–16%.

Estimates of exposure for Belgium from Cimenci et al. (2013) and EFSA (2012) were similar. The estimates conducted by the Committee were similar for the LB exposures, although the UB estimates were higher (up to 82 ng/kg bw per day for children and 25 ng/kg bw per day for adults at the mean). Despite the same consumption data set being used by EFSA (2012) and the Committee, the concentration data set was different, and foods may have been assigned differently to food groups. LOQs in the GEMS/Food concentration database ranged from 0.05 up to 3.3 µg/kg (fresh weight basis, when results with high LOQs over 3.5 µg/kg were excluded), whereas in the EFSA (2012) monitoring data, LOQs were <0.001–1.5 µg/kg on a fresh weight basis, which would have a large impact on the UB estimates, especially when 65% of the GEMS/Food data had non-detect values. The main contributors to dietary exposure, based on the calculations conducted by the Committee, were milk (60–65% children, 30–45% adults), cheese (10–36% children, 18–20% adults) and eggs for adults (15%) (see Appendix 3).

(c) China

The estimated dietary exposures for China that were calculated by the Committee were very low, at a mean of 1.0 ng/kg bw per day for children and 0.5 ng/kg bw per day for the general population. The concentration data set for China included a broad range of foods, including a range of animal foods. The low exposure is a result of the very low LOD used for the analysis of the foods.

The main contributors to dietary exposure for children were freshwater fish (26%), marine fish (13%), pork (13%), chicken eggs (12%), rice (10%) and wheat (10%). For the general population, the main contributors were freshwater fish (27%), marine fish (17%), pork (12%), rice (10%) and wheat (10%).

For the Hong Kong Special Administrative Region of China, there was one study from the literature that estimated dietary exposure to the sum of the six indicator PCBs (Xu & Cai, 2015). Dietary exposures were based on the concentrations analysed in a range of eight groups of animal-based foods. Mean dietary exposure was estimated as 2.83 ng/kg bw per day and 95th percentile exposure as 9.48 ng/kg bw per day for the Hong Kong Special Administrative Region adult population. The major contributors to dietary exposure were fish (60.3%), other seafood (9.0%), poultry (8.6%) and pork (7.5%).

(d) Cyprus

The dietary exposure to NDL-PCBs for Cyprus was estimated by the Committee. Consumption data were available only for adolescents, and dietary exposures (LB–UB) were 4–17 ng/kg bw per day at the mean and 7–35 ng/kg bw per day for a high exposure. The main contributors to dietary exposure were milk (44%), chicken (36%) and pork (17%).

EFSA (2012) also estimated dietary exposure for adolescents in Cyprus based on monitoring data. Mean exposures (LB–UB) were 4.7–5.9 ng/kg bw per day, and 95th percentile exposures were 15.9–17.1 ng/kg bw per day. The major contributors to dietary exposure were fish (45%), meat (32%) and milk (20%).

The exposure estimates from the Committee and EFSA (2012) were based on the same consumption data, but different concentration data sets made up of different foods. There was a limited range of fish data in the GEMS/Food database that matched with consumption data; therefore, the Committee's estimates did not show fish as a major contributor. The estimated exposures were similar for LB means; however, the Committee's UB estimates were higher. This could be attributed to the different data sets and the more stringent criteria used by EFSA (2012) to exclude data (i.e. results removed included those above LOQ 2 µg/kg, where there was a high per cent difference between LB and UB results and outliers).

(e) Czech Republic

Dietary exposure to NDL-PCBs for the Czech Republic was estimated by the Committee for children, adolescents and adults. Mean dietary exposures (LB–UB) for children were 0.7–5.2 ng/kg bw per day, for adolescents, 0.6–3.5 ng/kg bw per day, and for adults, 0.3–1.8 ng/kg bw per day. High-percentile exposures for children were 1.4–10.4 ng/kg bw per day, for adolescents, 1.1–6.9 ng/kg bw per day, and for adults, 0.7–3.6 ng/kg bw per day. The main contributors to dietary exposure were butter (27–35%), pork (19–28%), eggs (18–20%) and unprocessed meat not further specified (8–12%).

EFSA (2012) also estimated dietary exposure to the sum of the six indicator PCBs. Mean exposures (LB–UB) were, for children, 12.4–15.5 ng/kg bw per day, for adolescents, 9.3–11.0 ng/kg bw per day, and for adults, 6.2–7.4 ng/kg bw per day. Ninety-fifth percentile exposures were estimated for children as 41.7–44.7 ng/kg bw per day, for adolescents, 29.2–30.8 ng/kg bw per day, and for adults, 19.7–21.3 ng/kg bw per day. The main contributors to dietary exposure were meat (39–46%), fish (33–34%) and milk (11–15%).

(f) **Denmark**

EFSA (2012) estimated dietary exposure to the sum of the six indicator PCBs for children, adolescents, adults, the elderly and the very elderly. For children and adolescents, mean exposures (LB–UB) ranged between 6.0 and 12.8 ng/kg bw per day, and 95th percentile exposures ranged between 11.8 and 26.7 ng/kg bw per day. For all adult and elderly population groups, mean exposures ranged between 6.2 and 10.3 ng/kg bw per day, and 95th percentile exposures ranged between 10.8 and 36.5 ng/kg bw per day. The main contributors to dietary exposure for children and adolescents were meat (36–40%), fish (25–27%), milk (19–20%) and fats (14–16%); for adults and the elderly, the main contributors were fish (36–54%), meat (21–34%), milk (11–15%) and fats (12–14%).

(g) **Egypt**

One estimate of dietary exposure for the sum of the six indicator PCBs for Egypt was reported in the literature (Loutfy et al., 2008). Mean exposure based on food balance sheet consumption data using concentrations from meat, seafood and dairy (excluding milk) was 4.36 ng/kg bw per day. Although the use of food balance sheet consumption data usually leads to an overestimate of dietary exposure, this estimate does not include other food groups known to contribute to NDL-PCB exposures, such as eggs and milk; therefore, actual exposures may be higher than those estimated.

(h) **Finland**

Dietary exposures for a range of population subgroups were estimated by the Committee for Finland for the sum of the six indicator PCBs. Toddlers had the highest mean exposure, at 11 ng/kg bw per day. Mean exposure for adults was 0.8 ng/kg bw per day, and for the elderly, 1.7 ng/kg bw per day. For children, there were two consumption surveys; using the Finnish Type I Diabetes Prediction and Prevention Nutrition Study (DIPP) survey, the mean exposure was 1.4 ng/kg bw per day, and using the Turku Coronary Risk Factor Intervention Project for Children (STRIP) survey, it was 9.5 ng/kg bw per day. There was a large difference between the exposure estimates, which was the result of a high concentration

in a fish-based meal for which one of the surveys had a consumption value and the other did not. For the STRIP survey, 81% of the exposure was from fish-based meals, whereas for the DIPP survey, 54% of the exposure was from cheese and 30% from fish. High contributors to dietary exposure for adults were cheese (59%) and fish and seafood (40%), and for the elderly, fish and seafood (82%) and cheese (18%). Ready-to-eat meals containing meat/fish were the main contributor (92%) for toddlers.

EFSA (2012) also estimated dietary exposures for Finland. Exposures (LB–UB) for toddlers were 13.6–15.9 ng/kg bw per day (mean) and 41.0–46.1 ng/kg bw per day (95th percentile); for children in the DIPP survey, 13.5–15.6 ng/kg bw per day (mean) and 33.8–37.0 ng/kg bw per day (95th percentile); for children in the STRIP survey, 7.4–8.2 ng/kg bw per day (mean) and 19.9–21.7 ng/kg bw per day (95th percentile); for adults, 6.1–6.9 ng/kg bw per day (mean) and 18.6–19.7 ng/kg bw per day (95th percentile); and for the elderly, 7.5–8.1 ng/kg bw per day (mean) and 23.0–23.2 ng/kg bw per day (95th percentile). The food groups contributing to dietary exposure for toddlers were fish (40%), meat (33%) and milk (17%); for children, the two surveys produced similar contributions for fish (36–38%), meat (34–35%) and milk (18%). For adults and the elderly, the main contributor was fish (49% and 65%, respectively).

(i) France

For France, there were two estimates from the literature. Arnich et al. (2009) estimated dietary exposures to the sum of the six indicator PCBs to be 12.9 ng/kg bw per day (mean) and 27.3 ng/kg bw per day (95th percentile) for children, 7.6 ng/kg bw per day (mean) and 16 ng/kg bw per day (95th percentile) for females aged 19–44 years, and 7.7 ng/kg bw per day (mean) and 16 ng/kg bw per day (95th percentile) for other adults. Fish products were the highest contributor to dietary exposure for all population groups (38–47%), followed by meat products (21–24%) and dairy products (18–21%).

Sirot et al. (2012), from the French Total Diet Study, estimated dietary exposures for children and teenagers to be 3.77 ng/kg bw per day (mean) and 11.7 ng/kg bw per day (95th percentile) and for adults, 2.71 ng/kg bw per day (mean) and 7.90 ng/kg bw per day (95th percentile). The main contributor to dietary exposure was fish (48% for children and teenagers and 59% for adults).

The dietary exposures estimated by the Committee for France were much lower, ranging from 0.6 to 3.3 ng/kg bw per day for children and adolescents, including both LB and UB and mean and high percentile, and ranging from 0.7 to 2.3 for adults and the elderly for the same range. The main contributors to dietary exposure for all population groups were butter (28–54%) and fish (34–69%).

EFSA (2012) also estimated dietary exposures for the sum of the six indicator PCBs (LB–UB) for children as 14.7–17.1 ng/kg bw per day (mean) and 31.6–33.6 ng/kg bw per day (95th percentile), for adolescents, 7.4–8.8 ng/kg bw per day (mean) and 16.7–18.2 ng/kg bw per day (95th percentile), and for adults/elderly/very elderly, 6.7–8.4 ng/kg bw per day (mean) and 14.3–18.1 ng/kg bw per day (95th percentile). The main contributors to dietary exposure for all population subgroups were fish (39–51%) followed by meat (28–40%).

(j) **Germany**

From the literature, estimated dietary exposures for Germany (Fromme et al., 2007, 2009b) were 5.6 ng/kg bw per day (mean) and 8.9 ng/kg bw per day (95th percentile) for adults. Slightly higher estimates were generated from another study (Schwarz et al., 2010, 2014), where the mean for the general population was 10.9 ng/kg bw per day and for the high consumer, 22.6 ng/kg bw per day.

Estimates of dietary exposure derived by the Committee were in a similar range, with means (LB–UB) for toddlers and children of 5.9–10.8 ng/kg bw per day, for adolescents, 2.6–2.8 ng/kg bw per day, and for adults/elderly/very elderly, 3.4–4.2 ng/kg bw per day. Estimates for high consuming adults were slightly lower than the published estimates, at 6.7–8.4 ng/kg bw per day. The major contributors to dietary exposure for adults and the elderly were fish (21–33%), then butter (14–15%). For children, meat was the highest contributor (29%); for toddlers, it was infant foods (23%).

EFSA (2012) estimated dietary exposures for German population subgroups, with mean exposures (LB–UB) for children and toddlers of 8.8–11.8 ng/kg bw per day, for adolescents, 3.3–4.3 ng/kg bw per day, and for adults and the elderly, 4.3–6.2 ng/kg bw per day. Ninety-fifth percentile exposures (LB–UB) were, for toddlers and children, 19.2–23.4 ng/kg bw per day, for adolescents, 8.5–11.3 ng/kg bw per day, and for adults and the elderly, 14.4–18.6 ng/kg bw per day. The major contributors to dietary exposure were milk for toddlers (28%), meat for children and adolescents (35–50%) and both meat (27–39%) and fish (37–51%) for adults and the elderly.

(k) **Greece**

Dietary exposures for Greek children (not including toddlers and infants) were estimated by the Committee. Mean exposures (LB–UB) were estimated as 10–14 ng/kg bw per day, with high consumer exposures at 21–27 ng/kg bw per day. Milk contributed 80% to the exposure, eggs 10% and fish 6%.

EFSA (2012) also estimated dietary exposures for children. Mean exposures (LB–UB) were 8.4–9.6 ng/kg bw per day, and 95th percentile exposures (LB–UB) were 22.7–24.1 ng/kg bw per day. These estimates were very similar

to those estimated by the Committee. Major contributors to dietary exposure were milk (41%), fish (30%) and meat (23%). The contribution from fish was higher from EFSA (2012), whereas there was a limited range of fish and seafood included in the estimates by the Committee.

(l) Ireland

Dietary exposures to the sum of the six indicator PCBs for Ireland were estimated by the Committee for adults only. Dietary exposures (LB–UB) were very low, with a mean exposure of 0.8–1.2 ng/kg bw per day and a high exposure of 1.6–2.4 ng/kg bw per day. Major contributors were dietary supplements (32%), fish (22%), eggs (14%), butter (13%) and cheese (8%). Dietary supplements are a main contributor as a result of a mean concentration of around 24 000 ng/kg for this group, which included fish oil supplements. However, this food category may include consumption of supplemental beverages, rather than only dietary supplements, and therefore may be an overestimation of consumption of dietary supplements. There was no meat in the concentration data set; therefore, these estimates are likely to be an underestimate of exposure.

EFSA (2012) also estimated dietary exposures for Irish adults. Mean exposures (LB–UB) were 4.8–6.7 ng/kg bw per day, and 95th percentile exposures (LB–UB) were 10.9–13.5 ng/kg bw per day. Major contributors were meat (49%), fish (25%) and milk (15%).

(m) Italy

From the literature, one estimate of dietary exposure for adults was reported (n = 20 from a duplicate diet study), with a mean of 18 ng/kg bw per day and a 95th percentile of 39 ng/kg bw per day (Zuccato et al., 1999). Another estimate reported for adults (based on national consumption data) was a mean exposure of 10.9 ng/kg bw per day and a 95th percentile exposure of 23.8 ng/kg bw per day (Fattore et al., 2008). From this second study, exposures for toddlers and young children were 24.6 ng/kg bw per day (mean) and 60.0 ng/kg bw per day (95th percentile), and for children (7–12 years), 16.1 ng/kg bw per day (mean) and 33.8 ng/kg bw per day (95th percentile). The main contributors to dietary exposure for toddlers and young children were milk (38%) and fish (36%). For children (7–12 years), the main contributors were fish (38%) and milk (28%). For adults, the main contributors were fish (42%) and milk (24%).

Estimates of dietary exposure for infants were calculated by the Committee. The estimated dietary exposure to the sum of the six indicator congeners was very low (mean LB–UB: 0.003–7.4 ng/kg bw per day). The GEMS/Food data set used for this assessment included concentration data for a range of animal-based foods, but the total exposure could be attributed to beef

consumption (LB scenario used) for infants and toddlers. NDL-PCBs were not detected in milk samples. There was a concentration assigned to milk at the UB resulting in a mean dietary exposure for infants of 7.4 ng/kg bw per day. Actual dietary exposures for infants are likely to fall somewhere between the LB and UB estimates, as they are not likely to consume all of their milk with a true zero concentration of NDL-PCBs, as is assumed in the LB scenario. For toddlers, mean exposures were 0.02–3.5 ng/kg bw per day, children, 0.6–2.7 ng/kg bw per day, adolescents, 0.3–1.1 ng/kg bw per day, and adults/elderly/very elderly, 0.1–1.0 ng/kg bw per day. The main contributor for adolescents and adults/elderly/very elderly was fish (≥92%).

EFSA (2012) also estimated dietary exposures for a range of population groups. Estimated dietary exposures (LB–UB) for infants were 8.3–8.5 ng/kg bw per day (mean) and 31.7–35.4 ng/kg bw per day (95th percentile), for toddlers, 16.9–19.2 ng/kg bw per day (mean) and 36.6–39.8 ng/kg bw per day (95th percentile), for children, 16.1–18.8 ng/kg bw per day (mean) and 45.4–47.2 ng/kg bw per day (95th percentile), for adolescents, 9.0–10.3 ng/kg bw per day (mean) and 36.4–36.4 ng/kg bw per day (95th percentile), and for adults and the elderly, 4.7–8.7 ng/kg bw per day (mean) and 13.2–33.0 ng/kg bw per day (95th percentile). The main contributors to dietary exposure were infant foods (39%) for infants, fish (37%) and milk (32%) for toddlers, and fish (51–58%) for children, adolescents, adults and the elderly.

(n) Netherlands

From the literature, the one estimate of dietary exposure was determined for the sum of seven PCB congeners (six indicator PCBs and PCB 118) (Bakker et al., 2003; Baars et al., 2004; EFSA, 2005). These were converted to the equivalent amount of the sum of the six indicator congeners by Σ7*0.85. Mean and 95th percentile exposures were, respectively, for 2-year-olds, 11.5 and 21.8 ng/kg bw per day, for children 10 years of age, 7.8 and 12.5 ng/kg bw per day, and for adults 40 years of age, 4.9 and 8.1 ng/kg bw per day; lifelong averaged median and 95th percentile exposures were 4.8 and 10.1 ng/kg bw per day, respectively.

Estimates of dietary exposure derived by the Committee were mean and high exposures, respectively, for toddlers of 3.7 and 7.5 ng/kg bw per day, for children, 3.5 and 7.0 ng/kg bw per day, and for adults, 2.6 and 5.2 ng/kg bw per day. The main contributors to dietary exposure were cheese for all population groups (23–49%), the highest being for toddlers. Fish was also a contributor for adults (16%).

EFSA (2012) estimated dietary exposures (LB–UB) to be, for toddlers, 8.3–8.8 ng/kg bw per day (mean) and 18.2–20.5 ng/kg bw per day (95th percentile), for children, 7.3–7.8 ng/kg bw per day (mean) and 16.6–16.7 ng/kg

bw per day (95th percentile), and for adults, 3.8–4.5 ng/kg bw per day (mean) and 8.1–9.5 ng/kg bw per day (95th percentile). The main contributor to dietary exposure was meat for toddlers and children (34%) and adults (43%).

(o) Norway

From the literature, Kvalem et al. (2009) estimated LB mean dietary exposure to be 4.3 ng/kg bw per day for a representative group in the population and 6.4 ng/kg bw per day for high consumers; a median dietary exposure of 5.2 ng/kg bw per day was estimated for the whole group. Semi-oily and oily fish were the key contributors to dietary exposure.

(p) Republic of Korea

The estimated dietary exposures for the Republic of Korea that were calculated by the Committee were very low: 0.2 ng/kg bw per day at the mean for children and 0.5–0.6 ng/kg bw per day at the mean for the general population.

Concentration data in the GEMS/Food database for the Republic of Korea were available only for fish and seafood. The consumption data for children included consumption only for "not specified marine fish", with the remaining foods being non-seafoods. However, there was no marine fish in the concentration database assigned to this "not specified" code. Therefore, all marine fish samples for the Republic of Korea were pooled to derive a concentration to use to determine an estimate of dietary exposure. As a result, 100% of the dietary exposure for children was from marine fish.

There were consumption data for the general population for meat, eggs, milk and other animal foods known to contain NDL-PCBs; however, there were no concentration data for these foods. The main contributors to dietary exposure for adults were squid (40%), mackerel (24%), tuna (9%), pollack, crabs and prawns (all 7%) and clams (5%).

The limited range of foods with concentration data for the Republic of Korea means that the estimated dietary exposures are likely to be underestimates for both population groups assessed, despite fish usually being a key contributor to NDL-PCB exposure.

(q) Serbia

Estimated dietary exposures to the six indicator PCBs from grain foods, oil, and sugar and sugar products in Serbia were calculated (Skrbic & Durisic-Mladenovic, 2007). Mean exposures (LB–UB) were 2.9–3.4 ng/kg bw per day. Wholegrain wheat flour contributed 79% to dietary exposure from the limited range of foods. This will likely be an underestimate of actual dietary exposures, as no animal-

based foods were included in the assessment, despite per capita consumption data being used, which usually tend to produce an overestimate of exposure.

(r) Slovakia

From the literature, one assessment based on foods of animal origin (Salgovicová & Pavlovicová, 2007) had estimated dietary exposures for adults of 17 ng/kg bw per day (mean) and 45 ng/kg bw per day (95th percentile). Children 4–6 years of age had a mean exposure of 30 ng/kg bw per day and a 95th percentile exposure of 87 ng/kg bw per day, children 7–11 years had a mean exposure of 20 ng/kg bw per day and a 95th percentile exposure of 56 ng/kg bw per day, and children 12–15 years had a mean exposure of 17 ng/kg bw per day and a 95th percentile exposure of 47 ng/kg bw per day. The main contributors to dietary exposure were fats (47%) and eggs and egg products (28%).

(s) Spain

Based on concentration data from individual congeners and consumption data provided in Llobet et al. (2008), the Committee was able to estimate dietary exposure for the sum of the six indicator PCBs as 15 ng/kg bw per day. The main contributor to dietary exposure was fish and seafood, at 91%.

EFSA (2012) estimated dietary exposures for a range of population subgroups (LB–UB) for toddlers as 18.9–25.7 ng/kg bw per day (mean) and 52.7–52.7 ng/kg bw per day (95th percentile), for children (two surveys), 13.7–18.5 ng/kg bw per day (mean) and 38.8–42.1 ng/kg bw per day (95th percentile), for adolescents, 8.3–10.3 ng/kg bw per day (mean) and 22.5–25.1 ng/kg bw per day (95th percentile), and for adults (from two different surveys), 8.0–11.5 ng/kg bw per day (mean) and 21.0–26.7 ng/kg bw per day (95th percentile). The main contributors to dietary exposure were meat (36–47%) for toddlers, children and adolescents, fish (40–43%) for children and adolescents and fish (50–52%) for adults.

(t) Sweden

The Committee estimated dietary exposures for a range of population subgroups. Mean and high consumer exposures (LB–UB) were, respectively, for children, 6.7–13.7 ng/kg bw per day and 13.3–27.4 ng/kg bw per day, for adolescents, 3.4–7.5 ng/kg bw per day and 6.7–15.0 ng/kg bw per day, and for adults, 5.3–7.1 ng/kg bw per day and 10.5–14.1 ng/kg bw per day. The main contributors to dietary exposure were fish-based meals (adults 72%, adolescents and children 43%), milk (adults and adolescents 39%, children 33%) and fish roe (children 49% and adults 7%).

Estimated dietary exposures by EFSA (2012) (LB–UB) were, for children, 9.2–10.3 ng/kg bw per day (mean) and 20.9–22.7 ng/kg bw per day

(95th percentile), for adolescents, 5.6–6.4 ng/kg bw per day (mean) and 14.2–15.1 ng/kg bw per day (95th percentile), and for adults, 5.7–6.0 ng/kg bw per day (mean) and 12.8–13.1 ng/kg bw per day (95th percentile). The main contributors to dietary exposure for children were fish (35%) and meat (35%), for adolescents, meat (37%) and fish (38%), and for adults, fish (52%).

(u) Turkey

Dietary exposure to the sum of the six indicator PCBs for the Turkish population was estimated from milk and dairy products, including butter, based on concentrations in butter and extrapolation to other dairy foods on a fat per cent basis (Uçar et al., 2011). Details of the consumption data used and exact population covered were not provided in the paper. Mean dietary exposure was estimated as 0.183 ng/kg bw per day. This will, however, likely be an underestimate, as it did not include other animal-based foods known to contain NDL-PCBs.

(v) United Kingdom

Estimated dietary exposures for adults in the United Kingdom were estimated using the CIFOCOss consumption data and GEMS/Food concentration data. Estimates of dietary exposure for the sum of the six indicator PCBs (LB–UB) were low for the mean, at 1.4–1.5 ng/kg bw per day, as well as for a high-percentile exposure, at 2.8–2.9 ng/kg bw per day. The highest contributor to dietary exposure was dietary supplements (e.g. fish oil supplements: 50%). Fish oils have a very high concentration of NDL-PCBs (mean around 63 000 ng/kg). The consumption category used (13.6; dietary supplements/food supplements) had a low reported level of consumption (0.01 g/kg bw per person per day). However, this food category may include consumption of supplemental beverages, rather than only dietary supplements, and may be an overestimation of consumption of dietary supplements. Other high contributors to dietary exposure were eggs (32%), cheese (8%) and fishes and aquatic animals not elsewhere specified (7%). There were no concentration data for milk in the data set, which may also mean that the exposures were underestimated.

EFSA (2012) also estimated dietary exposures to the sum of the six indicator PCBs for adults. Exposures (LB–UB) were 4.1–5.3 ng/kg bw per day (mean) and 9.8–11.7 ng/kg bw per day (95th percentile). Major contributors to dietary exposure were fish (53%), meat (23%) and milk (15%).

8.3.2 National estimates of dietary exposure for individual indicator PCBs

(a) Estimated dietary exposure to the six indicator PCBs individually

Dietary exposure based on national data was also estimated by the Committee for the six indicator PCBs individually using the same methodology as outlined for

the assessments in section 8.3.1. This was for use in the modelling of body burden from dietary exposure (section 9). The only methodological difference was that no unique identifiers for the samples were needed for summing concentrations for a number of congeners. Therefore, there may have been a different number of samples included in this analysis compared with the national estimates for the sum of the six congeners. It was also possible to assess more countries. For example, Japan had concentration data for five of the six indicator PCBs, so although dietary exposures could not be estimated for the sum of the six indicator PCBs, they could be estimated for the five congeners separately.

A summary of these estimates is shown in Table 21. Full results are shown in Appendix 4 for each country and population group assessed.

Some countries had very low estimates for the minimum exposures across all countries. This was often due to there being a small number of foods that were sampled (e.g. a specific type of fish) for which there were no consumption data for a country.

Only one paper was identified in the literature that included an estimate of dietary exposure for single congeners. That was for PCB 153 for Sweden (Darnerud et al., 2006), where the mean per capita exposure from a range of foods was 139 ng/day or 1.9 ng/kg bw per day, which is within the range of exposures estimated by the Committee.

(b) PCB 128

Given that there were some toxicological data available for PCB 128, estimated dietary exposures were also of relevance for the Committee's evaluation of this congener; however, the data were limited. Out of the total GEMS/Food concentration database (n = >125 000 data points), there were only 387 data points for PCB 128 from three countries (Estonia, n = 68; Finland, n = 199; and the United Kingdom, n = 120). There were CIFOCOss consumption data only for Finland and the United Kingdom. The concentration data for these two countries for this congener were only from fish (both countries) and other seafood (United Kingdom only). This was despite both of these countries having concentration data for a broad range of foods for the six indicator PCBs. The estimates of dietary exposure for Finland at the mean were, for children, 0.000 02 ng/kg bw per day and, for adults, up to 0.000 06 ng/kg bw per day (UB); for the high percentile, estimates of dietary exposure were up to 0.000 04 ng/kg bw per day (UB) for children and up to 0.000 12 ng/kg bw per day (UB) for adults. For the United Kingdom, for adults, estimated dietary exposures at the mean were 0.000 005 ng/kg bw per day and at the high percentile, 0.000 01 ng/kg bw per day. These results are based on very limited data and therefore will be an underestimate of actual dietary exposures to this congener.

Table 21

Summary of estimated dietary exposures for individual indicator PCBs showing minimum and maximum for adults and children from all countries assessed

PCB	Population group	Dietary exposure measure	Dietary exposure (ng/kg bw per day)			
			Mean		High percentile	
			LB	UB	LB	UB
28	Children (infant to adolescent)	Minimum	0.002	0.03	0.000 4	0.05
		Maximum	1.2	17.5	2.5	35.1
	Adults	Minimum	0.005	0.02	0.01	0.05
		Maximum	0.3	4.7	2.0	9.5
52	Children (infant to adolescent)	Minimum	0.000 7	0.03	0.001	0.05
		Maximum	2.4	17.2	4.8	34.3
	Adults	Minimum	0.01	0.04	0.02	0.08
		Maximum	1.2	4.6	2.3	9.2
101	Children (infant to adolescent)	Minimum	0.000 3	0.03	0.001	0.07
		Maximum	3.0	17.2	6.0	34.4
	Adults	Minimum	0.01	0.05	0.03	0.1
		Maximum	0.7	4.8	2.0	9.5
138	Children (infant to adolescent)	Minimum	0.000 6	0.04	0.001	0.08
		Maximum	4.3	17.5	8.6	35.0
	Adults	Minimum	0.03	0.1	0.06	0.3
		Maximum	1.7	4.7	3.5	9.3
153	Children (infant to adolescent)	Minimum	0.001	0.04	0.002	0.08
		Maximum	6.5	15.7	13.1	31.5
	Adults	Minimum	0.03	0.1	0.06	0.3
		Maximum	3.0	5.0	6.0	9.9
180	Children (infant to adolescent)	Minimum	0.001	0.03	0.002	0.05
		Maximum	2.0	17.3	4.1	34.5
	Adults	Minimum	0.01	0.07	0.03	0.1
		Maximum	0.7	4.7	1.5	9.4

LB: lower bound; UB: upper bound

Given that the estimated dietary exposures were limited and not likely to be a realistic estimate of dietary exposure, an alternative approach was used whereby the proportion that the concentration of PCB 128 represents of the six indicator PCBs considered individually was determined on the basis of data from GEMS/Food (the average was 16%). This was then applied to the average of the upper end of the range of all indicator PCB congeners for both mean and high-percentile exposures for adults from any of the individual indicator congeners, as a way of representing approximate PCB 128 exposure before estimating the MOE.

8.3.3 International estimates of dietary exposure

International dietary exposures to the sum of the six indicator PCBs were estimated using consumption data from the 17 GEMS/Food cluster diets and occurrence data for NDL-PCBs from the GEMS/Food concentration database, based on the methodology described above.

The consumption amount of each food group by cluster can be found in Appendix 5, along with the LB and UB concentrations for each food group, estimated dietary exposure from each food (for both the LB and UB scenarios) and the total mean dietary exposures from all foods. The contribution of each food group to the total exposure is shown in Table 22. The contributions were based on the LB scenario only so as to not overestimate the likely contribution of food groups for which there were not detectable concentrations of NDL-PCBs.

Concentrations varied widely between and within regions for the range of foods for which data were available. The highest concentrations were for fish up to LB mean concentrations of 82 000 ng/kg for clusters using data for all countries and around 100 000 ng/kg (cluster 7) and 200 000 ng/kg (cluster 11) for clusters with data from their own countries. Other food groups with high concentrations included marine animal fat, with a LB mean of around 20 000 ng/kg, milk fats, around 11 000 ng/kg, animal fats, up to around 60 000 ng/kg, and "foods out of classifying" (e.g. mixed dishes or foods that did not fit specifically within a specific food group), at around 13 000 ng/kg. Relatively lower levels (usually under 1000 ng/kg) were mainly found in fruits and vegetables, where data were available. Across all of the clusters, there were no data for the food groups egg products and processed eggs, hops, roots and tubers raw or boiled, and root vegetables not elsewhere specified (nes) (there were data for roots and tubers nes).

The majority of the food groups in the cluster diets are at the raw commodity level. There is a small number of minimally processed food categories in the cluster diets where the concentrations for some processed foods were captured. However, concentrations for many of the mixed dishes or highly processed foods were captured under Level 2 code 190 Out of Classifying.

Estimated mean dietary exposures to the sum of the six indicator PCBs are summarized in Table 23. The range between the clusters for the LB scenario was from 1 ng/kg bw per day (cluster 9) to 60 ng/kg bw per day (cluster 11). For UB mean exposures, the range between clusters was from 2 ng/kg bw per day (cluster 9) to 83 ng/kg bw per day (cluster 11).

Cluster 9 has the lowest estimate of dietary exposure (LB–UB mean: 1–2 ng/kg bw per day). The cluster is made up of Asian countries, and the concentration data came from China (including Hong Kong Special Administrative Region).

Table 22

Per cent contribution (from the LB scenario) of food groups (only where >1% for any one cluster or more) to the dietary exposure to the sum of the six indicator PCBs from GEMS/Food cluster diets

Food code	Food name	% contribution in following clusters:																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
12	Pome fruits, fresh	0.1	0.2	0.0	0.1	0.1	–	–	1.1	–	–	–	0.0	0.0	0.0	0.1	0.0	0.0
20	Pulses (dry, prepared and composites)	0.1	0.0	0.1	0.1	0.2	–	–	–	1.4	–	–	0.1	0.4	0.0	0.0	0.9	0.0
21	Oilseed (incl. flour)	0.1	0.0	0.2	0.1	0.1	–	–	–	–	–	–	0.0	0.4	0.0	0.1	1.5	0.0
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	0.1	0.3	0.0	0.1	0.2	–	2.2	0.2	3.4	–	–	0.1	0.1	0.0	0.2	0.0	–
42	Fruiting vegetables, cucurbits	0.4	1.1	0.2	0.5	0.2	–	–	1.3	3.7	–	–	0.3	0.2	0.1	0.0	0.6	0.0
43	Fruiting vegetables (other than cucurbits) and mushrooms	0.0	0.0	0.0	0.0	0.0	–	–	0.0	1.2	–	–	0.0	0.0	0.0	0.0	0.0	0.0
60	Cereal grains & flours	2.8	2.0	1.6	1.4	2.8	–	6.8	1.9	11.8	–	–	1.0	3.7	0.6	1.2	2.2	0.2
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	1.7	1.2	0.6	0.8	1.6	–	9.0	0.0	–	12.1	–	1.0	0.9	0.4	0.5	1.1	0.2
80	Milk fats	1.8	1.4	0.0	0.8	1.8	–	4.0	16.2	0.2	0.2	1.2	0.3	0.3	0.1	2.3	0.1	0.2
81	Mammalian fats (no milk fat)	0.3	0.4	0.1	0.1	0.2	–	–	–	–	–	0.3	0.4	0.2	0.0	3.3	0.2	0.1
84	Plant origin fat	6.0	4.5	4.1	4.5	5.4	5.1	7.2	–	–	0.4	0.3	1.5	6.5	0.5	0.7	6.0	0.7
85	Animal or vegetable fat, nes	0.1	1.2	0.2	0.4	0.1	0.3	1.3	11.6	–	–	4.3	5.9	0.3	0.0	0.4	0.3	0.7
90	Milks (no other ingredients)	15.7	21.8	1.3	4.1	11.2	35.2	0.6	13.9	1.4	9.5	12.0	3.1	9.1	0.3	7.9	7.6	0.3
91	Dairy products (incl. whey, excl. milk fats)	0.3	0.9	0.0	0.9	0.2	4.2	1.0	7.1	0.1	0.4	2.9	0.7	0.2	0.0	0.4	0.0	0.0
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	1.1	1.9	0.5	0.8	1.2	2.0	3.4	8.5	6.7	6.1	1.2	0.6	1.5	0.1	1.9	1.5	0.4
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	0.3	0.4	0.1	1.2	0.5	1.9	0.6	0.7	0.1	22.9	0.4	0.8	0.1	0.0	0.3	0.2	0.2
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	0.5	0.0	6.7	0.3	0.4	0.1	0.1	8.5	–	–	0.0	0.4	3.7	7.9	0.2	8.0	–
110	Eggs	2.4	5.7	0.9	2.4	3.2	32.1	2.2	5.3	5.6	37.7	8.4	1.5	1.8	0.2	9.8	0.8	0.4

Food code	Food name	% contribution in following clusters:																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
120	Freshwater fish, unprocessed (incl. home-cooked)	1.9	1.5	6.2	1.7	6.7	4.7	3.6	0.3	32.0	4.2	0.4	1.4	5.0	0.9	12.5	37.5	0.0
121	Marine fish, unprocessed (incl. home-cooked)	2.1	3.5	9.4	4.3	5.0	1.0	0.8	0.1	1.4	0.2	0.1	5.8	2.1	2.9	0.6	0.7	2.1
122	Crustaceans, unprocessed (incl. home-cooked)	0.0	0.1	0.0	0.1	0.1	–	0.1	0.0	2.7	0.4	0.0	0.3	0.0	0.0	–	0.0	0.0
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	0.0	0.0	0.0	0.0	0.1	1.0	0.2	0.0	20.6	2.2	0.1	0.3	0.0	0.0	0.5	0.0	0.1
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	60.3	44.6	62.0	67.3	56.1	12.0	27.4	21.0	6.3	3.2	68.4	60.0	57.6	83.9	35.2	26.7	89.5
127	Processed aquatic animals	0.7	5.1	4.7	3.5	1.5	–	7.0	–	–	–	–	3.1	3.9	1.4	0.0	2.3	2.5
190	Out of classifying	0.5	1.5	0.7	3.7	0.4	–	21.2	0.2	–	0.0	–	10.8	0.8	0.2	20.9	1.1	2.0

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; –: zero contribution, due to either no consumption or no concentration; 0.0: very small contribution

Table 23
Summary of estimated dietary exposures to the sum of the six indicator PCBs for the GEMS/ Food cluster diets

	Mean exposure (ng/kg bw per day)[b]		
Cluster number[a]	LB	UB	Source of concentration data
1	9	20	All countries
2	11	23	All countries
3	9	13	All countries
4	17	28	All countries
5	8	18	All countries
6	3	3	Countries from own cluster
7	17	19	Countries from own cluster
8[c]	37	39	Countries from own cluster
9	1	2	Countries from own cluster
10	5	46	Countries from own cluster
11	60	83	Countries from own cluster
12	16	31	All countries
13	6	11	All countries
14	39	50	All countries
15	5	11	Countries from own cluster
16	4	9	All countries
17	52	61	All countries

LB: lower bound; UB: upper bound
[a] Countries in each cluster are given in Appendix 6.
[b] Body weight = 60 kg.
[c] Excluding outlier for plant fats and oils.

The concentrations for the sum of the six indicator PCBs were low across all foods, but they were detectable because of the extremely low LODs used. The low LODs used also meant that a low number was substituted for the UB scenario for not detected results, so UB estimates of exposure would not be overestimated. The samples included a wide range of foods, including fish and seafood, meat and offal, milk, eggs, fruit and vegetables.

Cluster 6 also had a low estimate of dietary exposure, at 3 ng/kg bw per day at both the LB and UB. The concentration data for this cluster were only from Greece. There was a wide representation of animal foods in the samples, including meat and meat products, milk and dairy products, eggs, fish and seafood, as well as plant-based fats. Therefore, this estimate should not be underestimated to a large degree. Apart from higher concentrations in "animal and plant fats nes", all food groups had mean concentrations under 5200 ng/kg.

Cluster 11 had the highest LB estimate of dietary exposure of any cluster (60 ng/kg bw per day). This cluster is made up of European countries. The

concentration data were from Belgium and the Netherlands. Neither of these countries contributed concentration data with extremely high LODs; however, Belgium did have a higher proportion of data that were not detected. This cluster had around 70% of its dietary exposure from the "other fish" food group, for which it has a consumption level around midway between the highest and lowest clusters for this food. The mean concentration for this food group was the highest for any cluster, at around 200 000 ng/kg. The food samples that contributed to this were some very high concentrations of NDL-PCBs in eels from the Netherlands. EFSA (2012) also noted the high concentration of NDL-PCBs in eel. This cluster also had 12% of the exposure coming from milk. This food was the highest contributor in the national estimates of exposure for Belgium owing to a high concentration in milk relative to the concentrations in milk in other countries.

Table 22 shows the details of the food group contributions to estimated dietary exposure to the sum of the six indicator PCBs based on the LB scenario. The main food groups contributing to estimated dietary exposure for the majority of clusters were the fish and seafood groups. This was due to either their high NDL-PCB concentrations or high consumption. Contributions from "other fishes and aquatic animals" ranged from 3% in cluster 10, 6% in cluster 9, 12% in cluster 6, 21% in cluster 8, 27% in clusters 7 and 16, 35% in cluster 15 and 45% in cluster 2 to around 60% or above for the remaining clusters, with the highest contribution at 90% for cluster 17. The clusters with the highest consumption of fish had the highest contribution. Cluster 17 had the highest consumption by far compared with the other clusters. Freshwater fish were also a contributor for a number of clusters: 6% in cluster 3, 7% in cluster 5, 32% in cluster 9, 13% in cluster 15 and 38% in cluster 16. Marine fish contributed to a number of clusters: 9% in cluster 3, 6% in cluster 12 and 5% in cluster 5. Processed aquatic animals contributed 7% for cluster 7 and 5% for clusters 2 and 3. Molluscs were a high contributor for cluster 9 (21%).

There were also contributions to dietary exposure (5% or greater) for a number of clusters for milk, eggs, and plant fats and oils, and a small number of clusters had marked contributions from meat or poultry, sugars/chocolates and cereal grains. Milks contributed 35% for cluster 6, 22% for cluster 2, between 10% and 20% for clusters 1, 5, 8 and 11, and between 5% and 10% for clusters 10, 13, 15 and 16. Eggs contributed 38% for cluster 10, 32% for cluster 6, 10% for cluster 15, 8% for cluster 11 and 6% for clusters 2 and 9. Meat and offal not further specified contributed 8% for clusters 8, 14 and 16 and 7% for cluster 3. Poultry contributed for only one cluster (23% for cluster 10). Mammalian meat contributed 9% for cluster 8, 7% for cluster 9 and 6% for cluster 10. For fats, plant fats contributed 5–7% for clusters 1, 2, 4, 5, 6, 7, 13 and 16; milk fats contributed 16% for cluster 8; and animal or plant fats not further specified contributed 6% for cluster 12 and 12% for cluster 8. Sugars/honey/candies (excluding chocolate)

contributed 9% for cluster 7 and 12% for cluster 10. Cereal grains contributed 7% for cluster 7 and 12% for cluster 9. In most cases, the high contribution was for the clusters with the higher consumption amounts of the food group across the clusters; however, this was not always the case.

The dietary exposure estimates are likely to be an overestimate, as the food balance sheet data on which they are based are amounts of food "available for consumption", and waste is not taken into account. The results do provide useful comparative information about the areas of the world that may have potentially higher dietary exposures. For the clusters that employed the same concentration data (clusters 1, 2, 3, 4, 5, 12, 13, 14, 16 and 17; pooled data from all countries), there were higher exposures for cluster 14, which is made up primarily of Pacific Island countries and has a high consumption of marine fish and other fish, both categories that had high concentrations.

However, when making comparisons between clusters, it must be considered that for many of the clusters, the whole data set of concentration data was combined and used for the calculations. Therefore, for these clusters, differences in dietary exposure will solely reflect differences in food consumption patterns. Therefore, a limitation of this methodology is that comparison across clusters is not on the same basis.

8.3.4 Dietary exposures for infants

PCBs are transferred from mother to child through breastfeeding. Concentrations of PCBs in breast milk can depend on a number of factors, including the maternal place of residence, diet and the number of previous children. Occurrence data also show detectable concentrations of NDL-PCBs in infant formula. Exposure of an infant to PCBs is an important contributor to the total body burden. Therefore, infants were included in the evaluation of dietary exposure to the six indicator PCBs where possible. Estimated dietary exposures from both breast milk and infant formula were relevant to the evaluation.

There were approximately 900 data points for NDL-PCBs in the GEMS/Food concentration data set for foods for infants (cereal-, vegetable-, dairy- or meat-based foods, etc.). However, national consumption data were not available for infants other than for Italy, which had no concentration data for infant foods; therefore, no estimates of dietary exposure could be calculated for infants consuming a diet that includes milk and solid foods.

(a) Estimated dietary exposure for breastfed infants

Breast milk has many beneficial aspects, including nutritional and immunological benefits, despite containing environmental contaminants, such as NDL-PCBs. However, based on present knowledge, the benefits of breastfeeding (WHO, 2015)

are considered to outweigh the possible disadvantages that may be associated with the presence of NDL-PCBs in breast milk. Concentrations of PCBs in human milk are highly variable both between and within countries. European countries have reported higher concentrations of NDL-PCBs in breast milk than in other parts of the world. Liem, Fürst & Rappe (2000) included a summary of concentrations of the sum of the six indicator PCBs in breast milk from a number of countries across the world. These ranged between 19 and 1068 ng/g in the fat for LB mean concentrations. Highest concentrations were found in the Czech Republic (1068 ng/g fat) and Slovakia (1015 ng/g fat), with all other countries having concentrations of 682 ng/g fat or less.

The biomonitoring section of this report (section 2.3.1) noted the WHO worldwide measurement campaigns to determine the exposure of infants to the 12 DL-PCBs and the six indicator PCBs over time, where five rounds of monitoring have been conducted to date (UNEP/WHO, 2013). For the sum of the six indicator PCBs, the median concentration in breast milk over the 12 years of the survey was between 10.8 and 30.7 ng/g lipid, with maximum concentrations between 37.1 and 65.8 ng/g lipid.

Data on human milk were submitted to the GEMS/Food concentration database by New Zealand. These were aggregate data for only two of the indicator PCBs, where the mean concentration for PCB 28 was 90 ng/kg (fresh weight) (from 50 samples) and the UB mean concentration for PCB 101 was 10 ng/kg (fresh weight) (from 15 samples). Therefore, it was not possible to use these data in this evaluation for calculating estimates of dietary exposure, as the focus was on the sum of the six indicator PCBs.

Estimating dietary exposures to any chemical in breast milk is difficult to do because of variation in the duration of breastfeeding, the number of children fed by the mother, the duration of each single feed, the volume consumed, the variable fat content in the milk, the age of the child, etc.

For breastfed infants, the most recent WHO study of PCB exposure reported a mean dietary exposure of about 1600 ng/kg bw per day (range of 230–7300 ng/kg bw per day) for the sum of the six indicator PCBs (IARC, 2015).

Based on data from 58 human milk pools from 18 European countries, it has been estimated that the dietary exposure to the sum of the six indicator PCBs for exclusively breastfed infants is a median exposure of 984 ng/kg bw per day or a mean exposure of 1177 ng/kg bw per day, assuming a milk intake of 800 mL/day with a fat content of 3.5% and a body weight of 5 kg. A maximum exposure of 5651 ng/kg bw per day was estimated (EFSA, 2005). These values are within the range reported by IARC (2015). This is significantly higher than estimates of dietary exposure for the rest of the population on a body weight basis.

In a study from Slovakia, a median dietary exposure to the sum of the six indicator PCBs for fully breastfed infants of 1608 ng/kg bw per day was reported

(Drobna et al., 2011). Another study from Sweden estimated that the mean exposures to the sum of five NDL-PCBs (PCBs 28, 138, 153, 170 and 180) in 1-, 3- and 6-month-old infants were 418, 294 and 165 ng/kg bw per day, respectively. This showed a clear trend in the reduction of NDL-PCB exposure over the breastfeeding period (Bergkvist et al., 2010).

(b) Estimated dietary exposure for fully formula-fed infants

Some data were submitted to the GEMS/Food concentration data set on NDL-PCB concentrations in infant formula. A summary of these data is shown in Table 24. Concentrations were provided for infant formula (0–6 months) in both liquid and powdered forms and follow-on formula (usually 6 months and above) in liquid form. No estimates of dietary exposure for formula-fed infants were derived using these data for a number of reasons, including that there were only a small number of countries with concentration data, that the majority of those had only a small number of samples and that some surveys had very high LODs or included only some of the six indicator PCBs.

There have been some estimates of dietary exposure of infants to NDL-PCBs from infant formula reported in the literature. One study from Spain (Lorán et al., 2009) estimated dietary exposure for 3-month-olds to the sum of the six indicator PCBs (estimated from Σ7*0.85) for boys of 6.9–9.2 ng/kg bw per day (LB–middle bound [MB]), and the equivalent for girls of 7.5–10.0 ng/kg bw per day, based on consumption of 841 mL formula and concentrations of 51 ng/kg (LB) and 68 ng/kg (MB).

A study from a PCB-contaminated area in Slovakia (Drobna et al., 2011) provided a comparison between dietary exposure to total summed PCBs over 10 months for exclusively breastfed infants compared with exclusively formula-fed infants. The results provided equated to a dietary exposure for the breastfed infants of 1286 ng/kg bw per day, compared with 2.8 ng/kg bw per day for formula-fed infants in the same area.

From the Hong Kong Special Administrative Region of China (Xu & Cai, 2015), concentrations in infant formula samples were reported as 0.065–1.15 ng/g fat. For exclusively formula-fed infants, the estimated dietary exposures based on the analysed infant formula concentrations ranged from 2.42 ng/kg bw per day during the first month of life to 1.70 ng/kg bw per day in the sixth month of life. These values were reported as being 1 order of magnitude lower than exposures for breastfed infants.

8.3.5 Dietary exposures for specific population subgroups

The occurrence data for NDL-PCBs show high concentrations in animal-based foods, particularly fish and seafood. Therefore, populations with high

Table 24
Summary of infant formula data submitted to the GEMS/Food concentration database

Country	PCBs	Food	Number of data points	Concentration data
Canada	20 congeners; however, only 5 of the 6 indicators	Infant formula liquid	80 (no sample unique identifiers provided)	LOQs up to 0.13 ng/kg.
China	6 indicators	Infant formula powder	822 (137 samples)	23% ND. LOQs 0.9 ng/kg or less. Range of detected values 0.17–153 ng/kg for individual congeners.
Czech Republic	6 indicators	Infant formula powder	12 (2 samples)	75% ND. LOQs up to 33 ng/kg. Range of detected values 0.10–0.14 ng/kg based on individual congeners.
France	6 indicators	Infant formula powder	24 (4 samples)	0% ND. Range 0.002–0.05 ng/kg based on individual congeners.
France	6 indicators	Follow-on formula liquid	6 (1 sample)	0% ND. Range 0.000 6–0.011 ng/kg.
Greece	6 indicators	Follow-on formula liquid	6 (1 sample)	0% ND. Range of values for individual congeners 0.07–0.3 ng/kg.
Singapore	6 indicators	Infant formula powder	35 (5 samples/different products)	All ND. High LOQs for all of the samples, ranging from 35 to 75 µg/kg, depending on the congener.
Sweden	6 indicators	Infant formula powder	30 (5 samples)	40% ND. LOQ 0.14 ng/kg or less. Range of detected values 0.001–0.03 ng/kg.

LOQ: limit of quantification; ND: not detected

consumption of fish and seafood were also assessed, where information was available.

EFSA (2005) provided a good summary of exposures for population subgroups with higher exposures than for the general population. These included Baltic fishermen who consumed fish more frequently and in greater quantities compared with the general population in the same region. Fish from the Baltic Sea also contain higher PCB concentrations compared with other regions of the world. Dietary exposure to the sum of the six indicator PCBs by fishermen from the Swedish coasts were approximately 5- to 10-fold higher than the corresponding exposure from fish estimated for the average male adult population in Sweden (e.g. east coast fishermen had an exposure up to 41.5 ng/kg bw per day, compared with 5.3 ng/kg bw per day for males in the general population).

Residents of the Faroe Islands have a high consumption of seafood and a higher dietary exposure to PCBs. A major contributor to the exposure is pilot whale blubber, which contains an average PCB concentration of 20 000 µg/kg.

Residents living in areas where PCBs had been previously produced, where waste may have contaminated locally grown and consumed agricultural crops and livestock, can have higher dietary exposures. Concentrations of three of the indicator PCBs (PCBs 138, 153 and 180) in blood from adults and children

in the Michalovce district of Slovakia were 2–2.5 times higher than those in residents from a control area.

A study in an area that recycles transformers showed that mean exposures to 37 PCBs in lactating women were 92.8 ng/kg bw per day, compared with a reference site with exposures of 7.3 ng/kg bw per day (Xing, Wu & Wong, 2010). Residents consuming fish and produce from the locally contaminated area had higher dietary exposures as a result.

The information on higher dietary exposures in these population subgroups is consistent with the higher blood/serum concentrations in these subgroups, as shown in the biomonitoring data evaluated by the Committee (see section 2.3.1).

8.4 Other routes of exposure

The major source of exposure to PCBs, including NDL-PCBs, is via the diet, with more than 90% coming from food (IPCS, 1993; EFSA, 2005; Loutfy et al., 2008). Dermal and inhalation exposure may also occur, usually making a small contribution to exposure. Occupational exposure can be an important source.

IARC (2015) undertook a large review of environmental sources of contamination and routes of exposure to PCBs, including inhalation and dermal routes. Dermal absorption of PCBs may occur via the occupational setting or other means, such as contact with contaminated sediments or soil or topical applications to the skin. Estimates of the concentrations in air, dust and soil were provided by IARC (2015) and EFSA (2005). Indoor air can contain PCBs where they are released into the environment as a result of being incorporated into building materials, such as sealants and paints. Residents living in contaminated buildings have higher PCB concentrations in blood compared with residents living in control buildings, as do pupils and teachers in contaminated schools compared with controls (EFSA, 2005). In one study where the sum of the six indicator PCBs was investigated, median concentrations in plasma were 3.4 times higher in residents living in buildings containing PCBs than in residents not exposed from their dwellings (Meyer et al., 2013). The differences were usually observed for the lower chlorinated congeners (PCBs 28, 52 and 101). Inhalation may account for 4–63% (median 15%) of overall exposure in humans (IARC, 2015).

IARC (2015) reviewed a large number of studies of concentrations of total and individual PCB congeners, covering both DL- and NDL-PCBs, in blood. These clearly showed higher concentrations in those who are occupationally exposed compared with controls. Whereas occupational exposure many years ago would have occurred during the manufacturing process and capacitor and

transformer repair, more recent exposures occur from waste incineration, fires and waste recycling (IARC, 2015).

EFSA (2005) calculated the relative contribution to exposure from air and soil compared with food. Exposure to PCBs (not specifically the NDL-PCBs in this case) via inhalation was estimated to be 0.05–0.5 ng/kg bw per day for children and 0.03–0.3 ng/kg bw per day for adults. Exposures from soil or dust would be small, at around 0.06–0.6 ng/kg bw per day for children. Dermal absorption was estimated to be around 5 pg/kg bw per day for children and 0.76 pg/kg bw per day for adults. From these values, ESFA (2005) concluded that exposure from these sources was around 3–4 orders of magnitude lower than exposure from food. Ingestion of contaminated soil or dust can be a minor source of exposure for children.

The information on higher exposures through the skin and inhalation in population subgroups living or working in contaminated sites or buildings is consistent with the higher blood/serum concentrations in these subgroups, shown in the biomonitoring section of this monograph (section 2.3.1).

8.5 Temporal trends in dietary exposure

A number of papers and reviews have indicated that dietary exposure to PCBs is decreasing over time.

Concentrations in foods have been demonstrated to be dropping over time. In Belgium, Cimenci et al. (2013) showed decreasing concentrations in milk and dairy products and eggs and egg products. The Chinese Total Diet Study (Y. Wu, personal communication, 2015) demonstrated an apparent approximate halving of the sum of the concentrations of the six indicator PCBs in milk, from a mean of 11.7 µg/kg in 2007 (12 provinces, n = 1237 milk samples, concentration range 2.4–28.8 ng/g lipid weight) to a mean of 6.6 µg/kg in 2011 (16 provinces, n = 1760 milk samples, concentration range 2.3–19.0 ng/g lipid weight). EFSA (2012) conducted a time trend analysis where three groups of foods (eggs, fish, and milk and dairy products) showed a decreasing trend in median concentrations for the sum of the six indicator PCBs over time. This was statistically significant for milk and dairy products, with a 64% reduction in 15 years.

Dietary exposures have been demonstrated to be dropping in a number of countries. In Italy, in 2008, dietary exposures to NDL-PCBs were estimated to be 30% lower than found in a corresponding study in the mid-1990s (Fattore et al., 2008). In the Netherlands, exposures to the sum of the six indicator PCBs have been decreasing over time, although this trend has been slower in more recent years, with a flattening out over the preceding decade. Exposures declined from around 80 ng/kg bw per day between 1975 and 1980 to 39 ng/kg bw per day in 1984–1985 to 10 ng/kg bw per day in 1994 (Bakker et al., 2003; Baars et

al., 2004). Mean exposures to the sum of the six indicator PCBs for adults in Slovakia decreased from 26 ng/kg bw per day in 1994 to 17 ng/kg bw per day in 2004 (Salgovicová & Pavlovicová, 2007). The National Monitoring Program in the Czech Republic showed a decreasing trend in exposures from 1994 to 2003 (EFSA, 2005). Studies in Sweden have also indicated a decrease in exposure over time; 28 PCBs, including DL- and NDL-PCBs, had mean MB concentrations of 8.3 ng/kg bw per day in 1999 and 4.9 ng/kg bw per day in 2011. This was proposed to be due to the drop in concentrations in foods over time and more specific analytical methods (Törnkvist et al., 2011). In France, dietary exposures to total PCBs decreased 3-fold between 2005 and 2012 (Sirot et al., 2012). EFSA (2012) also showed a statistically significant drop in dietary exposures over time (2002–2010) across all population subgroups and all countries.

Liem, Fürst & Rappe (2000) noted that countries that started to implement measures to reduce dioxin emissions in the late 1980s, such as the Netherlands, the United Kingdom and Germany, showed a decrease in PCB concentrations in food and therefore a lower dietary exposure, by almost a factor of 2, within the preceding 7 years.

Concentrations in human milk have also been dropping over time (IARC, 2015). Therefore, the dietary exposures for breastfed infants will also decrease, as has been reported by a number of European countries. In the Federal Republic of Germany before reunification, for example, PCB exposures decreased by 80% between 1984 and 2003 (EFSA, 2005). In Sweden, a significant decrease was estimated for mean exposures of breastfed infants between 2000 and 2006, by a factor of 1.5 (Bergkvist et al., 2010).

Reductions in concentrations in foods and therefore estimated dietary exposures over time could be due to a number of reasons, including reduced concentrations of PCBs over time, better analytical methods that report lower concentrations in foods (this will reduce the level of uncertainty and decrease UB estimates of exposure) and risk management measures, such as the implementation of maximum levels in Europe.

The evidence supporting a decrease in dietary exposure to PCBs over time is consistent with information summarized in the biomonitoring section of this monograph (section 2.3.1).

8.6 Limitations and uncertainties associated with the exposure estimates

A number of limitations and uncertainties in the dietary exposure estimates exist for NDL-PCBs. These include the following:

- Some LOQs in the GEMS/Food database were very high (up to 83 µg/kg). A reliable sensitive method of analysis for NDL-PCBs was determined to be one with an LOQ of 3.5 µg/kg or less. Leaving all data points in the data set can lead to a higher UB estimate of the dietary exposure and a wider LB–UB range. Eliminating results with LOQs over the specified cut-off of 3.5 µg/kg will affect the dietary exposures estimated for countries that have high LOQs, but may introduce some bias into the data set by eliminating parts of data sets. This variation in concentration data was one of the largest areas of uncertainty for the estimates of dietary exposure conducted by the Committee.
- Not all data points in the GEMS/Food database had unique identifiers for each sample. This made it difficult to sum the six indicator PCB congeners for each individual sample before deriving mean concentrations per food group, which is the ideal approach to summarizing the data for the congeners of interest. Therefore, in some instances, the mean concentration across the food group was obtained for each congener separately, which may or may not have been based on the same number of samples, and the sum of the mean concentrations was calculated from there.
- Concentration data submitted to the GEMS/Food database in some cases were only for a limited range of foods. Some of the estimates of dietary exposure in the literature were also based on only a limited range of foods. These estimates would therefore tend to be an underestimate of dietary exposure.
- Not all countries that provided concentration data to the GEMS/Food contaminants database provided country-specific consumption data for inclusion in the FAO/WHO CIFOCOss database. Therefore, specific country exposure assessments could not be undertaken for all countries providing concentration data.
- Concentration data for NDL-PCBs in the GEMS/Food contaminants database were available only from countries from seven out of the 17 clusters, meaning that concentration data for all submitting countries were used for dietary exposure estimation for clusters without specific concentration data. This limits the comparability of results across clusters and the robustness of the conclusions drawn from the assessment. For clusters using global concentration data, differences in dietary exposure estimates for NDL-PCBs will reflect differences in food consumption patterns only.
- Concentration data submitted to the GEMS/Food database were primarily from European countries (90%). Therefore, the majority of

the dietary exposures estimated by the Committee were for European countries. From the literature, the estimates were also predominantly from Europe, with a small number from Asian countries. Information from a broader range of countries around the world is needed in order to provide a more globally representative assessment of dietary exposure.

- Food groups in the CIFOCOss consumption data set and the GEMS/Food concentration data may have been given different classification codes. Whereas codes for the concentration data were reassigned if the original code was not appropriate, there was often still some mismatch between the two data sets. This made it difficult to match the two sets of data for the exposure calculations, and some assumptions had to be made about what concentration data were matched with what consumption data. For example, the concentration data set may have had data for "liquid milk" with no indication of origin; however, the only consumption value in the data set was "cow's milk", and therefore these may have been matched together in order to include an estimate of exposure and contribution from this food. This often led to lower national exposures being estimated by the Committee compared with other sources, and having better metadata for both the concentration and consumption data sets would enable better matching between and use of the two input data sets.
- Concentrations of NDL-PCBs have been shown to be decreasing over time. Therefore, older concentration data from the GEMS/Food contaminants database may be less representative for contemporary dietary exposure estimates, particularly estimates for children who are unlikely to have consumed foods containing concentrations of NDL-PCBs represented in the older concentration data. Inclusion of these older concentration data will lead to a more conservative (higher) estimate of dietary exposures for children.
- As outlined in section 5 on effects of processing, there are some decreases in NDL-PCB concentrations due to cooking of food, depending on the cooking method, but particularly where the cooking method results in loss of fat. Therefore, estimated dietary exposures, where not based on foods prepared ready for consumption, may be slight overestimates. However, it is not expected that this would change the general range of estimated exposures to NDL-PCBs in this evaluation or change the conclusions based on the estimates provided.

Despite these limitations, the estimates of dietary exposure were generally within the same ranges across all estimates of dietary exposure assessed, particularly for LB means.

9. Modelling of body burden from dietary exposure

PCBs, including NDL-PCBs, are known to be slowly eliminated from the body, as shown by the very long half-lives of some congeners (Ritter et al., 2011). As a consequence, recurrent exposure results in bioaccumulation – that is, increasing body burden over time. For this reason, the accumulated amount in the body (body burden), rather than the daily exposure, is typically considered a more relevant exposure end-point to be used in risk assessment for these chemicals (Van Leeuwen & Younes, 2000; USEPA, 2010; Annex 1, references *154* and *155*).

The objective of this section is to estimate the body burden corresponding to the dietary exposure as assessed in section 8. Body burden estimation becomes particularly relevant if tolerable daily intakes (TDIs) are set, but not if an MOE approach is taken.

9.1 Dynamic modelling of exposure from food

In order to estimate the body burden corresponding to the dietary exposure assessed in section 8, the Kinetic Dietary Exposure Model was used (Verger, Tressou & Clémençon, 2007). This model describes the dynamic evolution of internal exposure over time using a dynamic exposure process (mathematically detailed in Bertail, Clémençon & Tressou, 2010), which is determined by the accumulation due to recurrent dietary exposures and by the elimination process that occurs over time. Such a model was previously used to estimate the body burden of PCDDs, PCDFs and DL-PCBs in France and validated with biomonitoring data for these chemicals (Béchaux et al., 2014).

Body burdens for each congener were estimated in child and adult populations in the countries from which dietary exposure data were available (China, Czech Republic, Finland, France, Germany, Ireland, Italy, Japan, the Netherlands, the Republic of Korea, Sweden and the United Kingdom). No modelled body burdens for PCB 128 could be developed owing to the lack of half-life information.

Between exposures, the change in the body burden is described by a simple one-compartment, first-order toxicokinetic model that is commonly used for chemicals with long half-lives, such as PCBs (Lorber, 2008; Amzal et al., 2009; Fromme et al., 2009a). Consequently, the kinetics of elimination is described with two parameters – namely, half-life and absorption rate. A more complex kinetic model is available for PCB 153 (Redding, 2010). However, in order to retain consistency across the different congeners, it was decided to implement the same single-compartment model for each congener.

9.1.1 Model parameters

(a) Absorption

Absorption of PCBs following dietary exposure is congener specific and varies according to age and exposure level. Indeed, Moser & McLachlan (2001) showed that absorption varies with dietary exposure in the range 90–100%. Based on the difference between the amount ingested and the unabsorbed PCB fraction excreted in the faeces, McLachlan (1993) estimated the absorption of NDL-PCBs in a breastfed child to be 96–98% for the main congeners present in the mother's milk. Alcock et al. (2000) also calculated absorption of around 80% for adults and 95% for infants for PCB 101. Finally, in rats, lower chlorinated congeners with six or fewer chlorine atoms have greater than 90% absorption, and higher chlorinated congeners have about 75% absorption (Albro & Fishbein, 1972; ATSDR, 2000; EFSA, 2005). Consequently, two scenarios were envisioned for the model:

- Scenario 1 (base case): A conservative scenario was defined by setting absorption to 100%.
- Scenario 2 (sensitivity analysis): A more realistic scenario was defined by setting absorption potentially varying from 75% to 100%.

(b) Half-life

As highlighted in Table 2 and discussed in section 2.1.1, the published estimates of PCB half-lives in humans vary considerably. Ritter et al. (2011) proposed intrinsic elimination half-lives for the different congeners. Such half-lives differ from most empirical estimates of human elimination kinetics for persistent chemicals (i.e. apparent elimination half-lives) that represent the aggregated effect of intrinsic elimination, ongoing exposure and changes in body weight. The approach taken by Ritter et al. (2011) is therefore more accurate and was used to define the base case scenario.

As a consequence:

- Scenario 1 (base case) is defined with the use of half-lives as estimated from Ritter et al. (2011) where available (i.e. for PCBs 28, 58, 138, 153 and 180). For PCB 101, the single study proposing a human half-life is used (Wolff, Fischbein & Selikoff, 1992). However, this half-life has been calculated jointly for both PCB 99 and PCB 101.
- Scenario 2 (sensitivity analysis) is defined to reflect uncertainty and variability in estimated absorption and half-lives across the published studies. A normal distribution of half-lives is considered to describe the uncertainty and variability for each congener. The distribution mean is set to the half-life mean as provided by the literature (Table

2), weighted by the respective study sample sizes. The distribution standard deviation is set to (maximum – mean)/8 (i.e. the *z*-score between the minimum and the maximum of a normal distribution).

(c) Dietary exposure

The dietary exposures (in ng/kg bw per day) estimated in section 8 are used for each country and population subgroup for which there were consumption data.

9.2 Estimates of body burden

With scenario 1, described in Table 25, body burdens (in ng/kg bw) associated with dietary exposure (mean and high consumers) are calculated for each of the six indicator PCBs for children and adults and are shown in Tables 26–32.

With scenario 2, described in Table 33, body burdens associated with dietary exposure are calculated for each of the six indicator PCBs for adults who are average consumers and are shown in Tables 34–35.

The body burden of children who are average consumers is estimated assuming a dietary exposure equal to the average dietary exposure every day. The body burden of children who are high consumers is estimated assuming a dietary exposure equal to the high consumer dietary exposure every day. The body burden of adults who are average consumers is estimated assuming a dietary exposure equal to the dietary exposure for children who are average consumers every day until 18 years and then the dietary exposure for adults who are average consumers every day until 50 years. The body burden of adults who are high consumers is estimated assuming a dietary exposure equal to the dietary exposure for children who are high consumers every day until the age of 18 years and then to the dietary exposure for adults who are high consumers every day until the age of 50 years.

Table 25
Values for the parameters of the model to estimate body burdens with scenario 1

PCB congener	Absorption (%)	Half-life (years)	Exposure (ng/kg bw per day)
28	100	5.6[a]	From Table 21 (mean and high consumer, LB and UB)
52	100	2.6[a]	From Table 21 (mean and high consumer, LB and UB)
101	100	5.7[b]	From Table 21 (mean and high consumer, LB and UB)
138	100	10.8[a]	From Table 21 (mean and high consumer, LB and UB)
153	100	14.4[a]	From Table 21 (mean and high consumer, LB and UB)
180	100	11.5[a]	From Table 21 (mean and high consumer, LB and UB)

LB: lower bound; UB: upper bound
[a] Ritter et al. (2011).
[b] Wolff, Fischbein & Selikoff (1992) (co-elution between PCB 99 and PCB 101).

Table 26
PCB 28: estimated body burdens with scenario 1

		Body burden (ng/kg bw)			
Country	**Population group**	**M_LB_28**	**M_UB_28**	**H_LB_28**	**H_UB_28**
Belgium	Other children	589	36 825	1 179	73 652
China	Children	676	676	1 353	1 355
Czech Republic	Other children	292	2 231	584	4 463
Finland	Other children	563	563	1 129	1 129
France	Other children	89	271	6 710	27 546
Greece	Other children	1 087	2 737	2 174	5 473
Italy	Other children	76	968	153	1 937
Japan	Children	71	71	142	142
Netherlands	Other children	347	384	695	768
Republic of Korea	Children	76	89	150	176
Sweden	Other children	324	5 597	647	11 197
Belgium	Adults	633	13 224	1 266	26 449
China	General population	386	386	771	771
Czech Republic	Adults	168	877	336	1 757
France	Adults	68	156	4 347	13 725
Germany	Adults	736	933	1 472	1 869
Ireland	Adults	109	317	218	633
Italy	Adults	41	377	85	751
Japan	General population	53	53	103	103
Netherlands	Adults	286	294	574	586
Republic of Korea	General population	297	353	597	706
Sweden	Adults	224	1 698	447	3 397
United Kingdom	Adults	32	68	65	135

H: high consumer; LB: lower bound; M: mean; UB: upper bound

Table 27
PCB 52: estimated body burdens with scenario 1

		Body burden (ng/kg bw)			
Country	**Population group**	**M_LB_52**	**M_UB_52**	**H_LB_52**	**H_UB_52**
Belgium	Children	2 215	18 627	4 431	37 255
China	Children	141	143	283	285
Czech Republic	Children	58	1 080	117	2 161
Finland	Children	87	87	174	174
France	Children	45	139	3 464	14 219
Greece	Children	2 100	2 776	4 200	5 553
Italy	Children	95	557	182	1 104
Netherlands	Children	152	171	306	344
Republic of Korea	Children	33	35	65	69
Sweden	Children	232	2 251	466	4 500

		Body burden (ng/kg bw)			
Country	**Population group**	**M_LB_52**	**M_UB_52**	**H_LB_52**	**H_UB_52**
Belgium	Adults	1 579	6 099	3 160	12 198
China	General population	79	79	159	160
Czech Republic	Adults	32	367	63	733
France	Adults	33	73	2 023	6 387
Germany	Adults	260	430	519	860
Ireland	Adults	60	158	121	315
Italy	Adults	41	205	90	401
Netherlands	Adults	138	142	278	286
Republic of Korea	General population	95	104	189	207
Sweden	Adults	214	726	426	1 452
United Kingdom	Adults	67	88	133	175

H: high consumer; LB: lower bound; M: mean; UB: upper bound

Table 28
PCB 101: estimated body burdens with scenario 1

		Body burden (ng/kg bw)			
Country	**Population group**	**M_LB_101**	**M_UB_101**	**H_LB_101**	**H_UB_101**
Belgium	Children	3 161	36 737	6 323	73 476
China	Children	341	344	682	685
Czech Republic	Children	229	2 164	458	4 329
Finland	Children	504	506	1 008	1 013
France	Children	224	413	6 797	27 903
Greece	Children	7 938	8 935	15 876	17 867
Italy	Children	232	1 136	464	2 274
Japan	Children	416	416	832	832
Netherlands	Children	331	410	658	824
Republic of Korea	Children	75	88	152	176
Sweden	Children	1 575	8 002	3 151	16 004
Belgium	Adults	1 962	13 266	3 921	26 531
China	General population	216	216	428	431
Czech Republic	Adults	165	881	332	1 761
France	Adults	186	279	4 424	13 966
Germany	Adults	1 024	1 147	2 052	2 297
Ireland	Adults	306	509	614	1 021
Italy	Adults	132	470	261	940
Japan	General population	306	306	611	611
Netherlands	Adults	437	470	875	943
Republic of Korea	General population	237	282	476	563
Sweden	Adults	1 893	3 723	3 783	7 449
United Kingdom	Adults	204	240	407	476

H: high consumer; LB: lower bound; M: mean; UB: upper bound

Table 29
PCB 138: estimated body burdens with scenario 1

		Body burden (ng/kg bw)			
Country	**Population group**	**M_LB_138**	**M_UB_138**	**H_LB_138**	**H_UB_138**
Belgium	Children	12 291	55 157	24 583	110 310
China	Children	764	764	1 527	1 531
Czech Republic	Children	397	3 346	791	6 689
Finland	Children	1 788	1 788	3 576	3 576
France	Children	1 500	1 773	9 934	40 781
Greece	Children	16 768	18 287	33 539	36 578
Italy	Children	705	2 026	1 410	4 056
Japan	Children	577	577	1 153	1 153
Netherlands	Children	4 114	4 114	8 228	8 228
Republic of Korea	Children	136	148	269	296
Sweden	Children	8 431	9 930	16 865	19 861
Belgium	Adults	9 267	23 998	18 535	48 001
China	General population	562	562	1 124	1 130
Czech Republic	Adults	251	1 588	502	3 182
France	Adults	1 135	1 299	8 061	25 450
Germany	Adults	4 776	4 868	9 551	9 737
Ireland	Adults	1 015	1 370	2 030	2 740
Italy	Adults	497	1 113	988	2 227
Japan	General population	529	529	1 053	1 053
Netherlands	Adults	4 115	4 126	8 236	8 258
Republic of Korea	General population	431	486	857	977
Sweden	Adults	9 431	9 999	18 857	20 003
United Kingdom	Adults	1 812	1 828	3 619	3 657

H: high consumer; LB: lower bound; M: mean; UB: upper bound

Table 30
PCB 153: estimated body burdens with scenario 1

		Body burden (ng/kg bw)			
Country	**Population group**	**M_LB_153**	**M_UB_153**	**H_LB_153**	**H_UB_153**
Belgium	Children	21 660	53 173	43 321	106 347
China	Children	927	927	1 854	1 859
Czech Republic	Children	1 143	4 570	2 290	9 141
Finland	Children	2 575	2 575	5 146	5 146
France	Children	2 544	2 839	11 206	46 002
Greece	Children	2 307	5 058	4 614	10 112
Italy	Children	809	2 298	1 617	4 601
Japan	Children	1 116	1 116	2 237	2 237
Netherlands	Children	6 258	6 258	12 516	12 516
Republic of Korea	Children	167	185	334	365
Sweden	Children	11 918	14 563	23 831	29 127

		Body burden (ng/kg bw)			
Country	**Population group**	**M_LB_153**	**M_UB_153**	**H_LB_153**	**H_UB_153**
Belgium	Adults	20 789	33 064	41 579	66 129
China	General population	807	807	1 608	1 615
Czech Republic	Adults	793	2 498	1 587	4 989
France	Adults	2 318	2 518	10 191	32 174
Germany	Adults	7 631	7 900	15 269	15 801
Ireland	Adults	1 808	2 256	3 616	4 513
Italy	Adults	635	1 414	1 270	2 829
Japan	General population	1 145	1 145	2 298	2 298
Netherlands	Adults	7 162	7 162	14 317	14 317
Republic of Korea	General population	580	662	1 152	1 325
Sweden	Adults	13 758	14 862	27 524	29 718
United Kingdom	Adults	2 725	2 753	5 451	5 499

H: high consumer; LB: lower bound; M: mean; UB: upper bound

Table 31
PCB 180: estimated body burdens with scenario 1

		Body burden (ng/kg bw)			
Country	**Population group**	**M_LB_180**	**M_UB_180**	**H_LB_180**	**H_UB_180**
Belgium	Children	6 419	55 421	12 842	110 842
China	Children	313	313	621	629
Czech Republic	Children	421	3 436	846	6 872
Finland	Children	914	914	1 824	1 824
France	Children	778	1 050	1 548	6 940
Greece	Children	2 915	4 984	5 830	9 967
Italy	Children	289	1 652	581	3 304
Japan	Children	285	285	569	569
Netherlands	Children	2 434	2 434	4 867	4 867
Republic of Korea	Children	76	100	156	204
Sweden	Children	3 584	4 210	7 169	8 420
Belgium	Adults	4 313	25 828	8 627	51 656
China	General population	248	248	495	495
Czech Republic	Adults	265	1 670	536	3 340
France	Adults	610	783	1 209	4 342
Germany	Adults	3 265	3 778	6 530	7 555
Ireland	Adults	680	1 054	1 359	2 108
Italy	Adults	207	858	409	1 716
Japan	General population	265	265	536	536
Netherlands	Adults	2 528	2 534	5 062	5 068
Republic of Korea	General population	346	449	697	904
Sweden	Adults	3 927	4 169	7 855	8 344
United Kingdom	Adults	553	610	1 106	1 227

H: high consumer; LB: lower bound; M: mean; UB: upper bound

Table 32
Sum of the six indicator PCBs: estimated body burdens with scenario 1

Country	Population group	Body burden (ng/kg bw)			
		M_LB_Sum	M_UB_Sum	H_LB_Sum	H_UB_Sum
Belgium	Children	46 337	255 939	92 678	511 882
China	Children	3 162	3 166	6 321	6 345
Czech Republic	Children	2 541	16 829	5 086	33 655
Finland	Children	6 431	6 434	12 857	12 862
France	Children	5 180	6 485	39 659	163 391
Greece	Children	33 114	42 777	66 232	85 550
Italy	Children	2 206	8 637	4 407	17 275
Netherlands	Children	13 635	13 771	27 270	27 546
Republic of Korea	Children	563	646	1 126	1 287
Sweden	Children	26 064	44 553	52 129	89 108
Belgium	Adults	38 544	115 479	77 086	230 964
China	General population	2 298	2 298	4 586	4 602
Czech Republic	Adults	1 673	7 881	3 356	15 762
France	Adults	4 350	5 108	30 256	96 044
Germany	Adults	17 692	19 057	35 393	38 119
Ireland	Adults	3 977	5 664	7 957	11 329
Italy	Adults	1 553	4 438	3 103	8 864
Netherlands	Adults	14 667	14 729	29 342	29 458
Republic of Korea	General population	1 985	2 336	3 969	4 682
Sweden	Adults	29 447	35 178	58 892	70 363
United Kingdom	Adults	5 393	5 587	10 780	11 170

H: high consumer; LB: lower bound; M: mean; UB: upper bound

Table 33
Values for the parameters of the model to estimate body burdens with scenario 2

PCB congener	Absorption	Half-life (years)	Exposure (ng/kg bw per day)
28	Sampled from uniform (75–100%)	Sampled from normal (3.5 ; 0.5)	From Table 21 (mean consumer, sampled between LB and UB)
52	Sampled from uniform (75–100%)	Sampled from normal (3.8 ; 0.4)	From Table 21 (mean consumer, sampled between LB and UB)
101	Sampled from uniform (75–100%)	Sampled from normal (5.7 ; 2)	From Table 21 (mean consumer, sampled between LB and UB)
138	Sampled from uniform (75–100%)	Sampled from normal (10.7 ; 3.5)	From Table 21 (mean consumer, sampled between LB and UB)
153	Sampled from uniform (75–100%)	Sampled from normal (14.3 ; 5.5)	From Table 21 (mean consumer, sampled between LB and UB)
180	Sampled from uniform (75–100%)	Sampled from normal (7.4 ; 1.5)	From Table 21 (mean consumer, sampled between LB and UB)

LB: lower bound; UB: upper bound
[a] Ritter et al. (2011).
[b] Wolff, Fischbein & Selikoff (1992) (co-elution between PCB 99 and PCB 101).

Table 34
PCBs 28, 52 and 101: estimated body burdens with scenario 2

		Body burden (ng/kg bw)								
		PCB 28			PCB 52			PCB 101		
Country	Population group	Median	P5	P95	Median	P5	P95	Median	P5	P95
Belgium	Adults	4 048	544	8 512	5 822	3 075	9 793	7 336	1 908	15 975
China	General population	4 108	990	7 104	4 671	2 533	7 808	5 308	1 821	13 062
Czech Republic	Adults	3 710	590	7 015	4 498	2 077	8 007	6 036	1 828	13 045
France	Adults	11 546	2 382	21 382	12 637	3 845	24 034	15 474	3 319	39 306
Germany	Adults	14 823	1 240	29 432	16 278	5 591	31 283	19 313	5 780	47 271
Ireland	Adults	3 783	625	7 204	4 583	2 165	8 123	5 668	1 367	13 484
Italy	Adults	421	322	539	180	152	231	327	140	497
Japan	General population	214	164	275	100	84	128	183	79	278
Netherlands	Adults	2 692	1 018	4 734	2 482	774	4 499	3 313	679	7 417
Republic of Korea	General population	476	216	937	505	96	874	752	205	1 662
Sweden	Adults	260	97	498	216	50	528	391	135	881
United Kingdom	Adults	858	266	1 445	727	208	1 431	946	186	2 534

P5: 5th percentile; P95: 95th percentile

Table 35
PCBs 138, 153 and 180: estimated body burdens with scenario 2

		Body burden (ng/kg bw)								
		PCB 138			PCB 153			PCB 180		
Country	Population group	Median	P5	P95	Median	P5	P95	Median	P5	P95
Belgium	Adults	16 579	8 771	30 440	31 872	12 838	47 274	9 709	4 484	20 054
China	General population	12 748	5 083	22 192	23 651	9 535	34 152	7 874	3 050	16 838
Czech Republic	Adults	11 956	4 367	21 408	20 941	8 306	31 050	7 688	2 630	15 322
France	Adults	33 707	12 409	70 877	49 028	23 030	90 673	20 469	7 000	49 988
Germany	Adults	47 259	13 471	85 140	64 046	24 925	104 586	27 781	7 983	62 036
Ireland	Adults	13 250	5 928	23 731	21 627	10 403	32 897	8 125	2 838	16 670
Italy	Adults	901	428	1 274	1 312	570	1 755	264	175	355
Japan	General population	473	225	670	728	316	973	145	97	195
Netherlands	Adults	8 292	3 851	18 305	13 171	4 631	24 049	4 982	1 764	9 178
Republic of Korea	General population	1 200	383	2 731	2 465	1 095	4 792	1 149	433	2 203
Sweden	Adults	790	186	1 505	1 351	627	2 396	565	229	1 128
United Kingdom	Adults	1 932	417	4 627	3 905	1 208	7 358	1 488	549	3 067

P5: 5th percentile; P95: 95th percentile

9.3 Contribution of congeners to the total body burden

The contribution of the different congeners to the total body burden (sum of the six indicator PCBs) varies from one country to another. However, on average, PCB 153 is the main contributor (41%), followed by PCB 138 (28%), PCB 180 (14%), PCB 101 (8%), PCB 28 (6%) and PCB 52 (3%). These contributions are explained by both the dietary exposure and the kinetics of the congeners. Indeed, regarding dietary exposure only, PCB 153 is also the main contributor (33%), followed by PCB 138 (26%), PCB 180 (12%), PCB 101 (12%), PCB 28 (9%) and PCB 52 (7%). The contributions of PCBs 153, 138 and 180 are higher when considering the body burden, as they have the longest half-lives and thus are accumulated more in the human body.

9.4 Comparison with biomonitoring data

The comparison of the body burden estimated from dietary exposure with biomonitoring data cannot be conducted directly. Indeed, because of the accumulation of PCBs throughout life, the body burden measured through biomonitoring studies reflects not only the current exposure, but also previous exposure, including the past few decades. As was highlighted previously in sections 2 and 8, exposure to PCBs has varied substantially over past decades and is known to have been much higher in the 1970s. Consequently, for some countries in which exposure has varied a lot in the past, the actual measured body burden is higher than the body burden estimated in this work, especially for the congeners with the longest half-lives.

However, a crude comparison with biomonitoring data shows that the body burdens estimated from the model are of the same order of magnitude as the body burdens estimated from biomonitoring data. As PCBs accumulate in fat, human milk is often used as an indicator of steady-state body burden. Based on the median total concentration of about 240 ng/g fat for all NDL-PCBs measured in human milk sampled in European countries and assuming 20% fat content in the human body, a median human body burden of about 50 000 ng/kg bw was estimated (EFSA, 2005). A comparison of estimated body burdens for adults (Tables 26–32) with concentrations in human milk (Table 13) shows that estimation of body burden from current dietary exposure is in the same order of magnitude, although a little lower for some countries, as expected (Table 32: Belgium: 38 544–230 964 ng/kg bw; Czech Republic: 1673–15 762 ng/kg bw; France: 4350–96 044 ng/kg bw; Germany: 17 692–38 119 ng/kg bw; Ireland: 3977–11 329 ng/kg bw; Italy: 1553–8864 ng/kg bw; Netherlands: 14 667–29 458 ng/kg bw; Sweden: 29 447–70 363 ng/kg bw; United Kingdom: 5393–11 170 ng/kg bw).

As the concentration in adipose tissue is also known to be a good indicator of steady-state body burden, Table 12 from section 2 can be used for comparison,

congener by congener. For PCB 28, still assuming 20% fat content in the human body, these results provide body burdens of around 260 ng/kg bw for Belgium, 2580 ng/kg bw for China and 400 ng/kg bw for the Czech Republic. This is in the same order of magnitude as the results for PCB 28 from Table 26, except for China, where the body burden estimated from current dietary exposure is lower. Regarding PCB 52, concentrations in adipose tissue provide a body burden of 120 ng/kg bw for China and 320 ng/kg bw for the Czech Republic, which are in the same order of magnitude as the predictions from dietary exposure. The same results can be expected for PCB 101 for Belgium, where the body burden estimated from dietary exposure seems to be higher than the one estimated from adipose tissue concentrations. Finally, for PCBs 138, 153 and 180, the comparison highlights that the body burdens estimated from current dietary exposure are much lower for China and the Czech Republic than the body burdens estimated from concentrations in adipose tissue (10 400 ng/kg bw versus 532–1130 ng/kg bw for China and 24 000 ng/kg bw versus 793–4989 ng/kg bw for the Czech Republic), whereas the two estimates are closer for Belgium (42 000 ng/kg bw versus 9267–48 000 ng/kg bw).

Overall, the comparison with biomonitoring data shows some differences that can be mainly explained by the trend in exposure to PCBs over the last decades and also by the uncertainty around the dietary exposure estimations and the kinetic model used, especially around the half-life.

9.5 Uncertainty around the estimated body burdens (scenario 2)

With scenario 2, three sources of uncertainty were taken into account in the estimation of the body burdens for the mean consumer: (1) the uncertainty around the absorption of PCBs, (2) the uncertainty around the half-life of PCBs and (3) the uncertainty around the true level of exposure due to data below the LODs. Tables 34 and 35 address that by taking into account this uncertainty; the confidence interval around the estimate of the body burdens is large, but still within a reasonable order of magnitude. This result is even more obvious for PCBs 138 and 153, and this can be explained by the great uncertainty around the half-life, which was considered with scenario 2. Indeed, as shown in Table 2 discussed in section 2, the half-lives provided by the literature vary a lot from one study to another and lead to a significant uncertainty.

In this modelling, the interindividual variability in kinetics and especially in half-lives was not taken into account, as data on these apects were not available in the literature. However, as a large distribution was used in scenario 2 for half-life and absorption, it seems reasonable to assume that the interindividual variability would be covered by such a distribution.

10. Dose–response analysis

Following a review of both the experimental and human data on NDL-PCBs, the Committee noted that there are a large number of in vivo and in vitro studies available covering several of the indicator PCBs with respect to possible hepatotoxicity, thyroid toxicity, and neurodevelopmental or neurotoxic effects. However, there is a general lack of in vivo toxicity data for two of the indicator PCBs (PCB 101 and PCB 138).

Given that some of the experimental toxicological data on NDL-PCBs indicate some common targets for toxicity, the Committee considered whether a group evaluation could be undertaken. Noting the lack of data on PCB 101 and PCB 138, the latter being one of the major contributors to dietary exposure to the six indicator PCBs, and that there is not enough information on relative potencies for each congener with respect to receptor interactions and the downstream consequences, it was decided not to undertake a group evaluation.

The Committee further concluded that none of the available short-term toxicity studies on four of the indicator PCBs and PCB 128 was suitable for the derivation of health-based guidance values (e.g. provisional tolerable monthly intakes) or assessment of their relative potency compared with a reference compound, such as PCB 153. Therefore, a comparative approach using the minimal effect doses from the available studies was developed in order to estimate MOEs to provide guidance on human health risk.

The available rat toxicological data on individual congeners showed that minimal changes in liver and thyroid histopathology were evident from the lowest doses tested of 2.8–7 μg/kg bw per day and were similar across the short-term and long-term studies of toxicity. Bearing in mind that, with the exception of PCB 153, the available studies on individual NDL-PCB congeners were of relatively short duration (28 or 90 days), the Committee decided to take the lower end of the range of administered (external) doses used for each congener at which these minimal changes occurred as a conservative point of departure for estimating MOEs. Given the major difference in dosing regimens between the 28-day and 90-day studies and the bioaccumulative nature of PCBs, MOEs were estimated on the basis of both external dose and internal dose.

Table 36 shows the ranges of administered doses in rats and the corresponding measured internal doses (adipose tissue concentrations). Fig. 7 shows the same information in graphical form for easier comparison. The internal dose MOEs based on amounts present in adipose tissue were considered the most appropriate comparison, particularly because they also eliminate interspecies differences in toxicokinetics.

Table 36

NDL-PCB concentrations in fat tissue in critical studies in rats

PCB congener Reference Study duration	Daily dose or total dose administered (units)	Concentration of PCB in lipid (µg/g)
Males		
PCB 28	Daily dose (µg/kg bw per day)	
Chu et al. (1996a)	0	0.32
90 days	2.8	0.74
	36	4.6
	359	48
	3 783	531
PCB 128	Daily dose (µg/kg bw per day)	
Lecavalier et al. (1997)	0	0.02
90 days	4.2	0.67
	42	8.12
	425	69.8
	4 210	531
PCB 153	Daily dose (µg/kg bw per day)	
Chu et al. (1996b)	0	0.03
90 days	3.6	1.2
	34	11.6
	346	89
	3 534	866
PCB 180	Total dose (mg/kg bw)	
Viluksela et al. (2014)	0	0.26
28 days	3	15.7
	10	36.4
	30	122
	100	372
	300	1 320
	1 000	3 920
	1 700	7 390
Females		
PCB 28	Daily dose (µg/kg bw per day)	
Chu et al. (1996a)	0	0.47
90 days	2.9	0.49
	37	4
	365	40
	3 956	563
PCB 128	Daily dose (µg/kg bw per day)	
Lecavalier et al. (1997)	0	0.16
90 days	4.5	0.97
	45	12.8
	441	125
	4 397	1 006
PCB 153	Daily dose (µg/kg bw per day)	
Chu et al. (1996b)	0	0.16
90 days	4.2	2.5
	42	36
	428	157
	4 125	1 840

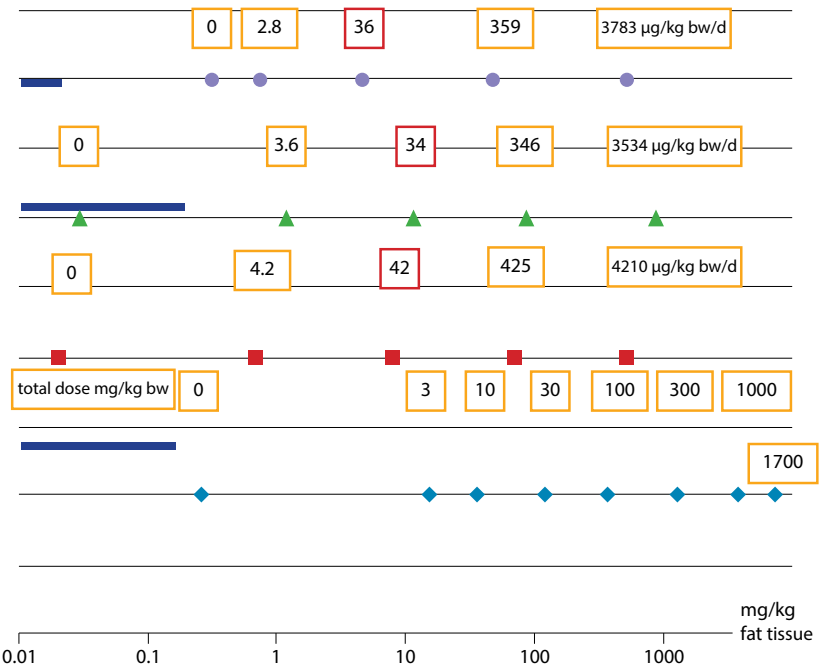
Table 36 (continued)

PCB congener Reference Study duration	Daily dose or total dose administered (units)	Concentration of PCB in lipid (µg/g)
PCB 153	Daily dose (µg/kg bw per day)	
NTP (2006a)	0	0.436
2 years	10[a]	20.1
	100[a]	158
	300[a]	519
	1 000[a]	1 557
	3 000[a]	4 292
PCB 180	Total dose (mg/kg bw)	
Viluksela et al. (2014)	0	0.29
28 days	3	15.5
	10	42.9
	30	165
	100	435
	300	1 380
	1 000	4 930
	1 700	11 300

[a] These doses were given on 5 days/week. If adjusted for 7 days/week dosing, the doses are equivalent to approximately 0, 7, 71, 214, 714 and 2143 µg/kg bw per day, respectively.

Fig. 7

Comparison of adipose tissue concentrations of PCBs in critical studies on male rats and indicative concentrations of the same congeners in human fat



Legend
Figures in boxes represent administered doses in each study.
Symbols represent the corresponding concentrations of PCB congeners in adipose tissue.

- PCB 28, Chu et al. (1996a), 90 days
- PCB 153, Chu et al. (1996b), 90 days
- PCB 128, Lecavalier et al. (1997), 90 days
- PCB 180, Viluksela et al. (2014), 28 days
- Average concentration in human fat (not available for PCB 128)

11. Comments

11.1 Toxicokinetics and mode of action

The main determinants of the fate and behaviour of PCB congeners in the body are their lipid solubility and their rate of metabolism. In general, PCBs are lipid soluble and are well absorbed from the gastrointestinal tract in mammalian species. They are rapidly distributed to all body compartments, especially the liver and muscle. The highest amounts of PCBs are usually found in the liver, fat, skin and breast milk. Rates of metabolism of PCBs vary greatly across species and also vary with the number and position of the chlorine atoms in the different congeners. In all species studied, PCB congeners with adjacent unsubstituted carbon atoms in the *meta* and *para* positions are more readily metabolized, whereas congeners without such adjacent unsubstituted carbon atoms are generally metabolized and cleared very slowly. PCBs with higher numbers of chlorine atoms are generally metabolized more slowly than those with lower numbers of chlorine atoms. Some PCBs with few chlorine atoms have apparent half-lives in blood as short as a week in experimental animals. However, many higher chlorinated PCB congeners have half-lives in humans that are much longer and therefore accumulate in the body. Depending on the species, half-lives vary from several months (e.g. rat) or a year or more (e.g. monkey) to over a decade (humans). The long half-lives in humans compared with rodents have been attributed to the poor metabolism of these compounds, and this, combined with the high lipid solubility of PCBs, results in high PCB content in the adipose tissue of humans. In terms of PCB metabolites, the hydroxy metabolites tend to be polar and more readily excreted, whereas the methyl sulfone metabolites are lipophilic and can be retained in adipose tissue.

PCBs are potent inducers of both phase I and phase II enzymes in the liver, and there are several routes of metabolism for PCBs. Biotransformation involves initial phase I oxidation by cytochrome P450 enzymes. PCBs can be oxidized across the aromatic ring to one or more unstable intermediate arene oxides, which can spontaneously rearrange to produce hydroxy metabolites. PCBs that oxidize to more stable arene oxides are subsequently reduced to dihydroxy metabolites. Dihydroxy metabolites can then be dehydrogenated to form catechols, which are in equilibrium with their oxidized forms, the corresponding hydroquinones and quinones. In these metabolic processes, dechlorination and shift of chlorine atoms may also occur. Thus, lower chlorinated NDL-PCB congeners can be metabolized to reactive intermediates, such as epoxides, quinones and reactive oxygen species, that can form adducts with macromolecules, such as proteins, DNA, RNA and lipids. PCB congeners lacking adjacent unsubstituted hydrogen atoms do not easily form arene oxides but can be metabolized by an alternative

pathway of direct insertion of a hydroxyl group to form a monohydroxy metabolite. Hydroxy metabolites are excreted as such, or the lower chlorinated PCBs can be conjugated with glucuronide or sulfate by the phase II enzymes UGT and SULT. Another route of metabolism for PCBs, which involves GST, is the formation of methyl sulfones. Methyl sulfones are the final product of the most rapidly metabolized PCBs.

Approximately 40 of the hundreds of potential hydroxy metabolites have been identified in human blood. Of these, only five persist in the blood, and these are hydroxy metabolites that are substituted in the *para* position, with chlorine atoms on each side of the hydroxyl group. In blood, they are bound to transthyretin, which normally binds T_4. Concentrations of hydroxy metabolites in human blood are approximately 5–10 times lower than those of the most persistent parent PCB congeners. Methyl sulfones undergo enterohepatic recirculation, and this, together with their lipophilicity, may account for some of the long retention times for methyl sulfone metabolites. Fifty or more methyl sulfone metabolites have been detected in human blood, but their concentrations in blood are low (generally less than 1% of the concentration of the most persistent PCB congeners), and much lower than those of the hydroxy metabolites. For both hydroxy and methyl sulfone metabolites, it may be more relevant to assess the effects of those metabolites with the highest retention potential than to assess the effects of the parent congener.

PCBs can interact with several cellular receptors, including CAR, PXR and AhR. The induction profile for these receptors differs between NDL-PCBs and DL-PCBs: NDL-PCBs most typically activate CAR and PXR, whereas DL-PCBs induce a pronounced activation of AhR, but not of CAR or PXR. Activation of either CAR and PXR or AhR results in different cytochrome P450 enzyme induction profiles. PXR and CAR activation induces CYP3A and CYP2B isoforms, respectively, whereas AhR activation induces CYP1A1, CYP1A2 and CYP1B1 isoforms. These differing cytochrome P450 induction profiles have traditionally been used to differentiate between NDL-PCB and DL-PCB congeners for toxicological purposes.

Interactions with CAR and PXR are crucial in the biotransformation and elimination of NDL-PCBs, because they can induce the relevant cytochrome P450 enzymes that metabolize NDL-PCBs. The activation of CAR and PXR also has potential toxicological implications, as these receptors play a significant role in the metabolism of endogenous molecules, such as hormones and vitamins. For example, induction of cytochrome P450 and conjugation enzymes by NDL-PCBs can influence hormonal homeostasis, as demonstrated in animal experiments for thyroid and steroid hormones, corticosteroids and retinoids. Recent studies have also indicated that CAR and PXR play an important role in the development of diabetes and inflammation.

NDL-PCBs also induce conjugation enzymes, such as UGTs, SULTs and GSTs. All these enzymes play important roles in the metabolism of NDL-PCBs, which is not only an important detoxification process, but also a route for the formation of transient reactive intermediates and more persistent hydroxy and methyl sulfone metabolites that are toxicologically relevant. Hydroxy metabolites can be agonists or antagonists for estrogen receptors, can interfere with thyroid hormone homeostasis and have neurotoxic potential. Methyl sulfone metabolites also interfere with thyroid hormone homeostasis and have been shown in vitro to have anti-estrogenic activity and to act as antagonists for glucocorticoid receptors. Based on the above mechanisms, a sustained exposure to NDL-PCBs may have toxicological implications.

In addition, there is cross-talk between PXR or CAR and other nuclear receptors, but the full scope of these interactions has not yet been fully elucidated. NDL-PCBs also activate RyR, which plays a crucial role in calcium signalling and in the decrease of brain dopamine levels. These mechanisms are thought to be major pathways leading to the observed neurobehavioural toxicity of NDL-PCBs in experimental animals. In general, the interactions of NDL-PCBs with these receptors and the enzyme activation reported in animal studies are considered to have human relevance.

11.2 Toxicological data

11.2.1 Acute toxicity and short-term studies of toxicity

There is no information on the acute toxicity of individual NDL-PCB congeners. The available data are mainly on rats and include 28-day studies on PCB 52 and PCB 180 and 90-day studies on PCB 28, PCB 128 and PCB 153. There are no short-term studies on two of the indicator PCBs, PCB 101 and PCB 138. In the two 28-day studies, the doses were expressed as total doses administered by oral gavage over the entire study period; the total dose comprised four (PCB 52) or six (PCB 180) higher daily loading doses during week 1, followed by three lower maintenance doses given 3 times per week during weeks 2–4. The total doses over the entire study period ranged from 3 to 3000 mg/kg bw for PCB 52 and from 3 to 1700 mg/kg bw for PCB 180. In the 90-day studies, fixed concentrations were administered in the diet and expressed as daily doses, which were similar for all three congeners, ranging from approximately 0.003 to 4.4 mg/kg bw per day. The main effects observed in these repeated-dose studies were on liver and thyroid and were fairly consistent across studies. Body weight was not affected in any of the 90-day studies.

In the liver, one of the most sensitive responses to exposure to NDL-PCBs is induction of phase I and phase II enzymes. In the short-term studies, this was reflected in structural changes, such as hepatocyte hypertrophy, cellular

vacuolation and alterations in cytoplasm density and homogeneity, which are well-recognized adaptive signs of increased liver activity following exposure to xenobiotics. The pattern of effects was similar for the five congeners tested, with effects being observed at most doses in both the 28-day and 90-day studies, usually from the lowest dose tested, and with males tending to be more sensitive than females. In many instances, there was little or no dose–response relationship in either incidence or severity of these minimal changes over the entire dose range covering 3 orders of magnitude (whether expressed as administered dose or as adipose tissue concentration at the end of dosing). In the 28-day studies, liver weight was increased at the highest total dose of 3000 mg/kg bw for PCB 52 and with a dose–response relationship for PCB 180 at doses of 300 mg/kg bw and higher. In the 90-day studies, liver weight was increased at the highest dose of 4.4 mg/kg bw per day for PCB 128 and at the highest dose of 4.1 mg/kg bw per day for PCB 153.

Studies on individual NDL-PCB congeners have shown effects on thyroid histology and/or circulating thyroid hormone concentrations in adults. Effects on thyroid histology were seen in all the 28-day and 90-day studies from the lowest doses tested. The effects included reductions in the size of large follicles, collapsed follicles, increases in epithelial height and cytoplasmic vacuolation. Blood thyroid hormone levels were measured in the two 28-day studies, with reductions in T_4 levels at and above 300 mg/kg bw total dose for PCB 52 and dose-related reductions at and above 100 mg/kg bw total dose for PCB 180. Effects on the thyroid are potentially important, particularly because of the sensitivity of the developing brain to reductions in maternal and early postnatal thyroid hormone levels. It should be noted that both DL-PCBs and NDL-PCBs (and their hydroxy metabolites) can have effects on the thyroid and/or circulating thyroid hormone levels. In rodents, commercial mixtures of PCBs reduce circulating total T_4 and free T_4, but have little or no effect on total or free T_3 or on TSH. Studies on NDL-PCBs also show effects on T_3, but these are usually less marked than those on T_4. The precise mechanisms underlying these changes and their relative contributions to NDL-PCB-induced thyroid effects are not yet clear.

11.2.2 Long-term studies of toxicity and carcinogenicity

The only NDL-PCB congener studied for long-term toxicity and carcinogenicity is PCB 153 (NTP, 2006a). Analytical checks of the test material for purity showed no contamination with DL-PCBs and only minor contamination with PCB 101 (0.21%) and PCB 180 (0.002%). Male animals were not used. Female rats were administered PCB 153 by oral gavage at 0, 10, 100, 300, 1000 or 3000 μg/kg bw per day, 5 days/week, for up to 105 weeks (equivalent to 0, 7, 70, 200, 700 or 2000 μg/kg bw per day when adjusted for 5 days/week dosing). These doses resulted in a

linear increase in concentrations in fat; at the end of the study, concentrations were approximately 440, 20 000, 160 000, 520 000, 1 600 000 and 4 300 000 ng/g lipid for the 0, 10, 100, 300, 1000 and 3000 μg/kg bw per day dose groups, respectively. There was equivocal evidence of carcinogenic activity of PCB 153, based on the occurrence of a small number of cholangiomas of the liver in two animals in each of the two highest dose groups. The study authors considered that the occurrence of bile duct hyperplasia at doses of 300 μg/kg bw per day and above could have contributed to cholangioma formation, and so the tumours may have been treatment related. The Committee noted that "bile duct hyperplasia" might better be described as atypical tubular epithelial cell hyperplasia.

It is notable that in this study, there was no increase in hepatic cell proliferation or any increases in hepatocellular adenomas or carcinomas. This is despite dose-related increases in hepatocyte hypertrophy, which were seen from the lowest dose of 10 μg/kg bw per day, equivalent to 7 μg/kg bw per day when adjusted for 5 days/week dosing, and which became statistically significant at doses of 300 μg/kg bw per day and above during the first year of the study and at all dose levels by the end of the study. There were also statistically significant increases in absolute and/or relative liver weights at 1000 and 3000 μg/kg bw per day at weeks 14 and 31 and at doses of 100 μg/kg bw per day and above at week 53 of the study; there was also evidence of diffuse fatty change in the liver at doses of 300 μg/kg bw per day and above at the end of the study. Concerning the thyroid, there were no increases in thyroid tumours, despite statistically significant reductions in serum thyroid hormone concentrations (total T_4, free T_4, free T_3) in the 3000 μg/kg bw per day group during the first year of the study and a significant increase in follicular cell hypertrophy in the mid-dose group (300 μg/kg bw per day) and highest-dose group (3000 μg/kg bw per day) at the end of the study. There were no effects on thyroid weight. The observations from this long-term study support the view that the liver and thyroid changes observed in the short-term studies on PCB 153 and the four other NDL-PCBs, at lower dose levels than those used in this study, are unlikely to lead to major pathological changes over the long term.

NDL-PCBs may have weak tumour promotion effects in the liver, based on studies in rodents using DEN as an inducer.

11.2.3 Genotoxicity

Genotoxicity studies on individual NDL-PCB congeners have produced both positive and negative results. Some in vitro tests on PCB 3/PCB 3 metabolites, PCB 52/PCB 52 metabolites, PCB 101, PCB 138 and PCB 153 were positive for genotoxicity. In vivo studies have been conducted only on PCB 52 and PCB 153, and these were negative. The positive results in vitro may be due to the formation

of reactive intermediates and induction of oxidative stress. It seems likely that some NDL-PCBs may be indirect-acting genotoxicants.

11.2.4 Reproductive and developmental toxicity

There are no oral reproductive toxicity studies on individual NDL-PCB congeners.

In developmental toxicity studies on individual NDL-PCB congeners (PCB 28, PCB 153 and PCB 180) in rodents, reduced birth weight and increases in offspring liver weight were seen only at high doses of 32 mg/kg bw per day and above. The majority of developmental toxicity studies have focused on neurodevelopmental outcomes. Rodent studies have shown that prenatal and/or postnatal exposures to NDL-PCBs cause effects on end-points such as spontaneous (locomotor) activity, habituation capability, spatial learning and anxiety-like behaviour at maternal doses ranging from 0.2 to 1000 mg/kg bw per day. A limitation of many of the neurobehavioural studies is that they used only one or two dose levels and effects were seen at the lowest dose or at the only dose tested, which does not allow derivation of a NOAEL. The Committee noted that the administered doses used in the developmental neurobehavioural studies were considerably higher than those used in the short- and long-term studies of toxicity and that the lowest effect level in the developmental neurobehavioural studies was at least 2 orders of magnitude higher than the lowest doses that induced minimal changes in liver and thyroid in the short-term studies of toxicity. Internal dose data (concentrations in fat) are not available for the developmental toxicity studies.

In vitro studies also indicate a potential role of hydroxylated metabolites of NDL-PCBs in neurodevelopmental mechanisms of toxicity, but support from in vivo studies is very limited. These results from developmental neurobehavioural studies in rodents indicate similar patterns of effects, albeit with congener-specific differences. Based on in vivo studies, a distinct mechanism of action for the neurodevelopmental effects of NDL-PCBs cannot be established. However, results from in vitro or ex vivo studies using neuronal cells indicate mechanistic pathways that involve disruption of intracellular calcium or thyroid hormone homeostasis. Based on available data, the Committee concluded that neurodevelopmental outcomes are not the most sensitive end-points for the toxicity of NDL-PCBs in rodents.

11.2.5 Immunological studies

In vitro and in vivo studies using doses ranging from 0.1 mg/kg bw per day up to several hundred milligrams per kilogram of body weight per day have shown that NDL-PCBs can exert immunological effects. In these studies, a comparison was often made between TCDD and an NDL-PCB, such as PCB 153. Results from in

vivo studies in mice indicate that the mechanism of action for immunological effects differs between dioxin-like and non-dioxin-like compounds. For example, PCB 153 significantly enhanced splenic PFC responses to SRBCs injected into mice, whereas TCDD induced an opposite response. Moreover, in studies of the effects of co-administration of TCDD and PCB 153, it has been shown that PCB 153 can counteract the AhR-mediated effects of TCDD on PFC responses. The results of repeated-dose studies in rodents suggest that PCB 153 can induce a proinflammatory response in various tissues (e.g. liver, spleen, lungs and uterus), which is not seen with TCDD. From the doses used in the immunological studies, such effects seem unlikely to be the most sensitive end-points for NDL-PCBs, but the data relate mostly to PCB 153.

11.3 Observations in humans

11.3.1 Biomonitoring and modelling of body burden

The most commonly used biomarkers of PCB exposure in humans are PCB concentrations in adipose tissue, serum, plasma and milk. These mainly reflect exposure from the diet. There is a strong correlation between serum and adipose tissue concentrations, when expressed on a lipid basis, and both are widely regarded as useful biomarkers of PCB body burden. In general, concentrations in blood lipids reflect more recent exposures, as well as the full spectrum of PCB congeners to which a person has been exposed, whereas the pattern of PCB congeners in adipose tissue reflects long-term exposure and, to a lesser degree, the extent to which a particular congener is metabolized. Concentrations in human milk largely reflect the pattern and amounts of PCB congeners present in maternal adipose tissue and blood, when expressed on a lipid basis.

Numerous publications confirm that PCB 138, PCB 153 and PCB 180 are the most consistently detected and quantitatively dominant PCB congeners found in human blood and tissues, accounting for 65–80% of total PCBs in human serum. If only one congener is to be used as a marker of total PCB exposure, then PCB 153 is a good choice, because it is very stable and often the most abundant congener. PCB 153 has been shown to have a high correlation with the total amount of PCBs in human milk, plasma and serum. However, if a more complete profile of congeners is considered, the correlations are lower, and either total PCBs or PCB 153 as a marker of the total could be misleading indicators of the differential exposure to other individual or groups of congeners of toxicological significance (ATSDR, 2000).

The total body burden of PCBs and their metabolites generally increases with age, and this is reflected in blood and adipose tissue biomarker concentrations. With the phasing out of the production of PCBs since the 1980s, results of studies conducted since that time show clear trends for decreasing concentrations of

PCBs in blood and human milk: in Europe, mean concentrations of PCB 138, PCB 153 and PCB 180 in blood appear to have decreased by approximately 80% in 20 years; in WHO surveys on human milk, concentrations of the six indicator PCBs have steadily decreased by approximately 10-fold over the decade 2000–2010.

Biomonitoring results from numerous countries over the preceding decade illustrate a wide range of concentrations for individual congeners in human serum, adipose tissue and milk. The results are summarized in Table 37, together with equivalent and modelled body burdens. The concentrations of hydroxy metabolites of PCBs in human serum are not shown, but are in a similar range to the concentrations of many parent PCB congeners, except for those PCBs that are the most prevalent or persistent. Human milk, serum and adipose tissue are all considered to be relevant matrices for assessment of body burdens of PCBs. Human milk has been recognized by WHO as the preferred matrix for monitoring levels of environmental contaminants. In Table 37, ranges of equivalent body burdens were derived using the available range of mean PCB concentrations reported in human milk, as the Committee considered that the milk values were more representative, reflecting both adult (maternal) and infant exposures.

The Kinetic Dietary Exposure Model (Verger, Tressou & Clémençon, 2007) was used to simulate body burdens in adult populations in the countries from which dietary exposure data (see below) were available (China, Czech Republic, Finland, France, Germany, Ireland, Italy, Japan, the Netherlands, the Republic of Korea, Sweden and the United Kingdom). Based on UB mean dietary exposures, body burdens were also modelled for each congener and each country. Ranges of modelled body burden estimates across countries are reported in Table 37. No modelled body burdens for PCB 128 could be developed owing to the lack of half-life information.

The human body burden for each congener was predicted using a one-compartment model, an assumption of 20% body fat and information on dietary exposure (see below). Half-life estimates were drawn from Ritter et al. (2011), and sensitivity analyses were performed to take into account the large variability in half-life data across other publications. The modelling predicted body burdens of the same order of magnitude as those reported in human biomonitoring data.

11.3.2 Epidemiology

Humans are exposed to complex mixtures of PCBs. The epidemiological literature covers studies that have analysed outcomes according to both exposure to complex mixtures of PCBs and exposure to specific marker NDL-PCBs. The studies included a broad range of potential outcomes, including growth and

Table 37

Summary of human biomonitoring results on selected NDL-PCBs from studies published in the last decade and body burden estimates

NDL-PCB congener	Range of mean concentrations (ng/g lipid)			Range of equivalent body burden[c] (µg/kg bw) across studies	Range of modelled body burden[d] (µg/kg bw) across countries
	Serum[a]	Adipose tissue	Milk[b]		
28	1–14	0.7–39	0.6–7.8	0.12–1.6	0.05–1.7
52	0.2–26	0.3–72	0.2–15.8	0.04–3.6	0.06–0.7
101	0.1–5.2	0.2–58	0.3–8.3	0.06–1.7	0.14–3.7
128[e]	NA	NA	0.2–4.0	0.04–0.8	NA
138	3.6–186	3.6–181	1.6–98	0.32–20.1	0.49–10.0
153	11–423	0.9–310	3.4–130	0.68–26.7	0.66–14.9
180	6–374	1.7–245	1.6–96	0.32–19.7	0.25–4.2

NA: not available

[a] The majority of serum samples were at the low end of the range.

[b] Excludes results from the upper end of the range in Czech Republic, as the data set included results from an industrial area with a former PCB-based paint production plant.

[c] Body burdens based on reported range of concentrations in human milk; 65 kg bw adult; 20% lipid.

[d] Model-based estimates using upper-bound mean dietary exposure in China, Czech Republic, Finland, France, Germany, Ireland, Italy, Japan, the Netherlands, the Republic of Korea, Sweden and the United Kingdom.

[e] Based on limited human milk analysis (Koopman-Esseboom et al., 1994; Todaka et al., 2010; Ryan & Rawn, 2014).

development, neurodevelopment and neurobehaviour in childhood, neurotoxic effects in adults, cancer, endocrine and metabolic effects (e.g. on thyroid hormone homeostasis, diabetes, obesity, insulin resistance and metabolic syndrome), reproductive effects in males and females, immunological effects and infections, respiratory diseases, cardiovascular diseases, hepatic effects, musculoskeletal effects and endometriosis. However, methodological issues and some study design features must be considered for a proper interpretation of human studies. Of particular concern is the extensive use of cross-sectional studies reporting associations between exposure and outcome, in which the exposure measurements are taken at the same time as the outcome is ascertained. A cross-sectional estimate of body burden may not reflect the exposure during the time period critical for the development of a particular outcome. Exceptions are in cases when the exposure and response are known to occur during a defined short period (e.g. prenatal exposure measured in cord blood in relation to effects in newborns). Other than this, cross-sectional studies are of little value. In case–control studies, major drawbacks arise from the fact that measurement may be affected by the disease and treatments, as well as the potential for selection and information bias in hospital-based studies. The degree of control of relevant confounders is highly variable across studies, including exposure to other contaminants, and the potential for confounding by factors not explicitly considered in the analysis cannot be ruled out. Finally, there is always co-exposure to dioxin-like congeners;

given the strong collinearity between exposure to DL-PCBs and NDL-PCBs, this makes it very difficult to make a valid estimate of the independent effect of NDL-PCBs.

In spite of all the limitations, some well-designed and well-conducted studies have identified potential health effects associated with exposure to NDL-PCBs, including changes in thyroid hormone homeostasis, neurodevelopmental effects, immunological effects and some types of cancer. Some of the results offer support for the toxicological findings, especially regarding thyroid effects, identified as potentially relevant for NDL-PCBs in animal studies. The results of prospective (Chevrier et al., 2007; Herbtsman et al., 2008; Darnerud et al., 2010) and cross-sectional studies in newborns (Takser et al., 2005; Wang et al., 2005; Herbstman et al., 2008) and children (Álvarez-Pedrerol et al., 2008; Schell et al., 2008) suggest that increasing concentrations of NDL-PCBs are correlated with lower levels of T_4 and higher levels of TSH in the blood, although there are some inconsistencies between results across studies. Perinatal exposure to NDL-PCBs in birth cohorts was found to be associated with increased incidence of acute respiratory infections in children (Dallaire et al., 2006; Glynn et al., 2008; Stølevik et al., 2013). Maternal and early postnatal exposure to NDL-PCBs in some birth cohorts was associated with impaired behavioural, cognitive and psychomotor development (Stewart et al., 2005; Park et al., 2010; Forns et al., 2012b; Lynch et al., 2012; Gascon et al., 2013; Tatsuta et al., 2014) and with alteration of VEPs (Saint-Amour et al., 2006).

Regarding cancer, the recent evaluation by IARC (2015) reported an association between melanoma and PCB exposure, mainly based upon cohort studies of exposed workers in various industries, for whom exposure would be by multiple routes. IARC (2015) also considered studies in the general population with different study designs. Only one population-based case–control study (Gallagher et al., 2011) reported specific results for NDL-PCBs, showing a significantly increased risk of melanoma for a group of 11 NDL-PCBs, as well as for some individual congeners. In this study, a similar increased risk was also observed for two DL-PCB congeners. The association between NDL-PCBs and NHL has also been assessed in several prospective cohorts (Engel et al., 2007; Bertrand et al., 2010; Laden et al., 2010; Bräuner et al., 2012), but the results were not consistent.

11.4 Analytical methods

The methodologies used for the analysis of NDL-PCBs are largely similar regardless of the laboratory performing the analysis. Although some agencies (e.g. AOAC International, International Organization for Standardization) have developed validated matrix-specific methods of analysis that may be followed for the analysis

of NDL-PCBs and DL-PCBs, others have developed a set of performance criteria to ensure that laboratories develop data of acceptable quality. The use of automated solid-phase extraction systems for the extraction and/or cleanup of samples has increased, which has improved efficiency. GC coupled to ^{63}Ni ECDs and mass spectrometers (including ion trap, low-resolution, high-resolution and tandem mass spectrometers) have been used in the analysis of NDL-PCBs.

The availability and use of stable isotope internal standards and certified reference materials lead to improved accuracy of analytical results. The use of analytical methods with satisfactory performance characteristics, as well as methods subjected to interlaboratory comparison studies, should be considered, as appropriate, to ensure that the data submitted for evaluation are of adequate quality.

11.5 Sampling protocols

Although there are no established protocols set specifically for the collection and storage of samples for NDL-PCB analysis, best practices have been established for other POPs present at ultra-trace levels (e.g. PCDDs/PCDFs, DL-PCBs). These practices include the collection of samples using containers that are non-reactive (e.g. glass, aluminium) and that have been chemically cleaned or certified to be free of contaminants.

11.6 Effects of processing

NDL-PCBs are thermally stable and resistant to degradation. Studies on the impact of processing in relation to PCB concentrations have been largely focused on the cooking techniques used to prepare foods and techniques that change the fat content (e.g. PCB levels are lowered in skimmed milk, but increased concentrations are found in foods with higher fat content, such as cheese or cream). Although the studies related to the impact of processing on PCB concentrations include both DL-PCBs and NDL-PCBs, the impact on the concentrations is similar for both groups. Ultimately, processing that results in the removal of lipids will lead to a decrease in PCB concentrations in the final food product.

11.7 Prevention and control

The focus of efforts related to preventing exposure to POPs, including NDL-PCBs, is on limiting contamination of the food-chain, including exposure of food-producing animals to PCBs. With the knowledge that fish, meat and dairy product consumption makes the most significant contribution to human PCB exposure, methods of PCB reduction in animals from which these foods are derived are of primary interest. Transfer of DL-PCBs and NDL-PCBs from

feed to animal-based food products (e.g. milk) occurs; transfer of PCB 138, PCB 153 and PCB 180 is greater than that observed for PCB 28, PCB 52 and PCB 101. Adherence to good agricultural practices and good animal feeding practices will contribute to the efforts to reduce PCB concentrations in food for human consumption. PCB contamination of animal housing and/or buildings (e.g. silos) near animal pastures may contribute to animal exposure levels, as does the pasturing of animals on lands contaminated with PCBs. It is therefore important to identify contaminated pastures to ensure that they are not used for grazing. PCB contamination can be further reduced by establishing and adhering to soil guidelines for agricultural purposes, performing diligent monitoring programmes to confirm compliance and establishing critical control points for the feed manufacturing process where PCB concentrations can be reduced. Additionally, farming practices should include plans for isolation, among other procedures, if PCB contamination is detected.

11.8 Levels and patterns of food contamination

Thirty countries (Australia, Austria, Belgium, Canada, China, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Poland, the Republic of Korea, Romania, Singapore, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) provided data to the Committee for its review of NDL-PCBs. The submissions from Europe were received through EFSA. Those data that were not in an acceptable format for evaluation by the Committee were removed from the data set. Submitted data included results from sample collection periods extending from 1995 to 2014. Most (90.5%) of the data were submitted from Europe; the Pacific region contributed 8.5% of the submissions, and 1% of the data were provided from North America.

The food categories having elevated NDL-PCB concentrations were fish/fish products, meat/meat products, egg/egg products and milk/milk products. Concentrations of the six indicator PCBs in these food categories varied widely (Table 38). Few occurrence data were submitted for PCB 128, and lower concentrations of this congener were reported relative to the indicator congeners (Table 38). It was noted that concentrations of the higher chlorinated indicator congeners (PCB 101, PCB 138, PCB 153 and PCB 180) were higher than those of the trichlorinated PCB 28 and tetrachlorinated PCB 52, particularly in fish/fish products. The maximum concentration reported in fish/fish products exceeded 1 000 000 ng/kg expressed on a wet weight basis, whereas the median concentrations remained very low for all six congeners (PCB 28: 0.73 ng/kg ww; PCB 52: 2.6 ng/kg ww; PCB 101: 8.9 ng/kg ww; PCB 138: 30 ng/kg ww; PCB 153: 50 ng/kg ww; PCB 180: 7.5 ng/kg ww).

Table 38
Concentrations of the six indicator PCBs and PCB 128 in specific foods

Food category	*n*	*n* < LOD	Concentration range (ng/kg ww)
PCB 28			
Eggs	1 086	392	ND–6 800
Fish	7 146	2 119	ND–103 000
Meat	2 488	1 473	ND–16 100
Milk	6 510	736	ND–5 250
PCB 52			
Eggs	1 069	484	ND–6 710
Fish	7 045	1 875	ND–610 000
Meat	2 506	1 495	ND–9 440
Milk	6 513	716	ND–4 600
PCB 101			
Eggs	1 085	508	ND–8 410
Fish	7 137	1 762	ND–1 200 000
Meat	2 463	1 478	ND–240 000
Milk	6 481	741	ND–1 850
PCB 138			
Eggs	1 090	312	ND–34 800
Fish	7 144	1 543	ND–482 000
Meat	2 521	1 013	ND–12 900
Milk	6 531	524	ND–5 740
PCB 153			
Eggs	1 092	294	ND–31 000
Fish	7 147	1 463	ND–812 000
Meat	2 521	993	ND–17 300
Milk	6 534	429	ND–16 900
PCB 180			
Eggs	1 092	310	ND–34 700
Fish	7 145	1 777	ND–280 000
Meat	2 517	1 074	ND–198 000
Milk	6 528	571	ND–4 210
PCB 128			
Eggs	2	1	ND–0.002
Fish	356	2	ND–6.63
Meat	13	4	ND–0.017
Milk	15	3	ND–1.29

LOD: limit of detection; *n*: number of samples; ND: not detected; ww: wet weight

11.9 Dietary exposure assessment

Estimates of dietary exposure were evaluated by the Committee, focusing on the six indicator PCBs, singly and in combination. Only chronic dietary exposure assessments were included in the evaluation. Dietary exposure estimates from the literature were reviewed. Both national and international estimates of dietary exposure were made by the Committee based on consumption and concentration data available from the GEMS/Food database. The concentration data submitted

(as shown at a major food group level in Table 38 above) were summarized by specific food type (e.g. for herring or cow's milk) for use in the exposure calculations conducted by the Committee. Estimates of dietary exposure for the six indicator PCBs were also calculated individually for countries that provided concentration and consumption data, for both body burden modelling and risk characterization purposes. Exposures to PCB 128 were also estimated, as relevant toxicity data were available for this congener for risk characterization purposes.

11.9.1 National estimates of dietary exposure

Estimated national dietary exposures for the sum of the six indicator PCBs are shown in Table 39.

National estimates of dietary exposure were also calculated for each of the six indicator PCBs individually. Exposures were highly variable, depending on the congener, concentration data, country and population subgroup assessed. As a result of a high proportion of "non-detects" (concentrations below the LOQ) across a wide range of food groups, high LOQs and similar LOQs across congeners, the exposures based on data from one country were excluded from the evaluation. The estimates are summarized in Table 40 for the remaining countries. Mean and high-percentile exposures, including LB and UB estimates, across all countries and population groups and individual congeners ranged between <1 and 4.7 ng/kg bw per day at the mean and 9.4 ng/kg bw per day at the high percentile.

For PCB 128, dietary exposure estimates were available for only two countries (Finland and the United Kingdom), based on concentration data for limited food commodities. For this reason, the estimated dietary exposures were not used to determine the body burden modelled from external dose for PCB 128. An alternative approach was used, whereby the proportion that the concentration of PCB 128 represents of the six indicator PCBs considered individually was determined on the basis of data from GEMS/Food (the average was 16%). To represent approximate PCB 128 exposure, 16% of the average of the upper-bound exposures for each individual indicator PCB for both mean and high percentile for adults was used (mean 0.2 ng/kg bw per day, high percentile 0.4 ng/kg bw per day).

Lower estimates of dietary exposure to the six indicator PCBs were determined where methods with lower LODs were used for the food analysis and low concentrations in foods were determined. This highlights the importance of using specific analytical techniques for this group of contaminants. Higher estimates of dietary exposure, particularly at the UB, were strongly influenced by the sensitivity of the analytical method and therefore the concentration assigned to "non-detects" for UB scenarios.

Table 39
Overall range of estimated national dietary exposures to the sum of the six indicator PCBs

Source	Population group	LB–UB dietary exposures[a] (ng/kg bw per day)	
		Mean exposure	High-percentile exposure[b]
Literature	Children[c]	3–24	12–87
	Adults	1–18	8–45
Estimated by the Committee	Children[c]	<1–82	1–163
	Adults	<1–25	<1–51

LB: lower bound; LOD: limit of detection; LOQ: limit of quantification; UB: upper bound
[a] LB where "non-detects" were assigned a zero concentration; UB where "non-detects" were assigned either the LOD or LOQ.
[b] Usually 90th or 95th percentile reported. The estimates calculated by the Committee were 90th percentiles.
[c] Includes infants consuming a mixed diet; excludes infants solely breastfed or formula fed.

Table 40
Summary of the range of estimated dietary exposures for individual indicator PCBs for adults and children[a] from all countries assessed

NDL-PCB	Population group[b]	Estimated dietary exposure (ng/kg bw per day)	
		Mean (LB–UB)	High percentile (LB–UB)
28	Children (infants to adolescents)	<1–2.8	<1–5.7
	Adults	<1–<1	<1–1.1
52	Children (infants to adolescents)	<1–2.6	<1–5.3
	Adults	<1–<1	<1–1.1
101	Children (infants to adolescents)	<1–3.4	<1–6.7
	Adults	<1–1.2	<1–2.5
138	Children (infants to adolescents)	<1–4.7	<1–9.4
	Adults	<1–1.8	<1–3.7
153	Children (infants to adolescents)	<1–3.5	<1–7.1
	Adults	<1–2.2	<1–4.3
180	Children (infants to adolescents)	<1–2.7	<1–5.4
	Adults	<1–<1	<1–1.5

LB: lower bound; UB: upper bound
[a] Includes infants consuming a mixed diet; does not include infants exclusively breastfed or formula fed.
[b] Where defined for the consumption survey, infants are <1 year, toddlers 1 to <3 years, children 3 to <10 years, adolescents 10–<18 years, adults 18+ years.

Despite variations in methodologies used to estimate dietary exposure, the majority of national estimates of dietary exposure to the NDL-PCBs assessed were in the same ranges, with slightly more variation in the estimates of UB levels of dietary exposure than in the LB estimates.

The main contributor to dietary exposure to the sum of the six indicator PCBs at the national level was fish and seafood, followed by meat or meat products. Milk and dairy products also contributed for some populations and population subgroups, particularly children. The differences in the main contributors

between countries depended on the importance of the food in the countries' diets as well as the concentration of the NDL-PCBs in the food used in the estimate.

11.9.2 International estimates of dietary exposure

Estimates of international mean dietary exposure per capita for the sum of the six indicator PCBs were calculated by the Committee using concentration data submitted to the GEMS/Food contaminants database and consumption data from the GEMS/Food cluster diets.

The range of estimated dietary exposure to the sum of the six indicator PCBs between clusters for the LB scenario was 1–60 ng/kg bw per day. For UB exposures, the range between clusters was 2–83 ng/kg bw per day. Fish was a major contributor to dietary exposure across the majority of the clusters, contributing up to about 90% of dietary exposure for one cluster. This was due to the higher concentration of NDL-PCBs in fish and/or the higher consumption of fish for the cluster.

11.9.3 Dietary exposure of infants

Mean dietary exposure of breastfed infants to the sum of the six indicator PCBs was reported for 11 European countries by EFSA (2005) to be 1200 ng/kg bw per day. The most recent review reported a mean dietary exposure for breastfed infants of 1600 ng/kg bw per day, with a wide range of means from around 200 to 7000 ng/kg bw per day (IARC, 2015). Estimated dietary exposures of breastfed infants to NDL-PCBs are up to 2 orders of magnitude higher than those for the rest of the population. Biomonitoring data indicate that breastfed infants have higher body burdens of NDL-PCBs compared with formula-fed infants.

11.9.4 Contribution of individual congeners to total exposures from all sources

For the sum of the six indicator PCBs, the contribution of each of the individual congeners differs between countries and population subgroups. However, for both dietary exposure and body burden estimates (which also take into consideration kinetics and half-lives), the main contributor is PCB 153 (41%), followed by PCB 138 (28%), PCB 180 (14%), PCB 101 (8%) and PCB 28 (6%), with the lowest contribution from PCB 52 (3%).

With the exception of those individuals with high occupational exposure, total exposures from all sources are likely to be only slightly higher than those predicted from the diet alone. Dietary exposures to NDL-PCBs have been decreasing over time, as indicated in studies from a number of countries, owing primarily to the phasing out of the manufacture and use of PCBs.

11.10 Estimation of margins of exposure

For non-genotoxic substances, the Committee would normally develop health-based guidance values using the most sensitive adverse effect in the most sensitive species as a point of departure. The Committee therefore considered whether the toxicological information available for the six indicator PCBs (PCB 28, PCB 52, PCB 101, PCB 138, PCB 153, PCB 180) and PCB 128 was sufficient and appropriate for such an approach. It was noted that there are a large number of in vivo and in vitro studies available with respect to possible hepatotoxicity, thyroid toxicity, and neurodevelopmental or neurotoxic effects, but that there is a general lack of in vivo toxicity data for two of the indicator PCBs (PCB 101 and PCB 138). In addition, there is not enough information on relative potencies for each congener with respect to receptor interactions and the downstream consequences.

The Committee considered whether it would be possible to undertake a group evaluation for NDL-PCBs using the available information for the indicator congeners. Such an approach should be based on internal rather than external dose because of the species differences in half-lives for these congeners. Owing to the lack of relevant toxicological data for two congeners (PCB 101 and PCB 138), the Committee decided not to undertake such a group evaluation.

The Committee further concluded that none of the available short-term toxicity studies on four of the six indicator PCBs and PCB 128 were suitable for the derivation of health-based guidance values (e.g. provisional tolerable monthly intakes) or assessment of their relative potency compared with a reference compound, such as PCB 153. This conclusion was based on the lack of clear dose–response relationships, doubts about the toxicological relevance of the observed minimal effects on the liver and thyroid and the limited experimental time periods of most of the studies (28 or 90 days). The Committee considered whether the 2-year NTP study on PCB 153 might form a basis for deriving a BMDL that could be used as a point of departure for a health-based guidance value for that congener. From a human exposure and risk assessment point of view, PCB 153 is highly relevant, as it represents up to 40% of the six indicator PCBs that are present in the diet or in human milk. The most sensitive end-point in the 2-year study was hepatocyte hypertrophy, observed at and above 7 µg/kg bw per day. After critical evaluation of these results, the Committee concluded that the hepatocyte hypertrophy should not be modelled to derive a BMDL, as the end-point may not be toxicologically relevant. Hence, data from the long-term NTP study with PCB 153 were not considered suitable to derive a health-based guidance value. Therefore, a comparative approach using the minimal effect doses from the available studies was developed in order to estimate MOEs to provide guidance on human health risk.

The available rat toxicological data on individual congeners showed that minimal changes in liver and thyroid histopathology were evident from the lowest doses tested of 2.8–7 μg/kg bw per day in the 90-day studies (PCB 28, PCB 128, PCB 153) and 3 mg/kg bw total dose in the 28-day studies (PCB 52, PCB 180) and were similar across the short-term and long-term toxicity studies. Bearing in mind that, with the exception of PCB 153, the available studies on individual NDL-PCB congeners were of relatively short duration (28 or 90 days), the Committee decided to take the lower end of the range of test doses used for each congener at which these minimal changes occurred as a conservative point of departure for estimating MOEs. Given the major difference in dosing regimens between the 28-day and 90-day studies and the bioaccumulative nature of PCBs, MOEs have been estimated on the basis of both external dose and internal dose. The internal dose MOEs based on amounts present in fat are considered the most appropriate comparison, particularly because they also eliminate interspecies differences in toxicokinetics.

The MOEs obtained for adults are shown in Table 41. The MOE comparisons for internal dose are based on the range of reported mean values for human milk expressed on a fat basis, which should reflect both fetal and adult (maternal) body burdens. The biomonitoring data on concentrations in human adipose tissue were not used because they represent far fewer, non-random samples derived from postmortem tissues from non-homogenous populations.

Table 41
Estimated MOEs for adults from repeated-dose studies on individual NDL-PCB congeners in rats

NDL-PCB congener Study duration Reference Mode of administration	Minimal effect dose expressed as external dose (µg/kg bw per day)	Minimal effect dose expressed as body burden[a] (mg/kg bw)	External dose MOE[b]	Body burden MOE (based on human milk)[c]	Body burden MOE (modelled from external dose)[c]
28 90 days Chu et al. (1996a) Diet	2.8	0.07	2 500–5 600	44–580	41–1 400
52 28 days Unpublished data provided to WHO by ATHON project study authors Gavage	3.0[d]	NA	97 000–210 000	NA	NA
101	NA	NA	NA	NA	NA
128 90 days Lecavalier et al. (1997) Diet	4.2	0.07	11 000–21 000	88–1 700	NA
138	NA	NA	NA	NA	NA
153 90 days Chu et al. (1996b) Diet	7[e]	2.0	1 600–3 100	75–2 900	130–3 000
180 28 days Viluksela et al. (2014) Gavage	3.0[d]	1.6	71 000–150 000	81–5 000	380–6 400

MOE: margin of exposure; NA: not available; UB: upper bound
[a] Body burden based on reported concentration of NDL-PCB congener in adipose tissue; 350 g rat with 10% lipid.
[b] For MOEs expressed as a range, the lower end of the range relates to UB adult high-percentile exposure, and the higher end of the range relates to UB adult mean exposure (see Table 40). The dietary exposure estimate for PCB 128 is based on it making, on average, a contribution equal to 16% of the total exposure to the six indicator PCBs.
[c] See Table 37.
[d] Total dose (mg/kg bw) administered over the whole study.
[e] Dose adjusted to 7 µg/kg bw per day from 10 µg/kg bw per day to take account of 5 days/week dosing.

12. Evaluation

The body burden MOEs for adults derived from the range of reported mean human milk concentrations range from 4.5 to 5000. The Committee noted that for some of the NDL-PCBs, these body burden estimates were developed from experimental studies with a less than chronic duration of exposure. For PCB 153, the lower end of the body burden MOE range based on human milk was 4.5 when derived from the short-term study, whereas in the long-term study it was 75, which is a 16-fold difference. The lower end of the range of body burden MOEs modelled from external dose also gave a 16-fold difference between long- and short-term studies on PCB 153. Thus, in the long-term study, similar hepatic effects to those seen in the short-term study were observed only at an internal dose that was substantially higher. Use of the MOE value from the long-term study on PCB 153 would give lower-end MOEs for all congeners in the range 44–88 for adults. MOEs for breastfed infants, which may have a body burden up to 2-fold higher than that for adults, would be approximately half of the adult values. The MOEs for children would be expected to be intermediate between those for adults and those for breastfed infants, owing to the initial contribution from breastfeeding and the subsequent lower dietary contribution compared with human milk.

As the MOEs are based on minimal effect doses, they were considered to be adequate and to give some assurance that dietary exposures to NDL-PCBs are unlikely to be of health concern for adults and children, based on the available data. For breastfed infants, the MOEs would be expected to be lower. However, based on present knowledge, the benefits of breastfeeding (WHO, 2015) are considered to outweigh the possible disadvantages that may be associated with the presence of NDL-PCBs in breast milk.

The Committee recognized that there are similarities in some of the reported effects for NDL-PCBs and that, ideally, risk estimates for combined exposure are desirable. The Committee concluded that this cannot be done on the basis of currently available data, but noted that the points of departure selected for derivation of the MOEs were particularly conservative, as they were based on effects on liver and thyroid that were not of clear toxicological significance, the changes were minimal and the lowest doses at which they were seen were used for the points of departure, combined with UB estimates of body burden.

12.1 Recommendations

A more complete toxicological database, including mechanistic studies on both parent congeners and hydroxy metabolites, would have allowed a more definitive assessment. The Committee recommended that further toxicological studies

should be done, particularly in vivo studies for those congeners, such as PCB 101 and PCB 138, that contribute significantly to dietary exposure and human body burden.

There were some limitations with the exposure assessment where there was a limited range of countries and/or foods for which concentration data were provided. This meant that some assumptions needed to be made for estimating dietary exposures for national and international assessments. To ensure better estimates of dietary exposure with a lower degree of uncertainty, the Committee recommends the following:

- As the risk characterization is driven mainly by dietary exposure estimates from European countries, information from a broader range of countries would be desirable to provide a more globally representative conclusion.
- More countries should submit concentration data to the GEMS/Food contaminants database (with as specific details as possible, including unique sample identifiers, specific food details, lower LODs, form of the food, etc.).
- National food consumption data should also be submitted by more countries to CIFOCOss to allow a broader range of country-specific exposure assessments to be undertaken in the future.
- For analytical surveys on NDL-PCBs, it is important to ensure the generation of occurrence data for congeners beyond the six indicator PCBs for a broad range of foods and to include all key congeners and sources of dietary exposure to NDL-PCBs.
- More concentration data in infant formula as well as data from a broader range of countries would assist in determining more reliable estimates of dietary exposure for formula-fed infants.

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Appendix 1. Indicator PCB concentrations for each food category tested by country

Note: In some cases, items have been moved to a different category to more accurately reflect food type (e.g. olive oil moved from fruit and fruit products to fats and oils).

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Australia												
Fish and products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Austria												
Cereals and products	0.009	0.032	0.007	0.020	0.007	0.066	0.008	0.541	0.007	0.976	0.003	190
Eggs and egg products	0.010	730	0.003	190	0.009	530	0.022	960	0.045	1 300	0.014	760
Fish and products	0.023	3.20	0.012	57.0	0.009	200	0.012	370	0.020	550	0.009	220
Food for the very young	0.006	0.320	0.006	0.160	0.009	0.110	0.010	0.092	0.019	0.170	0.008	0.051
Herbs, spices, etc.	65.0	80.0	47.0	60.0	41.0	100	30.0	330	36.0	490	8.90	190
Meat and meat products	0.006	3 000	0.005	670	0.005	890	0.004	4 000	0.008	6 600	0.002	2 000
Milk and dairy products	0.003	280	0.002	180	0.003	680	0.006	2 400	0.010	400	0.004	1 500
Special nutritional use	0.052	0.170	0.027	0.29	0.080	1.00	0.140	2.10	0.370	4.40	0.210	1.70
Belgium												
Eggs and egg products	ND	3 400	ND	3 450	ND	5 590	ND	34 820	ND	31 000	ND	34 680
Fats and oils	ND	3 000	ND	12 000	ND	5 000	ND	25 000	ND	32 000	ND	21 000
Fish and products	ND	5 440	ND	10 600	ND	23 500	ND	72 800	ND	126 000	ND	25 700
Food for the very young	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Legumes and pulses	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Meat and meat products	ND	300	ND	300	ND	477	ND	300	ND	1 050	ND	600
Milk and dairy products	ND	300	ND	4 600	ND	1 850	ND	3 310	ND	4 800	ND	1 900
Other foods	ND	ND	ND	310	ND	ND	ND	ND	ND	ND	ND	ND
Special nutritional use	ND	686	ND	4 500	ND	16 100	ND	4 110	ND	5 060	ND	3 820

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Canada												
Composite food	0.220	9.10	0.142	7.51	NR	NR	0.142	44.2	0.140	48.8	0.056	32.2
Eggs and egg products	14.6	45.9	2.09	2.68	NR	NR	14.5	34.2	15.4	33.0	8.09	16.8
Fats and oils	1.91	15.1	2.21	7.45	NR	NR	2.36	7.78	2.21	5.99	0.779	4.34
Fish and products	2.65	126	1.75	344	NR	NR	20.0	1 240	21.4	1 180	9.06	478
Food for the very young	0.466	8.76	0.485	14.7	NR	NR	0.415	12.0	0.414	14.3	0.236	4.87
Herbs, spices, etc.	2.90	3.77	1.74	3.24	NR	NR	0.142	42.9	4.68	8.18	1.53	4.55
Meat and meat products	1.88	21.0	1.53	51.8	NR	NR	5.16	72.6	5.25	69.7	2.87	30.9
Milk and dairy products	0.103	11.1	0.115	12.3	NR	NR	0.126	181	0.122	205	0.041	58.4
Nuts and oilseeds	6.44	14.9	4.92	8.41	NR	NR	4.30	7.66	2.10	8.63	1.10	6.14
Snacks and desserts	28.8	32.0	17.7	84.8	NR	NR	2.20	8.49	4.74	8.16	2.16	4.17
Starchy roots and tubers	4.31	8.86	9.19	16.1	NR	NR	0.793	11.5	0.693	13.3	0.325	7.70
Sugar and confectionary	8.19	11.3	6.54	10.2	NR	NR	41.1	44.2	45.6	51.8	17.3	18.6
China, mainland												
Cereals and products	ND	33.9	ND	14.7	ND	55.5	ND	39.5	ND	99.7	ND	39.6
Eggs and egg products	ND	498	ND	22.2	ND	66.7	ND	1 250	ND	84.4	ND	43.8
Fish and products	ND	5 420	ND	2 960	ND	2 850	ND	3 850	ND	4 750	ND	4 250
Food for the very young	ND	74.3	ND	43.2	ND	16.6	ND	153	ND	67.1	ND	24.3
Legumes and pulses	ND	74.6	ND	24.9	ND	101	ND	39.5	ND	168	ND	49.6
Meat and meat products	ND	191	ND	83.8	ND	45.2	ND	410	ND	305	ND	116
Milk and dairy products	ND	67.2	ND	61.9	ND	70.0	ND	223	ND	102	ND	89.8
Starchy roots and tubers	ND	70.5	ND	30.5	ND	39.8	ND	12.2	ND	14.1	ND	5.59
Vegetables and products	ND	73.6	ND	13.1	ND	12.7	ND	11.4	ND	16.2	ND	11.8
China, Hong Kong SAR												
Cereals and products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Composite food	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Eggs and egg products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Fats and oils	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Fish and products	ND	870	ND	850	ND	1 500	ND	1 500	ND	2 400	ND	840
Herbs, spices, etc.	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Meat and meat products	ND	ND	ND	ND	ND	ND	ND	60.0	ND	130	ND	ND
Milk and dairy products	ND	ND	ND	ND	ND	ND	ND	200	ND	280	ND	ND
Non-alcoholic beverages	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Snacks and desserts	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Starchy roots and tubers	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Stimulant beverages	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	ND	ND	ND	ND	ND	ND	40.0	ND	60.0	ND	ND
Cyprus												
Eggs and egg products	ND	377	ND	82.1	ND	94.1	ND	249	ND	406	ND	1 000
Fish and products	ND	19 900	ND	4 650	ND	5 220	ND	15 010	ND	34 900	ND	7 910
Food for the very young	0.013	0.026	0.006	0.012	0.004	0.010	0.008	0.015	0.008	0.016	0.003	0.006
Meat and meat products	ND	609	ND	725	ND	675	ND	1 050	ND	2 290	ND	928
Milk and dairy products	ND	252	ND	104	ND	120	ND	567	ND	702	ND	165
Other foods	0.050	0.084	0.011	0.020	0.007	0.015	0.009	0.021	0.016	0.025	0.006	0.011
Czech Republic												
Alcoholic beverages	ND	ND	ND	ND	ND	0.005	ND	0.007	ND	0.010	ND	ND
Cereals and products	ND	85.1	ND	12.8	ND	38.8	ND	14.7	ND	44.8	ND	183
Composite food	ND	0.043	ND	0.595	ND	1.78	ND	2.92	ND	3.99	ND	1.35
Drinking-water	ND	ND	ND	ND	0.005	0.009	ND	0.016	ND	ND	ND	0.004
Eggs and egg products	ND	96.1	ND	10.0	ND	10.0	0.040	0.136	ND	258	ND	74.8

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Fats and oils	ND	214	ND	20.0	ND	20.0	ND	29.2	ND	184	ND	27.3
Fish and products	ND	20.0	ND	20.0	ND	101	ND	147	ND	531	ND	201
Food for the very young	ND	0.101	ND	ND	ND	ND	ND	0.139	ND	0.139	ND	0.102
Fruit and fruit products	ND	0.045	ND	ND	ND	0.050	ND	0.081	ND	0.086	ND	ND
Fruit and vegetable juices	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Herbs, spices, etc.	ND	0.178	ND	0.053	ND	0.131	ND	ND	ND	ND	ND	0.010
Legumes and pulses	ND	0.062	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Meat and meat products	ND	1 370	ND	2 830	ND	1 960	ND	449	ND	815	ND	206
Milk and dairy products	ND	180	ND	15.0	ND	128	ND	282	ND	529	ND	247
Non-alcoholic beverages	ND	0.004	ND	0.011	ND	ND	ND	0.007	ND	0.004	ND	ND
Nuts and oilseeds	0.236	0.763	ND	ND	ND	0.092	ND	0.184	ND	0.188	ND	0.178
Snacks and desserts	ND	0.072	ND	0.344	ND	0.056	ND	0.061	ND	0.128	ND	0.059
Starchy roots and tubers	ND	0.079	ND	ND	ND	0.027	ND	0.056	ND	0.064	ND	0.007
Stimulant beverages	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	0.192	ND	0.290	ND	0.492	ND	0.486	ND	0.407	ND	0.404
Vegetables and products	ND	111	ND	20	ND	20.0	ND	20.0	ND	20.0	ND	20.0
Estonia												
Eggs and egg products	ND	1 630	ND	1 260	ND	860	ND	2 640	ND	3 130	ND	1 310
Fats and oils	ND	1.60	ND	3.13	ND	5.55	0.006	9.04	ND	10.6	ND	2.61
Fish and products	ND	1 010	ND	2 320	ND	1 250	ND	2 810	ND	2 300	ND	549
Meat and meat products	ND	0.024	ND	0.023	ND	0.002	ND	0.156	ND	0.231	ND	0.072
Milk and dairy products	ND	0.003	ND	0.038	ND	0.120	ND	0.565	ND	0.465	ND	0.074
Sugar and confectionary	ND	1 000	ND	1 100	ND	1 400	ND	1 000	ND	1 000	ND	1 000
Finland												
Composite food	825	825	974	974	3 630	3 630	6 740	6 740	10 300	10 300	3 850	3 850

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Eggs and egg products	19.3	121	3.68	6.82	4.90	15.0	30.8	209	42.7	261	15.5	82.9
Fish and products	ND	3 050	ND	5 790	ND	25 500	ND	223 000	ND	359 000	ND	130 000
Food for the very young	346	1 110	308	1 510	423	3 140	385	4 143	577	5 920	115	1 740
Meat and meat products	3.85	563	1.28	71.6	0.836	8.44	2.31	287	3.74	796	0.900	840
Milk and dairy products	ND	1 020	ND	77.5	ND	13.8	ND	442	ND	529	ND	190
France												
Eggs and egg products	ND	52.0	ND	81.9	ND	66.0	ND	1 000	ND	1 120	ND	1 170
Fats and oils	0.006	0.17	0.005	0.269	0.008	0.291	0.006	0.141	0.010	0.275	0.004	0.068
Fish and products	ND	9 700	ND	25 870	ND	31 100	ND	70 400	ND	134 000	ND	29 300
Food for the very young	<0.001	0.016	0.001	0.028	0.001	0.061	0.002	0.088	0.008	0.216	0.002	0.028
Meat and meat products	ND	400	ND	14.2	ND	14.6	ND	3 150	ND	3 270	ND	90.9
Milk and dairy products	ND	0.785	ND	0.720	ND	1.54	ND	64.2	ND	68.7	ND	34.2
Germany												
Alcoholic beverages	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Cereals and products	ND	12.3	ND	8.43	ND	13	ND	18.8	ND	18.6	ND	9.93
Composite food	ND	400	ND	600	ND	150	ND	1 300	ND	1 800	ND	900
Eggs and egg products	ND	4 070	ND	912	ND	287	ND	5 000	ND	4 000	ND	5 990
Fats and oils	ND	15 300	ND	10 800	ND	22 600	ND	37 800	ND	44 800	ND	21 800
Fish and products	ND	59 100	ND	189 000	ND	243 000	ND	255 000	ND	411 000	ND	165 000
Food for the very young	ND	70	ND	150	ND	90.0	20.0	50.0	20.0	70.0	10.0	40.0
Fruit and fruit products	1.16	175	ND	33.1	ND	31.0	ND	30.8	ND	31.0	ND	10.4
Fruit and vegetable juices	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Legumes and pulses	2.83	15.2	2.24	9.40	5.82	19.9	7.24	40.4	6.15	32.9	1.78	14.7
Meat and meat products	ND	16 100	ND	2 710	ND	240 000	ND	12 900	ND	17 300	ND	198 000
Milk and dairy products	ND	822	ND	308	ND	855	ND	5 740	ND	16 900	ND	4 210

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Special nutritional use	ND	300	ND	1 400	ND	4 800	330	7 900	300	10 900	450	4 000
Starchy roots and tubers	1.37	62.9	0.750	14.1	1.65	20.0	1.84	34.6	1.74	30.4	0.530	10.2
Stimulant beverages	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Vegetables and products	ND	85.5	ND	81.8	ND	246	ND	494	ND	323	ND	79.3
Greece												
Eggs and egg products	ND	6 800	ND	6 710	ND	8 410	ND	3 480	ND	1 700	ND	7 490
Fats and oils	ND	18 900	ND	62 300	ND	20 600	ND	58 400	ND	36 900	ND	16 500
Fish and products	ND	444	ND	9 060	ND	3 110	ND	3 730	ND	4160	ND	1 300
Food for the very young	0.006	0.053	0.010	0.111	0.009	0.109	0.007	0.126	0.009	0.155	0.004	0.052
Meat and meat products	ND	2 700	ND	2 710	ND	10 400	ND	10 730	ND	14 400	ND	9 110
Milk and dairy products	ND	5 250	ND	1 250	ND	1 820	ND	2 240	ND	797	ND	456
Iceland												
Cereals and products	353	353	75.1	75.1	ND	ND	ND	ND	ND	ND	ND	ND
Eggs and egg products	ND	37.0	ND	6.88	ND	13.5	243	987	251	1 020	85.9	634
Fats and oils	100	4 530	520	19 700	1 660	35 400	2 720	77 200	3 550	66 100	1 190	25 100
Fish and products	ND	1 600	ND	6 230	ND	9 130	ND	14 700	ND	17 000	ND	5 650
Meat and meat products	ND	96.3	ND	28	ND	73.5	ND	222	19.7	232	5.23	114
Milk and dairy products	ND	ND	ND	52.8	ND	52.8	33.2	1 670	38.0	2 110	12.2	807
Special nutritional use	ND	500	417	6 580	15 700	57 100	33 200	373 500	129 000	499 000	115 000	365 000
Starchy roots and tubers	8.00	8.00	4.00	4.00	4.00	4.00	4.00	4.00	ND	ND	ND	ND
Ireland												
Cereals and products	10.0	10.0	10.0	10.0	50.0	60.0	10.0	10.0	10.0	10.0	10.0	10.0
Composite food	10.0	10.0	10.0	10.0	20.0	20.0	10.0	10.0	10.0	10.0	10.0	10.0
Eggs and egg products	ND	3 230	ND	53.0	ND	88.7	8.78	5 490	8.78	10 100	3.25	15 800

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Fats and oils	ND	396	ND	145	ND	307	ND	1 410	ND	1 480	ND	355
Fish and products	ND	742	ND	1 840	ND	3 730	ND	5 700	ND	9 460	ND	2 360
Fruit and fruit products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Herbs, spices, etc.	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Meat and meat products	0.955	39.0	0.477	21.9	0.477	9.50	4.56	119	3.05	188	2.03	73.6
Milk and dairy products	0.525	47.5	0.316	112	0.316	183	1.88	199	2.45	239	0.840	87.7
Special nutritional use	ND	2 330	ND	8 260	ND	22 700	ND	33 800	ND	51 100	ND	14 900
Starchy roots and tubers	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Vegetables and products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Italy												
Eggs and egg products	ND	490	ND	490	ND	490	ND	490	ND	490	ND	1 270
Fats and oils	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Fish and products	ND	2 500	ND	5 700	ND	15 200	ND	31 000	ND	51 000	ND	6 500
Meat and meat products	ND	5.63	ND	20.2	ND	75.0	ND	28.2	ND	45.5	ND	41.4
Milk and dairy products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Japan												
Fish and products	4.7	1 000	NR	NR	ND	5 700	ND	5 800	57	10 000	16	2 400
Luxembourg												
Fish and products	262	3 630	ND	5 700	1 230	11 700	3 700	21 500	2 780	17 200	1 500	14 300
Netherlands												
Eggs and egg products	66.1	100	21.2	47.5	21.2	95.0	208	745	267	985	160	768
Fats and oils	111	991	ND	314	ND	140	ND	148	51.0	357	ND	123
Fish and products	<0.001	19 400	0.001	120 000	0.001	230 000	0.003	482 000	0.005	650 000	0.002	280 000
Meat and meat products	30.8	158	16.0	96.4	9.12	110	286	656	378	718	170	392

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Milk and dairy products	ND	431	ND	281	ND	319	32.9	1 370	40.3	1 800	13.7	732
Snacks and desserts	200	220	80	100	100	160	680	860	1 000	1 200	400	520
New Zealand												
Milk and dairy products	ND	ND	NR	NR	ND	ND	NR	NR	NR	NR	NR	NR
Norway												
Cereals and products	11.1	45.4	12.8	228	9.98	384	8.66	252	12.8	390	8.45	73.7
Eggs and egg products	ND	89.9	ND	63.3	ND	67.4	9.20	645	18.7	514	ND	249
Fats and oils	ND	524	ND	1 770	ND	2 910	ND	7 060	ND	7 950	ND	2 100
Fish and products	ND	15 000	ND	48 000	ND	125 000	ND	237 000	ND	300 000	ND	65 000
Fruit and fruit products	3.80	3.80	5.34	5.34	3.32	3.32	2.54	2.54	3.62	3.62	1.23	1.23
Legumes and pulses	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Meat and meat products	ND	273	ND	378	ND	681	ND	4 190	ND	4 750	ND	1 750
Milk and dairy products	ND	251	ND	44.0	ND	157	ND	1 090	ND	944	ND	566
Other foods	13.4	13.4	26.1	26.1	34.8	34.8	167	167	221	221	104	104
Snacks and desserts	56.6	56.6	61.2	61.2	48.1	48.1	229	229	321	321	141	141
Vegetables and products	41.6	41.6	186	186	301	301	210	210	331	331	60.8	60.8
Poland												
Composite food	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Eggs and egg products	ND	150	ND	19.2	ND	11.1	ND	68.6	ND	103	ND	58.6
Fish and products	ND	2 230	0.009	2 700	ND	9 570	ND	19 200	ND	22 500	ND	6 230
Meat and meat products	0.002	296	<0.001	106	ND	87.9	ND	312	0.005	766	ND	502
Milk and dairy products	0.003	55.8	ND	9.28	ND	4.88	ND	45.0	0.009	46.4	0.002	32.5
Sugar and confectionary	ND	ND	ND	ND	ND	0.009	ND	ND	ND	0.015	ND	ND
Republic of Korea												
Fish and products	ND	15 300	ND	1 280	ND	3 230	ND	4 540	ND	6 480	ND	2 770

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Romania												
Cereals and products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Composite food	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Fats and oils	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Fish and products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Meat and meat products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Milk and dairy products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Other foods	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Stimulant beverages	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Singapore												
Food for the very young	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Slovakia												
Eggs and egg products	ND	0.288	ND	0.042	ND	0.044	ND	0.657	ND	1.01	ND	0.587
Fats and oils	ND	0.081	ND	0.017	ND	0.016	ND	0.063	ND	0.092	ND	0.036
Fish and products	ND	7.70	ND	6.36	ND	7.03	ND	16.2	ND	40.8	ND	12.6
Meat and meat products	ND	0.150	ND	0.056	ND	0.046	ND	0.299	ND	0.571	ND	0.195
Milk and dairy products	ND	0.064	ND	0.004	ND	0.006	ND	0.626	ND	0.908	ND	0.312
Slovenia												
Eggs and egg products	35	679	ND	2 540	ND	2 500	ND	1 580	ND	1 370	ND	244
Fats and oils	ND	272	ND	0.017	ND	60.0	ND	1 800	ND	2 000	ND	562
Fish and products	ND	103 000	ND	610 000	ND	1 200 000	ND	250 000	ND	812 000	ND	68 000
Food for the very young	ND	0.001	ND	0.001	ND	0.001	ND	50.0	ND	70.0	ND	0.001
Meat and meat products	ND	70	ND	70	ND	1 020	60.0	980	60.0	1 200	ND	500
Milk and dairy products	ND	317	ND	ND	ND	ND	101	358	133	449	45.0	157

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**	**Min**	**Max**
Nuts and oilseeds	ND	37	ND	ND	ND	ND	ND	703	ND	624	ND	464
Special nutritional use	0.004	30	0.014	120	0.143	750	0.728	2 000	0.638	2 300	0.360	1 500
Sugar and confectionary	ND	193	ND	ND	ND	44.0	ND	195	ND	230	ND	147
Vegetables and products	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Spain												
Eggs and egg products	ND	ND	NR	NR	ND	ND	ND	ND	ND	ND	ND	ND
Fats and oils	ND	ND	NR	NR	ND	ND	ND	ND	ND	ND	ND	ND
Fish and products	<0.001	<0.001	<0.001	<0.001	0.001	0.001	0.003	0.003	0.001	0.001	0.001	0.001
Milk and dairy products	ND	ND	N R	N R	ND	ND	ND	ND	ND	ND	ND	ND
Sweden												
Cereals and products	ND	11	ND	13.0	ND	24.0	ND	22	ND	36.0	ND	14.0
Composite food	510	730	1 500	2 100	6 200	8 800	15 000	22 000	16 000	23 000	5 400	8 500
Eggs and egg products	ND	220	ND	20.3	ND	210	ND	4 200	ND	4 900	ND	2 400
Fats and oils	ND	174	ND	109	ND	1 430	ND	5 630	ND	7 900	ND	4 790
Fish and products	ND	1 500	ND	4 610	ND	18 200	ND	36 000	ND	56 000	ND	21 400
Food for the very young	ND	33	ND	69.0	ND	160	ND	200	ND	290	ND	75.0
Fruit and fruit products	<0.001	5.6	0.002	3.00	0.003	3.60	0.002	5.60	0.002	6.50	0.001	2.80
Meat and meat products	ND	297	ND	99.6	ND	99.6	ND	1 200	ND	2 760	ND	1 210
Milk and dairy products	ND	97.8	ND	97.8	ND	97.8	ND	364	ND	485	ND	240
Special nutritional use	ND	190	ND	630	ND	3 100	ND	7 900	ND	10 400	ND	7 850
Starchy roots and tubers	<0.001	6.1	0.001	2.60	0.002	2.10	0.001	1.20	0.002	2.00	<0.001	0.680
Vegetables and products	<0.001	2.3	0.001	1.5	0.005	2.20	0.002	0.880	0.003	1.60	0.001	0.650
United Kingdom												
Cereals and products	0.367	33.1	ND	22.5	ND	21.3	ND	18.6	ND	25.6	ND	0.370
Composite food	ND	439	ND	1 100	ND	2 040	ND	5 360	ND	6 730	ND	2 730

	Concentration (ng/kg ww)											
	PCB 28		PCB 52		PCB 101		PCB 138		PCB 153		PCB 180	
Country / food category	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Eggs and egg products	2.72	374	ND	29.4	ND	233	3.88	15 800	3.88	16 200	ND	8 790
Fats and oils	ND	1 150	ND	1 740	ND	4 980	ND	13 690	ND	12 100	ND	4 360
Fish and products	ND	1 110	ND	1 630	ND	3 540	ND	7 050	ND	8 310	ND	8 150
Fruit and fruit products	ND	12	ND	8.5	ND	11.9	ND	8.70	ND	11.8	ND	0.093
Meat and meat products	ND	664	ND	18.7	ND	39.3	ND	1 320	ND	1 720	ND	403
Milk and dairy products	ND	60.3	ND	92.7	ND	218	0.960	543	ND	821	ND	190
Nuts and oilseeds	26.6	26.6	11.6	11.6	ND	ND	ND	ND	9.97	9.97	8.31	8.31
Special nutritional use	ND	1 280	ND	14 510	ND	15 100	ND	57 000	ND	71 000	ND	15 100
Starchy roots and tubers	0.423	0.423	0.264	0.264	0.116	0.116	0.095	0.095	0.106	0.106	ND	ND
Sugar and confectionary	160	160	110	110	80	80	220	220	240	240	140	140
Vegetables and products	ND	27.7	ND	21.1	ND	32.1	ND	27.9	ND	32.5	ND	10.3

Max: maximum; Min: minimum; ND: not detected; NR: not reported; SAR: Special Administrative Region; ww: wet weight

Appendix 2. Mean indicator PCB concentrations in foods reported by countries responding to JECFA call for data

Note: In some cases, items have been moved to a different category to more accurately reflect food type (e.g. olive oil moved from fruit and fruit products to fats and oils).

	Mean concentration (ng/kg ww)					
Country / food category	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**
Australia						
Fish and products	ND	ND	ND	ND	ND	ND
Austria						
Cereals and products	0.020	0.014	0.036	0.274	0.491	0.192
Eggs and egg products	95.0	28.6	81.4	224	294	149
Fish and products	0.278	ND	9.55	17.6	26.4	10.4
Food for the very young	0.058	0.029	0.034	0.040	0.069	0.028
Herbs, spices, etc.	72.5	53.5	70.5	180	263	99.5
Meat and products	113	47.7	67.0	278	445	166
Milk and dairy products	19.7	13.2	40.6	160	250	99.4
Specialty products	0.093	0.12	0.504	0.820	1.65	0.792
Belgium						
Eggs and egg products	287	328	396	1 660	2 320	1 420
Fats and oils	430	588	467	936	1 530	793
Fish and products	158	2.81	1 740	960	1 940	427
Food for the very young	ND	ND	ND	ND	ND	ND
Legumes and pulses	ND	ND	ND	ND	ND	ND
Meat and products	14.5	19.8	39.9	14.5	54.8	25.6
Milk and dairy products	19.0	281	107	305	547	131
Other foods	ND	62.0	ND	ND	ND	ND
Specialty products	97.9	321	1 290	349	718	469
Canada						
Composite food	3.70	3.19	NR	9.72	10.9	6.02
Eggs and egg products	30.3	2.38	NR	24.4	24.2	12.4
Fats and oils	6.03	4.12	NR	5.28	4.39	3.05
Fish and products	32.3	75.6	NR	266	283	93.4
Food for the very young	2.36	3.36	NR	2.97	3.49	1.46
Herbs, spices, etc.	3.33	2.49	NR	5.98	6.43	3.04
Meat and products	6.07	6.89	NR	23.3	26.1	12.8
Milk and dairy products	1.97	2.52	NR	26.1	29.8	9.57
Nuts and oilseeds	10.7	6.66	NR	5.35	5.37	3.62
Snacks and desserts	30.4	51.3	NR	6.34	6.45	3.17
Starchy roots, tubers	6.58	12.6	NR	6.16	6.98	4.01
Sugar and confectionary	9.74	8.37	NR	42.7	48.7	18.0
China, mainland						
Cereals and products	4.43	1.50	5.25	2.40	5.82	1.87
Eggs and egg products	53.1	2.70	5.30	37.4	16.1	6.11

	Mean concentration (ng/kg ww)					
Country / food category	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**
Fish and products	97.8	75.9	76.5	131	129	52.3
Food for the very young	9.86	7.47	2.28	11.4	8.67	2.99
Legumes and pulses	13.6	3.77	5.98	2.90	7.25	2.03
Meat and products	11.3	5.38	2.32	12.2	9.82	3.51
Milk and dairy products	6.55	3.83	2.08	7.35	6.67	2.90
Starchy roots, tubers	7.54	2.57	3.14	1.62	1.86	0.768
Vegetables and products	9.82	2.51	2.08	1.27	1.69	0.670
China, Hong Kong SAR						
Cereals and products	ND	ND	ND	ND	ND	ND
Composite food	ND	ND	ND	ND	ND	ND
Eggs and egg products	ND	ND	ND	ND	ND	ND
Fats and oils	ND	ND	ND	ND	ND	ND
Fish and products	36.3	71.2	172	170	359	86.6
Herbs, spices, etc.	ND	ND	ND	ND	ND	ND
Meat and products	ND	ND	ND	2.92	6.88	ND
Milk and dairy products	ND	ND	ND	26.3	35.4	ND
Non-alcoholic beverages	ND	ND	ND	ND	ND	ND
Snacks and desserts	ND	ND	ND	ND	ND	ND
Starchy roots, tubers	ND	ND	ND	ND	ND	ND
Stimulant beverages	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	ND	ND	10	15	ND
Cyprus						
Eggs and egg products	21.1	6.06	7.23	15.3	24.2	47.0
Fish and products	1 550	376	484	1 350	3 170	629
Food for the very young	0.018	0.008	0.007	0.012	0.013	0.005
Meat and products	77.5	80.8	69.3	97.2	218	71.0
Milk and dairy products	17.9	6.57	7.41	23.7	40.5	11.2
Other foods	0.067	0.016	0.011	0.015	0.021	0.008
Czech Republic						
Alcoholic beverages	ND	ND	0.001	0.002	0.002	ND
Cereals and products	2.72	0.853	3.28	1.25	3.28	5.22
Composite food	0.145	0.122	0.305	0.406	0.546	0.183
Drinking-water	ND	ND	0.007	0.008	ND	0.002
Eggs and egg products	16.1	1.67	1.68	0.087	43.1	12.5
Fats and oils	17.8	1.45	1.47	3.83	16.5	3.72
Fish and products	0.498	0.503	2.49	4.32	13.0	5.12
Food for the very young	0.011	ND	ND	0.027	0.036	0.011
Fruit and fruit products	0.002	ND	0.002	0.007	0.013	ND
Herbs, spices, etc.	0.059	0.018	0.044	ND	ND	0.003
Legumes and pulses	0.010	ND	ND	ND	ND	ND
Meat and products	31.6	62.7	41.6	10.1	18.6	5.67
Milk and dairy products	6.24	0.686	3.10	10.8	18.5	8.29
Non-alcoholic drinks	0.001	0.003	ND	0.003	0.002	ND
Nuts and oilseeds	0.500	ND	0.046	0.092	0.094	0.089

	Mean concentration (ng/kg ww)					
Country / food category	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**
Snacks and desserts	0.012	0.057	0.009	0.020	0.039	0.010
Starchy roots, tubers	0.014	ND	0.002	0.003	0.010	<0.001
Stimulant beverages	ND	ND	ND	ND	ND	ND
Sugar and confectionary	0.009	0.008	0.018	0.017	0.016	0.018
Vegetables and products	4.06	0.874	0.873	0.881	0.889	0.875
Estonia						
Eggs and egg products	452	467	381	444	518	376
Fats and oils	0.738	1.52	2.48	4.07	5.27	1.38
Fish and products	59.3	78.0	90.2	181	207	57.5
Meat and products	0.006	0.004	<0.001	0.028	0.056	0.015
Milk and dairy products	<0.001	0.003	0.011	0.197	0.162	0.029
Sugar and confectionary	83.3	91.7	117	83.3	83.3	83.3
Finland						
Composite food	825	974	3 630	6 740	10 300	3 850
Eggs and egg products	36.6	5.19	8.22	119	152	53.7
Fish and products	350	628	2 700	6 640	8 870	3 350
Food for the very young	797	999	1 840	2 590	3 640	1 070
Meat and products	62.8	10.3	3.88	28.8	74.3	51.6
Milk and dairy products	177	16.6	0.922	46.3	53.0	17.8
France						
Eggs and egg products	8.94	3.85	5.52	42.5	50.3	26.0
Fats and oils	0.045	0.052	0.061	0.042	0.067	0.019
Fish and products	60.4	134	356	817	1540	473
Food for the very young	0.006	0.009	0.016	0.028	0.056	0.011
Meat and products	2.61	0.142	0.147	13.2	13.9	0.382
Milk and dairy products	0.108	0.112	0.146	5.58	6.55	2.88
Germany						
Alcoholic beverages	ND	ND	ND	ND	ND	ND
Cereals and products	6.26	3.98	7.43	9.38	9.68	3.35
Composite food	80.0	120	30.0	260	360	180
Eggs and egg products	60.6	43.2	14.2	339	351	269
Fats and oils	1 100	1 060	3 310	13 600	22 300	7 060
Fish and products	363	2 820	5 190	6 090	6 300	5 390
Food for the very young	37.0	77.0	31.9	28.9	38.9	21.5
Fruit and fruit products	25.7	8.01	9.77	9.51	10.2	2.67
Fruit, vegetable juices	ND	ND	ND	ND	ND	ND
Legumes and pulses	6.42	4.71	10.6	15.5	13.7	4.62
Meat and products	273	127	526	280	358	460
Milk and dairy products	51.7	0.347	30.5	105	136	59.2
Specialty products	64.3	254	936	1 930	2 650	1 280
Starchy roots, tubers	10.7	3.37	6.01	7.52	7.27	2.23
Stimulant beverages	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	ND	ND	ND	ND	ND
Vegetables and products	9.21	6.48	17.9	33.6	25.6	7.48

	Mean concentration (ng/kg ww)					
Country / food category	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**
Greece						
Eggs and egg products	292	787	1 170	387	105	317
Fats and oils	285	1 340	553	602	495	160
Fish and products	38.4	196	179	311	361	105
Food for the very young	0.031	0.068	0.072	0.071	0.100	0.031
Meat and products	24.8	37.1	124	188	161	74.0
Milk and dairy products	113	52.0	83.8	102	24.6	23.6
Iceland						
Cereals and products	210	75.1	ND	ND	ND	ND
Eggs and egg products	13.7	2.53	4.76	448	466	233
Fats and oils	1 100	5 890	10 800	20 300	22 500	8 420
Fish and products	106	287	464	803	872	292
Meat and products	23.7	7.35	14.3	72.7	86.5	34.9
Milk and dairy products	ND	6.21	11.7	403	495	171
Specialty products	225	3 520	35 650	185 000	329 000	265 000
Starchy roots, tubers	8.00	4.00	4.00	4.00	ND	ND
Ireland						
Cereals and products	10.0	10.0	53.3	10.0	10.0	10.0
Composite food	10.0	10.0	20.0	10.0	10.0	10.0
Eggs and egg products	75.2	4.46	7.83	227	380	479
Fats and oils	67.8	22.8	65.1	266	367	131
Fish and products	241	654	1 430	2 080	3 180	863
Fruit and fruit products	ND	ND	ND	ND	ND	ND
Herbs, spices, etc.	ND	ND	ND	ND	ND	ND
Meat and products	8.88	5.16	2.99	29.6	54.0	13.9
Milk and dairy products	5.07	6.90	11.2	13.7	16.3	5.10
Specialty products	360	1 230	2 650	6 790	9 680	3 110
Starchy roots, tubers	ND	ND	ND	ND	ND	ND
Vegetables and products	ND	ND	ND	ND	ND	ND
Italy						
Eggs and egg products	18.1	18.1	18.1	18.1	18.1	47.2
Fats and oils	ND	ND	ND	ND	ND	ND
Fish and products	224	392	740	2 390	2 210	535
Meat and products	0.158	0.453	1.45	0.553	0.901	0.785
Milk and dairy products	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	ND	ND	ND	ND	ND
Japan						
Fish and products	89.4	NR	458	517	878	273
Luxembourg						
Fish and products	740	1 490	5 000	11 400	8 620	6 050
Netherlands						
Eggs and egg products	83.0	34.4	58.1	476	626	464
Fats and oils	362	96.3	75.2	63.8	154	45.4
Fish and products	2 450	12 590	23 500	58 300	77 000	28 800

	Mean concentration (ng/kg ww)					
Country / food category	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**
Meat and products	71.1	40.3	56.1	424	562	279
Milk and dairy products	147	82.4	72.8	562	776	290
Snacks and desserts	210	90.0	130	770	100	ND
New Zealand						
Milk and dairy products	ND	NR	ND	NR	NR	NR
Norway						
Cereals and products	22.7	68.0	107	74.2	111	28.6
Eggs and egg products	39.6	13.6	12.9	337	280	97.7
Fats and oils	54.4	80.1	122	613	412	211
Fish and products	2 420	4 860	14 700	30 200	37 200	7 730
Fruit and fruit products	3.80	5.34	3.32	2.54	3.62	1.23
Legumes and pulses	ND	ND	ND	ND	ND	ND
Meat and products	43.5	37.7	53.9	402	516	196
Milk and dairy products	64.6	11.0	33.4	342	344	178
Other foods	13.4	26.1	34.8	167	221	104
Snacks and desserts	56.6	61.2	48.1	229	321	141
Vegetables and products	41.6	186	301	210	331	60.8
Poland						
Composite food	ND	ND	ND	ND	ND	ND
Eggs and egg products	20.9	2.72	1.49	8.50	18.3	11.6
Fish and products	158	272	1 080	2 050	2 560	571
Meat and products	7.95	3.05	2.86	23.3	51.7	25.5
Milk and dairy products	4.84	1.09	0.590	8.90	12.5	4.75
Sugar and confectionary	ND	ND	0.002	ND	0.009	ND
Republic of Korea						
Fish and products	234	163	170	194	216	136
Romania						
Cereals and products	ND	ND	ND	ND	ND	ND
Composite food	ND	ND	ND	ND	ND	ND
Fats and oils	ND	ND	ND	ND	ND	ND
Fish and products	ND	ND	ND	ND	ND	ND
Meat and products	ND	ND	ND	ND	ND	ND
Milk and dairy products	ND	ND	ND	ND	ND	ND
Other foods	ND	ND	ND	ND	ND	ND
Stimulant beverages	ND	ND	ND	ND	ND	ND
Sugar and confectionary	ND	ND	ND	ND	ND	ND
Singapore						
Food for the very young	ND	ND	ND	ND	ND	ND
Slovakia						
Eggs and egg products	0.067	0.008	0.012	0.079	0.132	0.061
Fats and oils	0.020	0.004	0.003	0.016	0.023	0.009
Fish and products	0.310	0.201	0.231	0.519	1.16	0.373
Meat and products	0.011	0.002	0.003	0.017	0.033	0.017
Milk and dairy products	0.006	0.001	0.002	0.024	0.064	0.026

	Mean concentration (ng/kg ww)					
Country / food category	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**
Slovenia						
Eggs and egg products	189	508	500	388	336	80.2
Fats and oils	52.6	1.90	4.48	238	429	148
Fish and products	2 150	10 800	19 600	8 850	14 100	1 430
Food for the very young	<0.001	<0.001	<0.001	1.79	2.50	<0.001
Meat and products	24.2	26.6	246	353	452	174
Milk and dairy products	45.3	ND	ND	199	285	99.3
Nuts and oilseeds	4.63	ND	ND	87.9	78.0	58.0
Specialty products	12.0	46.1	262	701	781	501
Sugar and confectionary	38.6	ND	8.80	39	46.0	29.4
Vegetables and products	ND	ND	ND	ND	ND	ND
Spain						
Eggs and egg products	ND	NR	ND	ND	ND	ND
Fats and oils	ND	NR	ND	ND	ND	ND
Fish and products	<0.001	0.001	0.001	0.003	0.001	0.001
Milk and dairy products	ND	NR	ND	ND	ND	ND
Sweden						
Cereals and products	0.657	0.663	1.20	1.10	1.80	0.701
Composite food	655	1 830	7 880	19 800	20 800	7 230
Eggs and egg products	35.8	3.84	23.4	394	499	168
Fats and oils	18.3	8.15	31.2	189	361	155
Fish and products	344	795	3 300	6 050	9 560	3 120
Food for the very young	4.34	7.39	13.6	16.5	24.8	6.68
Fruit and fruit products	2.44	1.24	1.73	1.58	2.26	0.875
Meat and products	15.9	7.76	7.90	79.6	144	56.9
Milk and dairy products	4.55	4.49	3.91	87.5	116	42.1
Specialty products	17.3	57.3	282	719	947	714
Starchy roots, tubers	2.73	1.20	0.901	0.533	0.926	0.280
Vegetables and products	0.714	0.463	0.705	0.318	0.543	0.188
United Kingdom						
Cereals and products	11.9	7.64	6.55	3.84	6.39	0.086
Composite food	67.2	170	344	805	898	243
Eggs and egg products	52.5	2.91	10.9	729	844	370
Fats and oils	110	155	372	1 180	1 090	575
Fish and products	112	184	295	722	875	427
Fruit and fruit products	3.48	1.70	2.38	1.75	2.37	0.020
Meat and products	7.93	1.57	2.28	77.2	99.4	33.8
Milk and dairy products	5.76	2.83	6.02	85.2	99.0	36.4
Nuts and oilseeds	26.6	11.6	ND	ND	9.97	8.31
Specialty products	332	3 810	4 960	21 600	26 600	6 010
Starchy roots, tubers	0.423	0.264	0.116	0.095	0.106	ND
Sugar and confectionary	160	110	80.0	220	240	140
Vegetables and products	2.00	1.52	2.30	2.02	2.35	0.778

ND: not detected; NR: not reported; SAR: Special Administrative Region; ww: wet weight

Appendix 3. Summary of the concentration data for food groups and major contributors to dietary exposure for the national dietary exposure estimates for the sum of the six indicator PCB congeners estimated by the Committee using the CIFOCOss consumption data and concentration data from the GEMS/Food database

Note: A blank per cent contribution in the tables below either represents a zero lower-bound concentration or indicates that the food group was not consumed by the population group.

Table A3.1
Concentration and dietary exposure data for Belgium

		Mean concentration (ng/kg)		Contribution to dietary exposure (%)					
Food code	Food name	Lower bound	Upper bound	Toddlers	Other children	Adoles-cents	Adults	Elderly	Very elderly
01.0	Dairy products, nes	416	766	<1	<1	<1	<1	<1	<1
01.2.1	Fermented milks (plain)	0	4 000						
01.6	Cheese	2 214	5 238	36	30	10	18	20	19
02.1	Animal or vegetable fats, nes	17 772	19 865	<1	<1	9	10	10	9
02.2.1	Butter	1 161	10 458	<1	<1	<1	1	3	4
06.8.3	Soya bean curd (tofu)	0	1 000						
08.0	Unprocessed meat and offal, nes	338	3 671	1	<1	<1	<1	<1	<1
09.0	Fishes and aquatic animals, nes	4 000	4 000	<1	3	1	3	5	4
13.6	Dietary supplements, food supplements	3 249	9 082						
13.7	Food for infants and small children, nes	0	2 875						
17	Other foods (foods which cannot be included in any other group)	62	3 929	2	1	<1	<1	2	2
FA 0142	Marine animal fats, nes	0	1 980						
IM 0150	Molluscs, including cephalopods, nes	157	3 934			<1	<1	<1	
IM 1003	Mussels	2 877	4 811		<1	<1	<1	1	<1
IM 1005	Scallops	499	3 832		<1	<1	<1	<1	<1
IM 1008	Squids	0	4 000						
MF 0100	Mammalian fats (except milk fats), and skin, nes	756	10 200						
ML 0106	Other and nes milks	485	848	58	61	<1	<1	<1	<1

Table A3.1 (continued)

Food code	Food name	Mean concentration (ng/kg)		Contribution to dietary exposure (%)					
		Lower bound	Upper bound	Toddlers	Other children	Adoles-cents	Adults	Elderly	Very elderly
ML 0106	Other and nes milks	485	848	58	61	<1	<1	<1	<1
ML 0812	Cow milk	2 935	6 760			64	45	33	40
ML 0814	Goat milk	378	378						<1
ML 0822	Sheep milk	910	910						
MM 0816	Horse and other equines	139	286	<1	<1	<1	<1	<1	<1
MM 0822	Sheep and other ovines	317	850		<1	<1	<1	<1	<1
OR 0172	Vegetable oils, nes	0	1 740						
OR 0305	Olive oil	236	5 208	<1	<1	<1	<1	<1	<1
OR 0495	Rape seed oil (incl. canola)	0	1 981						
OR 0541	Soya bean oil	0	1 715						
OR 0645	Maize oil	0	1 030						
OR 0665	Coconut oil	0	1 605						
OR 0696	Palm oil	0	1 477						
OR 0697	Peanut oil and butter	3 546	10 213	<1	<1	<1	<1		
OR 0702	Sunflower seed oil	233	3 855	<1	<1	<1	<1	<1	<1
PE 0112	Eggs, nes	3 373	3 373			<1	<1	<1	<1
PE 0840	Chicken eggs	8 095	14 031		<1	11	15	15	14
PM 0840	Chicken meat	53	2 712	<1	<1	<1	<1	<1	<1
WC 0143	Crustaceans, nes	401	3 401			<1	<1		
WC 0978	Lobsters	0	4 000						
WD 0123	Trout	2 374	4 435						
WD 0890	Eels	6 800	8 400				<1	<1	<1
WF 0115	Freshwater fish, nes	7 316	9 418						
WF 0864	Perch	0	4 000						
WS 0927	Cod	624	3 291	<1	<1	<1	<1	<1	<1
WS 0937	Herring	7 595	7 995	<1	<1	<1	1	4	2
WS 0941	Mackerel	10 272	11 072		1		1	2	<1
WS 0945	Plaice	182	3 682		<1	<1	<1	<1	<1
WS 0948	Rays	379	4 045						
WS 0951	Sole	4 123	5 723			<1	<1	3	1

incl.: including; nes: not elsewhere specified

Table A3.2
Concentration and dietary exposure data for China

		Mean concentration (ng/kg)		Contribution to dietary exposure (%)	
Food code	**Food name**	**Lower bound**	**Upper bound**	**Children**	**General population**
01.0	Dairy products, nes	57	57		
13.1.1.1	Ready-to-eat meal for infants and young children	43	43		
CF 1211	Wheat flour	36	36	10	10
GC 0649	Rice (excl. wild)	14	14	10	10
IM 1000	Clams	769	769	<1	<1
IM 1003	Mussels	798	798	<1	<1
ML 0812	Cow milk	20	20	3	2
MM 0812	Beef and other bovine meat	29	29	<1	<1
MM 0818	Pork and other porcines	61	61	13	12
MM 0822	Sheep and other ovines	0	1		
MO 1284	Pig kidney	5	5	<1	<1
MO 1285	Pig liver	4	4	<1	<1
PE 0840	Chicken eggs	100	101	12	8
PM 0840	Chicken meat	3	5	<1	<1
PE 0841	Duck eggs	344	345	2	1
PM 0841	Duck meat	7	9	<1	<1
VB 0041	Cabbages, head	37	37	<1	<1
VC 0046	Melons, except watermelon	41	41	<1	<1
VC 0424	Cucumber	22	22	<1	<1
VC 0427	Loofah, angled	63	63	<1	<1
VD 0541	Soya bean	37	37	<1	<1
VL 0053	Leafy vegetables, unprocessed, nes	17	17	<1	<1
VL 0466	Chinese cabbage, type pak-choi	0	1		
VL 0467	Chinese cabbage, type pe-tsai	8	8	2	2
VL 0483	Lettuce, leaf	0	1		
VL 0485	Mustard greens	0	1		
VL 0502	Spinach	10	10	<1	<1
VO 0448	Tomato	11	12	<1	<1
VP 0064	Peas, shelled (succulent seeds)	28	28	<1	<1
VR 0075	Root vegetables, unprocessed, nes	0	0.4		
VR 0506	Turnip, garden	0	0.4		
VR 0577	Carrot	0	0.3		
VR 0589	Potato	21	21	3	3
VS 0622	Bamboo shoots	12	12	<1	<1

Table A3.2 (continued)

		Mean concentration (ng/kg)		Contribution to dietary exposure (%)	
Food code	Food name	Lower bound	Upper bound	Children	General population
WC 0979	Shrimps or prawns	147	147	2	1
WC 0978	Lobsters	608	608		<1
WC 0146	Crabs	488	488	2	3
WD 0890	Eels	0	0.9		
WF 0115	Freshwater fish, nes	580	581	26	27
WS 0125	Marine fish, nes	663	663	13	17
WF 0859	Carps	0	0.4		
WC 0143	Crustaceans, nes	555	555		

excl.: excluding; nes: not elsewhere specified

Table A3.3
Concentration and dietary exposure data for Cyprus

		Mean concentration (ng/kg)		Contribution to dietary exposure (%)
Food code	Food name	Lower bound	Upper bound	Adolescents
01.0	Dairy products, nes	0.1	0.1	<1
01.6	Cheese	1	1	<1
09.0	Fishes and aquatic animals, nes	3	3	<1
13.2b	Cereal-based food for infants and young children	0.1	0.1	<1
13.7	Food for infants and small children, nes	0.1	0.1	
17	Other foods (foods which cannot be included in any other group)	0.1	0.1	<1
IM 0150	Molluscs, including cephalopods, nes	4	4	<1
ML 0812	Cow milk	536	3 870	56
ML 0814	Goat milk	820	7 820	
ML 0822	Sheep milk	0	18 600	
MM 0095	Meat from mammals other than marine mammals, nes	0.6	0.6	
MM 0812	Beef and other bovine meat	0	10 000	
MM 0818	Pork and other porcines	882	2 882	14
MM 0819	Rabbit meat	1 931	5 265	1
MM 0822	Sheep and other ovines	768	768	<1
PE 0112	Eggs, nes	756	756	1
PM 0840	Chicken meat	1 901	1 901	28
WF 0115	Freshwater fish, nes	27 460	27 460	
WS 0130	Sardine and sardine-like fishes	3	3	
WS 0952	Tuna	12	12	<1

nes: not elsewhere specified

Table A3.4
Concentration and dietary exposure data for Czech Republic

		Mean concentration (ng/kg)		Contribution to dietary exposure (%)		
Food code	Food name	Lower bound	Upper bound	Other children	Adolescents	Adults
01.0	Dairy products, nes	196	836	5	4	5
01.4.1	Cream	3	4			
01.6	Cheese	1	215	<1	<1	<1
02.1	Animal or vegetable fats, nes	16	61			
01.2.1	Fermented milks (plain)	0.13	161	<1	<1	<1
02.2.1	Butter	402	402	35	32	27
02.2.2	Margarine	1	1			
03.0	Edible ices, including sherbet and sorbet	0.18	400	<1	<1	<1
04.1.2.4	Canned or bottled (pasteurized) fruits	0	0.8			
04.1.2.5	Jams, jellies, marmalades	0	0.8			
04.2.2	Other vegetables, nes, other processing	70	71	3	5	7
05.1	Other cocoa products (incl. chocolate), nes	0.26	0.5	<1	<1	<1
07.2.1	Cakes, cookies and pies (e.g. fruit-filled or custard types)	0.32	0.4	<1	<1	<1
08.0	Unprocessed meat and offal, nes	385	477	8	12	9
09.0	Fishes and aquatic animals, nes	0	0.8			
11.5	Honey	0	17			
12.6.1a	Mustard sauce	0.18	0.8			
12.6.1b	Mayonnaise	0	0.6			
13.1.1.1	Ready-to-eat meal for infants and young children	0.11	172	<1	<1	<1
13.7	Food for infants and small children, nes	0	2			
14.1	Non-alcoholic ("soft") beverages, nes	0.01	20	<1	<1	<1
14.1.1.1	Natural mineral waters and source waters	0.03	0	<1	<1	<1
14.1.1.6	Water, nes	0.01	0			
14.2.1	Beer and malt beverages, nes	0	0			
14.2.3.1	Still grape wine	0.01	0	<1	<1	<1
14.2.6	Distilled spirituous beverages containing more than 15% alcohol	0.01	20	<1	<1	<1
15.1	Potato crisps	0.17	0.6	<1	<1	<1
15.4	Snacks, nes	0	800			
16.1	Cereal-based composite food	0.09	0.2	<1	<1	<1
16.2	Vegetable-based composite food (incl. mushroom-based)	0.36	201		<1	<1
16.8	Fish-based composite food	4	338			
16.10	Composite food, nes	0.39	0.8	<1	<1	<1
CF 1211	Wheat flour	0.02	0.3	<1	<1	<1

Table A3.4 (continued)

		Mean concentration (ng/kg)		Contribution to dietary exposure (%)		
Food code	Food name	Lower bound	Upper bound	Other children	Adolescents	Adults
CP 0179	Hominy/mugunzá	30	143			
CP 0179a	Wheat white bread	40	40	<1	<1	<1
DF 5259	Vine fruits (currants, raisins and sultanas), dried	0	400			
DM 0659	Sugarcane molasses	0	220			
DM 0715	Cocoa powder	1	201	<1	<1	<1
DT 1114	Tea, dried leaves	0	20			
FB 0269	Grapes	0.04	0.4	<1	<1	<1
FB 0275	Strawberry	0.04	400	<1	<1	<1
FC 0001	Citrus fruits, nes	0	400			
FC 0004	Orange, sweet, sour + orange-like hybrid	0.01	267	<1	<1	<1
FI 0327	Banana	0.02	267	<1	<1	<1
FI 0341	Kiwi fruit	0	0.8			
FP 0226	Apple	0.04	267	<1	<1	<1
FP 0230	Pear	0	400			
FS 0014	Plums (incl. prunes)	0	0.8			
FS 0240	Apricot	0.06	400	<1	<1	<1
FS 0247	Peach	0.07	400	<1	<1	<1
GC 0080	Cereals grains, nes	0.02	150	<1	<1	<1
GC 0649	Rice (excl. wild)	0	267			
HS 0093	Spices and condiments, nes	0.19	0.6	<1	<1	<1
JF 0175	Fruit juice, nes	0	0			
ML 0106	Other and nes milks	0.31	134	<1	<1	<1
ML 0812	Cow milk	3	39	4	2	1
MM 0095	Meat from mammals other than marine mammals, nes	0.04	5			
MM 0812	Beef and other bovine meat	0.78	134	<1	<1	<1
MM 0814	Goat and other caprines	0	0.9			
MM 0818	Pork and other porcines	211	244	19	22	28
MM 0819	Rabbit meat	0.09	51	<1	<1	<1
MO 0105	Offal from mammals, nes	1	1	<1		<1
MO 1285	Pig liver	50	51	<1	<1	<1
OR 0172	Vegetable oils, nes	0	0.4			
PE 0112	Eggs, nes	0.48	0.6			
PE 0840	Chicken eggs	230	430	21	18	18
PF 0840	Chicken fat	478	478			
PM 0110	Poultry meat, nes	0	3			
PM 0840	Chicken meat	22	122	4	3	3
PM 0847	Quail meat	0	3			
PM 0848	Turkey meat	30	31	<1	<1	<1
SO 0697	Peanut	0.33	0.9	<1	<1	<1

		Mean concentration (ng/kg)		Contribution to dietary exposure (%)		
Food code	Food name	Lower bound	Upper bound	Other children	Adolescents	Adults
TN 0664	Chestnuts	1	2			
VA 0035	Bulb vegetables, unprocessed, nes	2	336			
VB 0041	Cabbages, head	28	162	<1	<1	<1
VB 0400	Broccoli	0.03	267	<1	<1	<1
VB 0404	Cauliflower	0.02	267	<1	<1	<1
VB 0405	Kohlrabi	0.04	267	<1	<1	<1
VC 0424	Cucumber	0.03	267	<1	<1	<1
VC 0432	Watermelon	0.06	0.5	<1	<1	<1
VD 0070	Pulses, nes	0	0.8			
VD 0533	Lentil	0	0.8			
VD 0541	Soya bean	0.03	400			<1
VL 0466	Chinese cabbage, type pak-choi	0.02	267			
VL 0470	Corn salad (lamb's lettuce)	0.11	0.6			
VL 0480	Kale	0.26	267			
VL 0483	Lettuce, leaf	0	800			
VL 0502	Spinach	0.02	200			
VO 0448	Tomato	0.01	400	<1	<1	<1
VO 0450	Mushrooms and fungi	0.07	400	<1	<1	<1
VP 0061	Beans, except broad bean and soya bean	0	400			
VR 0494	Radish	0.03	267	<1	<1	<1
VR 0577	Carrot	0.05	267	<1	<1	<1
VR 0578	Celeriac	0	800			
VR 0587	Parsley, turnip-rooted	0.04	0.6	<1	<1	<1
VR 0589	Potato	0.03	267	<1	<1	<1
VR 0596	Sugar beet	0.02	0.1	<1	<1	<1
VS 0624	Celery	0.05	0.5			
WD 0123	Trout	0.8	3			
WF 0115	Freshwater fish, nes	3	97			
WF 0858	Bream	2	2			
WF 0859	Carps	51	52	<1	<1	<1
WS 0941	Mackerel	4	337	<1	<1	<1

excl.: excluding; incl.: including; nes: not elsewhere specified

Table A3.5
Concentration and dietary exposure data for Finland

		Mean concentration (ng/kg)		Contribution to dietary exposure (%)				
Food code	Food name	Lower bound	Upper bound	Toddlers	Other children (DIPP)	Other children (STRIP)	Adults	Elderly
01.6	Cheese	988	990	5	54	6	59	18
13.1.1.1	Ready-to-eat meal for infants and young children	10 927	10 927	92	15	9		
16.8	Fish-based composite food	26 319	26 319			81		
ML 0106	Other and nes milks	23	118	<1	<1	<1	<1	<1
MM 0095	Meat from mammals other than marine mammals, nes	329	329					
MM 0095a	Game (mammalian) meat	96	96	<1	<1	<1	<1	<1
MM 0819	Rabbit meat	129	129					
MO 1280	Cattle, kidney	18	18				<1	
MO 1281	Cattle, liver	91	91	<1	<1		<1	<1
MO 1284	Pig kidney	29	29					
MO 1285	Pig liver	45	45	<1	<1			
MO 1289	Sheep liver	191	191					
PE 0112	Eggs, nes	428	428					
PM 0841	Duck meat	47	47					
WC 0143	Crustaceans, nes	314	317				<1	<1
WD 0123	Trout	43 815	43 817					
WF 0115	Freshwater fish, nes	24 839	24 839					
WF 0858	Bream	15 436	15 436		1	<1		3
WF 0864	Perch	6 921	6 921	<1	6	1	3	9
WS 0130	Sardine and sardine-like fishes	7 471	7 471					
WS 0932	Flounders	14 233	14 233	<1	1		2	
WS 0937	Herring	23 799	23 799	2	22	2	33	70
WR 0140	Fish roe, nes	5 980	5 980			<1	1	<1

DIPP: Finnish Type I Diabetes Prediction and Prevention Nutrition Study; nes: not elsewhere specified; STRIP: Turku Coronary Risk Factor Intervention Project for Children

Table A3.6
Concentration and dietary exposure data for France

		Mean concentration (ng/kg)		Contribution to exposure (%)				
Food code	Food name	Lower bound	Upper bound	Other children	Adoles-cents	Adults	Elderly	Very elderly
02.2.1	Butter	1 716	1 716	54	52	40	34	28
13.1.1.1	Ready-to-eat meal for infants and young children	0.1	0.1	<1				
IM 0150	Molluscs, including cephalo-pods, nes	28	28		<1	<1	<1	<1
IM 1003	Mussels	28	28	<1	<1	<1	<1	<1
IM 1004	Oysters (incl. cupped oysters)	439	439	<1	<1	<1	<1	<1
IM 1005	Scallops	0.7	0.7	<1	<1	<1	<1	<1
IM 1008	Squids	3	3	<1	<1	<1	<1	
IM 5173	Octopuses	547	547					
ML 0106	Other and nes milks	4	4	<1	<1	<1	<1	<1
ML 0812	Cow milk	0.1	8	<1	<1	<1	<1	<1
ML 0814	Goat milk	0	162					
MM 0095	Meat from mammals other than marine mammals, nes	0	660					
MM 0095a	Game (mammalian) meat	1	1	<1	<1	<1	<1	<1
MM 0812	Beef and other bovine meat	0.8	0.8	<1	<1	<1	<1	<1
MM 0818	Pork and other porcines	1	1	<1	<1	<1	<1	<1
MM 0819	Rabbit meat	0.2	141	<1	<1	<1	<1	<1
MM 0822	Sheep and other ovines	0.7	0.7	<1	<1	<1	<1	<1
MO 0105	Offal from mammals, nes	583	583	<1	1	2	2	2
MO 1284	Pig kidney	0	660					
MO 1289	Sheep liver	0.5	0.5	<1	<1	<1	<1	
OR 0172	Vegetable oils, nes	0.2	0.2	<1	<1	<1	<1	<1
OR 0305	Olive oil	0.6	0.6	<1	<1	<1	<1	<1
OR 0495	Rape seed oil (incl. canola)	0.3	0.3	<1	<1	<1	<1	<1
OR 0541	Soya bean oil	0.2	0.2	<1	<1	<1		<1
OR 0696	Palm oil	0.3	0.3			<1		
OR 0702	Sunflower seed oil	0.1	0.1	<1	<1	<1	<1	<1
PE 0112	Eggs, nes	327	327					
PE 0840	Chicken eggs	0.6	379	<1	<1	<1	<1	<1
PE 0847	Quail eggs	0	1 578					
PM 0110	Poultry meat, nes	0.2	128	<1	<1	<1	<1	<1
PM 0840	Chicken meat	10	79	<1	<1	<1	<1	<1
PM 0841	Duck meat	0.1	402	<1	<1	<1	<1	<1
PM 0847	Quail meat	0	2					
PM 0848	Turkey meat	18	105	<1	<1	<1	<1	<1
WC 0979	Shrimps or prawns	6	6	<1	<1	<1	<1	<1
WC 0143	Crustaceans, nes	38	38	<1	<1	<1	<1	
WC 0146	Crabs	2	2	<1	<1	<1	<1	<1

Table A3.6 (continued)

Food code	Food name	Mean concentration (ng/kg)		Contribution to exposure (%)				
		Lower bound	Upper bound	Other children	Adoles-cents	Adults	Elderly	Very elderly
WC 0978	Lobsters	1 948	1 948	<1	<1	<1	<1	<1
WD 0123	Trout	196	1 261					
WD 0890	Eels	66	66			<1	<1	
WF 0115	Freshwater fish, nes	6 673	7 416					
WF 0858	Bream	137	137	<1	<1	<1	<1	<1
WF 0859	Carps	0	15 333					
WF 0864	Perch	0.4	0.4	<1	<1	<1	<1	<1
WS 0125	Marine fish, nes	6	6	<1	<1	<1	<1	<1
WS 0130	Sardine and sardine-like fishes	3 235	3 235					
WS 0920	Anchovies	15 334	15 334					
WS 0927	Cod	5 346	5 346	24	27	28	36	30
WS 0937	Herring	8	8	<1	<1	<1	<1	<1
WS 0941	Mackerel	17 840	17 840	15	10	24	22	35
WS 0948	Rays	2 506	2 506	<1	2	1	2	1
WS 0945	Plaice	5 800	5 800		2	<1		
WS 0952	Tuna	358	358	2	2	2	1	<1
WS 0951	Sole	1 068	1 068	2	<1	1	2	2

incl.: including; nes: not elsewhere specified

Table A3.7
Concentration and dietary exposure data for Germany

Food code	Food name	Mean concentration (ng/kg)		Contribution to exposure (%)					
		Lower bound	Upper bound	Toddlers (DONALD 2008)	Other children (DONALD 2008)	Adoles-cents	Adults	Elderly	Very elderly
01.0	Dairy products, nes	228	255	<1	<1	<1	<1	<1	<1
01.2.1	Fermented milks (plain)	317	317	8	12	6	6	6	5
01.4.1	Cream	1 770	1 770						
01.6	Cheese	6	12	<1	<1	<1	<1	<1	<1
02.1	Animal or vegetable fats, nes	61 515	61 515	5	3	21	19	12	13
02.2.1	Butter	3 608	3 719	9	14	20	15	16	19
02.2.2	Margarine	120 650	120 650						
13.6	Dietary supplements, food supplements	7 107	7 726						

		Mean concentration (ng/kg)		Contribution to exposure (%)					
Food code	Food name	Lower bound	Upper bound	Toddlers (DONALD 2008)	Other children (DONALD 2008)	Adoles-cents	Adults	Elderly	Very elderly
08.0	Unprocessed meat and offal, nes	13 112	13 118	18	29	12	12	11	6
09.0	Fishes and aquatic animals, nes	2	3	<1	<1	<1	<1	<1	<1
11.5	Honey	0	4						
13.1.1.1	Ready-to-eat meal for infants and young children	253	309	23	1				
13.7	Food for infants and small children, nes	221	665	4	<1				
14.1.2	Fruit juice and herbal tea for infants and young children	0	10						
14.2.3.1	Still grape wine	0	10						
16.10	Composite food, nes	0	2						
16.6	Meat-based composite food (incl. seafood)	5 150	5 150	10	11	16	9	5	5
FB 0275	Strawberry	25	25	<1	<1	<1	<1	<1	<1
FP 0226	Apple	105	105	2	4	4	3	4	4
GC 0650	Rye	30	30		<1		<1		
GC 0654	Wheat	46	46	<1	<1	<1	<1	<1	<1
JF 0175	Fruit juice, nes	0	10						
JF 0226	Apple juice	0	10						
JF 0269	Grape juice	0	10						
IM 0150	Molluscs, including cephalopods, nes	0.05	3			<1	<1	<1	
IM 1003	Mussels	3	3			<1	<1	<1	
IM 1005	Scallops	0.04	0.1			<1	<1	<1	
ML 0106	Other and nes milks	337	337	9	5	1	1	1	1
ML 0812	Cow milk	23	26	4	3	2	<1	<1	<1
ML 0814	Goat milk	142	151		<1		<1	<1	<1
MM 0095	Meat from mammals other than marine mammals, nes	49	112	<1	<1				
MM 0095a	Game (mammalian) meat	0.2	186			<1	<1	<1	<1
MM 0812	Beef and other bovine meat	216	288	<1	<1	1	<1	<1	<1
MM 0814	Goat and other caprines	0	0.7						
MM 0816	Horse and other equines	0	1						
MM 0818	Pork and other porcines	794	795	<1	3	9	7	5	4
MM 0819	Rabbit meat	0	0.9						
MM 0822	Sheep and other ovines	174	328		<1	<1	<1	<1	<1
MO 1281	Cattle, liver	916	1 015				<1	<1	<1
MO 1285	Pig liver	0	160						

Table A3.7 (continued)

Food code	Food name	Mean concentration (ng/kg)		Contribution to exposure (%)					
		Lower bound	Upper bound	Toddlers (DONALD 2008)	Other children (DONALD 2008)	Adoles-cents	Adults	Elderly	Very elderly
MO 0105	Offal from mammals, nes	0.7	2				<1	<1	<1
MO 1289	Sheep liver	4	5				<1		
PE 0112	Eggs, nes	0.2	2						
PE 0840	Chicken eggs	1 226	1 415	7	11	3	4	3	3
PE 0847	Quail eggs	130	287					<1	
PM 0110	Poultry meat, nes	1	3			<1	<1	<1	<1
PM 0840	Chicken meat	5	27	<1	<1	<1	<1	<1	<1
PM 0841	Duck meat	38	115			<1	<1	<1	<1
PM 0848	Turkey meat	13	35	<1	<1	<1	<1	<1	<1
PO 0111	Offal from poultry, nes	0	4						
VB 0041	Cabbages, head	28	28	<1	<1	<1	<1	<1	<1
VB 0404	Cauliflower	45	45	<1	<1	<1	<1	<1	<1
VB 0405	Kohlrabi	24	24	<1	<1	<1	<1	<1	<1
VC 0431	Squash	219	219						
VL 0053	Leafy vegetables, unpro-cessed, nes	125	125	<1	<1	1	1	<1	<1
VP 0061	Beans, except broad bean and soya bean	55	55	<1	<1	<1	<1	<1	<1
VR 0589	Potato	19	19						
VR 0577	Carrot	56	56	<1	<1	<1	<1	<1	<1
WC 0143	Crustaceans, nes	0	1 541						
WC 0979	Shrimps or prawns	0.003	8		<1	<1	<1	<1	<1
WD 0123	Trout	1 435	2 878						
WD 0890	Eels	22 585	22 965				<1	1	1
WF 0115	Freshwater fish, nes	777	1 380						
WF 0858	Bream	61	65				<1		
WF 0859	Carps	669	2 966				<1	<1	<1
WF 0864	Perch	8	93	<1	<1	<1	<1	<1	<1
WS 0130	Sardine and sardine-like fishes	31 000	37 667						
WS 0952	Tuna	2 420	3 176	<1	<1	1	1	<1	<1
WS 0927	Cod	282	1 018		<1	<1	<1	<1	<1
WS 0932	Flounders	800	977						
WS 0941	Mackerel	84 907	93 646			2	8	14	8
WS 0945	Plaice	0	1 008						
WS 0937	Herring	12 548	15 275		1	3	12	18	23
WS 0951	Sole	7 056	9 989				<1	<1	1
WR 0140a	Offal of fish, nes	258 416	258 416				<1		3

incl.: including; nes: not elsewhere specified

Table A3.8
Concentration and dietary exposure data for Grecce

		Mean concentration (ng/kg)		Contribution to exposure (%)
Food code	**Food name**	**Lower bound**	**Upper bound**	**Other children**
01.0	Dairy products, nes	0.04	0.038	<1
01.1.2	Flavoured milk	36	38	
01.4.1	Cream	8 861	8 861	
01.6	Cheese	88	88	<1
02.1	Animal or vegetable fats, nes	3 967	22 839	<1
08.0	Unprocessed meat and offal, nes	602	2 532	
13.1.1.1	Ready-to-eat meal for infants and young children	0.2	0.2	<1
13.2b	Cereal-based food for infants and young children	0.5	0.5	<1
IM 0150	Molluscs, including cephalopods, nes	2 552	5 803	
IM 1003	Mussels	1 230	1 230	
ML 0106	Other and nes milks	1 210	1 611	79
ML 0812	Cow milk	27	28	1
ML 0814	Goat milk	38	38	<1
ML 0822	Sheep milk	0.2	0.2	<1
MM 0812	Beef and other bovine meat	136	136	<1
MM 0818	Pork and other porcines	31	31	<1
MM 0822	Sheep and other ovines	259	260	<1
MO 0105	Offal from mammals, nes	0.2	0.2	<1
MO 1281	Cattle, liver	723	723	
OR 0172	Vegetable oils, nes	0.4	0.4	<1
OR 0305	Olive oil	649	649	2
OR 0645	Maize oil	259	259	
OR 0702	Sunflower seed oil	274	296	<1
PE 0112	Eggs, nes	3 221	4 073	10
PE 0840	Chicken eggs	0.3	0.3	<1
PM 0840	Chicken meat	89	89	<1
WD 0123	Trout	2 923	2 923	
WD 0890	Eels	20	20	
WF 0115	Freshwater fish, nes	365	558	
WF 0858	Bream	4 445	4 445	
WS 0927	Cod	2 568	2 568	6
WS 0941	Mackerel	1 225	1 225	<1

nes: not elsewhere specified

Table A3.9
Concentration and dietary exposure data for Ireland

		Mean concentration (ng/kg)		Contribution to exposure (%)
Food code	**Food name**	**Lower bound**	**Upper bound**	**Other children**
01.0	Dairy products, nes	29	29	<1
01.2.1	Fermented milks (plain)	29	29	<1
01.6	Cheese	284	284	8
02.2.1	Butter	880	880	13
02.1	Animal or vegetable fats, nes	1 131	1 131	<1
12.1.1	Salt	0	1 000	
13.6	Dietary supplements, food supplements	23 820	24 436	32
16.10	Composite food, nes	70	70	<1
FB 0272	Raspberries, red, black	0	200	
FB 0275	Strawberry	0	200	
FP 0226	Apple	0	200	
GC 0080	Cereals grains, nes	103	103	<1
IM 1004	Oysters (incl. cupped oysters)	1 008	1 008	
MF 0100	Mammalian fats (except milk fats), and skin, nes	759	1 176	<1
ML 0812	Cow milk	19	19	8
ML 0814	Goat milk	33	33	<1
MO 0105	Offal from mammals, nes	121	121	<1
MO 1281	Cattle, liver	248	248	<1
MO 1285	Pig liver	22	22	<1
MO 1289	Sheep liver	158	158	<1
OR 0172	Vegetable oils, nes	257	1 090	2
PE 0112	Eggs, nes	1 909	1 909	
PE 0840	Chicken eggs	713	752	14
PF 0111	Poultry fat and skin, nes	1 387	1 387	
PF 0840	Chicken fat	917	917	
PO 0840a	Chicken liver only	46	46	
PO 0848	Turkey, offal of	154	154	
VA 0387	Onion, Welsh	0	200	
VB 0041	Cabbages, head	0	200	
VL 0053	Leafy vegetables, unprocessed, nes	0	200	
VL 0502	Spinach	0	200	
VO 0448	Tomato	0	200	
VO 0450	Mushrooms and fungi	0	200	
VR 0577	Carrot	0	200	<1
VR 0589	Potato	0	200	
WD 0123	Trout	9 669	9 669	
WS 0937	Herring	6 012	6 012	
WS 0130	Sardine and sardine-like fishes	2 626	2 626	
WS 0941	Mackerel	6 479	6 479	<1
WS 0952	Tuna	3 970	3 988	32

incl.: including; nes: not elsewhere specified

Table A3.10
Concentration and dietary exposure data for Italy

		Mean concentration (ng/kg)		Contribution to exposure (%)						
Food code	Food name	Lower bound	Upper bound	Infants	Toddlers	Other children	Adoles-cents	Adults	Elderly	Very elderly
02.1	Animal or vegetable fats, nes	0	12 793							
11.5	Honey	0	12 500							
ML 0106	Other and nes milks	0	104							
ML 0812	Cow milk	0	58							
MM 0095	Meat from mammals other than marine mammals, nes	0	118							
MM 0812	Beef and other bovine meat	15	225	100	100	4	5	3	4	8
MM 0818	Pork and other porcines	0	290							
MM 0819	Rabbit meat	0	106							
MM 0822	Sheep and other ovines	0	375							
MO 0105	Offal from mammals, nes	0	10							
MO 1280	Cattle, kidney	0	33							
MO 1285	Pig liver	0	74							
PE 0112	Eggs, nes	28	335							
PM 0840	Chicken meat	0	120							
WD 0123	Trout	1 905	2 375							
WD 0890	Eels	1 845	5 345			<1	<1	1	1	
WF 0115	Freshwater fish, nes	9 637	9 978							
WF 0858	Bream	6 553	10 124			96	95	96	95	92

nes: not elsewhere specified

Table A3.11
Concentration and dietary exposure data for the Netherlands

		Mean concentration (ng/kg)		Contribution to exposure (%)		
Food code	Food name	Lower bound	Upper bound	Toddlers	Other children	Adults
01.6	Cheese	1 149	1 169	49	39	23
02.2.1	Butter	3 945	3 945	2	3	5
02.2.2	Margarine	1 860	2 047			
15.4	Snacks, nes	2 760	2 760	9	9	2
IM 0150	Molluscs, including cephalopods, nes	11 900	11 900			

Table A3.11 (continued)

		Mean concentration (ng/kg)		Contribution to exposure (%)		
Food code	Food name	Lower bound	Upper bound	Toddlers	Other children	Adults
ML 0106	Other and nes milks	112	124	7	10	2
MM 0812	Beef and other bovine meat	929	929	9	8	8
MM 0818	Pork and other porcines	570	570	3	3	11
OR 0172	Vegetable oils, nes	1 030	1 330		<1	<1
PE 0112	Eggs, nes	1 397	1 397			<1
PM 0840	Chicken meat	1 398	1 398	11	12	17
WC 0143	Crustaceans, nes	7 502	7 502			2
WC 0979	Shrimps or prawns	1 475	1 475	<1	<1	<1
WD 0123	Trout	13 133	13 133			
WD 0890	Eels	247 901	247 901		5	14
WF 0115	Freshwater fish, nes	28 864	28 864			
WF 0864	Perch	50 460	50 460			
WR 0140a	Offal of fish, nes	267 173	267 173			
WS 0125	Marine fish, nes	33 100	33 100	2		2
WS 0130	Sardine and sardine-like fishes	32 350	32 350			
WS 0920	Anchovies	63 900	63 900			
WS 0927	Cod	25	25	<1	<1	<1
WS 0937	Herring	15 500	15 500	5	2	2
WS 0941	Mackerel	10 000	10 000		2	1
WS 0952	Tuna	23 867	23 867	3	6	10

nes: not elsewhere specified

Table A3.12
Concentration and dietary exposure data for Republic of Korea

		Mean concentration (ng/kg)		Contribution to exposure (%)	
Food code	Food name	Lower bound	Upper bound	Children	General population
09.0	Fishes and aquatic animals, nes	1 259	1 480		
IM 0150	Molluscs, including cephalopods, nes	1 211	1 438		
IM 1000	Clams	1 026	1 266		5
IM 1003	Mussels	1 214	1 441		
IM 1004	Oysters (incl. cupped oysters)	1 584	1 792		
IM 1005	Scallops	831	1 087		
IM 1008	Squids	1 436	1 641		40
IM 5173	Octopuses	1 982	2 104		
WC 0146	Crabs	1 474	1 640		7
WC 0978	Lobsters	0	364		
WC 0979	Shrimps or prawns	978	1 235		7
WD 0123	Trout	927	1 000		
WD 0890	Eels	806	948		

		Mean concentration (ng/kg)		Contribution to exposure (%)	
Food code	Food name	Lower bound	Upper bound	Children	General population
WD 4917	Salmon, Pacific	1 644	1 720		
WF 0115	Freshwater fish, nes	1 084	1 202		
WF 0858	Bream	386	586		
WM 0141	Marine mammals, nes	3 408	3 450		
WS 0125	Marine fish, nes	878	999	100	
WS 0927	Cod	513	670		
WS 0932	Flounders	558	711		
WS 0937	Herring	2 184	2 197		
WS 0941	Mackerel	1 311	1 372		24
WS 0945	Plaice	936	1 033		
WS 0946	Pollack	367	605		7
WS 0951	Sole	648	721		
WS 0952	Tuna	747	906		9
WS 5015	Shark	642	779		

incl.: including; nes: not elsewhere specified

Table A3.13
Concentration and dietary exposure data for Sweden

		Mean concentration (ng/kg)		Contribution to exposure (%)[a]		
Food code	Food name	Lower bound	Upper bound	Other children	Adolescents	Adults
01.0	Dairy products, nes	3	3	<1	<1	<1
01.6	Cheese	0.3	0.3	<1	<1	<1
02.1	Animal or vegetable fats, nes	789	928	<1	<1	
02.2.1	Butter	520	645	<1	<1	<1
06.3b	Porridge	20	22			
08.0	Unprocessed meat and offal, nes	35	35	<1	<1	
13.1.1.1	Ready-to-eat meal for infants and young children	73	73			
13.6	Dietary supplements, food supplements	2 736	2 737	1	<1	
16.8	Fish-based composite food	58 080	58 080	43	43	72
CP 0179	Hominy/mugunzá	0	800			
FA 0142	Marine animal fats, nes	9 904	9 988			
FB 0275	Strawberry	5	5	<1	<1	<1
FP 0226	Apple	12	12	<1	<1	<1
GC 0650	Rye	0.03	0.03	<1		
GC 0654	Wheat	0.02	0.02			
ML 0106	Other and nes milks	39	39	1	1	<1
ML 0812	Cow milk	172	694	34	39	11
MM 0095	Meat from mammals other than marine mammals, nes	67	67			

Table A3.13 (continued)

		Mean concentration (ng/kg)		Contribution to exposure (%)[a]		
Food code	Food name	Lower bound	Upper bound	Other children	Adolescents	Adults
MM 0818	Pork and other porcines	0	405			
MO 0105	Offal from mammals, nes	28	28			<1
MO 1281	Cattle, liver	79	79			
MO 1289	Sheep liver	2	2			
OR 0172	Vegetable oils, nes	0.3	0.3	<1	<1	<1
OR 0665	Coconut oil	0	2 160			
OR 0696	Palm oil	0	2 203			
PE 0112	Eggs, nes	1 402	2 076	3	3	
PE 0840	Chicken eggs	776	789	<1	<1	3
PF 0111	Poultry fat and skin, nes	1	2			
PF 0840	Chicken fat	981	981			
PO 0840a	Chicken liver only	69	69			
VB 0041	Cabbages, head	8	8	<1	<1	<1
VB 0402	Brussels sprouts	0.01	0.01	<1	<1	<1
VB 0404	Cauliflower	8	8	<1	<1	<1
VL 0482	Lettuce, head	0.02	0.02			
VL 0496	Rucola	0.1	0.1			
VL 0502	Spinach	0.04	0.04	<1	<1	<1
VR 0577	Carrot	9	9	<1	<1	<1
VR 0589	Potato	0.01	0.01	<1	<1	<1
WD 0123	Trout	44 457	44 468			
WD 0890	Eels	15 561	15 587			<1
WF 0115	Freshwater fish, nes	10 719	10 730			
WF 0864	Perch	11 169	11 169	<1	<1	<1
WR 0140	Fish roe, nes	19 286	19 286	9	5	8
WS 0130	Sardine and sardine-like fishes	13 564	13 564			
WS 0927	Cod	2 589	2 622	4	4	<1
WS 0932	Flounders	7	7			<1
WS 0937	Herring	21 337	21 353	2	1	5
WS 0941	Mackerel	13 732	13 732	2	3	1

nes: not elsewhere specified

[a] Other children –National Food Agency survey, $n = 1473$; Adolescents – National Food Agency survey, $n = 1018$; Adults – survey Riksmaten (National Dietary Survey) 1997–1998, $n = 1210$.

Table A3.14
Concentration and dietary exposure data for the United Kingdom

		Mean concentration (ng/kg)		Contribution to exposure (%)[a]
Food code	**Food name**	**Lower bound**	**Upper bound**	**Adults**
01.0	Dairy products, nes	59	68	<1
01.6	Cheese	418	510	8
02.1	Animal or vegetable fats, nes	4 122	4 361	<1
04.1.1	Fruits	12	51	
04.2.2	Other vegetables, nes, other processing	11	24	<1
08.0	Unprocessed meat and offal, nes	203	240	<1
09.0	Fishes and aquatic animals, nes	2 429	2 443	7
11.1.3	Sugar products and confectionaries, nes	950	950	2
13.6	Dietary supplements, food supplements	63 258	63 705	50
16.8	Fish-based composite food	2 528	2 560	
CP 0179	Hominy/mugunzá	1	1	
GC 0080	Cereals grains, nes	45	95	<1
IM 0150	Molluscs, including cephalopods, nes	1 135	2 766	<1
IM 1003	Mussels	2	2	<1
IM 1004	Oysters (incl. cupped oysters)	2	2	<1
MM 0095a	Game (mammalian) meat	750	800	<1
MO 0105	Offal from mammals, nes	180	232	<1
OR 0172	Vegetable oils, nes	237	792	<1
PE 0840	Chicken eggs	2 041	2 057	32
PM 0110	Poultry meat, nes	52	68	<1
TN 0085	Tree nuts, nes	56	112	<1
VR 0589	Potato	1	1	<1
WD 0123	Trout	6	6	
WD 0890	Eels	66	66	<1
WF 0115	Freshwater fish, nes	4 224	4 557	
WF 0858	Bream	25	25	
WF 0859	Carps	54	54	
WF 0864	Perch	12	12	
WS 0927	Cod	0.2	0.2	<1
WS 0932	Flounders	9	9	
WS 0937	Herring	8	8	<1
WS 0941	Mackerel	4	4	<1

incl.: including; nes: not elsewhere specified
[a] Number of subjects = 1724. National Diet and Nutrition Survey.

Appendix 4. Details of the national dietary exposure for the six indicator PCB congeners individually as estimated by the Committee using the CIFOCOss consumption data and concentration data from the GEMS/Food database

Table A4.1
National dietary exposures to PCB 28

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
Belgium	Adolescents	0.2	5.7	0.4	11.3
	Adults	0.2	4.5	0.4	9.0
	Elderly	0.2	4.3	0.4	8.6
	Other children	0.2	14.0	0.4	28.0
	Toddlers	0.3	17.5	0.7	35.1
	Very elderly	0.2	4.7	0.4	9.5
China	Children	0.3	0.3	0.5	0.5
	General population	0.1	0.1	0.3	0.3
Cyprus	Adolescents	0.5	2.8	1.1	5.7
Czech Republic	Adolescents	0.1	0.6	0.2	1.1
	Adults	0.1	0.3	0.1	0.6
	Other children	0.1	0.8	0.2	1.7
Finland	Adults	0.3	0.3	0.6	0.6
	Elderly	0.2	0.2	0.4	0.4
	Other children (DIPP)	0.5	0.5	1.0	1.0
	Other children (STRIP)	0.7	0.7	1.3	1.3
	Toddlers	1.0	1.0	2.1	2.1
France	Adolescents	0.02	0.1	0.04	0.12
	Adults	0.02	0.1	0.05	0.11
	Elderly	0.03	0.1	0.05	0.11
	Other children	0.03	0.1	0.07	0.21
	Very elderly	0.02	0.05	0.05	0.1
Germany	Adolescents	0.2	0.2	0.4	0.5
	Adults	0.3	0.3	0.5	0.6
	Elderly	0.3	0.4	0.5	0.7
	Other children (DONALD 2006)	0.8	0.9	1.7	1.9
	Other children (DONALD 2007)	0.8	0.9	1.5	1.7
	Other children (DONALD 2008)	0.8	0.8	1.6	1.7
	Toddlers (DONALD 2006)	1.1	1.4	2.2	2.9
	Toddlers (DONALD 2007)	1.1	1.4	2.2	2.8
	Toddlers (DONALD 2008)	1.2	1.7	2.5	3.4
	Very elderly	0.2	0.3	0.5	0.7
Greece	Other children	0.4	1.0	0.8	2.1

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
Ireland	Adults	0.04	0.1	0.1	0.2
Italy	Adolescents	0.02	0.1	0.03	0.3
	Adults	0.01	0.1	0.03	0.3
	Elderly	0.01	0.1	0.02	0.2
	Infants	0.000 2	1.2	0.000 4	2.5
	Other children	0.03	0.4	0.1	0.7
	Toddlers	0.001	0.6	0.002	1.2
	Very elderly	0.005	0.1	0.01	0.2
Japan	Children	0.03	0.03	0.1	0.1
	General population	0.02	0.02	0.04	0.04
Netherlands	Adults	0.1	0.1	0.2	0.2
	Other children	0.1	0.1	0.3	0.3
	Toddlers	0.1	0.2	0.3	0.3
Republic of Korea	Children	0.03	0.03	0.1	0.1
	General population	0.1	0.1	0.2	0.2
Sweden	Adolescents	0.1	1.2	0.1	2.5
	Adults	0.1	0.6	0.2	1.2
	Other children	0.1	2.1	0.2	4.3
United Kingdom	Adults	0.01	0.02	0.02	0.05

DIPP: Finnish Type I Diabetes Prediction and Prevention Nutrition Study; STRIP: Turku Coronary Risk Factor Intervention Project for Children

Table A4.2
National dietary exposures to PCB 52

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
Belgium	Adolescents	1.5	5.6	3.1	11.3
	Adults	1.2	4.5	2.3	8.9
	Elderly	1.0	4.2	2.0	8.4
	Other children	1.6	13.7	3.3	27.4
	Toddlers	2.4	17.2	4.8	34.3
	Very elderly	1.1	4.6	2.1	9.2
China	Children	0.1	0.1	0.2	0.2
	General population	0.1	0.1	0.1	0.1
Cyprus	Adolescents	0.3	2.6	0.7	5.3
Czech Republic	Adolescents	0.04	0.5	0.1	1.1
	Adults	0.02	0.3	0.05	0.5
	Other children	0.04	0.8	0.1	1.6
Finland	Adults	0.04	0.04	0.1	0.1
	Elderly	0.1	0.1	0.1	0.1

Table A4.2 (continued)

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
	Other children (DIPP)	0.1	0.1	0.2	0.2
	Other children (STRIP)	0.4	0.4	0.8	0.8
	Toddlers	0.9	0.9	1.9	1.9
France	Adolescents	0.02	0.1	0.04	0.1
	Adults	0.02	0.1	0.05	0.1
	Elderly	0.03	0.1	0.07	0.1
	Other children	0.03	0.1	0.07	0.2
	Very elderly	0.03	0.1	0.07	0.1
Germany	Adolescents	0.1	0.3	0.3	0.5
	Adults	0.2	0.3	0.4	0.6
	Elderly	0.2	0.4	0.5	0.8
	Other children (DONALD 2006)	0.5	0.9	1.0	1.9
	Other children (DONALD 2007)	0.7	1.2	1.4	2.4
	Other children (DONALD 2008)	0.4	0.8	0.8	1.7
	Toddlers (DONALD 2006)	1.3	2.2	2.5	4.3
	Toddlers (DONALD 2007)	1.0	2.0	2.0	4.1
	Toddlers (DONALD 2008)	1.2	2.3	2.5	4.5
	Very elderly	0.2	0.4	0.4	0.7
Greece	Other children	1.5	2.0	3.1	4.1
Ireland	Adults	0.04	0.1	0.1	0.2
Italy	Adolescents	0.04	0.2	0.1	0.3
	Adults	0.03	0.1	0.1	0.3
	Elderly	0.02	0.1	0.05	0.3
	Infants	0.001	1.2	0.001	2.5
	Other children	0.1	0.4	0.1	0.8
	Toddlers	0.004	0.6	0.01	1.2
	Very elderly	0.01	0.1	0.02	0.2
Netherlands	Adults	0.1	0.1	0.2	0.2
	Other children	0.1	0.1	0.2	0.3
	Toddlers	0.1	0.1	0.2	0.2
Republic of Korea	Children	0.02	0.03	0.05	0.1
	General population	0.1	0.1	0.1	0.2
Sweden	Adolescents	0.1	1.0	0.2	1.9
	Adults	0.2	0.5	0.3	1.1
	Other children	0.2	1.7	0.3	3.3
United Kingdom	Adults	0.05	0.1	0.1	0.1

DIPP: Finnish Type I Diabetes Prediction and Prevention Nutrition Study; STRIP: Turku Coronary Risk Factor Intervention Project for Children

Table A4.3
National dietary exposures to PCB 101

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
Belgium	Adolescents	0.8	5.4	1.5	10.8
	Adults	0.7	4.4	1.3	8.9
	Elderly	0.7	4.4	1.3	8.7
	Other children	1.2	13.8	2.4	27.6
	Toddlers	1.6	17.2	3.1	34.4
	Very elderly	0.6	4.8	1.3	9.5
China	Children	0.1	0.1	0.3	0.3
	General population	0.1	0.1	0.1	0.1
Cyprus	Adolescents	0.3	2.6	0.6	5.2
Czech Republic	Adolescents	0.1	0.6	0.2	1.1
	Adults	0.1	0.3	0.1	0.6
	Other children	0.1	0.8	0.2	1.6
Finland	Adults	0.05	0.05	0.1	0.1
	Elderly	0.2	0.2	0.4	0.4
	Other children (DIPP)	0.1	0.1	0.2	0.2
	Other children (STRIP)	1.3	1.3	2.5	2.5
	Toddlers	1.7	1.7	3.4	3.4
France	Adolescents	0.04	0.1	0.08	0.2
	Adults	0.1	0.1	0.1	0.2
	Elderly	0.1	0.1	0.2	0.2
	Other children	0.1	0.2	0.2	0.3
	Very elderly	0.1	0.1	0.2	0.3
Germany	Adolescents	0.2	0.2	0.4	0.5
	Adults	0.3	0.4	0.7	0.8
	Elderly	0.4	0.5	0.9	1.0
	Other children (DONALD 2006)	0.6	0.7	1.2	1.5
	Other children (DONALD 2007)	1.0	1.1	2.0	2.2
	Other children (DONALD 2008)	0.6	0.7	1.2	1.3
	Toddlers (DONALD 2006)	0.8	1.6	1.7	3.2
	Toddlers (DONALD 2007)	0.9	1.5	1.7	2.9
	Toddlers (DONALD 2008)	1.0	1.7	2.0	3.5
	Very elderly	0.4	0.4	0.8	0.9
Greece	Other children	3.0	3.4	6.0	6.7
Ireland	Adults	0.1	0.2	0.2	0.3
Italy	Adolescents	0.05	0.2	0.1	0.4
	Adults	0.04	0.2	0.1	0.3
	Elderly	0.03	0.1	0.1	0.3
	Infants	0.000 3	1.2	0.001	2.5
	Other children	0.1	0.4	0.2	0.9
	Toddlers	0.002	0.6	0.004	1.2

Table A4.3 (continued)

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	**Population group (survey)**	**Lower bound**	**Upper bound**	**Lower bound**	**Upper bound**
	Very elderly	0.01	0.1	0.03	0.2
Japan	Children	0.2	0.2	0.3	0.3
	General population	0.1	0.1	0.2	0.2
Netherlands	Adults	0.1	0.2	0.3	0.3
	Other children	0.1	0.2	0.2	0.3
	Toddlers	0.1	0.1	0.2	0.3
Republic of Korea	Children	0.03	0.03	0.1	0.1
	General population	0.1	0.1	0.2	0.2
Sweden	Adolescents	0.3	1.7	0.6	3.4
	Adults	0.6	1.2	1.3	2.5
	Other children	0.6	3.0	1.2	6.0
United Kingdom	Adults	0.1	0.1	0.1	0.2

DIPP: Finnish Type I Diabetes Prediction and Prevention Nutrition Study; STRIP: Turku Coronary Risk Factor Intervention Project for Children

Table A4.4
National dietary exposures to PCB 138

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	**Population group (survey)**	**Lower bound**	**Upper bound**	**Lower bound**	**Upper bound**
Belgium	Adolescents	2.6	5.4	5.2	10.8
	Adults	1.7	4.4	3.4	8.8
	Elderly	1.3	4.2	2.6	8.5
	Other children	3.2	14.2	6.3	28.3
	Toddlers	4.1	17.5	8.1	35.0
	Very elderly	1.5	4.7	2.9	9.3
China	Children	0.2	0.2	0.4	0.4
	General population	0.1	0.1	0.2	0.2
Cyprus	Adolescents	0.8	3.1	1.6	6.2
Czech Republic	Adolescents	0.1	0.6	0.2	1.1
	Adults	0.05	0.3	0.1	0.6
	Other children	0.1	0.9	0.2	1.7
Finland	Adults	0.2	0.2	0.3	0.3
	Elderly	0.5	0.5	0.9	0.9
	Other children (DIPP)	0.3	0.3	0.6	0.6
	Other children (STRIP)	2.4	2.4	4.7	4.7
	Toddlers	2.5	2.5	4.9	5.0
France	Adolescents	0.2	0.2	0.4	0.5
	Adults	0.2	0.2	0.4	0.5

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
	Elderly	0.3	0.3	0.5	0.6
	Other children	0.4	0.5	0.8	0.9
	Very elderly	0.3	0.3	0.5	0.6
Germany	Adolescents	0.7	0.7	1.4	1.4
	Adults	0.9	0.9	1.7	1.8
	Elderly	1.0	1.0	2.0	2.0
	Other children (DONALD 2006)	1.7	1.8	3.5	3.5
	Other children (DONALD 2007)	1.9	2.0	3.8	3.9
	Other children (DONALD 2008)	1.5	1.6	3.1	3.1
	Toddlers (DONALD 2006)	2.1	2.1	4.2	4.2
	Toddlers (DONALD 2007)	2.0	2.0	3.9	4.0
	Toddlers (DONALD 2008)	2.1	2.2	4.3	4.3
	Very elderly	1.1	1.1	2.1	2.2
Greece	Other children	4.3	4.7	8.6	9.4
Ireland	Adults	0.2	0.3	0.4	0.5
Italy	Adolescents	0.1	0.2	0.2	0.5
	Adults	0.1	0.2	0.2	0.4
	Elderly	0.1	0.2	0.1	0.4
	Infants	0.001	1.2	0.001	2.5
	Other children	0.2	0.5	0.4	1.0
	Toddlers	0.003	0.6	0.01	1.2
	Very elderly	0.03	0.1	0.1	0.3
Japan	Children	0.1	0.1	0.3	0.3
	General population	0.1	0.1	0.2	0.2
Netherlands	Adults	0.8	0.8	1.5	1.5
	Other children	1.1	1.1	2.1	2.1
	Toddlers	1.1	1.1	2.3	2.3
Republic of Korea	Children	0.03	0.04	0.1	0.1
	General population	0.1	0.1	0.2	0.2
Sweden	Adolescents	1.1	1.3	2.2	2.7
	Adults	1.7	1.8	3.5	3.7
	Other children	2.2	2.5	4.3	5.1
United Kingdom	Adults	0.3	0.3	0.7	0.7

DIPP: Finnish Type I Diabetes Prediction and Prevention Nutrition Study; STRIP: Turku Coronary Risk Factor Intervention Project for Children

Table A4.5
National dietary exposures to PCB 153

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
Belgium	Adolescents	4.6	6.2	9.2	12.4
	Adults	3.0	4.8	6.0	9.6
	Elderly	2.3	4.4	4.7	8.9
	Other children	4.9	12.1	9.9	24.2
	Toddlers	6.5	15.7	13.1	31.5
	Very elderly	2.6	5.0	5.2	9.9
China	Children	0.2	0.2	0.4	0.4
	General population	0.1	0.1	0.2	0.2
Cyprus	Adolescents	1.2	3.5	2.4	7.0
Czech Republic	Adolescents	0.2	0.7	0.4	1.4
	Adults	0.1	0.4	0.2	0.7
	Other children	0.3	1.0	0.5	2.1
Finland	Adults	0.2	0.2	0.4	0.4
	Elderly	0.6	0.6	1.2	1.2
	Other children (DIPP)	0.4	0.4	0.7	0.7
	Other children (STRIP)	3.5	3.5	7.0	7.1
	Toddlers	3.4	3.5	6.9	6.9
France	Adolescents	0.3	0.3	0.6	0.7
	Adults	0.3	0.4	0.7	0.7
	Elderly	0.4	0.5	0.9	0.9
	Other children	0.6	0.6	1.2	1.3
	Very elderly	0.5	0.5	0.9	1.0
Germany	Adolescents	0.9	1.0	1.8	1.9
	Adults	1.1	1.1	2.2	2.3
	Elderly	1.2	1.2	2.4	2.4
	Other children (DONALD 2006)	2.2	2.4	4.4	4.7
	Other children (DONALD 2007)	2.4	2.6	4.7	5.1
	Other children (DONALD 2008)	1.9	2.1	3.8	4.2
	Toddlers (DONALD 2006)	2.8	3.1	5.6	6.1
	Toddlers (DONALD 2007)	2.6	3.0	5.3	6.0
	Toddlers (DONALD 2008)	2.8	3.1	5.6	6.3
	Very elderly	1.3	1.3	2.6	2.7
Greece	Other children	0.5	1.2	1.1	2.3
Ireland	Adults	0.3	0.3	0.5	0.7
Italy	Adolescents	0.1	0.2	0.2	0.5
	Adults	0.1	0.2	0.2	0.4
	Elderly	0.1	0.2	0.1	0.4
	Infants	0.001	1.2	0.002	2.5
	Other children	0.2	0.5	0.4	1.0
	Toddlers	0.01	0.6	0.01	1.2

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
	Very elderly	0.03	0.1	0.1	0.3
Japan	Children	0.3	0.3	0.5	0.5
	General population	0.2	0.2	0.3	0.3
Netherlands	Adults	1.0	1.0	2.1	2.1
	Other children	1.4	1.4	2.8	2.8
	Toddlers	1.5	1.5	3.1	3.1
Republic of Korea	Children	0.04	0.04	0.1	0.1
	General population	0.1	0.1	0.2	0.2
Sweden	Adolescents	1.4	1.7	2.8	3.5
	Adults	2.0	2.2	4.0	4.3
	Other children	2.7	3.3	5.4	6.6
United Kingdom	Adults	0.4	0.4	0.8	0.8

DIPP: Finnish Type I Diabetes Prediction and Prevention Nutrition Study; STRIP: Turku Coronary Risk Factor Intervention Project for Children

Table A4.6
National dietary exposures to PCB 180

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	Population group (survey)	Lower bound	Upper bound	Lower bound	Upper bound
Belgium	Adolescents	1.0	5.5	2.1	11.1
	Adults	0.7	4.5	1.5	9.0
	Elderly	0.6	4.3	1.2	8.6
	Other children	1.6	13.8	3.2	27.6
	Toddlers	2.0	17.3	4.1	34.5
	Very elderly	0.6	4.7	1.3	9.4
China	Children	0.1	0.1	0.2	0.2
	General population	0.04	0.04	0.1	0.1
Cyprus	Adolescents	0.4	2.7	0.8	5.4
Czech Republic	Adolescents	0.1	0.6	0.2	1.1
	Adults	0.05	0.3	0.1	0.6
	Other children	0.1	0.9	0.2	1.7
Finland	Adults	0.1	0.1	0.1	0.1
	Elderly	0.2	0.2	0.5	0.5
	Other children (DIPP)	0.1	0.1	0.2	0.2
	Other children (STRIP)	1.3	1.3	2.6	2.6
	Toddlers	1.0	1.0	2.0	2.1
France	Adolescents	0.1	0.1	0.2	0.3
	Adults	0.1	0.1	0.2	0.3
	Elderly	0.1	0.2	0.3	0.3
	Other children	0.2	0.3	0.4	0.5

Table A4.6 (continued)

		Dietary exposure (ng/kg bw per day)			
		Mean		High	
Country	**Population group (survey)**	**Lower bound**	**Upper bound**	**Lower bound**	**Upper bound**
	Very elderly	0.1	0.2	0.3	0.3
Germany	Adolescents	0.5	0.6	0.9	1.1
	Adults	0.6	0.7	1.1	1.3
	Elderly	0.6	0.7	1.3	1.5
	Other children (DONALD 2006)	1.1	1.5	2.2	3.0
	Other children (DONALD 2007)	1.5	2.0	3.1	3.9
	Other children (DONALD 2008)	1.0	1.4	2.0	2.7
	Toddlers (DONALD 2006)	1.3	2.0	2.7	4.0
	Toddlers (DONALD 2007)	1.2	2.0	2.4	4.0
	Toddlers (DONALD 2008)	1.3	2.1	2.7	4.1
	Very elderly	0.6	0.7	1.2	1.4
Greece	Other children	0.7	1.2	1.5	2.5
Ireland	Adults	0.1	0.2	0.2	0.4
Italy	Adolescents	0.04	0.2	0.1	0.3
	Adults	0.04	0.1	0.1	0.3
	Elderly	0.03	0.1	0.1	0.3
	Infants	0.001	1.2	0.002	2.5
	Other children	0.1	0.4	0.1	0.8
	Toddlers	0.005	0.6	0.01	1.2
	Very elderly	0.01	0.1	0.03	0.2
Japan	Children	0.1	0.1	0.1	0.1
	General population	0.05	0.05	0.1	0.1
Netherlands	Adults	0.4	0.4	0.9	0.9
	Other children	0.6	0.6	1.2	1.2
	Toddlers	0.7	0.7	1.3	1.3
Republic of Korea	Children	0.02	0.03	0.04	0.1
	General population	0.1	0.1	0.1	0.2
Sweden	Adolescents	0.4	0.5	0.9	1.1
	Adults	0.7	0.7	1.4	1.4
	Other children	0.9	1.1	1.8	2.1
United Kingdom	Adults	0.1	0.1	0.2	0.2

DIPP: Finnish Type I Diabetes Prediction and Prevention Nutrition Study; STRIP: Turku Coronary Risk Factor Intervention Project for Children

Appendix 5. Dietary exposure calculations for each cluster, including consumption, concentration (lower bound and upper bound) and dietary exposure (lower bound and upper bound)

Clusters with specific concentration data: Clusters 6, 7, 8, 9, 10, 11, 15
(only showing information for foods where concentration data were available)

Table A5.1
Dietary exposure calculations for cluster 6

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
84	Plant origin fat	33.5	22	249	250	8.3	8.4
85	Animal or vegetable fat, nes	0.1	133	3 967	22 839	0.4	2.4
90	Milks (no other ingredients)	146.9	20	390	531	57.3	77.9
91	Dairy products (incl. whey, excl. milk fats)	15.6	25	437	437	6.8	6.8
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	35.6	50	934	94	3.3	3.3
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	35.5	9	89	89	3.2	3.2
102	Mammalian offal, unprocessed (incl. home-cooked)	5.0	12	121	121	0.6	0.6
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	0.3	62	602	2 532	0.2	0.7
110	Eggs	17.6	41	2 986	3 775	52.4	66.3
120	Freshwater fish, unprocessed (incl. home-cooked)	8.7	55	885	1 053	7.7	9.2
121	Marine fish, unprocessed (incl. home-cooked)	0.8	4	1 897	1 897	1.6	1.6
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	0.7	7	2 363	5 150	1.7	3.6
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	8.4	5	2 342	2 342	19.6	19.6
170	Food for infants and small children	0.4	5	0.4	0.4	0.000 2	0.000 2
	Total	1 994				163	203
	Mean dietary exposure (ng/kg bw per day)					3	3

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.2
Dietary exposure calculations for cluster 7

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
15	Fresh fruit, nes	14.0	6	13	46	0.2	0.6
22	Tree nuts (excl. groundnut)	5.2	1	567	112	0.3	0.6
31	Roots and tubers, nes	0.1	2	11	182	0.001	0.001
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	20.7	1	1 130	1 130	23.4	23.4
48	Other and mixed vegetables	33.4	14	11	24	0.4	0.8
60	Cereal grains & flours	216.7	6	330	430	71.6	93.2
61	Further processed cereals and by-products	30.1	4	69	69	2.1	2.1
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	98.9	1	950	950	93.9	93.9
80	Milk fats	21.0	18	1 987	2 342	41.7	49.2
83	Marine animal fat	0.0	44	22 242	22 265		
84	Plant origin fat	51.0	32	1 481	2 021	75.5	103.0
85	Animal or vegetable fat, nes	3.9	27	3 427	3 945	13.3	15.3
90	Milks (no other ingredients)	276.9	45	22	63	6.1	17.4
91	Dairy products (incl. whey, excl. milk fats)	48.1	80	219	248	10.5	11.9
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	126.6	131	286	334	36.1	42.3
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	67.9	102	889	168	6.0	11.4
102	Mammalian offal, unprocessed (incl. home-cooked)	15.2	194	159	241	2.4	3.7
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	3.9	80	203	240	0.8	0.9
105	Meat and offal, processed (excl. marine)	15.9	5	414	414	6.6	6.6
110	Eggs	28.8	201	811	947	23.3	27.3
120	Freshwater fish, unprocessed (incl. home-cooked)	5.3	771	7 071	7 457	37.3	39.3
121	Marine fish, unprocessed (incl. home-cooked)	0.6	560	13 448	13 482	8.6	8.7
122	Crustaceans, unprocessed (incl. home-cooked)	1.2	55	891	1 018	1.1	1.2
123	Molluscs ans cephalopods, unprocessed (incl. home-cooked)	5.9	296	273	439	1.6	2.6
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	3.1	1 014	92 734	92 837	287.8	288.2
127	Processed aquatic animals	29.2	163	2 528	2 560	73.8	74.7
170	Food for infants and small children	0.6	25	3 497	3 497	2.2	2.2
190	Out of classifying	16.5	2	13 443	13 443	222.3	222.3
	Total	1 994				1 049	1 143
	Mean dietary exposure (ng/kg bw per day)					17	19

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.3
Dietary exposure calculations for cluster 8

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
10	Berries and other small fruits, fresh	23.9	9	25	25	0.6	0.6
12	Pome fruits, fresh	57.8	11	105	105	6.1	6.1
31	Roots and tubers, nes	0.0	20	37	37	4.94E-05	4.94E-05
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	39.8	20	34	34	1.3	1.3
42	Fruiting vegetables, cucurbits	34.2	10	219	219	7.5	7.5
43	Fruiting vegetables (other than cucurbits) and mushrooms	61.0	1	0.04	0.04	0.002	0.002
44	Leafy vegetables (including brassica leafy vegetables and seaweed)	15.4	10	125	125	1.9	1.9
45	Legume vegetables (fresh/green)	8.9	10	55	55	0.5	0.5
50	Herbs	0.0	1	256	256	0	0
53	Spices & condiments	1.3	1	1 222	1 222	1.6	1.6
60	Cereal grains & flours	245.0	10	44	44	10.8	10.8
61	Further processed cereals and by-products	15.5	1	2	2	0.03	0.03
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	110.4	18	0	3	0.0	0.3
80	Milk fats	25.5	28	3 545	3 643	90.5	93.0
84	Plant origin fat	53.7	1	120 650	120 650	6 484.8	6 484.8
85	Animal or vegetable fat, nes	1.0	9	61 515	61 515	64.6	64.6
90	Milks (no other ingredients)	233.3	4 808	331	331	77.3	77.3
91	Dairy products (incl. whey, excl. milk fats)	53.3	431	741	743	39.5	39.6
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	146.9	422	322	374	47.3	55.0
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	50.9	159	72	93	3.7	4.7
102	Mammalian offal, unprocessed (incl. home-cooked)	5.2	44	459	520	2.4	2.7
103	Poultry offal, unprocessed (incl. home-cooked)	0.7	1	0	4	0	0.003
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	1.4	29	33 580	33 580	47.4	47.4
105	Meat and offal, processed (excl. marine)	4.6	48	1	9	0.004	0.04
110	Eggs	34.0	372	865	998	29.4	33.9
120	Freshwater fish, unprocessed (incl. home-cooked)	2.7	354	560	1 401	1.5	3.8
121	Marine fish, unprocessed (incl. home-cooked)	0.2	831	27 476	30 663	5.4	6.1
122	Crustaceans, unprocessed (incl. home-cooked)	0.1	39	0.002	519	2E-07	0.05
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	0.9	18	2	3	0.001	0.002

Table A5.3 (continued)

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	3.3	389	35 643	36 241	116.9	118.9
130	Fruit & vegetable juices	9.9	21	0	10	0	0.1
151	Other alcoholic beverages	67.7	11	0	10	0	0.7
170	Food for infants and small children	0.0	39	163	351	0.001	0.002
190	Out of classifying	1.4	6	858	1 083	1.2	1.5
	Total	1 994				7 042	7 065
	Mean dietary exposure (ng/kg bw per day)					117	118

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.4
Dietary exposure calculations for cluster 9

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
20	Pulses (dry, prepared and composites)	20.1	216	37	37	0.7	0.7
31	Roots and tubers, nes	0.4	276	16	42	0.01	0.02
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	50.6	12	37	37	1.9	1.9
42	Fruiting vegetables, cucurbits	56.7	42	36	36	2.0	2.0
43	Fruiting vegetables (other than cucurbits) and mushrooms	58.3	24	11	11	0.6	0.7
44	Leafy vegetables (including brassica leafy vegetables and seaweed)	33.4	162	13	14	0.4	0.5
45	Legume vegetables (fresh/green)	7.2	36	28	28	0.2	0.2
47	Stalk and stem vegetables	7.2	6	12	12	0.1	0.1
54	Sauces & vinegars	3.1	24	0	300	0	0.9
60	Cereal grains & flours	391.9	324	17	83	6.5	32.6
61	Further processed cereals and by-products	3.4	240	0	300	0	1.0
71	Cocoa, cola and their non-liquid derivates	0.3	24	25	300	0.0	0.1
80	Milk fats	0.4	24	343	543	0.1	0.2
84	Plant origin fat	19.4	24	0	300	0	5.8
90	Milks (no other ingredients)	40.3	1 698	19	28	0.8	1.1
91	Dairy products (incl. whey, excl. milk fats)	0.6	648	51	84	0.0	0.0
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	79.5	2 256	46	64	3.6	5.1
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	23.8	204	3	110	0.1	2.6

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
102	Mammalian offal, unprocessed (incl. home-cooked)	6.3	54	2	136	0.0	0.9
105	Meat and offal, processed (excl. marine)	1.7	72	0	300	0	0.5
110	Eggs	31.6	360	97	157	3.0	5.0
120	Freshwater fish, unprocessed (incl. home-cooked)	27.0	1 590	648	670	17.5	18.1
121	Marine fish, unprocessed (incl. home-cooked)	1.3	474	597	625	0.8	0.8
122	Crustaceans, unprocessed (incl. home-cooked)	5.3	276	280	318	1.5	1.7
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	12.2	180	922	1 015	11.3	12.4
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	7.2	12	483	484	3.5	3.5
131	Non-alcoholic beverages (excl. milk-based beverages, stimulants and water)	11.2	24	0	300	0	3.4
140	Coffee (or substitute) based beverages	0.7	24	0	300	0	0.2
142	Tea and mate beverages	1.1	24	0	300	0	0.3
170	Food for infants and small children	0.1	822	43	43	0.004	0.004
190	Out of classifying	0.5	240	0	300	0	0.2
	Total	1 994				55	103
	Mean dietary exposure (ng/kg bw per day)					1	2

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.5
Dietary exposure calculations for cluster 10

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
22	Tree nuts (excl. groundnut)	4.2	10	32	32	0.1	0.1
32	Roots and tubers processed	3.2	10	36	36	0.1	0.1
53	Spices & condiments	1.9	10	21	21	0.0	0.0
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	129.5	144	271	15 688	35.1	2 031.5
71	Cocoa, cola and their non-liquid derivates	4.1	10	128	128	0.5	0.5
80	Milk fats	8.7	58	80	81	0.7	0.7
83	Marine animal fat	0.0	18	24	25	0.0	0.0
84	Plant origin fat	59.7	26	18	18	1.1	1.1
85	Animal or vegetable fat, nes	1.1	66	0	12 793	0	13.6

Table A5.5 (continued)

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
90	Milks (no other ingredients)	246.2	304	112	1 706	27.7	420.0
91	Dairy products (incl. whey, excl. milk fats)	32.8	156	37	37	1.2	1.2
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	108.7	532	163	652	17.7	70.9
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	84.4	58	788	825	66.5	69.7
102	Mammalian offal, unprocessed (incl. home-cooked)	6.8	28	50	76	0.3	0.5
103	Poultry offal, unprocessed (incl. home-cooked)	0.3	10	88	88	0.03	0.03
105	Meat and offal, processed (excl. marine)	3.1	30	86	86	0.3	0.3
110	Eggs	39.1	364	2 796	2 933	109.5	114.8
120	Freshwater fish, unprocessed (incl. home-cooked)	3.8	2 738	3 149	3 395	12.1	13.0
121	Marine fish, unprocessed (incl. home-cooked)	0.5	1 510	1 084	1 255	0.5	0.6
122	Crustaceans, unprocessed (incl. home-cooked)	1.3	485	957	1 193	1.3	1.6
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	5.5	1 422	1 170	1 387	6.5	7.7
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	6.6	1 416	1 394	1 748	9.2	11.5
170	Food for infants and small children	0.3	68	11	11	0.003	0.003
190	Out of classifying	2.9	112	36	36	0.1	0.1
	Total	1 994				290	2 760
	Mean dietary exposure (ng/kg bw per day)					5	46

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.6
Dietary exposure calculations for cluster 11

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
20	Pulses (dry, prepared and composites)	6.4	1	0	1 000	0	6.4
80	Milk fats	21.2	7	1 956	8 597	41.5	182.6
81	Mammalian fats (no milk fat)	12.5	3	756	10 200	9.5	127.8
82	Poultry fats	0.6	5	4 355	11 688	2.5	6.8
83	Marine animal fat	0.0	2	0	1 980	0	0

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
84	Plant origin fat	55.7	100	161	2 529	9.0	140.9
85	Animal or vegetable fat, nes	8.7	43	17 772	19 865	155.4	173.7
90	Milks (no other ingredients)	266.9	91	1 609	3 552	429.4	947.9
91	Dairy products (incl. whey, excl. milk fats)	69.0	25	1 477	3 440	101.9	237.4
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	117.1	18	364	671	42.6	78.6
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	51.2	11	298	2 473	15.2	126.7
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	0.3	1	338	3 671	0.1	1.0
110	Eggs	42.1	60	7 163	12 012	301.8	506.1
120	Freshwater fish, unprocessed (incl. home-cooked)	1.2	129	12 186	13 943	14.6	16.7
121	Marine fish, unprocessed (incl. home-cooked)	0.2	32	8 891	10 162	1.9	2.1
122	Crustaceans, unprocessed (incl. home-cooked)	0.4	7	2 679	4 108	1.1	1.6
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	1.1	22	2 006	4 673	2.3	5.3
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	11.4	178	214 614	214 831	2 444.0	2 446.5
170	Food for infants and small children	0.0	8	0	2 875	0	0
190	Out of classifying	0.0	7	833	3 595	0	0
	Total	1 994				3 573	5 008
	Mean dietary exposure (ng/kg bw per day)					60	83

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.7

Dietary exposure calculations for cluster 15

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
10	Berries and other small fruits, fresh	22.1	7	1	173	0.0	3.8
11	Citrus fruits, fresh	29.0	5	0	321	0.0	9.3
12	Pome fruits, fresh	64.6	14	4	190	0.3	12.3
13	Stone fruits, fresh	31.4	5	0.1	320	0.0	10.1
14	Tropical and subtropical fruits, fresh	30.6	4	0	201	0.0	6.1
16	Dried fruits	2.2	2	0	400	0	0.9
17	Prepared fruits (no dried & juice)	8.4	1	0	0.8	0	0.01
20	Pulses (dry, prepared and composites)	10.5	4	0.02	201	0.000 2	2.1

Table A5.7 (continued)

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
21	Oilseed (incl. flour)	0.6	4	457	807	0.3	0.5
22	Tree nuts (excl. groundnut)	4.0	2	1	301	0.003	1.2
31	Roots and tubers, nes	0.0	21	1	249	2.15E-06	0.000 4
32	Roots and tubers processeded	9.5	2	0.1	1	0.000 9	0.005
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	58.7	18	11	200	0.6	11.7
41	Bulb vegetables	36.1	4	2	302	0.1	10.9
42	Fruiting vegetables, cucurbits	34.4	4	0.04	201	0.001	6.9
43	Fruiting vegetables (other than cucurbits) and mushrooms	73.9	8	0.02	350	0.002	25.9
44	Leafy vegetables (including brassica leafy vegetables and seaweed)	7.5	17	0.1	200	0.001	1.5
45	Legume vegetables (fresh/green)	10.4	2	0	400	0	4.2
47	Stalk and stem vegetables	0.3	2	0.05	1	1.28E-05	0.000 1
48	Other and mixed vegetables	40.8	7	30	31	1.2	1.3
53	Spices & condiments	3.3	7	0.1	172	0.000 2	0.6
60	Cereal grains & flours	262.3	21	15	210	3.9	55.1
61	Further processed cereals and by-products	19.4	42	18	147	0.4	2.9
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	87.4	47	17	815	1.5	71.2
71	Cocoa, cola and their non-liquid derivates	6.3	5	0.6	81	0.004	0.5
80	Milk fats	14.4	23	521	624	7.5	9.0
81	Mammalian fats (no milk fat)	14.1	6	759	1 176	10.7	16.6
82	Poultry fats	0.3	40	924	959	0.3	0.3
83	Marine animal fat	0.0	2	9 904	9 988	0	0
84	Plant origin fat	43.2	18	55	481	2.4	20.8
85	Animal or vegetable fat, nes	1.6	149	888	1 031	1.4	1.6
90	Milks (no other ingredients)	352.3	149	72	217	25.3	76.5
91	Dairy products (incl. whey, excl. milk fats)	35.8	51	38	288	1.4	10.3
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	114.1	160	52	211	5.9	24.0
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	55.6	38	20	101	1.1	5.6
102	Mammalian offal, unprocessed (incl. home-cooked)	10.0	66	77	121	0.8	1.2
103	Poultry offal, unprocessed (incl. home-cooked)	0.9	7	61	84	0.1	0.1
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	1.0	22	809	1 043	0.8	1.0
105	Meat and offal, processed (excl. marine)	7.5	37	1	80	0.01	0.6
110	Eggs	30.0	207	1 044	1 134	31.3	34.0
120	Freshwater fish, unprocessed (incl. home-cooked)	2.1	111	19 488	19 520	40.0	40.1

Lev2 CODE	Lev2NAME	Consumption (g/day)	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)	LB exposure (ng/day)	UB exposure (ng/day)
121	Marine fish, unprocessed (incl. home-cooked)	0.1	194	17 240	17 257	2.0	2.0
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	1.6	5	1 008	1 008	1.6	1.6
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	3.5	310	32 603	32 705	112.7	113.1
127	Processed aquatic animals	21.7	2	7	7	0.1	0.1
130	Fruit & vegetable juices	13.5	1	0	0.04	0	0.0
131	Non-alcoholic beverages (excl. milk based beverages, stimulants and water)	55.7	4	0.01	20	0.000 5	1.1
142	Tea and mate beverages	0.9	3	0	1 047	0	0.9
150	Beers	225.2	1	0	0.04	0	0.01
151	Other alcoholic beverages	61.4	3	0.01	13	0.000 4	0.8
160	Water	4.6	2	0.02	0.04	7.79E-05	0.000 2
170	Food for infants and small children	0.6	61	31	133	0.02	0.1
190	Out of classifying	6.1	21	11 066	11 986	67.0	72.6
	Total	1 994				321	673
	Mean dietary exposure (ng/kg bw per day)					5	11

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Clusters where concentration data from all countries were used for the dietary exposure calculations: Clusters 1, 2, 3, 4, 5, 12, 13, 14, 16, 17

Table A5.8

Concentration data used for the dietary exposure estimates for clusters with no concentration data

Lev2 CODE	Lev2NAME	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)
10	Berries and other small fruits, fresh	96	15	90
11	Citrus fruits, fresh	30	0.008	320
12	Pome fruits, fresh	150	49	153
13	Stone fruits, fresh	30	0.05	320
14	Tropical and subtropical fruits, fresh	24	0.02	201
15	Fresh fruit, nes	36	13	46
16	Dried fruits	12	0	400
17	Prepared fruits (no dried & juice)	6	0	0.8
20	Pulses (dry, prepared and composites)	246	32	76
21	Oilseed (incl. flour)	24	457	807
22	Tree nuts (excl. groundnut)	28	24	172

Table A5.8 (continued)

Lev2 CODE	Lev2NAME	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)
30	Roots and tubers raw or boiled	0		
31	Roots and tubers, nes	534	17	89
32	Roots and tubers processeded	22	18	19
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	246	50	133
41	Bulb vegetables	24	2	302
42	Fruiting vegetables, cucurbits	126	116	154
43	Fruiting vegetables (other than cucurbits) and mushrooms	78	3	219
44	Leafy vegetables (including brassica leafy vegetables and seaweed)	324	30	93
45	Legume vegetables (fresh/green)	108	40	85
46	Root vegetables	0		
47	Stalk and stem vegetables	18	4	4
48	Other and mixed vegetables	126	17	26
50	Herbs	6	256	256
52	Hops	0		
53	Spices & condiments	58	129	254
54	Sauces & vinegars	24	0	300
60	Cereal grains & flours	546	40	131
61	Further processed cereals and by-products	522	12	212
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	540	92	4 620
71	Cocoa, cola and their non-liquid derivates	64	33	174
80	Milk fats	566	1 815	2 884
81	Mammalian fats (no milk fat)	64	650	5 085
82	Poultry fats	275	1 280	2 291
83	Marine animal fat	306	19 579	19 680
84	Plant origin fat	1 115	1 026	2 585
85	Animal or vegetable fat, nes	2 261	5 894	13 323
90	Milks (no other ingredients)	33 046	327	412
91	Dairy products (incl. whey, excl. milk fats)	4 521	546	719
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	7 542	189	280
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	2 192	96	231
102	Mammalian offal, unprocessed (incl. home-cooked)	2 024	179	250
103	Poultry offal, unprocessed (incl. home-cooked)	58	61	78
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	1 169	5 366	6 053
105	Meat and offal, processed (excl. marine)	642	25	89
110	Eggs	6 072	1 431	1 927
111	Egg products and processed eggs	0		
120	Freshwater fish, unprocessed (incl. home-cooked)	12 848	5 154	5 599

Lev2 CODE	Lev2NAME	Number of samples	LB concentration (ng/kg)	UB concentration (ng/kg)
121	Marine fish, unprocessed (incl. home-cooked)	11 710	17 556	18 971
122	Crustaceans, unprocessed (incl. home-cooked)	1 367	693	948
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	3 690	734	1 029
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	12 806	73 356	73 589
127	Processed aquatic animals	990	2 497	2 529
130	Fruit & vegetable juices	132	0	10
131	Non-alcoholic beverages (excl. milk-based beverages, stimulants and water)	48	0.004	160
140	Coffee (or substitute) based beverages	24	0	300
142	Tea and mate beverages	42	0	620
150	Beers	6	0	0.04
151	Other alcoholic beverages	84	0.002	11
160	Water	12	0.02	0.04
170	Food for infants and small children	1 728	353	495
190	Out of classifying	568	2 859	3 412

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.9

Estimated dietary exposures for clusters 1, 2, 3 and 4 using concentration data from all countries

		Cluster 1			Cluster 2			Cluster 3			Cluster 4		
Lev2 CODE	Lev2NAME	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
10	Berries and other small fruits, fresh	14.4	0.2	1	13.4	0.2	1	0.1	0.001	0.007	18.4	0.3	2
11	Citrus fruits, fresh	31.7	0.000 3	10	11.4	0.000 1	4	16.7	0.000 1	5	72.7	0.000 6	23
12	Pome fruits, fresh	16.3	0.8	2	33.2	2	5	0.6	0.03	0.09	20.2	1	3
13	Stone fruits, fresh	10.8	0.000 6	3	22.7	0.001	7	0.2	1E-05	0.08	10.5	0.000 5	3
14	Tropical and subtropical fruits, fresh	32.8	0.000 6	7	9.0	0.000 2	2	123.1	0.002	25	117.0	0.002	23
15	Fresh fruit, nes	42.7	0.6	2	35.9	0.5	2	9.1	0.1	0.4	64.6	0.8	3
16	Dried fruits	1.3	0	0.5	0.9	0	0.4	0.1	0	0.03	2.9	0	1
17	Prepared fruits (no dried & juice)	1.6	0	0.001	1.4	0	0.001	0.6	0	0.000 5	13.5	0	0.01
20	Pulses (dry, prepared and composites)	15.6	0.5	1	7.1	0.2	0.5	23.7	0.8	2	19.2	0.6	1
21	Oilseed (incl. flour)	1.3	0.6	1	0.4	0.2	0.3	1.8	0.8	1	2.5	1	2
22	Tree nuts (excl. groundnut)	3.6	0.09	0.6	3.3	0.08	0.6	5.1	0.1	0.9	8.6	0.2	1
30	Roots and tubers raw or boiled	59.3	0	0	314.4	0	0	469.5	0	0	56.9	0	0
31	Roots and tubers, nes	3.1	0.05	0.3	0.0	6E-05	0.000 3	1.4	0.02	0.1	1.8	0.03	0.2
32	Roots and tubers processed	0.2	0.004	0.004	1.0	0.02	0.02	56.3	1	1	4.9	0.09	0.09
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	7.5	0.4	1	46.7	2	6	0.9	0.05	0.1	11.6	0.6	2
41	Bulb vegetables	34.3	0.05	10	46.4	0.07	14	4.7	0.007	1	41.4	0.06	12
42	Fruiting vegetables, cucurbits	20.7	2	3	61.8	7	10	7.9	0.9	1	43.2	5	7

Lev2 CODE	Lev2NAME	Cluster 1			Cluster 2			Cluster 3			Cluster 4		
		Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
43	Fruiting vegetables (other than cucurbits) and mushrooms	49.6	0.2	11	80.8	0.3	18	20.9	0.07	5	98.6	0.3	22
44	Leafy vegetables (including brassica leafy vegetables and seaweed)	1.3	0.04	0.1	0.6	0.02	0.06	0.8	0.03	0.08	7.9	0.2	0.7
45	Legume vegetables (fresh/ green)	7.7	0.3	0.7	1.5	0.06	0.1	0.5	0.02	0.04	3.0	0.1	0.2
46	Root vegetables	9.5	0	0	30.8	0	0	0.4	0	0	8.7	0	0
47	Stalk and stem vegetables	0.7	0.003	0.003	0.0	5E-05	5E-05	0.0	2E-05	2E-05	0.3	0.001	0.002
48	Other and mixed vegetables	23.4	0.4	0.6	46.3	0.8	1	29.4	0.5	0.8	52.2	0.9	1
50	Herbs	0.5	0.1	0.1	0.0	0.000 2	0.000 2	0.0	0	0	0.0	0	0
52	Hops	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0
53	Spices & condiments	2.1	0.3	0.5	1.3	0.2	0.3	2.0	0.3	0.5	6.5	0.8	2
54	Sauces & vinegars	2.3	0	0.7	1.3	0	0.4	1.6	0	0.5	4.6	0	1
60	Cereal grains & flours	372.4	15	49	337.8	13	44	205.9	8	27	355.3	14	47
61	Further processed cereals and by-products	7.2	0.09	2	13.0	0.2	3	4.0	0.05	0.8	21.9	0.3	5
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	101.5	9	469	91.5	8	423	32.9	3	152	85.3	8	394
71	Cocoa, cola and their non-liquid derivates	0.7	0.02	0.1	4.2	0.1	0.7	0.6	0.02	0.1	4.2	0.1	0.7
80	Milk fats	5.4	10	16	5.1	9	15	0.1	0.2	0.3	4.8	9	14
81	Mammalian fats (no milk fat)	2.1	1	11	4.4	3	22	0.7	0.4	3	1.0	0.6	5
82	Poultry fats	0.0	0.002	0.003	0.1	0.1	0.2	0.0	0	0	0.1	0.1	0.2
83	Marine animal fat	0.0	0.002	0.002	0.0	0	0	0.0	0	0	0.0	0.6	0.6
84	Plant origin fat	31.5	32	81	29.9	31	77	20.7	21	54	44.8	46	116

Table A5.9 (continued)

		Cluster 1			Cluster 2			Cluster 3			Cluster 4		
Lev2 CODE	Lev2NAME	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
85	Animal or vegetable fat, nes	0.1	0.7	1	1.4	8	18	0.1	0.9	2	0.7	4	10
90	Milks (no other ingredients)	258.4	84	106	456.5	149	188	20.4	7	8	126.8	41	52
91	Dairy products (incl. whey, excl. milk fats)	2.7	1	2	10.7	6	8	0.3	0.2	0.2	17.6	10	13
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	30.9	6	9	69.4	13	19	14.8	3	4	45.6	9	13
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	14.6	1	3	29.2	3	7	8.0	0.8	2	127.6	12	29
102	Mammalian offal, unprocessed (incl. home-cooked)	4.8	0.9	1	9.7	2	2	3.0	0.5	0.7	5.5	1	1
103	Poultry offal, unprocessed (incl. home-cooked)	0.1	0.007	0.009	0.1	0.005	0.007	0.1	0.007	0.009	5.4	0.3	0.4
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	0.5	3	3	0.0	0.09	0.1	6.5	35	39	0.6	3	3
105	Meat and offal, processed (excl. marine)	0.2	0.004	0.02	3.3	0.08	0.3	1.1	0.03	0.1	3.3	0.08	0.3
110	Eggs	9.1	13	18	27.1	39	52	3.4	5	7	17.1	24	33
111	Egg products and processed eggs	0.1			0.1			0.0			0.2		
120	Freshwater fish, unprocessed (incl. home-cooked)	2.0	10	11	1.9	10	11	6.3	32	35	3.5	18	19
121	Marine fish, unprocessed (incl. home-cooked)	0.6	11	12	1.4	24	26	2.8	49	53	2.5	44	48

Lev2 CODE	Lev2NAME	Cluster 1			Cluster 2			Cluster 3			Cluster 4		
		Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
122	Crustaceans, unprocessed (incl. home-cooked)	0.1	0.07	0.1	0.5	0.4	0.5	0.3	0.2	0.3	1.4	1	1
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	0.1	0.08	0.1	0.4	0.3	0.4	0.0	0.04	0.05	0.5	0.4	0.5
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	4.4	324	325	4.2	305	306	4.4	325	326	9.4	688	690
127	Processed aquatic animals	1.5	4	4	14.1	35	36	9.8	24	25	14.2	35	36
130	Fruit & vegetable juices	3.3	0	0.03	4.5	0	0.04	0.6	0	0.006	12.4	0	0.1
131	Non-alcoholic beverages (excl. milk-based beverages, stimulants and water)	7.7	3E-05	1	74.6	0.000 3	12	3.0	1E-05	0.5	17.2	7E-05	3
140	Coffee (or substitute) based beverages	1.2	0	0.4	2.0	0	0.6	1.3	0	0.4	3.6	0	1
142	Tea and mate beverages	2.4	0	1	2.0	0	1	1.5	0	0.9	2.5	0	2
150	Beers	4.9	0	0.000 2	93.8	0	0.004	50.3	0	0.002	12.8	0	0.000 5
151	Other alcoholic beverages	0.7	1E-06	0.008	12.7	2E-05	0.1	12.7	2E-05	0.1	1.4	2E-06	0.01
160	Water	0.2	4E-06	1E-05	39.7	0.000 7	0.002	0.5	8E-06	2E-05	7.4	0.000 1	0.000 3
170	Food for infants and small children	0.2	0.06	0.09	0.3	0.09	0.1	0.1	0.03	0.05	1.9	0.7	0.9
190	Out of classifying	1.0	3	4	3.7	11	13	1.2	4	4	13.4	38	46
	Total mean exposure (ng/day)	1 267	538	1 188	2 121	684	1 358	1 195	524	791	1 664	1 022	1 696
	Total mean exposure (ng/kg bw per day)		9	20		11	23		9	13		17	28

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.10

Estimated dietary exposures for clusters 5, 12, 13 and 14 using concentration data from all countries

		Cluster 5			Cluster 12			Cluster 13			Cluster 14		
Lev2 CODE	Lev2NAME	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
10	Berries and other small fruits, fresh	4.1	0.06	0.4	0.8	0.01	0.08	0.2	0.002	0.01	11.5	0.2	1
11	Citrus fruits, fresh	33.7	0.000 3	11	465.0	0.004	149	20.8	0.000 2	7	2.1	2E-05	0.7
12	Pome fruits, fresh	7.6	0.4	1	2.0	0.1	0.3	0.3	0.01	0.04	2.2	0.1	0.3
13	Stone fruits, fresh	2.2	0.000 1	0.7	0.1	5E-06	0.03	0.1	4E-06	0.03	0.0	1E-06	0.003
14	Tropical and subtropical fruits, fresh	93.1	0.002	19	135.8	0.002	27	74.5	0.001	15	132.4	0.002	27
15	Fresh fruit, nes	17.5	0.2	0.8	43.5	0.6	2	18.8	0.2	0.9	73.9	1	3
16	Dried fruits	0.3	0	0.1	1.8	0	0.7	0.1	0	0.05	0.6	0	0.3
17	Prepared fruits (no dried & juice)	1.4	0	0.001	2.6	0	0.002	1.1	0	0.000 8	1.3	0	0.001
20	Pulses (dry, prepared and composites)	33.1	1	3	36.7	1	3	41.1	1	3	17.1	0.6	1
21	Oilseed (incl. flour)	1.6	0.7	1	0.4	0.2	0.3	2.9	1	2	0.9	0.4	0.7
22	Tree nuts (excl. groundnut)	15.9	0.4	3	28.3	0.7	5	6.7	0.2	1	157.2	4	27
30	Roots and tubers raw or boiled	67.2	0	0	86.3	0	0	165.9	0	0	168.1	0	0
31	Roots and tubers, nes	0.8	0.01	0.07	0.6	0.01	0.05	28.0	0.5	2	4.9	0.08	0.4
32	Roots and tubers processed	5.1	0.09	0.09	6.6	0.1	0.1	23.6	0.4	0.4	8.7	0.2	0.2
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	17.8	0.9	2	19.4	1	3	6.3	0.3	0.8	5.0	0.3	0.7
41	Bulb vegetables	21.1	0.03	6	20.2	0.03	6	11.3	0.02	3	23.8	0.04	7
42	Fruiting vegetables, cucurbits	10.5	1	2	22.4	3	3	6.2	0.7	1	14.2	2	2

Lev2 CODE	Lev2NAME	Cluster 5			Cluster 12			Cluster 13			Cluster 14		
		Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
43	Fruiting vegetables (other than cucurbits) and mushrooms	46.1	0.2	10	10.4	0.03	2	24.2	0.08	5	33.7	0.1	7
44	Leafy vegetables (including brassica leafy vegetables and seaweed)	2.0	0.06	0.2	2.5	0.08	0.2	0.5	0.01	0.05	0.0	0.001	0.003
45	Legume vegetables (fresh/ green)	5.1	0.2	0.4	0.2	0.007	0.01	0.6	0.02	0.05	3.2	0.1	0.3
46	Root vegetables	2.8	0	0	8.7	0	0	2.1	0	0	3.0	0	0
47	Stalk and stem vegetables	0.3	0.001	0.001	0.0	0.000 2	0.000 2	0.0	2E-05	2E-05	0.0	2E-06	2E-06
48	Other and mixed vegetables	43.9	0.8	1	41.5	0.7	1	46.4	0.8	1	32.7	0.6	0.9
50	Herbs	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0
52	Hops	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0
53	Spices & condiments	4.4	0.6	1	2.5	0.3	0.6	2.2	0.3	0.6	7.0	0.9	2
54	Sauces & vinegars	0.4	0	0.1	1.2	0	0.4	0.6	0	0.2	0.3	0	0.1
60	Cereal grains & flours	358.4	14	47	247.0	10	32	330.5	13	43	321.3	13	42
61	Further processed cereals and by-products	6.6	0.08	1	26.0	0.3	6	2.8	0.03	0.6	3.6	0.04	0.8
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	86.2	8	398	107.2	10	495	35.8	3	166	107.7	10	498
71	Cocoa, cola and their non-liquid derivates	0.4	0.01	0.07	5.3	0.2	0.9	0.1	0.003	0.02	0.9	0.03	0.2
80	Milk fats	5.0	9	14	1.7	3	5	0.6	1	2	0.7	1	2
81	Mammalian fats (no milk fat)	1.6	1	8	5.5	4	28	0.9	0.6	5	0.9	0.6	5
82	Poultry fats	0.0	2E-06	4E-06	0.0	0	0	0.0	0	0	0.0	0	0
83	Marine animal fat	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0
84	Plant origin fat	26.9	28	70	14.4	15	37	22.4	23	58	10.7	11	28

Table A5.10 (continued)

		Cluster 5			Cluster 12			Cluster 13			Cluster 14		
Lev2 CODE	Lev2NAME	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
85	Animal or vegetable fat, nes	0.1	0.6	1	9.7	57	129	0.2	1	2	0.1	0.6	1
90	Milks (no other ingredients)	174.9	57	72	94.1	31	39	98.3	32	40	22.8	7	9
91	Dairy products (incl. whey, excl. milk fats)	1.8	1	1	12.0	7	9	1.5	0.8	1	0.4	0.2	0.3
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	33.0	6	9	30.8	6	9	27.0	5	8	16.8	3	5
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	24.9	2	6	82.6	8	19	3.9	0.4	0.9	11.8	1	3
102	Mammalian offal, unprocessed (incl. home-cooked)	3.8	0.7	1	3.2	0.6	0.8	4.6	0.8	1	2.0	0.4	0.5
103	Poultry offal, unprocessed (incl. home-cooked)	0.2	0.01	0.02	0.0	0	0	0.0	0.001	0.002	0.7	0.04	0.05
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	0.3	2	2	0.7	4	5	2.4	13	15	34.1	183	206
105	Meat and offal, processed (excl. marine)	0.4	0.009	0.03	18.8	0.5	2	0.3	0.009	0.03	0.6	0.01	0.05
110	Eggs	11.4	16	22	10.6	15	20	4.5	6	9	4.0	6	8
111	Egg products and processed eggs	0.2			0.0			0.0			1.0		
120	Freshwater fish, unprocessed (incl. home-cooked)	6.6	34	37	2.7	14	15	3.4	18	19	4.1	21	23
121	Marine fish, unprocessed (incl. home-cooked)	1.4	25	27	3.2	56	61	0.4	8	8	3.8	67	72

Lev2 CODE	Lev2NAME	Cluster 5			Cluster 12			Cluster 13			Cluster 14		
		Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
122	Crustaceans, unprocessed (incl. home-cooked)	1.0	0.7	1	4.2	3	4	0.2	0.1	0.2	0.8	0.6	0.8
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	0.7	0.5	0.7	4.2	3	4	0.0	0.03	0.04	0.2	0.2	0.2
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	3.9	285	286	8.0	586	588	2.8	203	204	26.5	1 946	1 952
127	Processed aquatic animals	3.0	8	8	12.0	30	30	5.5	14	14	12.7	32	32
130	Fruit & vegetable juices	1.5	0	0.01	27.9	0	0.3	1.1	0	0.01	1.1	0	0.01
131	Non-alcoholic beverages (excl. milk-based beverages, stimulants and water)	5.9	2E-05	0.9	43.1	0.000 2	7	2.1	9E-06	0.3	8.0	3E-05	1
140	Coffee (or substitute) based beverages	1.8	0	0.6	5.9	0	2	0.9	0	0.3	1.2	0	0.4
142	Tea and mate beverages	2.3	0	1	0.8	0	0.5	1.6	0	1	5.3	0	3
150	Beers	39.3	0	0.002	65.3	0	0.003	48.0	0	0.002	11.4	0	0.000 5
151	Other alcoholic beverages	3.6	6E-06	0.04	6.8	1E-05	0.07	49.1	8E-05	0.5	0.2	0	0.003
160	Water	0.6	1E-05	3E-05	1.4	2E-05	6E-05	0.4	6E-06	2E-05	0.2	4E-06	1E-05
170	Food for infants and small children	0.1	0.04	0.06	2.8	1	1	0.1	0.03	0.04	0.1	0.04	0.06
190	Out of classifying	0.6	2	2	37.1	106	127	1.0	3	3	1.6	5	5
	Total mean exposure (ng/day)	1 247	508	1 081	1 835	977	1 881	1 137	352	646	1 321	2 318	2 982
	Total mean exposure (ng/kg bw per day)		8	18		16	31		6	11		39	50

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Table A5.11

Estimated dietary exposures for clusters 16 and 17 using concentration data from all countries

		Cluster 16			Cluster 17		
Lev2 CODE	Lev2NAME	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)	Consumption (g/day)	LB exposure (ng/day)	UB exposure (ng/day)
10	Berries and other small fruits, fresh	0.0	0.000 2	0.001	0.3	0.004	0.03
11	Citrus fruits, fresh	0.1	1E-06	0.04	4.4	4E-05	1
12	Pome fruits, fresh	0.1	0.006	0.02	1.5	0.07	0.2
13	Stone fruits, fresh	0.0	0	0.000 8	0.0	0	0
14	Tropical and subtropical fruits, fresh	455.7	0.008	91	411.2	0.007	82
15	Fresh fruit, nes	8.2	0.1	0.4	23.6	0.3	1
16	Dried fruits	0.0	0	0.002	0.3	0	0.1
17	Prepared fruits (no dried & juice)	0.0	0	3E-05	18.9	0	0.02
20	Pulses (dry, prepared and composites)	70.1	2	5	9.0	0.3	0.7
21	Oilseed (incl. flour)	8.4	4	7	0.9	0.4	0.7
22	Tree nuts (excl. groundnut)	0.0	0.000 9	0.007	347.3	8	60
30	Roots and tubers raw or boiled	539.7	0	0	348.7	0	0
31	Roots and tubers, nes	0.0	0.000 3	0.002	39.7	0.7	4
32	Roots and tubers processed	19.7	0.4	0.4	0.2	0.004	0.004
40	Brassica (cole or cabbage) vegetables, head cabbages, flowerhead cabbages	0.0	0.001	0.003	0.0	0	0
41	Bulb vegetables	9.7	0.01	3	8.7	0.01	3
42	Fruiting vegetables, cucurbits	13.6	2	2	0.1	0.006	0.008
43	Fruiting vegetables (other than cucurbits) and mushrooms	1.0	0.003	0.2	0.3	0.000 9	0.06
44	Leafy vegetables (including brassica leafy vegetables and seaweed)	0.0	0.000 1	0.000 3	0.0	0	0
45	Legume vegetables (fresh/green)	0.0	0.002	0.003	0.0	0	0
46	Root vegetables	0.1	0	0	0.0	0	0
47	Stalk and stem vegetables	0.0	2E-06	2E-06	0.0	0	0
48	Other and mixed vegetables	31.2	0.5	0.8	61.6	1	2
50	Herbs	0.0	0	0	0.0	0	0
52	Hops	0.0	0	0	0.0	0	0
53	Spices & condiments	0.5	0.06	0.1	1.4	0.2	0.3
54	Sauces & vinegars	0.2	0	0.07	3.7	0	1
60	Cereal grains & flours	136.8	5	18	182.9	7	24
61	Further processed cereals and by-products	1.4	0.02	0.3	18.3	0.2	4
70	Sugars, honey, candies (excl. chocolate), sweeteners and molasses	29.7	3	137	59.8	5	276
71	Cocoa, cola and their non-liquid derivates	0.2	0.006	0.03	2.3	0.08	0.4
80	Milk fats	0.1	0.2	0.3	3.1	6	9
81	Mammalian fats (no milk fat)	0.9	0.6	5	2.5	2	13
82	Poultry fats	0.0	0	0	0.0	0	0
83	Marine animal fat	0.0	0	0	0.0	0	0

Lev2 CODE	Lev2NAME	Cluster 16 Consumption (g/day)	Cluster 16 LB exposure (ng/day)	Cluster 16 UB exposure (ng/day)	Cluster 17 Consumption (g/day)	Cluster 17 LB exposure (ng/day)	Cluster 17 UB exposure (ng/day)
84	Plant origin fat	14.8	15	38	22.6	23	58
85	Animal or vegetable fat, nes	0.1	0.7	2	3.7	22	49
90	Milks (no other ingredients)	59.0	19	24	27.7	9	11
91	Dairy products (incl. whey, excl. milk fats)	0.1	0.08	0.1	1.9	1	1
100	Mammalian (not marine) meat, unprocessed (incl. home-cooked)	20.4	4	6	66.3	13	19
101	Poultry (incl. pigeon) meat, unprocessed (incl. home-cooked)	5.0	0.5	1	55.2	5	13
102	Mammalian offal, unprocessed (incl. home-cooked)	3.3	0.6	0.8	4.0	0.7	1
103	Poultry offal, unprocessed (incl. home-cooked)	0.0	0.000 6	0.000 7	0.0	0	0
104	Meat and offal, nes (incl. reptiles and amphibians), unprocessed (incl. home-cooked)	3.8	20	23	0.0	0	0
105	Meat and offal, processed (excl. marine)	0.2	0.006	0.02	6.2	0.2	0.6
110	Eggs	1.3	2	3	8.8	13	17
111	Egg products and processed eggs	0.0	0	0	0.0	0	0
120	Freshwater fish, unprocessed (incl. home-cooked)	18.4	95	103	0.1	0.4	0.4
121	Marine fish, unprocessed (incl. home-cooked)	0.1	2	2	3.7	65	70
122	Crustaceans, unprocessed (incl. home-cooked)	0.0	0.03	0.04	1.4	1	1
123	Molluscs and cephalopods, unprocessed (incl. home-cooked)	0.0	0.03	0.04	4.9	4	5
124	Other fishes and aquatic animals, unprocessed (incl. home-cooked)	0.9	68	68	38.0	2 787	2 796
127	Processed aquatic animals	2.4	6	6	30.7	77	78
130	Fruit & vegetable juices	0.2	0	0.002	5.4	0	0.05
131	Non-alcoholic beverages (excl. milk-based beverages, stimulants and water)	7.0	3E-05	1	29.7	0.000 1	5
140	Coffee (or substitute) based beverages	2.9	0	0.9	6.4	0	2
142	Tea and mate beverages	0.6	0	0.3	0.9	0	0.5
150	Beers	153.7	0	0.006	52.2	0	0.002
151	Other alcoholic beverages	138.6	0.000 2	1	31.9	5E-05	0.3
160	Water	0.1	2E-06	5E-06	6.1	0.000 1	0.000 3
170	Food for infants and small children	0.1	0.03	0.05	1.0	0.4	0.5
190	Out of classifying	0.9	3	3	21.9	62	75
	Total mean exposure (ng/day)	1 762	253	554	1 981	3 115	3 686
	Total mean exposure (ng/kg bw per day)		4	9		52	61

excl.: excluding; incl.: including; LB: lower bound; nes: not elsewhere specified; UB: upper bound

Appendix 6. GEMS/Food cluster diets 2012 – Countries by cluster

Cluster	Country
1	Afghanistan, Algeria, Azerbaijan, Iraq, Jordan, Libya, Mauritania, Mongolia, Morocco, Occupied Paestinian Territory, Pakistan, Syrian Arab Republic, Tunisia, Turkmenistan, Uzbekistan, Yemen
2	Albania, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, Republic of Moldova, Ukraine
3	Angola, Benin, Burundi, Cameroon, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Ghana, Guinea, Liberia, Madagascar, Mozambique, Paraguay, Togo, Zambia
4	Antigua and Barbuda, Bahamas, Brunei Darussalam, French Polynesia, Grenada, Israel, Jamaica, Kuwait, Netherlands Antilles, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Saudi Arabia, United Arab Emirates
5	Argentina, Bolivia (Plurinational State of), Brazil, Cape Verde, Chile, Colombia, Costa Rica, Djibouti, Dominican Republic, Ecuador, El Salvador, Guatemala, Guyana, Honduras, India, Malaysia, Maldives, Mauritius, Mexico, New Caledonia, Nicaragua, Panama, Peru, Seychelles, South Africa, Suriname, Tajikistan, The former Yugoslav Republic of Macedonia, Trinidad and Tobago, Venezuela (Bolivarian Republic of)
6	Armenia, Cuba, Egypt, Greece, Iran (Islamic Republic of), Lebanon, Turkey
7	Australia, Bermuda, Finland, France, Iceland, Luxembourg, Norway, Switzerland, United Kingdom, Uruguay
8	Austria, Germany, Poland, Spain
9	Bangladesh, Cambodia, China, Democratic People's Republic of Korea, Guinea Bissau, Indonesia, Lao People's Democratic Republic, Myanmar, Nepal, Philippines, Sierra Leone, Thailand, Timor Leste, Viet Nam
10	Belarus, Bulgaria, Canada, Croatia, Cyprus, Estonia, Italy, Japan, Latvia, Malta, New Zealand, Republic of Korea, Russian Federation, United States of America
11	Belgium, Netherlands
12	Belize, Dominica
13	Botswana, Burkina Faso, Central African Republic, Chad, Ethiopia, Gambia, Haiti, Kenya, Malawi, Mali, Namibia, Niger, Nigeria, Senegal, Somalia, Sudan, Swaziland, United Republic of Tanzania, Zimbabwe
14	Comoros, Fiji Islands, Kiribati, Papua New Guinea, Solomon Islands, Sri Lanka, Vanuatu
15	Czech Republic, Denmark, Hungary, Ireland, Lithuania, Montenegro, Portugal, Romania, Serbia, Slovakia, Slovenia, Sweden
16	Gabon, Rwanda, Uganda
17	Samoa, Sao Tome and Principe

ANNEX 1

Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

1. General principles governing the use of food additives (First report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).
2. Procedures for the testing of intentional food additives to establish their safety for use (Second report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).
3. Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants) (Third report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. I. Antimicrobial preservatives and antioxidants, Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
4. Specifications for identity and purity of food additives (food colours) (Fourth report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. II. Food colours, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).
5. Evaluation of the carcinogenic hazards of food additives (Fifth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).
6. Evaluation of the toxicity of a number of antimicrobials and antioxidants (Sixth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962 (out of print).
7. Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents (Seventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).
8. Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants (Eighth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 38, 1965; WHO Technical Report Series, No. 309, 1965 (out of print).
9. Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants. FAO Nutrition Meetings Report Series, No. 38A, 1965; WHO/Food Add/24.65 (out of print).
10. Specifications for identity and purity and toxicological evaluation of food colours. FAO Nutrition Meetings Report Series, No. 38B, 1966; WHO/Food Add/66.25.

11. Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases (Ninth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).

12. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases. FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29.

13. Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances (Tenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.

14. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents (Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.

15. Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.

16. Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.

17. Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics (Twelfth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.

18. Specifications for the identity and purity of some antibiotics. FAO Nutrition Meetings Series, No. 45A, 1969; WHO/Food Add/69.34.

19. Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances (Thirteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.

20. Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances. FAO Nutrition Meetings Report Series, No. 46A, 1970; WHO/Food Add/70.36.

21. Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives. FAO Nutrition Meetings Report Series, No. 46B, 1970; WHO/Food Add/70.37.

22. Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents (Fourteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 48, 1971; WHO Technical Report Series, No. 462, 1971.

23. Toxicological evaluation of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.

24. Specifications for the identity and purity of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.

25. A review of the technological efficacy of some antimicrobial agents. FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.

26. Evaluation of food additives: some enzymes, modified starches, and certain other substances: Toxicological evaluations and specifications and a review of the technological efficacy of some antioxidants (Fifteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.

27. Toxicological evaluation of some enzymes, modified starches, and certain other substances. FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.

28. Specifications for the identity and purity of some enzymes and certain other substances. FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.

29. A review of the technological efficacy of some antioxidants and synergists. FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.

30. Evaluation of certain food additives and the contaminants mercury, lead, and cadmium (Sixteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.

31. Evaluation of mercury, lead, cadmium and the food additives amaranth, diethylpyrocarbamate, and octyl gallate. FAO Nutrition Meetings Report Series, No. 51A, 1972; WHO Food Additives Series, No. 4, 1972.

32. Toxicological evaluation of certain food additives with a review of general principles and of specifications (Seventeenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum (out of print).

33. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents. FAO Nutrition Meetings Report Series, No. 53A, 1974; WHO Food Additives Series, No. 5, 1974.

34. Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers. FAO Food and Nutrition Paper, No. 4, 1978.

35. Evaluation of certain food additives (Eighteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 54, 1974; WHO Technical Report Series, No. 557, 1974, and corrigendum.

36. Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives. FAO Nutrition Meetings Report Series, No. 54A, 1975; WHO Food Additives Series, No. 6, 1975.

37. Specifications for the identity and purity of some food colours, enhancers, thickening agents, and certain food additives. FAO Nutrition Meetings Report Series, No. 54B, 1975; WHO Food Additives Series, No. 7, 1975.

38. Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances (Nineteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 55, 1975; WHO Technical Report Series, No. 576, 1975.

39. Toxicological evaluation of some food colours, thickening agents, and certain other substances. FAO Nutrition Meetings Report Series, No. 55A, 1975; WHO Food Additives Series, No. 8, 1975.

40. Specifications for the identity and purity of certain food additives. FAO Nutrition Meetings Report Series, No. 55B, 1976; WHO Food Additives Series, No. 9, 1976.

41. Evaluation of certain food additives (Twentieth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Food and Nutrition Meetings Series, No. 1, 1976; WHO Technical Report Series, No. 599, 1976.

42. Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 10, 1976.

43. Specifications for the identity and purity of some food additives. FAO Food and Nutrition Series, No. 1B, 1977; WHO Food Additives Series, No. 11, 1977.

44. Evaluation of certain food additives (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.

45. Summary of toxicological data of certain food additives. WHO Food Additives Series, No. 12, 1977.

46. Specifications for identity and purity of some food additives, including antioxidants, food colours, thickeners, and others. FAO Nutrition Meetings Report Series, No. 57, 1977.

47. Evaluation of certain food additives and contaminants (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.

48. Summary of toxicological data of certain food additives and contaminants. WHO Food Additives Series, No. 13, 1978.

49. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 7, 1978.

50. Evaluation of certain food additives (Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 648, 1980, and corrigenda.

51. Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 14, 1980.

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54. Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 15, 1980.

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59. Evaluation of certain food additives and contaminants (Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 683, 1982.

60. Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 17, 1982.

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62. Evaluation of certain food additives and contaminants (Twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 696, 1983, and corrigenda.

63. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 18, 1983.

64. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 28, 1983.

65. Guide to specifications – General notices, general methods, identification tests, test solutions, and other reference materials. FAO Food and Nutrition Paper, No. 5, Rev. 1, 1983.

66. Evaluation of certain food additives and contaminants (Twenty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 710, 1984, and corrigendum.

67. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 19, 1984.

68. Specifications for the identity and purity of food colours. FAO Food and Nutrition Paper, No. 31/1, 1984.

69. Specifications for the identity and purity of food additives. FAO Food and Nutrition Paper, No. 31/2, 1984.

70. Evaluation of certain food additives and contaminants (Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 733, 1986, and corrigendum.

71. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 34, 1986.

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74. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 21. Cambridge University Press, 1987.

75. Specifications for the identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 37, 1986.

76. Principles for the safety assessment of food additives and contaminants in food. WHO Environmental Health Criteria, No. 70. Geneva, World Health Organization, 1987 (out of print). The full text is available electronically at www.who.int/pcs.

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82. Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper, No. 41, 1988.

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89. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 26, 1990.

90. Specifications for identity and purity of certain food additives. FAO Food and Nutrition Paper, No. 49, 1990.

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94. Evaluation of certain food additives and contaminants (Thirty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 806, 1991, and corrigenda.

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100. Guide to specifications – General notices, general analytical techniques, identification tests, test solutions, and other reference materials. FAO Food and Nutrition Paper, No. 5, Ref. 2, 1991.

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102. Toxicological evaluation of certain food additives and naturally occurring toxicants. WHO Food Additives Series, No. 30, 1993.

103. Compendium of food additive specifications: addendum 1. FAO Food and Nutrition Paper, No. 52, 1992.

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107. Evaluation of certain food additives and contaminants (Forty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 837, 1993.

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109. Compendium of food additive specifications: addendum 2. FAO Food and Nutrition Paper, No. 52, Add. 2, 1993.

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112. Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper, No. 41/6, 1994.

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116. Evaluation of certain food additives and contaminants (Forty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 859, 1995.

117. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 35, 1996.

118. Compendium of food additive specifications: addendum 3. FAO Food and Nutrition Paper, No. 52, Add. 3, 1995.

119. Evaluation of certain veterinary drug residues in food (Forty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 864, 1996.

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125. Evaluation of certain veterinary drug residues in food (Forty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 876, 1998.

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130. Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper, No. 41/10, 1998.

131. Evaluation of certain food additives and contaminants (Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 884, 1999.

132. Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 40, 1998.

133. Compendium of food additive specifications: addendum 5. FAO Food and Nutrition Paper, No. 52, Add. 5, 1997.

134. Evaluation of certain veterinary drug residues in food (Fiftieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 888, 1999.

135. Toxicological evaluation of certain veterinary drug residues in food. WHO Food Additives Series, No. 41, 1998.

136. Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper, No. 41/11, 1999.

137. Evaluation of certain food additives (Fifty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 891, 2000.

138. Safety evaluation of certain food additives. WHO Food Additives Series, No. 42, 1999.

139. Compendium of food additive specifications, addendum 6. FAO Food and Nutrition Paper, No. 52, Add. 6, 1998.

140. Evaluation of certain veterinary drug residues in food (Fifty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 893, 2000.

141. Toxicological evaluation of certain veterinary drug residues in food. WHO Food Additives Series, No. 43, 2000.

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144. Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 44, 2000.

145. Compendium of food additive specifications, addendum 7. FAO Food and Nutrition Paper, No. 52, Add. 7, 1999.

146. Evaluation of certain veterinary drug residues in food (Fifty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 900, 2001.

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148. Residues of some veterinary drugs in animals and foods. FAO Food and Nutrition Paper, No. 41/13, 2000.

149. Evaluation of certain food additives and contaminants (Fifty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 901, 2001.

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151. Compendium of food additive specifications: addendum 8. FAO Food and Nutrition Paper, No. 52, Add. 8, 2000.

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154. Evaluation of certain food additives and contaminants (Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 909, 2002.

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ANNEX 2

Abbreviations used in the monographs

ADHD	attention deficit hyperactivity disorder
AH	aniline hydroxylase; ancestral haplotype
AHH	acetanilide-4-hydroxylase
AhR	aryl hydrocarbon receptor
AMICS	Asthma Multicentre Infants Cohort Study
ANOVA	analysis of variance
APDM	aminopyrine *N*-demethylase
ATHON	Assessing the Toxicity and Hazard of Non-dioxin-like PCBs Present in Food
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BAEP	brainstem auditory evoked potential
BDE	brominated diphenyl ether
BDE-47	2,2′,4,4′-tetrabromodiphenyl ether
BF	breastfed as infants
BMD	benchmark dose
BMDL	lower 95% confidence limit on the benchmark dose
BMI	body mass index
BSID	Bayley Scales of Infant Development
bw	body weight
CAR	constitutive androstane receptor
CARDIA	Coronary Artery Risk Development in Young Adults
CDC	Centers for Disease Control and Prevention (USA)
cGMP	cyclic guanosine monophosphate
CED	critical effect dose
CEDL	lower bound of the confidence interval on the critical effect dose
CES	critical effect size
CI	confidence interval
CIFOCOss	FAO/WHO Chronic Individual Food Consumption database – summary statistics
CPT	Continuous Performance Test
CYP	cytochrome P450
DAT	dopamine transporter
DBP	diastolic blood pressure
DDE	1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene
DDT	2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane

DEN	diethylnitrosamine
DIPP	Finnish Type I Diabetes Prediction and Prevention Nutrition Study
DL-PCB	dioxin-like polychlorinated biphenyl
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
ECD	electron capture detection/detector
E-CPT	Extended Continuous Performance Test
EFSA	European Food Safety Authority
ELISA	enzyme-linked immunosorbent assay
ENRIECO	Environmental Health Risks in European Birth Cohorts
EPA	Environmental Protection Agency (USA)
EROD	ethoxyresorufin-*O*-deethylase
F	female
F_0	parental generation
F_1	first filial generation
FAO	Food and Agriculture Organization of the United Nations
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GC	gas chromatography
GD	gestation day
GEMS/Food	Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
GJIC	gap junctional intercellular communication
GR	glucocorticoid receptor
GST	glutathione *S*-transferase
HBCD	hexabromocyclododecane
HCB	hexachlorobenzene
HDL	high-density lipoprotein
HR	hazard ratio
HRGC-MS	high-resolution gas chromatography with mass spectrometry
HSD	hydroxysteroid dehydrogenase
IARC	International Agency for Research on Cancer
IC_{50}	median inhibitory concentration
ICAM-1	intercellular adhesion molecule-1
ICD-8	International Classification of Diseases, Eighth Revision
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IGF-1	insulin-like growth factor-1
IL	interleukin
IM-GSM	grey-scale median of the intima-media complex
IMT	intima-media thickness

INCA-2	Etude individuelle nationale des consommations alimentaires 2
INMA	INfancia y Medio Ambiente (Child and Environment)
IQ	intelligence quotient
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
K-ABC	Kaufman Assessment Battery for Children
LB	lower bound
LD_{50}	median lethal dose
LDL	low-density lipoprotein
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantification
M	male
MB	middle bound
MCP-1	monocyte chemoattractant protein-1
MDI	mental development index
MMP-7	matrix metalloproteinase-7
MNC	magnocellular neuroendocrine cell
MOE	margin of exposure
MR	muscarinic receptor
mRNA	messenger ribonucleic acid
MSCA	McCarthy Scales of Children's Abilities
NADPH	nicotinamide adenine dinucleotide phosphate (reduced)
NBF	non-breastfed as infants
ND	non-detects; not detected
NDL-PCB	non-dioxin-like polychlorinated biphenyl
nes	not elsewhere specified
NES2	Neurobehavioural Evaluation System 2
NHANES	National Health and Nutrition Examination Survey (USA)
NHL	non-Hodgkin lymphoma
NMDA	*N*-methyl-D-aspartate
NOAEL	no-observed-adverse-effect level
NOS	nitric oxide synthase
NTD	neural tube defect
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
OR	odds ratio
P5	5th percentile
P90	90th percentile

P95	95th percentile
P99	99th percentile
PBB	polybrominated biphenyl
PBDE	polybrominated diphenyl ether
PBK	physiologically based kinetic
PBPK	physiologically based pharmacokinetic
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-*p*-dioxin
PCDF	polychlorinated dibenzofuran
PDI	psychomotor development index
PFC	plaque-forming cell
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors
PKC	protein kinase C
PND	postnatal day
POPUP	Persistent Organic Pollutants in Uppsala Primiparas
PROD	pentoxyresorufin-*O*-deethylase
PXR	pregnane X receptor
POP	persistent organic pollutant
PPAR	peroxisome proliferator–activated receptor
QSAR	quantitative structure–activity relationship
ROCK	Rho-associated kinase
RR	relative risk
RyR	ryanodine receptor
SAR	structure–activity relationship; Special Administrative Region
SBP	systolic blood pressure
SD	standard deviation
SHBG	sex hormone binding globulin
SIR	standardized incidence rate
SMR	standardized mortality rate
SON	supraoptic nucleus
SRBC	sheep red blood cell
SRS	Social Responsiveness Scale
STEM	STatistical Exposure Model
STRIP	Turku Coronary Risk Factor Intervention Project for Children
SULT	sulfotransferase
T_3	triiodothyronine
T_4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxic equivalents

TSH	thyroid stimulating hormone
UB	upper bound
UDS	unscheduled DNA synthesis
UGT	uridine diphosphate-glucuronosyltransferase
UNEP	United Nations Environment Programme
USA	United States of America
USEPA	United States Environmental Protection Agency
VCAM-1	vascular cell adhesion molecule-1
VEP	visual evoked potential
VMAT	vesicular monoamine transporter
WAM	weighted arithmetic mean
WGM	weighted geometric mean
WHO	World Health Organization
w/w	weight per weight
ww	wet weight

ANNEX 3

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Rome, 16–25 June 2015

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This volume contains a monograph prepared at the eightieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which met in Rome, Italy, from 16 to 25 June 2015.

The toxicological and dietary exposure monograph in this volume summarizes the safety and dietary exposure data on a contaminant group (non-dioxin-like polychlorinated biphenyls) discussed at the eightieth meeting. Monographs on seven food additives discussed at that meeting have been previously published in the WHO Food Additives series (FAS 71), and a monograph on a second contaminant group (pyrrolizidine alkaloids) will be published as a separate supplement in the WHO Food Additives series.

This volume and others in the WHO Food Additives series contain information that is useful to those who produce and use food additives and veterinary drugs and those involved with controlling contaminants in food, government and food regulatory officers, industrial testing laboratories, toxicological laboratories and universities.

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