OPINION OF THE SCIENTIFIC PANEL ON CONTAMINANTS IN THE FOOD CHAIN ON A REQUEST FROM THE COMMISSION RELATED TO THE PRESENCE OF NON DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (PCB) IN FEED AND FOOD

(Question N° EFSA-Q-2003-114)

Adopted on 8 November 2005

SUMMARY

Polychlorinated biphenyls (PCB) cover a group of 209 different PCB congeners which can be divided into two groups according to their toxicological properties. One group, consisting of 12 congeners, show toxicological properties similar to dioxins, is therefore termed “dioxin-like PCB” (DL-PCB), and these have been included in the "Risk Assessment of Dioxins and Dioxin-Like PCBs in Food" performed by the EU Scientific Committee on Food (SCF). The other PCB, referred to as “non dioxin-like PCB” (NDL-PCB), have not been previously evaluated by the SCF or EFSA. Both groups of PCB, NDL-PCB as well DL-PCB, are usually found in feed and food.

PCB were widely used in a number of industrial and commercial applications. It is estimated that more than 1 million tons of technical PCB mixtures were produced world-wide since their first commercial use in the late 1920s. Although produced by comparable production processes, technical PCB mixtures contain both DL and NDL-PCB and may vary considerably with respect to their congener composition due to differences in the amount of chlorine and the reaction conditions applied. Moreover, technical PCB mixtures contain other dioxin-like compounds as impurities, such as polychlorinated dibenzofurans (PCDF). The different compositions as well as the presence of toxicologically relevant impurities may have a significant impact on the results of toxicological studies with technical PCB mixtures.

Although the manufacture, processing and distribution of PCB has been prohibited in almost all industrial countries since the late 1980s, their entry into the environment still occurs, especially due to improper disposal practices or leaks in electrical equipment and hydraulic systems still in use. PCB are highly persistent and are globally circulated by atmospheric transport and thus are present in all environmental media.

Data on the occurrence of NDL-PCB in food and feed have been reported in different ways for example as the sum of three PCB congeners (PCB 138, 153 and 180), as the sum of six PCB congeners (PCB 28, 52, 101, 138, 153, 180) often referred to as indicator PCB or as the sum of seven (sum of six indicator PCB plus PCB 118). This lack of consistency often hampers a direct comparison of occurrence data. The Panel decided to use the sum of the six indicator PCB as the basis for the evaluation in this opinion, because these congeners are appropriate indicators for different PCB patterns in various sample matrices and are most

suitable for a risk assessment of NDL-PCB on the basis of the available data. The Panel noted that the sum of the six indicator PCB represents about 50% of total NDL-PCB in food.

Following exposure of farm animals, NDL-PCB will accumulate in meat, liver and particularly in fat tissues. In addition, NDL-PCB will be transferred into milk and eggs, and levels in these products will reach a steady state following exposure over a period of several weeks. PCB 138 and 153, both with six chlorine atoms, show the highest carry-over into milk and eggs, in the order of 50-60%. After cessation of exposure, levels in eggs and milk initially decrease rapidly to about 50%, followed by a slower elimination phase. In fattened animals like calves, piglets, and poultry, and also farmed fish, no steady state is obtained, due to the fact that these animals are slaughtered at a young age.

For risk assessment of domestic animals, the Panel compared the effect concentrations in the experimental diet with the NDL-PCB concentration in animal feed. Following a conservative approach, the 90th percentile of the sum of six NDL-PCB in compound feed, 0.02 mg/kg feed was taken as the point of comparison. This figure corresponds to about 0.04 mg total NDL-PCB, which is more than two orders of magnitude below the concentrations causing effects in most domestic animals studied. Mink are usually given feed based on fish. The 90th percentile of the sum of the six NDL-PCB in fish and fish products is 0.067 mg/kg corresponding to 0.13 mg/kg total NDL-PCB. This is only about five times below the concentration of PCB in feed that produced pronounced effects on reproduction in mink. The Panel therefore concluded that current background levels of NDL-PCB in animal feed are of no health concern for most domestic animals, with the possible exception of mink.

Congener patterns in feed, particularly that of plant origin and in edible tissue may differ considerably. Due to the different sources of contamination, different origins of the feed and of food commodities, there is generally no correlation between the concentrations of NDL-PCB and DL-PCB Toxic Equivalents (TEQ) or the total TEQ (polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF) and DL-PCB) with the exception of samples where the circumstances of contamination are known.

More than 90% of the NDL-PCB exposure in the general population is via food. Average daily dietary intakes of total NDL-PCB can be estimated to be in the range of 10-45 ng/kg body weight (b.w.) per day. Limited exposure data for young children, up to six years of age, indicates that the average intake (breastfeeding excluded) of total NDL-PCB is about 27-50 ng/kg b.w. per day. However, where data on both adults and children within a specific population were available, in general children had exposure levels 2.5 fold higher than adults. In specific subpopulations with high dietary PCB exposure such as Baltic Sea fishermen the daily intake from fish of the sum of the six NDL-PCB could be about 40 ng/kg b.w., corresponding to an intake of total NDL-PCB of 80 ng/kg b.w. per day before taking into account the rest of the diet. Breastfed infants are a group of high NDL-PCB intake which might be two orders of magnitude higher than adult exposure.

Other routes of exposure such as ambient and indoor air, dust and soil, do not usually contribute significantly to the body burden of the general population. However, there are situations in which contribution from contaminated indoor air could be considerable.

Technical PCB mixtures used in toxicity studies contain both NDL-PCB and dioxin-like compounds such as DL-PCB. These mixtures exert a variety of toxicological effects such as effects on liver, thyroid, immune function, reproduction and behaviour as well as carcinogenicity. The adverse effects reported in laboratory animals following exposure to individual NDL-PCB were effects on the thyroid, liver and brain biochemistry, as well as immunotoxicity, oestrogenicity, and reproductive and neurodevelopmental effects. The latter effects are particularly found in the offspring of rodents following *in utero* exposure. However, these effects are not all specific for NDL-PCB but are also to be seen following exposure to polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and DL-PCB.

Several NDL-PCB congeners are metabolised to hydroxy-PCB and/or methylsulfonyl-PCB. Some of these metabolites may contribute to hormone-like effects seen with PCB.

Results of *in vitro* and *in vivo* genotoxicity studies indicate that PCB are not mutagenic at the gene or chromosome level. Some NDL-PCB, in particular the lower chlorinated congeners, caused DNA damage, probably resulting from the formation of reactive oxygen species. In two-stage initiation-promotion studies, technical PCB mixtures containing NDL-PCB as well as DL-PCB promote liver carcinogenesis in rats, following initiation with genotoxic carcinogens. Data from animal experiments with several technical mixtures (Aroclor 1016, 1242, 1254 and 1260) indicate that PCB can cause liver and thyroid neoplasms in rats. The International Agency for Research on Cancer (IARC) classified PCB in Group 2A (probably carcinogenic to humans), based on limited evidence in humans and sufficient evidence in animals. Evaluation of the cancer studies in rats with technical PCB mixtures, and comparison with data obtained with TCDD, indicate that the dioxin-like components in technical PCB mixtures are likely to be responsible for the carcinogenic response of these mixtures. No peer reviewed data are available on the carcinogenicity of individual NDL-PCB congeners.

Occupational exposures to PCB have been reported to be associated with an increased risk of cancer of the digestive system and possibly other sites. Some studies suggest that environmental PCB exposure may be linked to the development of breast cancer, although perhaps only in certain vulnerable sub-groups. Among non-cancer effects reported to be associated with environmental PCB exposure, adverse reproductive outcomes, delayed neurodevelopment and impairment of the immune system during development are considered to be the most important. The epidemiological studies however do not allow an estimation of the toxicity that may specifically be attributed to the NDL-PCB.

Benchmark dose calculations have been based on human studies on developmental neurotoxicity and immunotoxicity after perinatal exposure to total DL and NDL-PCB. The

95% lower confidence limit of benchmark dose (BMDL) of approximately 1 µg PCB/g lipid is only about four times higher than the current median concentration in human milk.

The Panel noted that the comprehensive toxicological database on health effects of technical PCB mixtures was not suitable for the separate assessment of NDL-PCB, and that the human data on exposure to environmental mixtures containing PCB could not differentiate between the effects of NDL-PCB and DL-PCB and polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans. Therefore, in its assessment the Panel concentrated on the toxicological information available for individual NDL-PCB congeners. Although the absence of mutagenicity indicates that a threshold approach is appropriate for the hazard characterisation, the toxicological database however, was considered to be too limited to allow the establishment of a health based guidance value for NDL-PCB. The Panel therefore decided to perform its health risk characterisation on the basis of a margin of exposure approach.

The most sensitive effects seen in studies with individual NDL-PCB congeners in experimental animals were liver and thyroid toxicity. The NOAELs for these effects in 90-day rat studies with the individual NDL-PCB congeners PCB 28, 128, and 153 were in the range of 30-40 µg/kg b.w. per day. For compounds that accumulate in the body, such as NDL-PCB, evaluations based on body burden (BB) calculations are considered more appropriate than evaluations based on the external dose. The Panel therefore applied a body burden approach to the results of the 90-day rat studies, and estimated body burdens at the "no observed adverse effect level" (NOAEL) of 400, 800, and 1,200 µg/kg b.w. for PCB 28, 128, and 153, respectively. The Panel compared estimated body burdens at the NOAEL for different effects in animals with the estimated median human body burden derived from the analyses of human milk. The "margin of body burdens" at the NOAEL (NOAEL MoBB) were calculated by dividing the estimated animal body burden with the estimated median human body burden.

NOAEL MoBBs of 900, 6,300, and 85 were obtained for the effects on liver and/or thyroid of PCB 28, 128, and 153, respectively. Although PCB 28, 128, and 153 showed similar potencies in the 90-day toxicity studies, PCB 153 had the lowest NOAEL MoBB due to its abundance in human tissues. Application of the same approach to experimental animal studies on reproductive and developmental effects, oestrogenicity, thyroid effects and effects on the immune system and the developing nervous system, revealed NOAEL MoBBs that were higher than 1,600.

In order to evaluate the impact of exposure to total NDL-PCB, the Panel noted that the available toxicological database on NDL-PCB covered a number of congeners present in food and human tissues. Considering that the "lowest observed adverse effect level " BB for the most sensitive effects (liver, thyroid) were 10 times higher than the NOAEL BB (400, 800, and 1,200 µg /kg b.w. for PCB 28, 128, and 153, respectively), the Panel chose an overall body burden of 500 µg /kg b.w. as a representative conservative body burden at the NOAEL (NOAEL BB) for all individual NDL-PCB and for the sum of NDL-PCB occurring in human tissues. Based on the median total concentration of all NDL-PCB measured in human milk

sampled in European countries of about 240 ng/g fat, and assuming 20% fat content in the human body, a median human body burden of about 50 µg/kg b.w. was estimated. Consequently the overall NOAEL MoBB is about 10.

Although this margin appears rather small, it should be stressed that the endpoints considered in the evaluation of the individual NDL-PCB congeners, can also be observed after treatment with polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, or DL-PCB. Since a number of these latter compounds have relatively high potencies for these effects in rats, minor contamination (in the range of 0.1%) of the NDL-PCB congeners studied with potent dioxin-like compounds might be sufficient to explain the effects observed. Thus, any estimate of a NOAEL for NDL-PCB is hampered by the uncertainty in the extent to which NDL-PCB congeners might have been contaminated with polychlorinated dibenzofurans and/or DL-PCB. Therefore the "true" NOAEL MoBB for NDL-PCB might be larger. On the other hand, the MoBB was calculated on the basis of the median concentrations of NDL-PCB in human milk, and some populations in Europe may have considerably higher body burdens.

During the nursing period, breastfed infants may have daily intakes, on a body weight basis, of NDL-PCB estimated to be about two orders of magnitude higher than the average adult intake. This elevated intake by the infants is related to the mother's long-term intake of NDL-PCB with food. However, the subtle neurodevelopmental effects that were reported in some studies of human infants were mainly associated with exposure to a mixture of NDL-PCB, DL-PCB, and polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans, and any causal role of NDL-PCB is unclear. The Panel noted that in many other studies of infants, breastfeeding was associated with beneficial effects, in spite of the contaminants present in human milk.

In conclusion, no health based guidance value for humans can be established for NDL-PCB because simultaneous exposure to NDL-PCB and dioxin-like compounds hampers the interpretation of the results of the toxicological and epidemiological studies, and the database on effects of individual NDL-PCB congeners is rather limited. There are however indications that subtle developmental effects, being caused by NDL-PCB, DL-PCB, or polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans alone, or in combination, may occur at maternal body burdens that are only slightly higher than those expected from the average daily intake in European countries. Because some individuals and some European (sub)-populations may be exposed to considerably higher average intakes, a continued effort to lower the levels of NDL-PCB in food is warranted.

KEY WORDS

Polychlorinated biphenyls (PCB), non dioxin-like PCB (NDL-PCB), dioxin-like PCB (DL-PCB), prenatal exposure delayed effects, occurrence, feed, food, human milk, carry-over, margin of body burden, MoBB, developmental effects, human health, animal health, toxicity, risk characterisation.

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List of Abbreviations

2,4,5-T	2,4,5-trichlorophenoxyacetic acid
AHH	arylhydrocarbon hydroxylase
ATSDR	Agency for Toxic Substances and Disease Registry
b.w.	body weight
BB	body burden
BMD	bench mark dose
BMDL	bench mark dose lower confidence limit
CYP	human cytochrome P450
DHEA	dehydroepiandrosterone
DHS	dehydroepiandrosterone sulfate
DL-PCB	dioxin-like PCB
ECD	electron capture detection
EI	electron impact
EPA	Environmental Protection Agency
EROD	ethoxyresorufin-O-deethylase
GC	gas chromatography
GD	gestation day
GGT	γ-glutamyltranspeptidase
HLA-DR	human leukocyte antigen DR
HpCDD	heptachlorodibenzo-p-dioxin
HpCDF	heptachlorodibenzofuran
HL-60	human acute promyelocytic leukemia cell line
HPRT	hypoxanthine-guanine phosphoribosyltransferase
HxCDD	hexachlorodibenzo-p-dioxin
HxCDF	hexachlorodibenzofuran
IARC	International Agency for the Research on Cancer
Ig	immunogluboline
IHNV	infectious haematopoietic necrosis virus
i.p.	intraperitoneal
IQ	intelligence quotient
LC_{50}	concentration that causes death among 50% of treated animals
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	lowest observable effect values
LOQ	limit of quantification
$MeSO_2$-PCB	PCB methylsulfones or methylsulfonyl-PCB
MS	mass spectrometry
MWI	municipal waste incinerator
MoBB	margin of body burden
NDL-PCB	non dioxin-like PCB
NIC	negative chemical ionization
NOAEL	no observed adverse effect level

NTP	National Toxicology Program
OCDD	octachlorodibenzo-p-dioxin
OCDF	octachlorodibenzofuran
OH-PCB	hydroxy-PCB
PB-PK	physiologically based pharmacokinetic
PCB	polychlorinated biphenyls
PCDD	polychlorinated dibenzo-p-dioxins
PCDF	polychlorinated dibenzofurans
PCN	polychlorinated naphthalenes
PeCDD	pentachlorodibenzo-*p*-dioxin
PeCDF	pentachlorodibenzofuran
PKC	protein kinase C
PND	postnatal day
RM	reconstituted PCB mixture
SCAN	Scientific Committee on Animal Nutrition
SCE	sister chromatid exchanges
SCF	Scientific Committee on Food
SRBC	sheep red blood cells
T3	triiodothyronine
T4	thyroxine
TCDD	tetrachlorodibenzo-p-dioxin
TeCDF	tetrachlorodibenzofuran
TEF	toxic equivalence factor
TEQ	toxic equivalents
TLC	thin layer chromatography
TPH	tryptophan hydroxylase
TSH	thyroid-stimulating hormone
UDP-GT	UDP-glucuronosyltransferase
UDS	unscheduled DNA synthesis
WHO-EURO	World Health Organization, Regional Office for Europe

BACKGROUND

1. General Background

Polychlorinated biphenyls (PCB) cover a group of 209 different PCB congeners which can be divided into two groups according to their toxicological properties. One group consists of 12 congeners that show toxicological properties similar to dioxins and is therefore termed "dioxin-like PCB". The other PCB do not show dioxin-like toxicity but have another toxicological profile. For this group of PCB, sometimes termed "non dioxin-like PCB", about 10 different toxicological endpoints have been identified. A risk assessment has to address all these different endpoints and identify the most relevant/sensitive endpoints for the PCB-congener patterns usually found in food.

The Scientific Committee on Food (SCF) assessed the risks for public health arising from the presence of dioxins and dioxin-like PCB in food in November 2000[1] and May 2001[2]. On 6 November 2000, the Scientific Committee on Animal Nutrition (SCAN) adopted an opinion on the dioxin contamination of feedingstuffs and their contribution to the contamination of food of animal origin[3]. These two opinions provided the scientific basis for the Community measures to limit the presence of these contaminants in feed and food as part of an overall strategy to reduce the presence of dioxins, furans and PCB in the environment, food and feed.

A community strategy for dioxins, furans and PCB[4] was adopted by the Commission on 24 October 2001, addressing measures to limit or to eliminate the emission of dioxins into the environment through source-directed measures and addressing the way to actively decrease the presence of dioxins in feedingstuffs and in foodstuffs.

The Commission developed this strategy in view of the general concern that at the current levels of exposure a considerable part of the European population would exceed the Tolerable Weekly Intake of 14 pg WHO-TEQ/kg body weight as derived by the SCF.

In the above mentioned SCF and SCAN opinions, the risk assessment was focused on dioxins, furans and dioxin-like PCB. For the *non dioxin-like ("classical" or "non-coplanar")* PCB, which have another toxicological profile and which could be several orders of magnitude more concentrated than dioxins in some feed and food matrices, a risk assessment needs still

[1] Scientific Committee on Food. Opinion on the risk assessment of dioxins and dioxin-like PCB in food (adopted on 22 November 2000) http://europa.eu.int/comm/food/fs/sc/scf/out78_en.pdf

[2] Scientific Committee on Food. Opinion on the risk assessment of dioxins and dioxins-like PCB in food (update based on the new scientific information available since the adoption of the SCF opinion of 22 November 2000) (adopted by the SCF on 30 May 2001) http://europa.eu.int/comm/food/fs/sc/scf/out90_en.pdf

[3] Scientific Committee on Animal Nutrition. Opinion on the „Dioxin contamination of feedingstuffs and their contribution to the contamination of food of animal origin" (Adopted on 06 November 2000). http://europa.eu.int/comm/food/fs/sc/scan/out55_en.pdf

[4] Communication from the Commission to the Council, Parliament and the Economic and Social Committee. Community strategy for dioxins, furans and polychlorinated biphenyls (2001/C 322/02) (COM (2001) 593 final). Official Journal of the European Communities, C322/2-18, 17.11.2001. http://europa.eu.int/eur-lex/en/com/pdf/2001/com2001_0593en01.pdf

to be carried out, as highlighted in the above mentioned Communication. Also, on 22 April 2002, the Committee on Environment, Public Health and Consumer policy of the European Parliament called upon the Commission to propose measures to limit the presence of the non dioxin-like PCB in food and feed.

A significant part of the human exposure to PCB derives from food. Food of animal origin is the main contributor to dietary PCB exposure. The PCB burden in animals derives mainly from feed. As food contamination is directly related to feed contamination, it seems appropriate to integrate/combine the risk assessment on the presence of non dioxin-like PCB in feed with the requested risk assessment on the presence of non dioxin-like PCB in food.

2. Specific Background

2.1 Non dioxin-like PCB in food

A request for a risk assessment on non dioxin-like PCB in food has already been put forward by the European Commission early in 2002.

The Commission requested the SCF to provide a scientific opinion on the risk assessment of NDL-PCB in food with the following terms of reference:
The scientific opinion on non dioxin-like PCB should comprise the:

- evaluation of the toxicity of the non dioxin-like PCB for humans, considering all relevant toxicological endpoints and identification of the PCB congeners of toxicological relevance with particular attention to the congeners occurring in food;
- evaluation of the relevance of the metabolites, such as hydroxyl- or methylsulfonyl-PCB, for the toxicity of PCB;
- exposure of the EU population to NDL-PCB, including the identification of the main sources of dietary exposure and the relative importance of dietary and non dietary sources;
- risk characterisation, including the identification of high risk groups of the population.

Particular attention should be paid to the fact that the PCB congener pattern present in food does not reflect in most cases the PCB congener patterns of technical mixtures.
The scientific opinion should furthermore contain an assessment of:

- the relevance of the current usual monitoring of the 7 (6) indicator PCB[5] in food as an indicator for the presence of total NDL-PCB and for the toxicity of the non dioxin-like PCB;
- the quantitative ratio in food between the presence of non dioxin-like PCB and dioxin-like PCB and non dioxin-like PCB and WHO-TEQs (dioxins, furans and dioxin-like PCB), respectively;

[5] PCB 28, PCB 52, PCB 101, PCB 118, PCB 138, PCB 153 and PCB 180. As the congener PCB 118 has also a dioxin-like activity and therefore belongs also to the dioxin-like PCB, PCB 118 is not always analysed together with the other 6 indicator PCB.

- whether an approach of protecting humans against WHO-TEQ exposure (dioxins/furans, dioxin-like PCB) is regarded as sufficient for protection against exposure to non dioxin-like PCB or if on the basis of exposure scenarios showing a relatively high ratio of non dioxin-like PCB versus dioxin-like PCB, a separate approach for the protection of humans against exposure to non dioxin-like PCB is appropriate.

It is evident that this is a very complex and time consuming exercise and even the SCF itself questioned whether it had the necessary capacity (human resources, means, time) to perform this task.

At the same time, other organizations such as the World Health Organization (WHO) and the United States Environmental Protection Agency (US-EPA), were also undertaking initiatives to perform a risk assessment on non dioxin-like PCB. Therefore, a co-operation has been put in place with the WHO and the US-EPA in order to make progress in this important issue and to avoid duplication of efforts. Progress within this joint working group has until now been limited.

Since May 2003, the European Food Safety Authority (EFSA) has taken over from the European Commission the responsibility for the scientific assessment of feed and food safety issues and therefore EFSA has been asked to carry out the risk assessment on non dioxin-like PCB in food.

2.2. Non dioxin-like PCB in feed

Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed[6] replaced, Council Directive 1999/29/EC of 22 April 1999 on the undesirable substances and products in animal nutrition[7] from 1 August 2003.

The main new requirements can be summarised as follows:

- extension of the scope of the Directive to include the possibility of establishing maximum limits for undesirable substances in feed additives;
- deletion of the existing possibility to dilute contaminated feed materials instead of decontamination or destruction (introduction of the principle of non-dilution);
- deletion of the possibility for derogation of the maximum limits for particular local reasons;
- introduction of the possibility for the establishment of an action threshold triggering an investigation to identify the source of contamination ("early warning system") and to take measures to reduce or eliminate the contamination ("pro-active approach").

[6] OJ L140, 30.5.2002, p. 10

[7] OJ L 115, 4.5.1999, p. 32

In particular, the introduction of the principle of non-dilution is an important and far- reaching measure. In order to protect public and animal health, it is important that the overall contamination of the food and feed chain is reduced to a level as low as reasonably achievable, providing a high level of public health and animal health protection. The deletion of the possibility of dilution is a powerful means to stimulate all operators throughout the chain to apply the necessary prevention measures to avoid contamination as much as possible. The prohibition of dilution, together with the necessary control measures, will effectively contribute to safer feed.

During discussions in the lead up to the adoption of Directive 2002/32/EC, the Commission made a commitment to review the maximum levels laid down in Annex I on the basis of updated scientific risk assessments and taking into account the prohibition of any dilution of contaminated non-complying products intended for animal feed. The Commission therefore requested the Scientific Committee on Animal Nutrition (SCAN) in March 2001 to provide these updated scientific risk assessments in order to enable the Commission to finalise this review as soon as possible (Question 121 on undesirable substances in feed)[8].

The opinion on undesirable substances in feed, adopted by SCAN on 20 February 2003, and updated on 25 April 2003[9], provides a comprehensive overview of the possible risks for animal and public health as the consequence of the presence of undesirable substances in animal feed.

It was nevertheless acknowledged by SCAN itself for several undesirable substances, and also by the Standing Committee on the Food Chain and Animal Health, that additional detailed risk assessments are necessary to enable a complete review of the provisions in the Annex, including the establishment of maximum levels for undesirable substances currently not listed.

With regard to PCB, SCAN concluded that they are ubiquitous, stable and lipophilic bio-accumulative contaminants that concentrate along the food chain. Their occurrence, together with their toxicity, justifies that such compounds be considered for possible inclusion in the list of undesirable substances and that a detailed risk assessment be undertaken regarding the presence of NDL-PCB in feed.

TERMS OF REFERENCE

The European Commission requests the EFSA to provide a scientific opinion on the presence of non dioxin-like PCB in feed and food

[8] Summary record of the 135th SCAN Plenary meeting, Brussels, 21-22 March 2001, point 8 – New questions. http://europa.eu.int/comm/food/fs/sc/scan/out61_en.pdf

[9] Opinion of the Scientific Committee on Animal Nutrition on Undesirable Substances in Feed, adopted on 20 February 2003, updated on 25 April 2003. http://europa.eu.int/comm/food/fs/sc/scan/out126_bis_en.pdf

The scientific opinion on non dioxin-like PCB in food should comprise the:

- evaluation of the toxicity of the NDL-PCB for humans, considering all relevant toxicological endpoints and identification of the PCB congeners of toxicological relevance with particular attention to the congeners occurring in food;
- evaluation of the relevance of the metabolites, such as hydroxyl or methylsulfonyl PCB, for the toxicity of PCB;
- exposure of the EU population to NDL-PCB, including the identification of the main sources of dietary exposure and the relative importance of dietary and non dietary sources;
- risk characterisation, including the identification of high risk groups of the population.

Particular attention should be paid to the fact that the PCB congener pattern present in food does not reflect, in most cases, reflect the PCB congener patterns of technical mixtures.

The scientific opinion should furthermore contain an assessment of:

- the relevance of the current usual monitoring of the 7 (6) indicator PCB[5] in food as an indicator for the presence of total NDL-PCB and for the toxicity of the non dioxin-like PCB;
- the quantitative ratio in food between the presence of non dioxin-like PCB and dioxin-like PCB and non dioxin-like PCB and WHO-TEQs (dioxins, furans and dioxin-like PCB), respectively;
- whether an approach of protecting humans against WHO-TEQ exposure (dioxins/furans, dioxin-like PCB) is regarded as sufficient for protection against exposure to non dioxin-like PCB or if on the basis of exposure scenarios showing a relatively high ratio of non dioxin-like PCB versus dioxin-like PCB, a separate approach for the protection of humans against exposure to non dioxin-like PCB is appropriate.

The scientific opinion on the presence of non dioxin-like PCB in animal feed should comprise the:

- determination of the toxic exposure levels (daily exposure) of non dioxin-like PCB for the different animal species of relevance (difference in sensitivity between animal species) above which:
  - signs of toxicity can be observed (animal health / impact on animal health)
  - the level of transfer/carry over of (the most relevant congeners of) non dioxin-like PCB from the feed to the products of animal origin results in unacceptable levels of non dioxin-like PCB or its metabolites in the products of animal origin in view of providing a high level of public health protection.
- identification of feed materials which could be considered as sources of contamination by non dioxin-like PCB and the characterisation, insofar as possible, of the distribution of levels of contamination;
- determination, insofar as possible, for the different feed materials/compound feedingstuffs of the carry-over/transfer rates from feed to the different food products

of animal origin of the relevant non dioxin-like PCB (relevant in view of their occurrence and/or specific toxicity);

- assessment of the contribution of the different identified feed materials as sources of contamination by non dioxin-like PCB:
  - to the overall exposure of the different relevant animal species to non dioxin-like PCB;
  - to the impact on animal health;
  - to the contamination of food of animal origin (the impact on public health), taking into account dietary variations and carry-over rates.
- identification of eventual gaps in the available data which need to be filled in order to complete the evaluation.

Particular attention should be paid to the fact that the PCB congener pattern present in feed does not in most cases reflect the PCB congener patterns of the technical mixtures.
The scientific opinion should furthermore contain an assessment of

- the relevance of the current usual monitoring of the 7 (6) indicator PCB[5] in feed as an indicator for the presence of total NDL-PCB and for the toxicity of the non dioxin-like PCB;
- the quantitative ratio in feed between the presence of non dioxin-like PCB and dioxin-like PCB and non dioxin-like PCB and WHO-TEQs (dioxins, furans and dioxin-like PCB), respectively.

ASSESSMENT

1. General introduction

Polychlorinated biphenyls (PCB) are synthesised by catalysed chlorination of biphenyl. Depending on the number of chlorine atoms (1-10) and their position at the two rings, 209 different compounds, PCB congeners, are theoretically possible. Figure 1 shows the structural formula of PCB and the numbering of the carbon atoms in the two rings. While positions 2, 2',6, 6' are called "*ortho*", positions 3, 3', 5, 5' are named "*meta*" and positions 4 and 4' are called "*para*" positions, respectively.

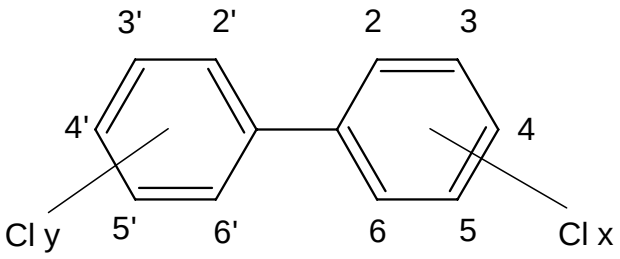


Figure 1. Structural formula of PCB and numbering of the carbon atoms ($Cl_x + Cl_y$ = 1-10).

Due to their physical and chemical properties, such as non-flammability, chemical stability, high boiling point, low heat conductivity and high dielectric constants, PCB were widely used in a number of industrial and commercial open and closed applications. Closed applications include the use of PCB in hydraulic and heat transfer systems as well as cooling and insulating fluids in transformers and capacitors. Use of PCB in pigments, dyes, repellents and carbonless copy paper or as plasticizers in paints, sealants, plastics and rubber products are typical open applications. For technical purposes, PCB have never been used as single compounds but as complex, technical mixtures. It is estimated, that more than 1 million tons of technical PCB mixtures were produced world-wide since their first commercial use in the late 1920s. These technical mixtures were liquids with different viscosity depending on the degree of chlorination (between 21 and 68% chlorine). Depending on the chlorine content and the production process, the composition of the technical mixtures, marketed under a large number of trade names, such as Aroclor, Clophen, Phenochlor, Kanechlor, Pyralene, Fenclor, Delor, may differ significantly as to the number and content of individual PCB congeners. Even mixtures with comparable chlorine content, but from different manufacturers (e.g. Aroclor 1260 and Clophen A 60), show varying compositions. The different technical mixtures are found to contain about 100-140 individual congeners.

PCB was identified as an environmental contaminant by Sören Jensen in 1966 (Jensen, 1966). Although the manufacture, processing and distribution of PCB has been prohibited in almost all industrial countries since the late 1980s, their entry into the environment still occurrs, especially due to improper disposal practices or leaks in electrical equipment and hydraulic systems still in use. PCB are globally circulated by atmospheric transport and thus present in all environmental media. Once released into the environment, individual PCB congeners may undergo biodegradation and photodegradation, which results in a change to the congener pattern compared with the original technical mixtures. This change in pattern is even more pronounced when PCB mixtures are taken up by animals, especially mammals, including humans. While certain lower chlorinated PCB congeners are metabolised quickly, higher chlorinated congeners with certain chlorine substitution patterns are notably more stable and accumulate within the food chain.

The main pathway of human exposure for the majority of the population is via food consumption with the exception of specific cases of accidental or occupational exposure.

Based on structural characteristics and toxicological effects, PCB can be divided into two groups. One group consists of 12 congeners that easily can adopt a coplanar structure and has the capability to bind to the Ah receptor, thus showing toxicological properties similar to dioxins (effects on liver, thyroid, immune function, reproduction and behaviour). This group of PCB is therefore called “dioxin-like PCB” (DL-PCB). The nomenclature as well as structure and toxic equivalency factors (TEF) assigned to these congeners by WHO in 1997 (Van den Berg *et al.*, 1998) is shown in Table 1. According to the WHO, a TEF indicates an order of magnitude estimate of the toxicity of a dioxin-like compound relative to TCDD. The shorthand nomenclature refers to the systematic numbering system proposed by Ballschmiter

and Zell in 1980 and modified by Ballschmiter *et al.* in 1987 b and 1992. Since then, this system is generally accepted.

Table 1. Nomenclature of DL-PCB congeners and assigned TEF by WHO (van den Berg *et al.*, 1998)

PCB number	Structure	TEF
non-ortho PCB		
77	3,3',4,4'-tetrachlorobiphenyl	0.0001
81	3,4,4',5-tetrachlorobiphenyl	0.0001
126	3,3',4,4',5-pentachlorobiphenyl	0.1
169	3,3',4,4',5,5'-hexachlorobiphenyl	0.01
mono-ortho PCB		
105	2,3,3',4,4'-pentachlorobiphenyl	0.0001
114	2,3,4,4',5-pentachlorobiphenyl	0.0005
118	2,3',4,4',5-pentachlorobiphenyl	0.0001
123	2',3,4,4',5'-pentachlorobiphenyl	0.0001
156	2,3,3',4,4',5-hexachlorobiphenyl	0.0005
157	2,3,3',4,4',5'-hexachlorobiphenyl	0.0005
167	2,3',4,4',5,5'-hexachlorobiphenyl	0.00001
189	2,3,3',4,4',5,5'-heptachlorobiphenyl	0.0001

The other PCB do not show dioxin-like toxicity but have a different toxicological profile, in particular with respect to effects on the developing nervous system and neurotransmitter function. This group of PCB, is called “non dioxin-like PCB” (NDL-PCB). Although NDL-PCB in this opinion are discussed as a group of PCB congeners, it is not likely that all these congeners have identical toxicological profiles. Mixtures used to study the toxicity of PCB contain both NDL- and DL-PCB and some PCB congeners may even possess both types of toxicity. It is therefore difficult to differentiate between the toxic effects of dioxins and DL-PCB and NDL-PCB.

Both NDL-PCB and DL-PCB accumulate in animals and humans and biomagnify in the food chain, although clear differences between individual congeners are observed.

2. Dioxin-like compounds in technical PCB mixtures

Although produced by similar production processes, the resulting mixtures may vary considerably with respect to their congener composition. Moreover, technical PCB mixtures may have contained other chlorinated compounds as impurities, such as polychlorinated naphthalenes (PCN) and polychlorinated dibenzofurans (PCDF). The different composition as

well as the presence of these toxicologically relevant impurities may have had a significant impact on the results of toxicological studies with technical PCB mixtures. A reliable interpretation of results of such studies, especially a differentiation of effects caused by NDL- and DL-PCB respectively, may only be achievable if the congener composition of these mixtures is known. Unfortunately, this is not the case for most of the animal studies performed. Moreover, it has to be considered that the manufacture of PCB had more or less ended by the late 1970s, before many of the analytical techniques, necessary for determining specific congeners, were developed. Therefore, almost all congener specific analyses of technical mixtures were carried out when production had already ceased.

The variation of congener composition as well as the amount of impurities in two Aroclor 1254 lots that were used for toxicological studies over the last few years, is shown in Table 2. Aroclor 1254 with lot numbers 6024 and 124-191 both had a purity >99% and were purchased from Accu Standard (New Haven, CT, USA).

The raw data for the various congeners of the two lots were extracted from the publication by Kodavanti *et al*. (2001) and transferred into toxic equivalents using the TEF values proposed by WHO in 1997. As can be seen, the proportions of non-ortho as well as mono-ortho PCB differed significantly between the two lots. As a consequence, the resulting TEQ values (38.3 vs. 395.1 µg WHO-TEQ/g) differ by more than one order of magnitude. The amounts of PCN and PCDF were also somewhat higher in Aroclor 1254 lot 6024. While lot 124-191 has the typical PCB congener distribution of "early" Aroclors 1254 types (G4 types), lot 6024 represents the "late" (1974-1976) production of Aroclor 1254 (A4 types) (Kodavanti *et al.*, 2001).

Frame *et al*. (1996) analysed different Aroclor 1254 lots for their individual PCB congener composition. Most of these lots were manufactured between 1937 and 1974. While four lots belonged to the late so called "A4" variant, the other 11 lots belonged to the more extensive "G4" type produced earlier. A4 and G4 type Aroclor 1254 were produced by different chlorination procedures (two step versus single step chlorination).

Table 2. DL-PCB, PCDD/PCDFand PCNs in 2 different Aroclor 1254 lots

Parameter	Lot 124-191	Lot 6024
non-ortho congeners		
PCB 77	0.01 mg/g	27.2 mg/g
PCB 81	0.01 mg/g	0.28 mg/g
PCB 126	0.17 mg/g	3.24 mg/g
PCB 169	0.01 mg/g	0.02 mg/g
mono-ortho congeners		
PCB 105	51.00 mg/g	130.00 mg/g
PCB 114	0.05 mg/g	0.78 mg/g
PCB 118	127.00 mg/g	124.00 mg/g
PCB 123	0.57 mg/g	2.14 mg/g
PCB 156	4.80 mg/g	51.00 mg/g
PCB 157	0.36 mg/g	26.30 mg/g
PCB 167	n.d.	n.d.
PCB 189	n.d.	n.d.
Σ polychlorinated dibenzo-*p*-dioxins	<2 ng/g	<2 ng/g
2,3,7,8 – TeCDF	129.9 ng/g	350.1 ng/g
1,2,3,7,8 – PeCDF	295 ng/g	1920.2 ng/g
2,3,4,7,8 – PeCDF	821 ng/g	4049.2 ng/g
1,2,3,4,7,8 – HxCDF	1638.1 ng/g	4571.4 ng/g
1,2,3,6,7,8 – HxCDF	733.7 ng/g	3190.5 ng/g
1,2,3,7,8,9 – HxCDF	n.d.	n.d.
2,3,4,6,7,8 – HxCDF	213.3 ng/g	1333.3 ng/g
1,2,3,4,6,7,8 – HpCDF	581.8 ng/g	1506.5 ng/g
1,2,3,4,7,8,9 – HpCDF	533.3 ng/g	1459.4 ng/g
1,2,3,4,6,7,8,9 – OCDF	356 ng/g	945.6 ng/g
Σ polychlorinated dibenzofurans	11.3 µg/g	38.7 µg/g
Σ Polychlorinated naphthalenes	155 µg/g	171 µg/g
Σ Non-ortho congeners-TEQ	17.1 µg WHO-TEQ/g	327 µg WHO-TEQ/g
Σ Mono-ortho congeners-TEQ	20.5 µg WHO-TEQ/g	65 µg WHO-TEQ/g
Σ PCDF-TEQ	0.7 µg WHO-TEQ/g	3.1 µg WHO-TEQ/g
Total PCDD/PCDF/PCB-TEQ	38.3 µg WHO-TEQ/g	395.1 µg WHO-TEQ/g

Table 3. DL-PCB (µg WHO-TEQ/g) in a number of Aroclor mixtures with different chlorine content

References	Aroclor								
	1016	**1221**	**1232**	**1242**	**1248**	**1254**	**1260**	**1262**	**1268**
	(µg WHO-TEQ/g Aroclor)								
1	Lot 129 **0.085**	Lot A 7080365 **0.051**	Lot A 7080363 **3.3**	Lot 01141 **5.2**	Lot A 7090364 **16**	Lot 124-191 **21**	Lot 023-150D **3.5**	Lot 106-262 **1.1**	Lot A 7080368 **0.21**
2		**0.85**		**3.3**	**6.2**	**32**	**15**		
3, 4		**0.14**	**0.78**	**1.8**	**5.3**	G 4 type **17** A 4 type **51.2** [a] G 4 type **18.6-24.2** A 4 type **37.9-76.4**	**3.5**	**1.2**	
5	**0.01**	**0.04**	**1.6**	**4.3**	**14**	**42.8** [b]	**4.7**	**4.0**	**0.61**
6				**3.3**	**13**	**18**	**2.0**		
7						Lot NT01719 **687** [b]			
8				Mean of 3 lots **1.7**	Lot A 3.5 **5.3** Lot G 3.5 **5.2**	Lot A 4 **51.2** [b] Lot G 4 **16.5**	Mean of 3 lots **3.5**		
9						Lot 124-191 **37** Lot 6024 **392**			

References 1-9:
1: Rushneck *et al.*, 2004; 2 Duinker *et al.*, 1988 (data cited in Rushneck *et al.*, 2004); 3: Frame *et al.*, 1996 (data cited in Rushneck *et al.*, 2004); 4: Frame, 1999; 5: Hong *et al.*, 1993 (data cited in Rushneck *et al.*, 2004); 6: Schwartz *et al.*, 1993 (data cited in Rushneck *et al.*, 2004); 7: Howard *et al.*, 2003; 8: Hansen, 1999 (data condensed from Frame *et al.*, 1996); 9: Kodavanti *et al.*, 2001
(a) TEQ values recalculated due to obvious calculation errors in Rushneck *et al.*, 2004
(b) TEQ calculation overestimated due to coelution of PCB 77, 126, 156, and 157 with other PCB congeners

Although both are chlorinated to 54% chlorine by weight, their congener composition differs slightly. A4 type contains higher levels of PCB 126 (5.3-43.2 vs. 3.2-5.7 µg TEQ/g) than G4 type, and consequently higher levels of PCB-TEQ (37.9-76.4 vs. 18.6-24.2 µg total-PCB-TEQ/g) (Frame *et al.,* 1996). These data in Table 3 are expressed in relation to the sum of PCB found, instead of the weight of Aroclor taken, because some of the commercial mixtures analysed were diluted with non PCB components. Data on possible impurities by polychlorinated dibenzofurans are not reported for these mixtures (Frame *et al*., 1996).

While production records suggest that the A4 pattern lots of Aroclor 1254 (e.g. lot 6024) represented less than 1% of the total Aroclor 1254 production, their availability during the final years of production resulted in a disproportionate use of them by suppliers of standards and researchers studying Aroclor 1254 toxicity. For example, the major chronic two year rat carcinogenicity study of Aroclors (Mayes, *et al.,* 1998) and an in vivo neurotoxicity study (Kodavanti *et al.*, 1998), both employed an Aroclor lot of this type (Frame, 1996, 1999).

A compilation of TEQ values based on the occurrence of DL-PCB in different technical mixtures such as Aroclor, Clophen, Delor and Kanechlor, is given in Tables 3 and 4. In some cases the levels of polychlorinated dibenzofurans and their contribution to the TEQ were also reported.

Table 4. DL-PCB and dioxins (expressed as µg WHO-TEQ/g product**)** in other technical PCB preparations with different chlorine content

Reference	**PCB-product (µg WHO-TEQ/g product)**			
1	Clophen A 30 **2.6**	Clophen A 40 **6.9**	Clophen A 50 **114**	Clophen A 60 **472**
2	Delor 103[a] DL- PCB: **2.2** PCDF: **not detected**	Delor 104[b] DL-PCB: **5.4** PCDF: **4.2**	Delor 105[c] DL-PCB: **25.5** PCDF: **0.8**	Delor 106[d] DL-PCB: **16.4** PCDF: **2.0**
3	Kanechlor 300 **0.71**	Kanechlor 400 **8.6**	Kanechlor 500 **14.2**	Kanechlor 600 **3.4**

References 1-3:
1: (Duinker *et al*., 1988); 2: (Taniyasu *et al*., 2003); 3: (Kim *et al*., 2004)
a) Delor 103 resembles Aroclor 1242
b) Delor 104 resembles Aroclor 1248
c) Delor 105 resembles Aroclor 1254
d) Delor 106 resembles Aroclor 1260

The data indicate that the TEQ values increase with increasing chlorine content, showing their maximum in products containing around 50% chlorine and declining with a further increase in chlorine content. This is however not the case for Clophen A60 where the relatively high TEQ value is caused by the contribution of PCB 126 with a relative amount of 0.46%. A special situation also seems to exist for the two different types of Aroclor 1254 (A4 vs. G4). In all other cases, the TEQ values of the various PCB mixtures with comparable chlorine content, but from different producers, show obvious similarities.

In summary, the data demonstrate that the presence of DL-PCB and PCDF in different technical PCB mixtures (expressed as WHO-TEQ) must be considered when interpreting toxicological animal studies aiming at assessing the toxic effects of NDL-PCB based on results obtained with technical PCB mixtures.

3. Methods of analysis

The complexity of the different technical PCB mixtures, and the change of composition after release into the environment, initially made quantitative analysis of PCB very difficult. The first attempts aimed at dechlorination to biphenyl with subsequent HPLC determination or perchlorination to decachlorobiphenyl using gas chromatography (GC) with electron capture detection (Crist and Moseman, 1977; De Kok *et al*., 1981; Lin and Que Hee, 1985; Kuchen *et al*., 1987) for quantification. These methods express the levels as total PCB and only allow a rough estimate because the calculation is highly dependent on the mixture that is used for calibration. Accuracy of early GC analyses was restricted due to limited resolution power of packed columns used for separation of the various congeners. Usually, the broad peaks detected consisted of a number of non-resolved PCB congeners and probably other interfering compounds. This approach does not account for the fact that the detector response of individual PCB congeners is not only dependent on the number of chlorine atoms, but also on their position at the biphenyl ring system. Consequently, two packed column GC peaks with the same detector signal (expressed as peak area) may contain variable amounts of individual congeners. For quantification, the areas of normally 3-6 peaks were compared with corresponding peaks of those technical mixtures which chromatographically fitted best, usually Clophen A60 and Aroclor 1260 for human specimens and samples of animal origin. As a result, the concentration was e.g. reported as “total-PCB, expressed as Clophen A60”. Such results are tainted with significant uncertainties because the PCB pattern found in environmental and biological samples seldom resembled the composition of the technical mixture which was used for calibration.

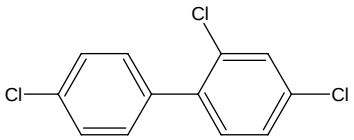
The breakthrough in PCB analysis can be attributed to the introduction of capillary columns for gas chromatographic separation (Schulte and Acker, 1980), synthesis and commercial availability of an increasing number of individual PCB congeners, and the determination of the relative retention times of all 209 congeners on a non-polar fused silica capillary column (Mullin *et al.*, 1984). This enabled the assignment of the composition of technical PCB mixtures, the identification of individual PCB in fly ash from municipal waste incinerators

and the congener specific PCB analysis in environmental, food and human samples (Ballschmiter *et al.*, 1987a,b; Schulte and Malisch, 1983, 1984).
In principle, a gas chromatographic determination of all 209 PCB congeners is possible. However, this is a very time-consuming task because it demands calibration for each analyte in question. This effort is considered unjustifiable. Instead, it was proposed to focus the analysis mainly on the six PCB congeners 28, 52, 101, 138, 153 and 180 (Beck and Mathar, 1985).

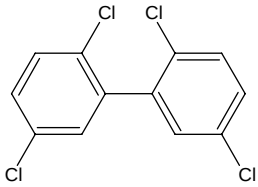
The six individual congeners (Figure 2) were not selected from a toxicological point of view, but were considered as indicators for the different PCB pattern in various sample types. This concerns technical mixtures as the main source of contamination as well as environmental and human samples where the pattern is significantly affected by biodegradation and photodegradation as well as bioaccumulation and metabolism. These six congeners are often termed "indicator-PCB" or "marker-PCB". In the past, this approach was adopted by a number of countries. Other investigations, especially in connexion with the Belgium PCB/dioxin case in 1999 also include PCB 118 (Figure 2) which is actually a DL-PCB, as a seventh congener into the group of indicator PCB. Meanwhile, the six or seven indicator PCB, either as individual congeners or as a sum, have found their way into numerous national regulations. A number of well proven and validated methods for the analysis of NDL-PCB in various environmental and biological matrices are available. Currently, high-resolution gas chromatography with electron capture detection (GC/ECD) is the analytical method of choice. This analytical technique not only allows differentiation between the various congeners, but also enables separation of them from possibly coeluting interfering compounds such as organochlorine pesticides or PCB substitutes. To check for compliance with given maximum levels, it has proven good to perform the gas chromatographic analyses on two capillary columns of different polarity. Special attention has to be paid to the determination of PCB 138, because this congener, which is part of many national PCB regulations, coelutes on several non-polar columns with PCB 163. This may lead to significant overestimation of the actual level of PCB 138. Potential coelution problems of PCB congeners with other organohalogen compounds can be overcome by applying combined capillary gas chromatography/mass spectrometry (GC/MS) in the electron impact (EI), or negative chemical ionization (NCI) mode as an alternative method.

During extraction and clean up of samples, care has to be taken to avoid losses of the lower chlorinated PCB congeners due to their relative high volatility. Moreover, each batch of samples should include a blank sample in order to check for possible PCB contamination originating from chemicals and devices used in the analytical procedure as well as the laboratory environment. This is especially true for the determination of lower chlorinated congeners in specimen where only a low sample quantity is available. For example, the analytical determination of PCB 28 and 52 in food, feed and human samples, may be significantly affected by volatilisation of these congeners from sealants used in the laboratory building. In addition, freeze drying applied during the analytical procedure, may be a potential

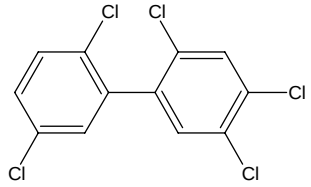
source of contamination with PCB 47. Therefore, comprehensive quality control measures are mandatory in order to ensure that the methodology applied is fit for the purpose.



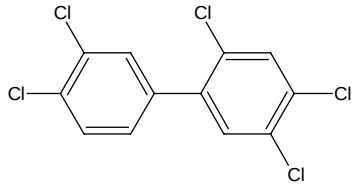
PCB 28 (2,4,4' – trichlorobiphenyl)



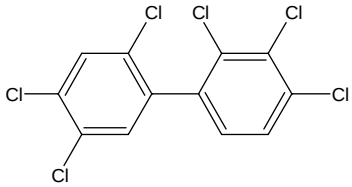
PCB 52 (2,2',5,5' – tetrachlorobiphenyl)



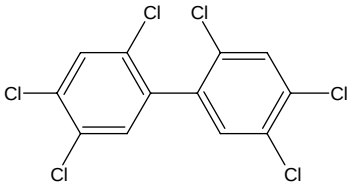
PCB 101 (2,2',4,5,5' – pentachlorobiphenyl)



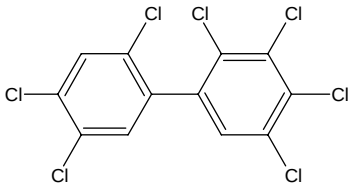
PCB 118 (2,3',4, 4',5, – pentachlorobiphenyl)
(dioxin-like PCB)



PCB 138 (2,2',3,4,4',5' – hexachlorobiphenyl)



PCB 153 (2,2',4,4',5,5' – hexachlorobiphenyl)



PCB 180 (2,2',3,4,4',5,5' – heptachlorobiphenyl)

Figure 2. Chemical structures of the seven indicator PCB

4. Attempts to estimate total PCB concentrations

Most analytical investigations for PCB are limited to the determination of a small number of congeners, which raises the question of the exent to which these results can be used for estimation of the total PCB concentration in a given sample. In this respect a number of attempts have been made in past decades in order to compare analytical results and to perform toxicological evaluations.

Based on the finding that the sum of PCB 138, 153 and 180 make up on average 61% of the human PCB body burden, it was proposed to multiply their summed concentration in human samples by 1.64 to give the total PCB concentration (Schulte and Malisch, 1984). For food samples of animal origin the factor of 1.64 was considered not appropiate. Therefore, a factor of four was proposed instead. This factor was derived from the occurrence of the three PCB congeners 138, 153 and 180 (approximately 25%) in the technical mixture Clophen A60 (DFG, 1988). Later investigations of different food categories indicated that the relative contribution of these three indicator PCB is in the range of 20-42% (Liem and Theelen, 1997).

The predominance of the three PCB congeners 138, 153 and 180 in highly chlorinated Clophen mixtures was also the basis for another estimation of the total PCB content in human samples using the following formula:

Total PCB = (conc. PCB 138 x 7.03 + conc. PCB 153 x 6.64 + conc. PCB 180 x 11.86)/3

This formula was used for years by a number of investigators for human PCB risk assessment purposes. However, it results in a significant overestimation of the total PCB concentration because it does not account for the fact that approximately 40% of the PCB congeners present in technical mixtures are metabolised within the food chain (Schulte and Malisch, 1984). This is demonstrated by converting the mean levels of the PCB congeners 138, 153 and 180 determined in the latest WHO human milk field study (see chapter 5.3) into total PCB. Using the afore mentioned formula, the sum of the three PCB congeners would result in a total PCB level of 562 ng/g fat which is almost twice the actually measured level of 313 ng/g fat.

While the above approaches estimate **total PCB** concentrations based on the determination of a limited number of congeners and subsequent transformation with empirical factors, other investigations express the PCB concentration in a given sample as a **sum of a number of selected congeners**. This is often done either as the sum of the three predominant PCB 138, 153 and 180, as the sum of six or seven indicator PCB or even as the sum of all PCB congeners quantified in the respective sample. Often, the sum of PCB is reported as such without giving any details on the kind and number of congeners analysed.

The situation becomes even more complicated when different matrices are looked at with the aim of tracing back contamination pathways or assessing different routes of human PCB exposure. When analysing indoor air, for example, it is common practise to measure six indicator PCB, add up their levels and multiply the sum by a factor of five to estimate the total

PCB concentration (VDI, 1997). Depending on the chlorine content of the PCB-containing sealant as the most likely contamination source, the results of air measurements in the respective building will lead to erroneous estimation of the real PCB concentration. This is especially important because air samples are mostly dominated by the highly volatile, lower chlorinated PCB congeners 28 and 52, while the more persistent PCB 138, 153 and 180 are normally of minor importance due to their lower volatility. In contrast, the latter ones are bioaccumulated within the food chain and predominate in human samples, whereas PCB 52, and to some extent PCB 28, are normally found at considerably lower levels.

It is obvious that approaches aiming to estimate the total PCB concentration in a given sample using transformation factors or reporting of PCB sums without stating the underlying number and kind of congeners, considerably hampers the interpretation of results and makes a reliable comparison of data - even for the same matrix - almost impossible. Consequently, all respective calculations are tainted with smaller or larger uncertainties. Therefore, a valid evaluation of analytical results and comparison of occurrence and exposure data is achievable only on an individual PCB congener basis.

Because PCB 118 is considered to be a DL-PCB it has been assigned a TEF value by WHO (see Table 1). Therefore, for the present opinion the Panel used, unless stated otherwise, the sum of the six indicator congeners PCB (Σ_6(PCB)) 28, 52, 101, 138, 153 and 180 to represent the sum of NDL-PCB.

5. Regulatory Status for NDL-PCB

5.1. Provisions at EU level

No maximum levels for NDL-PCB in feed and food have been set at Community level.

In 1999, contamination of feedingstuffs with PCB and dioxins happened in Belgium with serious consequences for the whole food chain. Analysis of dioxins requires sophisticated methods, which were at that time only available in a limited number of laboratories. Given the need for analysis, it was concluded that the level of the sum of seven indicator PCB (Σ_7(PCB))[10] could be reliably used as a surrogate for dioxins for that specific contamination incident in order to increase the analytical capacity for managing the contamination incident. As criteria for acceptability, maximum levels for the sum of seven PCB of 200 µg/kg fat for eggs, egg products, fresh poultry, beef and pig meat and derived products and of 100 µg/kg fat for raw milk, heat-treated milk and milk based products were established by Commission Decisions 1999/449/EC and 1999/788/EC[11]. Once the contamination incident was under

[10] Sum of the following PCB: 28, 52, 101, 118, 138, 153, 180

[11] Commission Decision 1999/449/EC of 9 July 1999 on protective measures with regard to contamination by dioxins of certain products of animal origin intended for human or animal consumption (OJ L 173, 10.7.1999, p. 70); Commission Decision 1999/788/EC of 3 December 1999 on protective measures with regard to contamination by dioxins of certain products of porcine and poultry origin intended for human or animal consumption (OJ L 310, 4.12.1999, p. 62)

control, these maximum levels were consequently repealed in April 2000 by Commission Decision 2000/301/EC[12] .

5.2. National provisions for feed

A limited number of Member States have national provisions in place as regards maximum levels for NDL-PCB in animal feed.

Belgium and Poland have established maximum levels for animal feed for the sum of seven indicator PCB (200 µg/kg fat) while Sweden has established a maximum level for total PCB (2000 µg/kg product in feed materials and 200 µg/kg product in other feedingstuffs); Germany has established orientation values for the PCB 138, 153 and 180 individually (5 µg/kg total daily feed supply).

5.3. National provisions for food

Several Member States have national provisions in place as regards maximum levels for NDL-PCB in foodstuffs.

For foodstuffs Belgium and France established maximum levels for the sum of seven indicator PCB of 100 or 200 µg/kg fat, depending on the type of product. In the Czech Republic maximum levels for the sum of seven indicator PCB for various foodstuffs have been set in the range of 50-5000 µg/kg fat. Maximum levels for total PCB have been established in Hungary (100 µg/kg fat for game and 500 µg/kg fat for other food products and of 1000 µg/kg product for fish and fish products) and Slovenia (1000 µg/kg fat for milk and milk products, 2000 µg/kg fat for meat and meat products, 300 µg/kg product for eggs and 3000 µg/kg edible part for fish and seafood). Sweden established maximum levels in food commodities for PCB 153 congener alone, ranging from 10-100 µg/kg product, depending on the food product and the fat content. Germany, The Netherlands and the Slovak Republic established maximum levels for the six indicator PCB on an individual basis for a whole range of foodstuffs. In addition, the Netherlands also established maximum levels for PCB 118 for foodstuffs.

6. Occurrence and exposure assessment

As part of the EC recommended monitoring programme for dioxins and PCB, 12 Member States as well as Iceland and Norway submitted data on the occurrence of these contaminants in various feed and food products to the Commission. In almost all cases, the determination of PCB was limited to the six or seven indicator PCB. Other congeners were rarely included.

[12] Commission Decision 2000/301/EC of 18 April 2000 repealing the protective measures with regard to contamination by dioxins of certain products of porcine and poultry origin intended for human or animal consumption (OJ L 97, 19.4.2000, p. 16)

When evaluating the data it was recognized that the objectives of the monitoring programmes in the contributing countries differed in many respects. While some countries applied highly sensitive analytical methods in order to also follow the temporal trend of contamination of feed and food with dioxins and PCB, others aimed only to check for compliance with national maximum limits using less sensitive methodologies. Moreover, some results originated from *ad hoc* studies and targeted sampling in areas which were considered to be contaminated. These variables, combined with a general lack of inter-laboratory analytical harmonization, hamper the comparability of the submitted results. It was therefore necessary to screen all raw data for consistency in order to increase the reliability of the evaluation.

The following selection criteria were applied:

- only results from samples collected and analysed between 1997 and 2004 were considered in order to evaluate and describe the actual occurrence situation;
- data relating to samples collected before 1997 were discarded because recent reports have shown that background levels of dioxins and PCB in feed and food have in general decreased over the past years;
- data for which all or most congeners were below the analytical limit of quantification (LOQ) were not included in the selected database;
- data for which some congeners were below LOQ but the LOQ was not indicated were not included in the database;
- data that exhibited relatively high LOQs for one or more congeners being more than 20 times higher than actual levels in corresponding feed and/or food samples were excluded;
- samples for which the ratio between upper bound and lower bound levels for the sum of the six indicator PCB are above three were not included either.

In a number of cases, it was necessary to resolve some uncertainties in the data submitted by the Member States to the Commission. Selection resulted in a remarkable reduction of the initial data base. In the end, only minor fractions of the data originally submitted were conveyed into the final feed and food databases (N = 171 and 4183, respectively). The summary tables for the various feed and food categories each contain the distribution of the six indicator PCB. Annex I also presents data on DL-PCB 118 because it is also included in numerous national monitoring programmes as a further indicator PCB.

6.1. Occurrence in feed

Commission Directive 2003/57/EC of 17 June 2003 amending Directive 2003/32/EC of the European Parliament and of the Council on undesirable substances in animal feed, provides a classification of feedingstuffs into ten categories which have been used in this opinion for summarizing the results of the various feed products. As can be seen from Table 5, the distribution of the PCB occurrence in the different feed categories for which data are available is based on 4-55 data sets with no less than four contributing countries. NDL-PCB levels appear to span approximately one order of magnitude for *Fish oil* and *Feedingstuffs for fish*,

one to two orders of magnitude for Materials of plant origin and Compound feedingstuffs, and more than two orders of magnitude for *Fish and fishery products*. The data set for Fish oil appears to be the most homogeneous and least spread in comparison with the other "Feed" data sets dealt with here.

Table 5 demonstrates that the congener pattern of the various feed categories show great similarity. While PCB 138 and 153 are always the most prominent congeners, PCB 28, 52, and in some instances 180, show the lowest levels. PCB 101 normally exhibits an intermediate level.

Table 5. Summary of PCB occurrence distribution medians (italics), means (bold), and 10^{th}-90^{th} percentile ranges in feeds and feed components. Values in ng/g product.[a]

		PCB CONGENERS						
FEEDS AND FEED COMPONENTS	**N**	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**	**Σ_6(PCB)**
Materials of plant origin	55	*0.40* **0.70** 0.10–1.66	*0.40* **0.76** 0.05–1.79	*0.40* **1.10** 0.20–2.60	*3.60* **3.45** 0.25–6.30	*2.80* **3.17** 0.25–7.14	*1.00* **1.56** 0.05–3.36	*10.0* **10.7** 0.99–19.6
Minerals	4	— **0.26** 0.02–0.50 [b]	— **0.25** 0.009–0.50 [b]	— **0.27** 0.03–0.50 [b]	— **1.07** 0.03–3.00 [b]	— **0.52** 0.03–1.40 [b]	— **0.26** 0.01–0.50 [b]	— **2.62** 0.13–6.40 [b]
Fish oil	29	*2.00* **3.30** 1.40–10.0	*6.68* **6.12** 2.00–10.0	*9.80* **10.5** 2.58–23.0	*11.4* **13.7** 5.79–20.9	*15.4* **16.7** 7.28–26.4	*3.20* **4.45** 2.00–10.0	*48.6* **54.7** 24.9–94.9
Fish and fishery products	17	*0.33* **1.10** 0.02–2.14	*0.73* **2.85** 0.03–8.68	*1.87* **4.65** 0.08–14.5	*1.75* **6.86** 0.08–19.9	*2.42* **8.12** 0.16–23.6	*0.76* **1.99** 0.06–5.14	*7.47* **25.6** 0.41–66.7
Compound feedingstuffs	20	*0.07* **0.71** 0.02–2.00	*0.07* **0.75** 0.03–2.00	*0.16* **0.94** 0.03–2.01	*0.24* **1.94** 0.06–4.15	*0.30* **1.68** 0.07–4.21	*0.09* **1.30** 0.02–3.03	*0.85* **7.31** 0.26–19.0
Feedingstuffs for fish	46	*0.65* **1.01** 0.21–2.00	*1.63* **1.63** 0.63–2.65	*2.77* **3.42** 0.93–6.05	*3.25* **5.71** 1.43–11.0	*4.28* **5.96** 1.54–14.1	*1.15* **1.65** 0.30–3.60	*13.9* **19.4** 5.48–40.1

(a) Values rounded off to a maximum of three figures and two decimals.
(b) X_{MIN}–X_{MAX} range.

Regarding the sum of the six indicator PCB, *Fish oil* as well as *Fish and fishery products,* show the highest mean levels being 54.7 and 25.6 ng/g product, respectively. Lowest levels were found in *Minerals* (2.62 ng/g product) and in *Compound feedingstuffs* (7.31 ng/g product). However, it has to be considered that the category *Minerals* was poorly characterized as to both the number of data (N = 4) and the number of contributing countries (only two).

Four of the above mentioned feed categories could not be evaluated due to a lack of PCB occurrence data submitted to the European Commission. This applies to:

- *binders, anti-caking agents* and coagulants
- *animal fat*
- *other land animal products*
- *fish protein hydrolysates containing more than 20% fat*.

6.2. Occurrence in food

Table 6 shows the summary of the PCB distributions in various food categories. In contrast to feed, the statistics are based on a considerably higher amount of individual data sets ranging up to a maximum number of 2155 samples. While the levels for food commodities of plant origin are given as pg/g product and for fish as ng/g fresh weight respectively, all other results are given as ng/g fat weight. NDL-PCB levels span approximately one to two orders of magnitude for *Vegetable oil*, *Animal fat*, *Ruminant meat*, *Pork meat*, *Eggs*, *Poultry meat, Milk and dairy products* and more than two orders of magnitude for *Fish oil*, and *Fish and fishery products*. The data sets for *Animal fat* and *Ruminant meat* appear to be the most comparatively homogeneous ones.

From the average concentration estimates summarized in Table 6, it can be seen that the congener profile in different food groups of animal origin are similar. PCB 138 and 153 are clearly the most prominent congeners, followed by PCB 101, and 180. PCB 28 and 52 normally contribute only minor amounts to the sum of the indicator PCB. A somewhat different profile can be seen in the food categories *Cereals and cereal products*, *Fruit and vegetables*, and in the subgroup *Vegetable oil,* which in contrast to animals, lacks the ability to metabolise the lower chlorinated congeners. As a consequence, the lower chlorinated congeners PCB 28, 52 and to a certain extent also PCB 101, are present at somewhat higher levels compared to food samples of animal origin.

Cereals and cereal products, *Fruit and vegetables*, and the subgroup *Liver* are only poorly characterized due to the small number of data (N = 6-7). In addition, the data on the first two food groups were obtained from fewer than three countries each. Therefore, only a limited number of descriptors were estimated for these categories in Table 6 in order to provide a general indication of PCB levels. Although only based on a limited number of samples and thus to be considered with care, the data indicate low background contamination of food of plant origin ranging up to approximately 0.1 ng/g fresh weight.

Table 6. Summary of PCB occurrence distribution medians (italics), means (bold), and 10th-90th percentile ranges in food groups and subgroups[a].

			PCB CONGENERS						
FOOD GROUPS	**UNITS[b]**	**N**	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**	**Σ_6(PCB)**
Cereals and cereal products	pg/g product	6	— **8.35** 0.03–37.1 [c]	— **5.01** 0.03–22.0 [c]	— **1.89** 0.08–7.54 [c]	— **2.17** 0.06–8.12 [c]	— **2.46** 0.06–8.70 [c]	— **1.41** 0.02–6.38 [c]	— **21.3** 0.28–89.9 [c]
Fruit and vegetables	pg/g product	6	— **6.32** 1.33–13.0 [c]	— **3.89** 0.77–8.13 [c]	— **2.62** 0.61–3.69 [c]	— **7.42** 2.05–17.6 [c]	— **10.5** 3.22–26.5 [c]	— **19.1** <2 [d]–50.9 [c]	— **49.5** 11.8–101 [c]
Eggs	ng/g fat	128	*0.23* **0.59** 0.10–1.87	*0.09* **0.41** 0.04–1.12	*0.10* **0.70** 0.06–2.03	*0.52* **1.81** 0.25–4.05	*0.69* **2.00** 0.32–5.13	*0.39* **1.05** 0.13–3.00	*2.42* **6.60** 1.03–21.9
Fats and oils	ng/g fat								
Vegetable oil		11	*0.32* **0.65** 0.24–2.40	*0.08* **0.35** 0.04–0.81	*0.18* **0.56** 0.04–1.63	*0.24* **1.42** 0.10–5.22	*0.26* **1.51** 0.12–4.13	*0.08* **0.57** 0.04–1.85	*1.56* **5.05** 0.66–13.7
Animal fat		11	*0.12* **0.13** 0.05–0.17	*0.12* **0.11** 0.09–0.12	*0.12* **0.13** 0.12–0.15	*0.54* **0.63** 0.11–1.44	*0.85* **1.16** 0.23–2.96	*0.35* **0.46** 0.08–1.08	*2.10* **2.61** 0.80–6.37
Fish oil		77	*0.27* **0.79** 0.05–2.12	*1.01* **3.44** 0.05–9.58	*4.80* **9.18** 0.06–24.0	*17.0* **23.2** 0.13–51.4	*15.9* **25.5** 0.12–61.8	*6.33* **8.09** 0.10–17.0	*44.4* **70.2** 0.53–169
Fish and fishery products	ng/g fresh weight	1620	*0.12* **0.29** 0.02–0.70	*0.23* **0.63** 0.04–1.85	*0.50* **1.64** 0.06–4.02	*1.10* **3.88** 0.10–9.61	*1.10* **4.41** 0.12–11.2	*0.34* **1.63** 0.03–4.21	*3.98* **12.5** 0.42–30.6
Meat and meat products	ng/g fat								
Poultry		68	*0.50* **0.77** 0.16–1.00	*0.50* **0.96** 0.10–1.45	*0.50* **0.89** 0.12–1.08	*1.00* **5.34** 0.25–7.76	*0.63* **2.31** 0.24–7.46	*0.30* **2.03** 0.10–5.51	*4.47* **12.7** 1.76–24.0
Ruminants		71	*0.50* **0.58** 0.19–1.00	*0.50* **0.96** 0.18–2.00	*0.50* **0.55** 0.14–0.50	*3.40* **3.74** 1.14–6.60	*3.00* **2.60** 0.30–5.00	*1.10* **1.10** 0.10–2.10	*9.40* **9.53** 2.80–16.8
Pork		23	*0.25* **0.45** 0.02–0.97	*0.24* **0.66** 0.02–1.49	*0.31* **0.58** 0.03–0.99	*1.50* **1.54** 0.16–2.29	*2.34* **2.34** 0.04–4.56	*0.92* **1.23** 0.36–1.67	*5.82* **6.80** 0.66–13.5
Liver (terrestrial animals)		7	— **0.50** <0.02–1.27 [c]	— **1.02** <0.02–3.12 [c]	— **0.52** <0.02–1.50 [c]	— **1.16** 0.11–2.69 [c]	— **2.88** 0.11–5.10 [c]	— **0.70** 0.03–1.23 [c]	— **6.79** 0.30–14.5 [c]
Milk and dairy products	ng/g fat	2155	*1.39* **1.48** 0.82–2.31	*1.00* **0.99** 1.00–1.00	*1.00* **1.01** 0.37–1.73	*2.50* **2.57** 1.00–4.12	*3.11* **3.21** 1.57–4.92	*1.38* **1.47** 0.67–2.29	*10.6* **10.7** 6.50–15.0

(a) Values rounded off to a maximum of three figures and two decimals.
(b) Unit relationship: 1 pg/g = 1 × 10^{-3} ng/g.
(c) X_{MIN}–X_{MAX} range.
(d) The sign "<" indicates below limit of determination.

Considerably higher mean levels for the sum of the six indicator PCB are found for food samples of animal origin. Except in fish, the mean levels for the sum of the six indicator PCB in the remaining food categories of animal origin range between 2.61 and 12.7 ng/g lipid. This

range of mean levels is remarkably narrow, considering the variety of the underlying food items.

A relatively uniform contamination of European dairy products was also found in a recent investigation, using butter as a widely available, homogeneous lipid-rich matrix for the determination of spatial distributions of persistent organic pollutants including PCB. The investigation comprised a total of 138 butter samples from 15 non-European and nine European countries (Austria, Czech Republic, Denmark, Germany, Italy, The Netherlands, Spain, Sweden and UK). While the samples from UK and the Czech Republic showed the lowest and highest levels for the sum of the seven indicator PCB 28, 52, 101, 118, 138, 153 and 180, being 2.6 and 27 ng/g lipid, respectively, the levels in the samples from the other seven European countries ranged from 3.35-10.0 ng/g lipid. Mean and median levels for the sum of the seven indicator PCB were calculated as 8.2 and 7.1 ng/g lipid, respectively (Santillo *et al.*, 2003).

Fish oil and *Fish and fishery products* are examples of foods having high contamination, with mean levels for the six indicator PCB of 70.2 ng/g lipid, and 12.5 ng/g whole weight, respectively (Table 6). The wide range of contamination which is 0.53-169 ng/g lipid for *Fish oil* and 0.42-30.6 ng/g wet weight for *Fish and fishery products* can be explained by the particularly large variety of species analysed. These include farmed as well as wild fish with significantly different fat content, fish from various geographical regions, and fish belonging to different levels of the trophic web up to high-level predators, which normally show a very pronounced biomagnification of lipophilic persistent contaminants.

Numerous reports have shown that Baltic fish samples may contain higher levels of persistent organic pollutants compared to corresponding species from other fishing areas. As the fish samples from the Baltic region were well defined, an evaluation, which focused on the geographical origin of the specimen group was carried out. The Baltic samples could be further broken down into the two sub-groups “herring” and “salmon”.

The summary of this evaluation is shown in Table 7. As can be seen, the total contribution of *Baltic fish* (N = 278) amounts to 17.2% of the whole database for *Fish and fishery products* (N = 1620). As regards different Baltic fish specimens, the highest levels of NDL-PCB were found in wild salmon and herring, ranging up to 145 and 82.5 ng/g wet weight for the sum of the six indicator PCB respectively. If Baltic fish is included in the statistical evaluation of the results of all fish samples, then the mean and median levels for the sum of the six indicator PCB are approximately 50% higher compared to the corresponding levels of all non Baltic fish samples.

Table 7. Summary of PCB occurrence distribution medians (italics), means (bold), and 10th-90th percentile ranges in fish, fishery products, and selected subgroups. Values in ng/g, fresh weight.[a]

		PCB CONGENERS						
GROUPS AND SUBGROUPS	**N**	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**	**Σ_6(PCB)**
Fish and fishery products (Baltic fish specimens included)	1620	*0.12* **0.29** 0.02–0.70	*0.23* **0.63** 0.04–1.85	*0.50* **1.64** 0.06–4.02	*1.10* **3.88** 0.10–9.61	*1.10* **4.41** 0.12–11.2	*0.34* **1.63** 0.03–4.21	*3.98* **12.5** 0.42–30.6
Fish and fishery products (Baltic fish specimens not included)	1342	*0.09* **0.24** 0.02–0.51	*0.16* **0.55** 0.04–1.70	*0.34* **1.06** 0.06–2.79	*0.70* **2.69** 0.10–6.31	*0.72* **2.74** 0.11–6.06	*0.19* **0.99** 0.02–2.25	*2.59* **8.27** 0.39–19.6
Baltic fish (herring and salmon included)	278	*0.43* **0.54** 0.04–1.17	*0.70* **1.06** 0.10–2.55	*2.35* **4.44** 0.42–11.1	*4.94* **9.63** 1.02–25.0	*6.53* **12.5** 1.43–31.7	*2.36* **4.73** 0.46–12.5	*16.7* **32.9** 3.54–83.3
Baltic fish (herring and salmon not included)	108	*0.13* **0.22** 0.02–0.61	*0.20* **0.38** 0.03–0.94	*0.86* **1.76** 0.17–4.46	*2.34* **4.29** 0.56–9.98	*3.73* **5.80** 0.68–11.7	*1.28* **2.24** 0.28–5.06	*8.98* **14.7** 1.88–31.3
Baltic herring	152	*0.56* **0.66** 0.22–1.23	*0.97* **1.27** 0.35–2.53	*3.93* **5.25** 1.37–9.80	*7.23* **11.4** 2.52–24.3	*9.87* **14.5** 3.31–31.3	*3.84* **5.67** 0.96–13.2	*25.4* **38.8** 9.17–82.5
Baltic salmon	18	*1.86* **1.52** 0.49–2.34	*3.60* **3.35** 1.27–4.76	*14.9* **13.8** 2.27–20.1	*32.7* **26.6** 2.60–43.0	*40.9* **35.0** 4.30–54.1	*12.1* **11.7** 1.11–21.4	*109* **92.0** 12.3–145

(a) Rounded off to a maximum of three figures and two decimals.

6.3. Occurrence in human milk

Between 1988 and 2001 the WHO conducted three world wide field studies on levels of PCB, PCDD (polychlorinated dibenzo-p-dioxins) and PCDF in human milk. The main objectives of these studies were:

- to produce reliable and comparable data on levels of the afore mentioned contaminants in human milk to further improve the health risk assessment for infants;
- to provide a better overview of exposure levels in various countries and geographical areas;
- to identify highly exposed local populations for immediate risk management actions, including epidemiological follow-up studies and;
- to determine trends in exposure levels in order to evaluate applied risk management measures.

In particular, the determination of time trends demands recruitment of well defined cohorts. Therefore, participating countries were asked to collect samples from the same locations as in

the previous rounds for purposes of comparison. Donors should be primiparae, exclusively breastfeeding one child only, and should not have resided for more than six months outside the sampling area during the last five years. In addition, both mother and child should be apparently healthy and the pregnancy should have been normal. Strict requirements were provided for collection, pooling, storage and transport of specimens to the analytical laboratory. In order to avoid uncertainties due to the different methodologies applied, analysis of the samples could only be performed by laboratories that had to qualify beforehand in a rigid interlaboratory quality control study.

In 2001/2002 the bulk of a total of 102 human milk pools from 26 countries world-wide was collected following the protocol outlined above, and analysed in the frame of the third round of the WHO field study on human milk (van Leeuwen and Malisch, 2002; Malisch and van Leeuwen, 2005) including 58 samples from 18 European countries (Belgium, Bulgaria, Croatia, Czech Republic, Finland, Germany, Hungary, Ireland, Italy, Luxemburg, Norway, Romania, Russia, Slovak Republic, Spain, Sweden, The Netherlands, and Ukraine). This comprehensive investigation comprised the determination of the following 38 PCB congeners:

- non-ortho PCB:
  37, 77, 81, 126, 169
- mono-ortho PCB:
  28, 33, 55, 60, 66, 74, 105, 110, 114, 118, 122, 123, 124, 156, 157, 167, 189
- di-ortho PCB:
  18, 52, 99, 101, 128, 138, 141, 153, 170, 180, 183, 187, 194, 206, 209

The mean, median, minimum and maximum levels of the 33 most abundant congeners determined in the European samples are presented in Table 8. All levels are given as ng/g fat. PCB congeners 55, 122, 123 and 124 could only occasionally be determined near the detection limit and therefore are not included in the table. PCB 47 was excluded from the study because its quantification in the milk samples was affected by contamination from a freeze drying process applied in the analytical procedure.

Regarding the occurrence of PCB, the mean and median values for almost all 33 congeners are relatively close together. With a few exceptions the minimum and maximum concentrations of most of congeners are within a factor of 50. While on a concentration basis non-ortho PCB only amount to 0.04% of all PCB congeners analysed, the contribution of mono-ortho and di-ortho PCB is 14.2% and 85.8%, respectively. Three mono-ortho PCB (74, 118, 156) and eight di-ortho congeners (99, 138, 153, 170, 180, 183, 187, 194) each contribute more than 1% to the sum of all 33 congeners determined. PCB 153, 138 and 180 are by far the most predominant congeners, making up on average more than 65%.

Table 8. PCB concentrations (ng/g fat) in 58 human milk pools from 18 European countries (Results from third WHO human milk field study; van Leeuwen and Malisch, 2002; Malisch and van Leeuwen, 2005).

PCB Congener	Mean	Median	Minimum	Maximum	Contribution
non-ortho	**ng/g fat**				**%**
37	0.025	0.013	0.005	0.576	0.01
77	0.011	0.006	0.003	0.173	<0.01
81	0.005	0.003	0.001	0.071	<0.01
126	0.049	0.046	0.012	0.108	0.02
169	0.031	0.029	0.007	0.080	0.01
mono-ortho	**ng/g fat**				**%**
28	4.6	2.2	0.90	92.1	0.88
33	0.11	0.06	<0.02	0.80	0.02
60*	0.87	0.41	0.14	11.3	0.16
66	2.3	1.2	0.39	33.4	0.48
74	8.4	6.8	1.9	29.8	2.72
105	3.0	2.1	0.51	12.2	0.84
110	0.28	0.21	0.05	1.2	0.08
114	0.70	0.53	<0.14	2.0	0.21
118	12.9	11.3	2.2	35.1	4.52
156	7.1	6.9	0.97	27.6	2.76
157	1.2	1.2	0.18	3.0	0.48
167	2.5	2.2	0.38	9.3	0.88
189	0.68	0.54	0.09	3.4	0.22
di-ortho	**ng/g fat**				**%**
18	0.13	0.09	0.01	0.90	0.04
52	0.51	0.32	0.09	4.6	0.13
99	9.2	6.2	1.6	27.1	2.48
101	0.86	0.69	0.16	3.0	0.28
128	0.79	0.63	<0.16	4.1	0.25
138	64.0	55.5	9.6	286.0	22.19
141	0.19	0.17	0.06	0.60	0.07
153	81.7	67.8	10.9	378.9	27.11
170	23.5	17.9	2.8	148.3	7.16
180	58.5	45.8	6.1	336.9	18.31
183	7.6	6.0	0.83	41.3	2.40
187	14.4	9.6	1.6	62.9	3.84
194	4.7	3.2	0.34	27.2	1.28
206	0.44	0.30	0.07	1.7	0.12
209	0.26	0.14	<0.04	2.9	0.06
Σ_6(PCB)**	210.1	175.7	29.1	1009.1	64.4
Σ_7(PCB) ***	223.0	186.2	31.3	1028.0	68.2
Σ_{25}(NDL-PCB)	282.8	241.7	40.7	1309.0	90.1
Σ_{12} (DL-PCB) ****	28.2	27.2	4.4	67.4	9.9
Σ_{37}(PCB)	311.1	271.6	45.1	1374.4	100.0
Σ (138+153+180)x 1.64	334.9	280.2	43.7	1643.0	102.6

60*: PCB 60 was only analysed in 27 samples
Σ_6(PCB) **: sum of indicator PCB 28, 52, 101, 138, 153 and 180
Σ_7(PCB) ***: sum of indicator PCB 28, 52, 101, 118, 138, 153 and 180
Σ_{12}(DL-PCB) ****: sum of PCB 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189

Figure 3 shows the results of the investigations of PCB in human milk from European countries where at least two measurements within the frame of the WHO field studies between 1988 and 2001 are available. In cases where samples from the same area were analysed at different time points, the name of the area is given in brackets behind the country. If in single cases for one country different pools were analysed and their results were averaged provided they did not differ significantly.

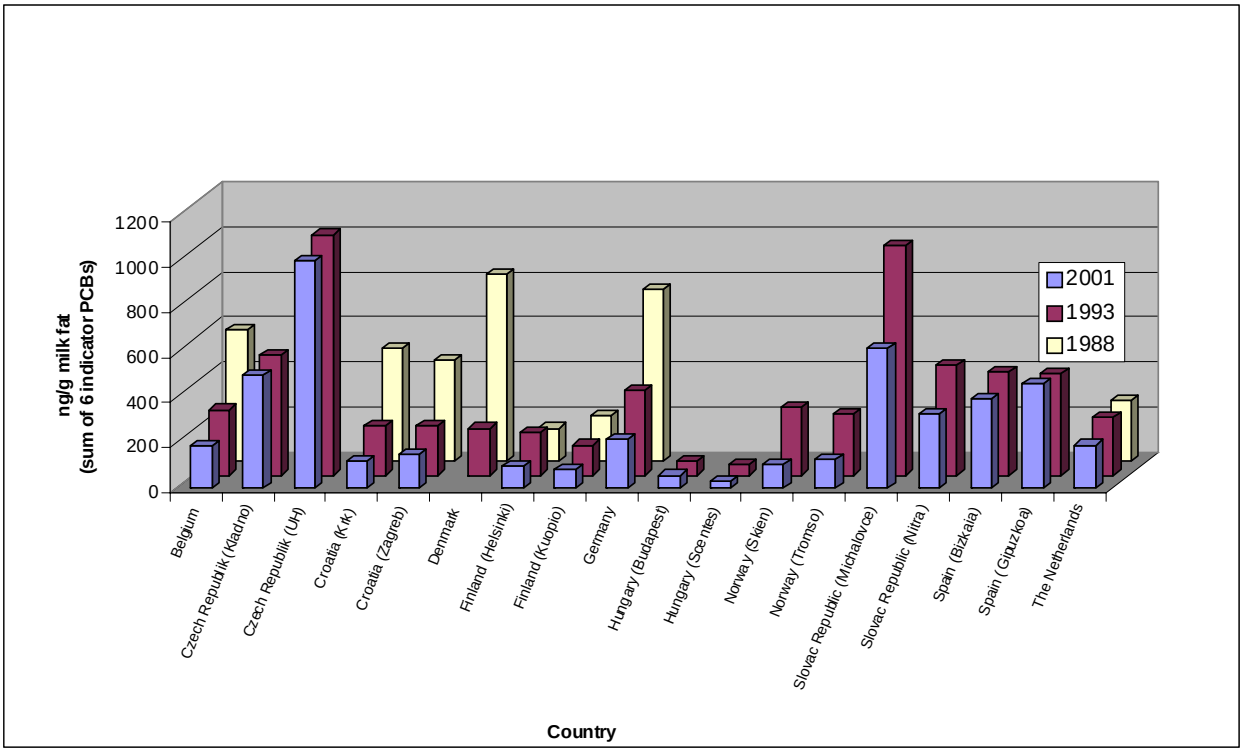


Figure 3. Sum of six indicator PCB in human milk samples from various European countries analysed in the WHO field studies 1988, 1993 and 2001. In cases where the samples originate from the same area rather than a nation wide collection the name of the area is given in brackets.

Figure 3 demonstrates the wide occurrence of PCB in human milk in various European countries. In most countries that took measures at an early stage to regulate the open and closed application of technical PCB mixtures, a more or less pronounced decline of PCB levels can be observed which is roughly in the range of 30-70%. While the lowest levels were found in human milk samples from Hungary, the human milk pools from the Czech Republic (Uherske Hradiste) show the highest levels. Both human milk pools from the Czech Republic collected and analysed in 1993 and 2001 reveal almost the same level, indicating no significant decline in exposure in these areas over the past 10 years. Although at a much lower level, the same holds true for the two observation areas in Spain. However, it should be noted, that these results can not be considered as being representative for all of the respective countries, because a number of pools originate from areas with well-known contamination and were selected specifically with the aim of following the exposure via breastfeeding over the

course of time. For example, analyses of 2595 milk samples performed between 1994 and 2000 in four districts of the Czech Republic that had different levels of industrialization, in contrast to the above finding, revealed a decline of the median levels from 1355 ng/g fat in 1994 to 653 ng/g fat in 2000. In this case, the sum of PCB was calculated by multiplying the sum of congeners 138, 153 and 180 by a factor of 1.7 (Cerna *et al.*, 2003). In this investigation, the strongest decrease was observed between 1994 and 1997. Thereafter, the levels remained almost constant.

6.4. Relationships between NDL-PCB, DL-PCB, PCDD and PCDF

The data submitted by the Member States were screened for possible correlations between NDL-PCB and DL-PCB on the one hand and between NDL-PCB and PCDD/PCDF on the other hand. Such correlations are more likely to be found where contamination of the food chain happened shortly before discovery, as was the case in the Belgian incident in 1999. However, there are many different sources for PCDD/PCDF and DL-PCB. Some of these sources such as pentachlorophenol, 2,4,5-T, trichlorophenol, kaolinitic clay and ball clay contain almost exclusively PCDD but no PCB as contaminants. In other cases, like depositions from waste incinerators, non-ortho PCB contribute significantly to the total TEQ levels, but levels of NDL-PCB are relatively low. Only in the case of incidents with technical PCB-mixtures are both NDL- and DL-PCB present at high levels. Depending on the type and production process as well as length of use, the technical PCB mixtures may also have contained considerable amounts of polychlorinated dibenzofurans. Consequently, this had a distinct effect on the congener profile of the feed and food commodities that are contaminated by these products.

6.4.1. Feed

The number of analyses of feed and feed components where NDL-PCB and DL-PCB as well as PCDD/PCDF were determined in the same sample is rather limited. Based on the available data a mean value for the ratio of the sum of the six PCB and DL-PCB TEQ of 18,000 (n=95) was calculated. The mean value for the ratio of the sum of the six PCB and total TEQ was 6,300 (n=83).

The Belgian incident in 1999 where feed was contaminated with a mixture of Aroclor 1254 and Aroclor 1260 represents a well defined contamination case. For that case a ratio of about 50,000 was calculated for the sum of the seven indicator PCB and the PCDD/PCDF TEQ in this PCB mixture. When including the DL-PCB, the ratio of the sum of the seven indicator PCB to total TEQ was about 25,000, with an important contribution to the TEQ from the mono-ortho PCB (Hoogenboom *et al.*, 2004). Following exposure of farm animals, ratios in tissue may further change, because the congeners that contribute most to the sum of indicator PCB, and to total TEQ, tend to accumulate in the food chain. A similar ratio for NDL-PCB to the PCDD/PCDF TEQ (about 25,000) was found in the fat of broilers that received

contaminated feed from the Belgian incident for one week. In young pigs a corresponding ratio of about 30,000 was found following a similar treatment. It should be understood, however, that these ratios were only valid for the distinct and well-known contamination case and therefore can not be applied for other cases.

6.4.2. Food

As mentioned above, background contamination of food may originate from many different sources and therefore no fixed ratio between PCDD/PCDF and PCB is expected. Figures 4 and 5 show the relation between the sum of the six indicator PCB and either DL-PCB TEQ (A), or total TEQ (B) in dairy products and eggs calculated for data reported to the Commission, extended with recent data from Germany. In principle, the data only cover samples from Western Europe. These graphs clearly demonstrate that the relationship may vary considerably between individual samples. The overall relations are relatively weak, both for DL-PCB and total TEQ. For PCDD/PCDF TEQ it was even less pronounced (data not shown), as can be expected because of the variety of sources for dioxin contamination.

Ratios calculated for the sum of the six PCB and DL-PCB TEQ or total TEQ in the set of dairy samples were on average 5,800 (3,600-9,600) and 3,800 (2,500-6,400) (5-95% confidence limits), respectively. For the egg samples, ratios for the sum of the six PCB versus DL-PCB TEQ and total TEQ were on average 12,500 (4,300-24,900) and 6,800 (2,300-17,400), respectively. For other food items the number of samples analysed for the different compounds was too limited and prevented a reliable estimate of ratios between NDL-PCB and either DL-PCB or total TEQ.

Some surveys conducted in well-defined sampling areas show good correlations for some food categories between levels of NDL-PCB and PCDD/PCDF and/or DL-PCB, respectively. However, the overall range of ratios for the above mentioned contaminants show great variations within Europe. Depending on the source, climate and length of vegetation period, the contaminant levels as well as the congener patterns of PCB and PCDD/PCDF in plants, vegetables and food samples of plant origin may differ significantly. Animals and food samples of animal origin are potentially affected by contaminated feedingstuffs, as well as by the conditions of the environment in which the animals are raised. Due to the differences in areas, methods and circumstances of production, definite relationships between PCB and PCDD/PCDF generally do not exist on a European level. Consequently, setting limits for PCDD/PCDF and DL-PCB might have different effects on the reduction of NDL-PCB in different foodstuffs from different geographical areas. Thus the possible reduction of human exposure to NDL-PCB by setting such limits is difficult to predict.

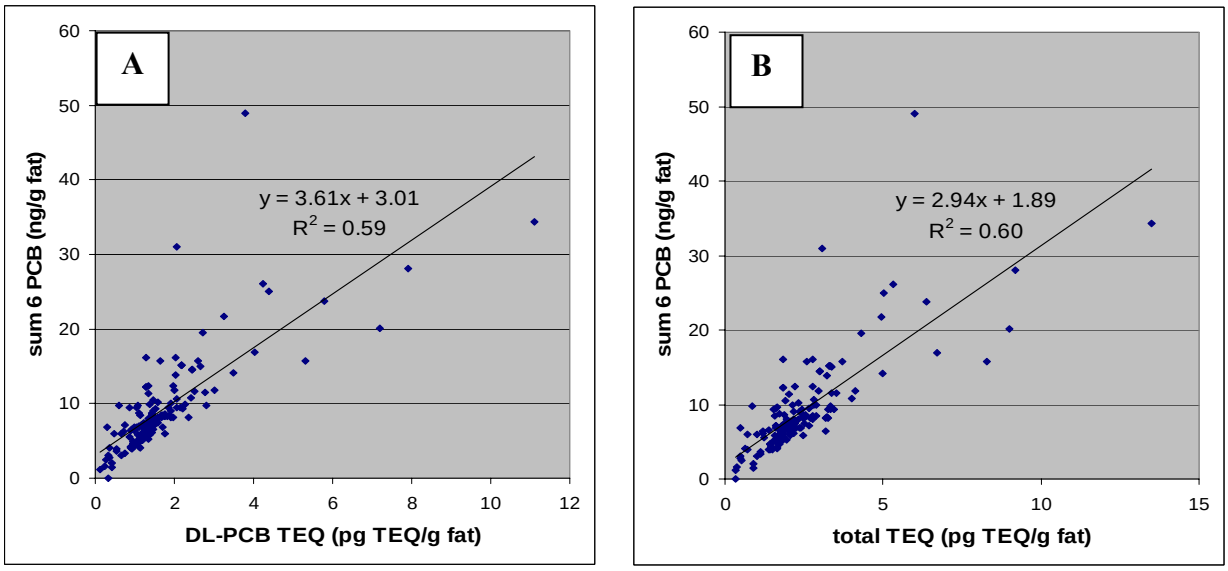


Figure 4. Relationship between either DL-PCB (A), or total TEQ (B) and the sum of the six indicator PCB in 170 samples of dairy products primarily obtained from Germany, Belgium, and Norway.

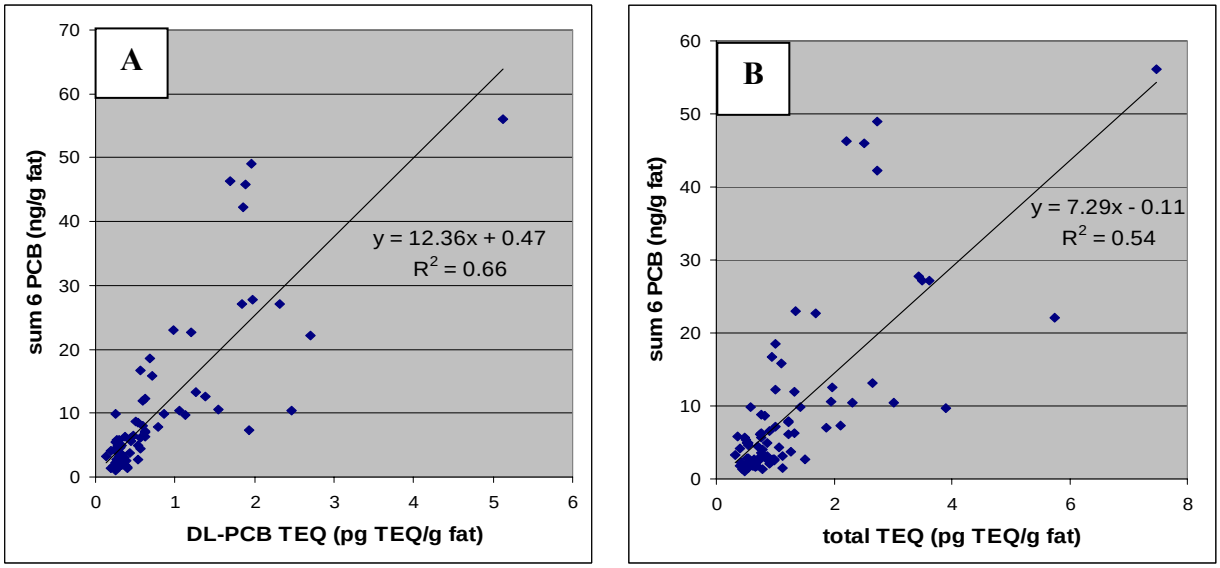


Figure 5. Relationship between either DL-PCB (A) or total TEQ (B), and the sum of the six indicator PCB in 85 samples of egg primarily obtained from Germany, Belgium, Ireland and Norway.

6.4.3. Human milk

The evaluation of the results of the human milk pools from 18 European countries analysed in the third round WHO field study revealed no statistically significant correlation between the NDL-PCB levels, PCDD/PCDF and DL-PCB, either on a concentration or on a TEQ basis. The wide range of ratios for the sum of the six indicator PCB and the PCDD/PCDF-TEQ (Table 9) indicates different sources and pathways for these contaminants and demonstrates a diverse human exposure to PCDD/PCDF and PCB in the various regions.

Table 9. Relationship of NDL-PCB versus DL-PCB and PCDD/PCDF in 58 human milk pools from 18 European countries and 38 pools from 12 EU Member States, respectively analysed in the third round of WHO human milk field studies.

Ratio	18 European countries		12 EU Member States	
	Median	Range	Median	Range
6 NDL-PCB (ng/g fat) vs. 12 DL-PCB (ng/g fat)	6.8	2.2-15.6	7.2	5.3-15.6
6 NDL-PCB (ng/g fat) vs. 12 DL-PCB (ng TEQ/g fat)	15,400	6,200-39,200	16,200	11,700-39,200
6 NDL-PCB (ng/g fat) vs. PCDD/F (ng TEQ/g fat)	15,700	4,900-94,000	16,900	4,900-94,000
6 NDL-PCB (ng/g fat) vs. PCDD/F/DL-PCB (ng TEQ/g fat)	7,800	3,500-25,700	8,100	3500-25,700

Figure 6 shows the correlation between the sum of the six indicator PCB, expressed as ng/g fat and the 12 DL-PCB, expressed on a concentration (A) and a TEQ (B) basis, for 58 milk pools from 18 European countries. As can be seen, the data are clustered with a number of samples that lie significantly above or below the trend line. Data points above the trend line are characterized by relatively high levels of indicator PCB and low levels of DL-PCB. The corresponding human milk samples mostly originate from the Czech and Slovak Republics. In contrast, the data points which lie significantly below the trend line are characterized by comparatively low levels of indicator PCB, but relatively high levels of DL-PCB. Most of the latter samples originate from Russia and the Ukraine. One explanation for the deviant congener pattern in human milk in these two groups compared to other European countries could be exposure to technical PCB mixtures of different composition, used in these countries. But differences in the pathways of these contaminants as well as differences in food composition patterns could also be of importance for the difference in congener patterns.

If only the human milk pools from the EU Member States are considered, the corresponding ratios between NDL-PCB and DL-PCB show a lower variation (Figure 7). Consequently, the coefficient of correlation of 0.7175 is higher compared to the corresponding value of 0.3138

for the entire European data set. A better correlation between NDL-PCB and DL-PCB can be found in human milk samples from individual countries. Analyses of human milk samples from Germany revealed a coefficient of correlation of 0.8549 for the ratio between the sum of six indicator PCB and 12 DL-PCB (Fürst, 2004). This higher coefficient of correlation reflects a more uniform contamination.

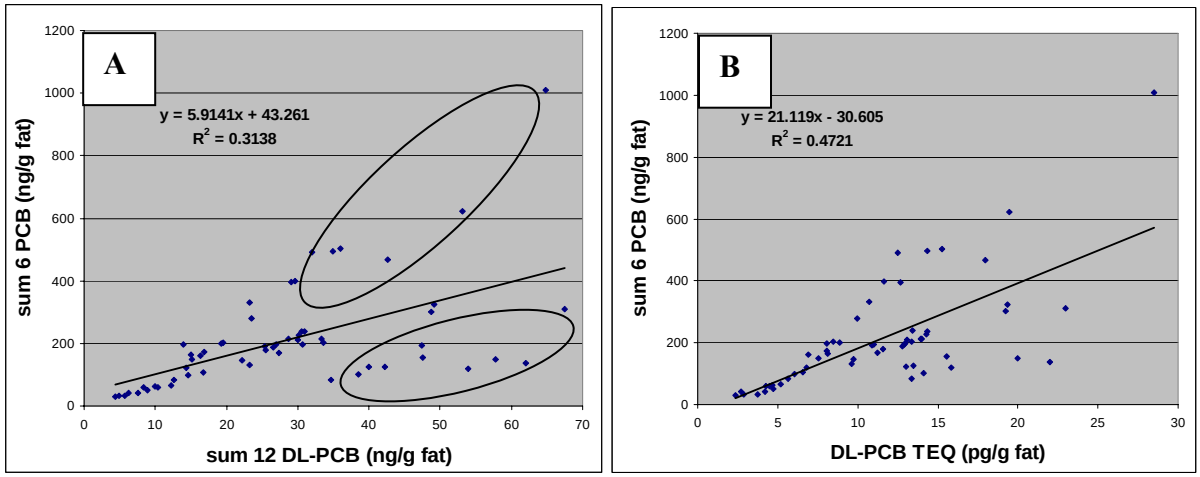


Figure 6. Relationship between the sum of six indicator PCB (28, 52, 101, 138, 153, 180; ng/g fat) and 12 DL-PCB (A ng/g fat; B: pg WHO-TEQ/g fat) in 58 human milk pools from 18 European countries analysed in the frame of the third round of WHO human milk field study.

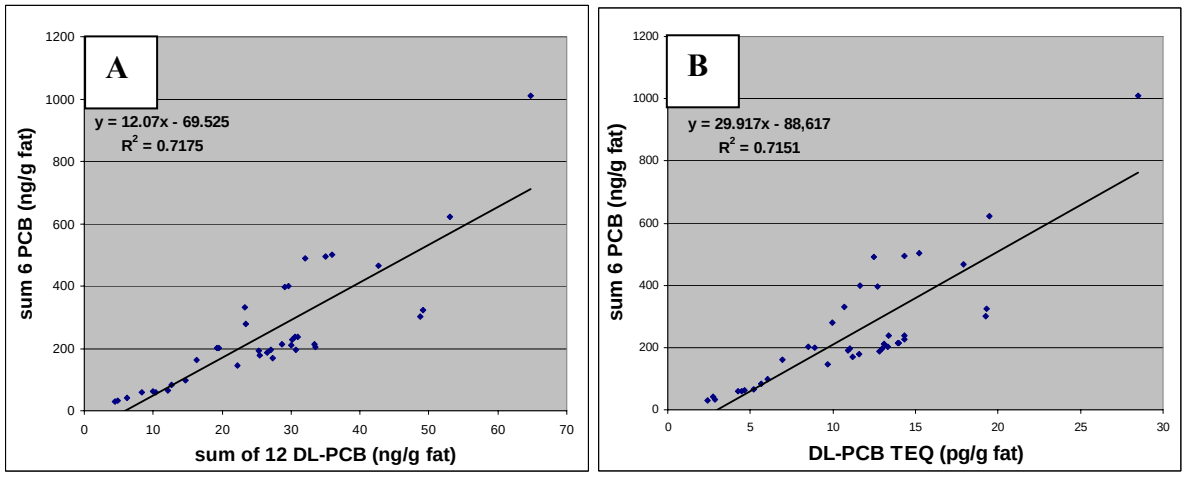


Figure 7. Relationship between the sum of six indicator PCB (28, 52, 101, 138, 153, 180; ng/g fat) and 12 DL-PCB (A: ng/g fat; B: pg WHO-TEQ/g fat) in 38 human milk pools from 12 EU Member States analysed in the frame of the third round of WHO human milk field study.

The data indicate that relatively high correlations between NDL-PCB and DL-PCB may exist in human milk from discrete areas and/or countries. However, these correlations become significantly weaker if samples from different countries are included in the assessment.

6.5 Human exposure

Human exposure occurs by three routes: (i) inhalation, (ii) dermal absorption and (iii) ingestion (food consumption and ingestion of contaminated soil/sediments). The most important source of PCB exposure of the general population is food of animal origin.

6.5.1 National dietary intake studies

Table 10 shows recent estimates of human NDL-PCB intake from different European countries. A recent and comprehensive study regarding occurrence of PCB in food and the resulting estimate of human dietary intake of PCB was published in The Netherlands (Bakker *et al.*, 2003). In this study, the PCB concentrations in composite food categories were measured and combined with the corresponding consumption data obtained from the Dutch National Food Consumption Database. The individual dietary intakes of the seven indicator PCB for 6250 individuals were calculated for two consecutive days and estimated as a function of age. Thereafter, the averaged life-long (70 years) intake was calculated. Median and 95th percentile intake values were found to be 5.6 and 11.9 ng/kg b.w. per day, respectively. Based on the assumption that PCB 118 contributes about 15% (a figure delineated from the raw data of the study) to the sum of the seven indicator PCB, it can be estimated that the median life-long averaged intake for the six indicator PCB would be about 4.8 ng/kg b.w. per day. These results are in line with earlier investigations conducted on duplicate diets in the Netherlands. This study covered 19 individual PCB which are considered to be the predominant congeners in food. Regarding the intake of six indicator PCB, a decline from 78 ng/kg b.w. per day in 1978 to 37 ng/kg b.w. per day in 1984/1985 and to 9 ng/kg b.w. per day in 1994 was determined. Based on data for all 19 NDL-PCB congeners determined in these studies, the total NDL-PCB intake decreased from 137 ng/kg b.w. per day in 1978 to 66 ng/kg b.w. per day in 1984/85 to 19 ng/kg body weight per day in 1994 (Liem and Theelen, 1997). From these figures it can be deduced that the relative contribution of the six indicator PCB to the sum of 19 NDL-PCB congeners ranged from 49 to 57%. Thus, for a rough estimate of total NDL-PCB intake, the sum of the six indicator PCB can be multiplied by a factor of two.

At the end of the 1990s, three duplicate diet studies were conducted in Germany. For the sum of the three PCB congeners 138, 153 and 180, Arnold *et al.* (1998) calculated average and maximum dietary PCB intakes of 15.3 and 133.3 ng/kg b.w. per day, respectively. While this cohort comprised an age range of 12-92 years, the seven day duplicate diet study by Schäfer *et al.* (2000) conducted in 1997 comprised seven women who were between 20 and 35 years old. For the sum of the three PCB congeners 138, 153 and 180 daily intake levels of 4.5 (median), 6.0 (average), 16.5 (95^{th} percentile) and 33.1 (maximum) ng/kg b.w. were calculated.

Table 10. Recent human NDL-PCB intake estimates from different European countries.

Country (Year)	PCB-Intake ng/kg body weight	Age (Years)	Remarks	Reference
The Netherlands				
1998/ 1999	12.1 (median) 13.5* (average) 21.9 (90th perc.) 25.7 (95th perc.)	2	Σ PCB 28, 52, 101, 118, 138, 153, 180 Survey carried out 1998/ 1999 on the basis of food consumption data from 1997/1998 (n = 6250 individuals)	Bakker *et al.*, 2003 * corrected figures provided by the authors
	6.9 (median) 9.4* (average) 12.5 (90th perc.) 14.7 (95th perc.)	10		
	5.2* (median) 5.8* (average) 8.6 (90th perc.) 10.1 (95th perc.)	40		
	5.6 (median) 11.9 (95th perc.)		estimated lifelong averaged intake	
Germany				
1995	15.9 (median) 30.5 (95th perc.)	1.5-5.3	Σ PCB 138, 153, 180 duplicate diet study, n = 14	Petzold *et al.*, 1999
1997	4.5 (median) 6.0 (average) 16.5 (95th perc) 33.1 (maximum)	20-35	Σ PCB 138, 153, 180 duplicate diet study, 7 days, n = 7 women	Schäfer *et al.*, 2000
1998	15.3 (average) 133 (maximum	12-92	Σ PCB 138, 153, 180 duplicate diet study n = 36, age = 61-92 years n = 21, age = 12-21 years	Arnold *et al.*, 1998
Sweden				
1997/ 1998	5.5 – 11.5 (median, women) 6.2 – 9.6 (median, men)	17-75	Σ 23 PCB congeners link of analytical data from different food groups with national dietary survey, n = 626 women and 581 men	Lind *et al.*, 2002
Italy				
mid 1990s	18.0 (mean) 39.0 (95th perc.)		Σ PCB 28, 52, 101, 138, 153, 180 duplicate diet study, 2 days, n = 20	Zuccato *et al.*, 1999
2004	24.6 (mean) 16.1 (mean) 10.9 (mean)	0-6 7-12 13-94	Σ PCB 28, 52, 101, 138, 153, 180 link of EU NDL-PCB occurrence data base with individual (n = 1940) consumption data (3-7 days)	Fattore *et al.*, 2005

Petzold *et al*. (1999) estimated the dietary PCB intake by young children (1.5-5.3 years) from a duplicate diet study with 14 individuals in 1995. For the sum of the three congeners 138, 153 and 180 the 95th percentile was reported as 30.5 ng/kg b.w. per day. If the results of these studies should be converted into total NDL-PCB a factor of 2.5-3 could be used. This factor could be derived from the occurrence data presented in Annex I and the assumption that the sum of the six indicator PCB contributes about 50% to the total NDL-PCB (see above).

In the Czech Republic, the National Monitoring Program recently pointed out that dietary exposure to NDL PCB over the 1994-2003 period exhibited a decreasing trend. The dietary exposure was estimated by combining measured indicator PCB concentrations in foodstuffs with average Czech food consumption data. For the sum of seven indicator PCB the average daily intake in 2003 was estimated to be less than 50 ng/kg b.w. (Czech SCF, 2004).

In Sweden a comprehensive investigation of the daily intake of a number of contaminants via food was carried out. The investigation was based on a national dietary survey from 1997-98 (Swedish Food Administration, 1999). These data were combined with analytical data from different food samples. In this way the daily intake of PCB (sum of 23 congeners) could be calculated for men and women of different age groups (17-20, 21-30, 31-40, 41-50, 51-60, 61-70 and 71-75 years). The total number of persons studied was 1207 (626 women and 581 men). The calculated median daily intake of total PCB (sum of 23) by women was found to be in the range 5.5-11.5 ng/kg b.w. where the group 21-30 years had the lowest intake and 61-70 years the highest. The median daily intake for men was 6.22-9.62 ng/kg b.w. where the age group 31-40 years had the lowest and 61-70 years the highest intake (Lind *et al.,* 2002).

Dietary exposure to PCB was also established in Italy in the mid-1990s (Zuccato *et al*., 1999). The method was based on collection of duplicate meals, on two non-consecutive days, in a group of twenty subjects consuming a typical central Italian diet. For the sum of the seven indicator PCB a mean daily intake of 19 ng/kg b.w., with a 95th percentile of 40 ng/kg b.w. was calculated. Without PCB 118 the mean and the 95th percentile values for the six indicator PCB were 18 and the 39 ng/kg b.w. per day, respectively.

A recent intake estimate for Italy was carried out by linking the EU NDL-PCB dataset (Table 6, Table 7, the latter for PCB concentrations in fish and fishery products without the Baltic contribution, Annex I) with national food consumption estimates. This assessment was based on individual consumption figures recorded over three to seven consecutive days for 1940 subjects (age 0-94 years). Subjects were grouped by age into small children (0-6 years, breastfeeding excluded), children (7-12 years), and adults (13-94 years). The mean dietary intakes of the sum of the six indicator PCB for the three age groups were 24.6, 16.1, and 10.9 ng/kg b.w. per day, respectively.

Another recent intake estimate of the sum of the six indicator NDL-PCB based on consumption data from a number of European countries resulted in an average daily intake

ranging from 14-17 ng/kg b.w. per day, corresponding to about 28-34 ng/kg b.w. per day total NDL-PCB (see Annex 1, part C).

The intake estimates presented in Table 10 result from several independent investigations, carried out in different years and with diverse methodologies. When all data are converted into total NDL-PCB by multiplying the "sum of the three" by 3, the "sum of the six" by 2 and the "sum of the seven" by 2 x 0.85 (the latter factor is a correction for the contribution of PCB 118) an average intake of 10-45 ng/kg b.w. for total NDL-PCB for the general adult population can be estimated. This figure corresponds well with the recent intake estimate by EFSA (see Annex 1, part C). The estimates of exposure for high level consumers of fish were in the region of 60-80 ng/kg b.w. per day for total NDL-PCB (Annex I, part C, Table 3).

Although populations with somewhat higher dietary intake were identified, such as in the Czech Republic and in the Slovak Republic, the above mentioned dietary intake range provides a fair indication of the average background dietary exposure to NDL-PCB in the general population in Europe. For young children (0-6 years, breastfeeding excluded) dietary intake values for the indicator PCB were reported in the range of 13.5-25 ng/kg b.w., corresponding to 27-50 ng/kg b.w. for total NDL-PCB. Where data on both adults and children within a specific population were available, in general children had exposure levels 2.5 fold higher than adults.

6.5.1.1. Sub-populations with high dietary exposure

Baltic fishermen

In Sweden in the 1990s, fishermen from the east coast (Baltic proper) and the west coast were interviewed about their preferences for 27 different food items as well as coffee, tobacco and alcohol consumption. Four categories of fish were included in the study, cod, herring, salmon and flatfish. Average weekly consumption figures for fish were calculated based on frequencies and portion size indicated.

As indicated in Table 11, intake of fish, expressed as average weekly intake of different fish species, is significantly higher among fishermen from the east coast than among the corresponding referents from the general population of the same region. East coast fishermen had a higher intake of both lean and fatty fish species compared to referents. Fishermen from the west coast also had fish meals more often than their referents but considering the fatty fish species herring and salmon, which contain higher contaminant levels, there were no significant differences between the fishermen and their referents. Similar results have also been reported for fishermen's wives (Rylander *et al.,* 1995).

Table 11. Estimated average fish consumption (g/week) by fishermen from the Swedish east and west coast. Standard deviation within brackets. From Svensson *et al.,* 1995.

	East Coast			**West Coast**		
	Fishermen N=150	Referents N=150	*p*	Fishermen N=100	Referents N=98	*p*
Cod filet	161 (145)	97 (99)	0.0001	270 (214)	128 (138)	0.0001
Flatfish	218 (282)	99 (148)	0.0003	487 (403)	161 (203)	0.0001
Salmon	119 (159)	54 (90)	0.0001	37 (108)	31 (52)	0.24
Herring	208 (253)	103 (121)	0.0001	73 (107)	59 (119)	0.24

The fish consumption habits in Table 11 provide a basis for estimating NDL-PCB intake with increasing fish consumption and contamination level. Based on the mean sum of the six indicator PCB occurrence value (12.5 ng/g fresh weight) for fish and fishery products (Table 6) and an average fish consumption in Sweden of 34 g/person per day (Swedish Food Administration, 1999), it can be estimated that the average Swedish male adult, assuming assuming a bodyweight of 80 kg, has a mean intake of 5.3 ng/kg b.w. per day. Using fish consumption rates according to Table 11, the average daily intakes of sum of the six indicator PCB from fish for west and east coast fishermen (assuming 80 kg b.w.) is 19.4 and 15.8 ng/kg b.w., respectively. If for the occurence data the mean concentration in Baltic fish, including herring and salmon of 32.9 ng/g fresh weight is used (see Table 7), the daily intake by east coast fishermen of the sum of the six indicator PCB from fish reach 41.5 ng/kg b.w. corresponding to some 80 ng/kg b.w. of total NDL-PCB. This figure is approximately 5 to 10 fold higher than the corresponding intake from fish estimated for the average male adult population in Sweden.

Faroe Islands

The population in the Faroe Islands has a high intake of seafood and PCB exposure is elevated, while exposure to PCDD/PCDF appears comparable to that occurring elsewhere in Northern Europe (Grandjean *et al.*, 1995). The major source of PCB exposure in the Faroes is pilot whale blubber, which contains an average PCB concentration of 20 µg/g (Borrell *et al.*, 1993). Pilot whale blubber is eaten as a traditional food item by many Faroese, with average intakes in the 1980s of about 7 g per day (Vestergaard and Zachariassen, 1987). A dietary survey was carried out among pregnant women in 2000-2001 subsequent to a governmental dietary advisory that women abstain from eating whale blubber until they had given birth to their children. This recent survey showed an average blubber consumption of about 0.6 g per day (Weihe *et al*., 2003).

Belgian PCB/dioxin incident 1999

In January 1999 a mixture of PCB contaminated with polychlorinated dibenzodioxins (PCDD) and polychlorinated dibenzofurans (PCDF) was accidentally added to recycled fat intended

for the production of animal feed. The PCB oil contained a congener pattern that closely matched to a mixture of Aroclor 1260 and Aroclor 1254 at a ratio of 75:25. It was estimated that the total amount of PCB added to the recycled fat was about 50 kg, expressed as the sum of seven indicator PCB or approximately 150 kg expressed as total PCB. The PCB oil contained a total amount of approximately 1 g PCDD/PCDF-TEQ and 2 g DL-PCB-TEQ (Bernard *et al*., 1999; van Larebeke *et al*., 2001). The incident was identified in May 1999 and subsequently traced back to PCB-contaminated fat that was sold to nine manufacturers of animal feed who in turn supplied a total of 2500 farms, in particular poultry and pig farms. (Bernard *et al*., 2002). It was concluded that the contamination of animal feed was limited to the period January to March 1999 and that the number of reproduction hens and chickens affected by the incident represented around 2% of the total number of chickens produced in Belgium during the respective time period. Because of the relatively short life cycle of broiler chicken, most of the contaminated poultry meat, but also eggs, were already consumed when the incident became public in May 1999. For animals with a longer life cycle, such as pigs, some of the contaminated animals and products could still be traced back and were destroyed (Bernard *et al*., 2002).

Taking into account that the incident was limited in time and in scale, Bernard and Fierens (2002) concluded in a worst case scenario that the consumption of the most contaminated food items during the period of the incident could have lead to a doubling of the PCB body burden. However, such an extreme scenario was considered quite improbable for the general population, maybe with the exception of farmers consuming exclusively their own contaminated products such as like eggs.

Slovak Republic

Human exposure to PCB as a consequence of former PCB production was recently assessed in the Michalovce district in the eastern part of the Slovak Republic. Discharge of PCB waste resulted in higher PCB levels in wild fish and food products derived from cattle, pigs and poultry kept in the polluted area and fed with locally produced feed (Kocan *et al*., 2004). A total of 2000 adults and 400 children (8-9 years old), selected equally from the polluted and from the control area were analysed for PCB[13] .

The most abundant congeners quantified in all samples are PCB 138, 153, 170 and 180. The median level for the sum of the three congeners (PCB 138, 153, 180) in adults from the contaminated area amounted to 1450 ng/g serum lipids. The corresponding value for the control area was 560 ng/g serum lipids. For children from the contaminated area, the median level for the sum of the three PCB congeners was found to be 390 ng/g serum lipids in comparison to 185 ng/g serum lipids in samples from the control area. Thus, on average, the sum of the three PCB congeners was a factor of two to three higher in blood samples from the contaminated area than from the control area. A similar finding was reported for the PCB

[13] www.pcbrisk.sk

metabolites which were also two to three fold higher in the cohort from the contaminated area compared to the control area (Hovander *et al*., 2004). The major hydroxy-PCB metabolites found were 4-OH-CB187, 4-OH-CB146 and 4-OH-CB107 with median levels of 140, 74 and 63 ng/g lipid in plasma samples from the contaminated area compared to 58, 26 and 26 ng/g lipids in samples from the control area. It is noteworthy, that the most abundant hydroxy-PCB metabolit amounted only to around 30% of the level of PCB congener 153.

Although a detailed evaluation of the different pathways of exposure was not carried out, it can be anticipated that dietary intake of locally grown and produced food represents the main route of PCB exposure in the contaminated area.

6.5.1.2. Exposure through breastfeeding

In comparison to adults and adolescents, the daily intake of PCB by breastfed infants is significantly higher. Table 12 shows the estimated intake of NDL-PCB for exclusively breastfed infants based on the results of the third round of the WHO human milk field study. In addition, the table also contains the intake estimates for PCDD/PCDF and the DL-PCB derived from the same data base.

The median daily intake for the sum of the six indicator PCB for an exclusively breastfed infant weighing five kg amounted to 984 ng/kg b.w. (range: 163-5650) considering a daily milk intake of 800 mL with a mean fat content of 3.5%. The corresponding median values for the sum of seven, sum of 25 NDL and the sum of all 37 measured PCB were 1043 ng/kg b.w. per day (range: 175-5757), 1354 ng/kg b.w. per day (range: 228-7330) and 1521 ng/kg b.w. per day (range: 253-7697), respectively.

The highest NDL-PCB intake values were determined for areas in the Czech Republic, Slovak Republic and for the Basque region in Spain, the lowest PCB intake was found for areas in Hungary and Bulgaria. However, as indicated before, these results can not be considered as fully representative for the entire country, because sampling sites were sometimes chosen in areas with well-known PCB contamination.

PCB exposure through breastfeeding decreased significantly during the past decades in those countries that took measures to regulate open and closed application of technical PCB mixtures. Based on the analysis of 2032 individual human samples from West Germany collected between 1984 and 2003, it was found that the intake of PCB by an exclusively breastfed infant decreased by approximately 80% in this period (Fürst, 2004). Similar results were reported for other European countries, such as The Netherlands, Norway and Sweden. The most recent estimated median PCB exposure of breastfed infants in West Germany still amounted to 778 ng/kg b.w. per day for the sum of the three (PCB 138+153+180) and to 1277 ng/kg b.w. per day for total PCB (Σ PCB (138+153+180) x 1,64), respectively.

Table 12. Estimated intake of PCB and PCDD/PCDF by exclusively breastfed babies based on the results of 58 human milk pools from 18 European countries

PCB - Congener	NDL-PCB intake of breastfed infants (milk intake: 800 mL; fat: 3.5%; body weight: 5 kg) ng/kg b.w. per day			
	Mean	Median	Minimum	Maximum
28	26	12	5.0	516
52	2.9	1,8	0.5	26
101	4.8	3,9	0.9	17
118	72	63	12	197
138	358	311	54	1602
153	458	380	61	2122
180	328	256	34	1887
Σ_6(PCB)[a]	1177	984	163	5651
Σ_7(PCB) [b]	1249	1043	175	5757
Σ_{25}(NDL-PCB)	1584	1354	228	7330
Σ_{37}(PCB)	1742	1521	253	7697
Σ (138+153+180) x 1,64	1875	1569	245	9201
Parameter	**PCDD/PCDF and DL-PCB intake of breastfed infants (milk intake: 800 mL; fat: 3.5%; body weight: 5 kg) pg/kg b.w. per day**			
PCDD/PCDF-TEQ	58.3	53.5	28.5	119
DL-PCB-TEQ	63.8	65.0	13.3	159
Total PCDD/PCDF/PCB-TEQ	122	123	42.8	220

(a) Σ_6(PCB): sum of indicator PCB 28, 52, 101, 138, 153 and 180
(b) Σ_7(PCB): sum of indicator PCB 28, 52, 101, 118, 138, 153 and 180

6.5.2 Exposure from other sources

6.5.2.1 Air

Lower-chlorinated PCB congeners have a considerably higher vapour pressure than the higher-chlorinated ones. Therefore, the composition in air is dominated by the lower-chlorinated congeners such as PCB 18, 28, 66, 52 and 74. Vapour pressure of the first three congeners has been reported to be 0.14, 0.026 and 0.001 Pa respectively which could be compared to the vapour pressure reported for PCB 153 of 0.00012 Pa (Hansen, 1999). PCB in air are likely to be found close to sources where technical mixtures are in direct contact with air. Such conditions are typical for occupational settings but have also been found in buildings with PCB-containing sealants or other kinds of PCB-containing building material.

Outdoor air

In outdoor air, lower chlorinated PCB occur in the gaseous phase while higher chlorinated congeners are adsorbed to particulate matter. PCB may be emitted directly into air from industrial processes or human activities (e.g. thermal processes) or they may be emitted from contaminated soil as particulate matter or gaseous PCB. Data on PCB concentrations in outdoor air are available for different European regions including a number of Central and East European countries. Levels up to 0.1 ng/m^3 have been reported for rural areas and levels higher than 1 ng/m^3 were found in industrial areas. The reported PCB concentrations in ambient air range from 0.01 up to 1 ng/m^3 in Western European countries and from 0.05 up to 10 ng/m^3 in Central and East European countries (EC, 2004). However, the data cannot be regarded as representative for the European region since most of the monitoring campaigns have focused on specific problem areas.

Indoor air

PCB were used in many countries during the 1950s until the early 1970s in different kinds of building material. Probably the most significant of these were sealants used between concrete blocks and around windows and doors, mainly on the outside of the building. Other open applications were in floor paints, as flame retardant in acoustic plates and in glue in insulating windows. The PCB concentration in remaining sealants can now be found to be anything up to around thirty percent.

It was generally considered likely that the PCB would remain in the sealant as long as the sealant was not removed. However, more recent investigations have shown that PCB could be found in indoor air, and that it could escape from buildings into the environment (Balfanz *et al.,* 1993; Benthe *et al.,* 1992; Jansson *et al.,* 1997; Zweiner, 1994).

Indoor air concentrations for total PCB of about 360 ng/m^3 have been reported in Sweden for flats containing PCB sealants or other kinds of PCB-containing building materials (Johansson *et al.*, 2001). In a number of schools in Germany, levels of 10,000 to 20,000 ng/m^3 have been reported (German Federal Environment Agency, 2003, Ewers *et al.,* 1998; Neisel *et al.*, 1999; Gabrio *et al.,* 2000; Liebl *et al.,* 2004). It is most likely that the transfer of PCB from the sealants to indoor air occurs as the result of volatilisation. This is supported by a study of Johansson *et al.* (2001) indicating very low levels of PCB on dust particles compared to the gaseous phase. Indoor air levels in buildings without such sealants do not generally differ from those found in ambient air from the same area.

Effect of contaminated indoor air on PCB body burden

Results from a Swedish study, where blood samples were taken from individuals living in contaminated and non-contaminated flats in the same residential area, show that the median blood levels of total PCB in people living in contaminated flats were about twice as high: 435

ng/g fat versus 225 ng/g fat (Johansson *et al.*, 2001, 2003). Particularly the levels of PCB 28 and 52 were considerably higher in individuals living in contaminated flats compared to those from control flats.

Despite the very high levels recorded in indoor air in contaminated German schools (about three orders of magnitude above background level) the levels of PCB in blood of teachers from these schools was only 4-7% higher than that in teachers from control schools. This increase was particularly due to the lower chlorinated PCB 28, 52 and 101 (Gabrio *et al*., 2000). Ewers *et al.* (1998) could not identify any of the low-chlorinated PCB in the blood samples, although in findings similar to those in the Swedish study, slightly elevated levels of PCB 153 and 138 were observed. Schwenk *et al.* (2002) report results that are more similar to the Swedish study, including an eight fold increase of PCB 28, a two fold increase for PCB 52 and 101. The difference for the higher-chlorinated congeners 138, 153 and 180 was less pronounced. In a recent study, Liebl *et al.* (2004) report statistically significantly elevated levels of PCB 28, 52 and 101 (sum 22 ng/L) in the blood of pupils exposed to high levels of PCB in indoor air in a contaminated school (ranging from 700 to 20,000 ng/m^3). Corresponding levels in the control group were all below 1 ng/L. No significant differences between the exposed and control group were found for the higher chlorinated congeners (PCB 138,153, 180), showing levels about one to two orders of magnitude higher than the lower chlorinated congeners in both groups. This indicates that total PCB concentrations in blood were only slightly affected by the contaminated indoor air.

The available results on PCB in indoor air and the impact on levels in blood show profound qualitative and quantitative differences, probably due to differences in technical PCB mixtures used, differences in construction materials and ventilation techniques etc. Despite these differences, it is clear that situations exist where part of the general population is exposed to significantly elevated levels of lower chlorinated NDL-PCB in indoor air. This exposure could contribute to the body burden of NDL-PCB, particularly of the lower chlorinated congeners, but the data on blood levels indicate that this contribution is far less than could be expected based on the levels measured in highly contaminated indoor air.

6.5.2.2. Soil

PCB are generally stable and stationary in soil. Therefore, the impact of local emission sources is of major importance for the contamination levels in soil. As a consequence the location of sampling can strongly influence the levels found in the direct vicinity of PCB emission sources. Such data should therefore not be used for averaging national contamination levels.

Based on data from national surveys provided to the European Commission (EC, 2004) and data reviewed by Buckland *et al.* (1998), it can be concluded that levels for total PCB in agricultural and rural areas usually range from 0.1 to 10 ng/g dry matter. Levels reported for urban/industrial sites usually range from 10-100 ng/g dry matter. In contaminated areas such

as industrial sites, military bases or dump sites of chemical waste, total PCB levels ranging from about 1000 ng/g dry matter up to 35,000 ng/g dry matter have been reported.

6.5.2.3. Relative importance of PCB exposure from air and soil compared to exposure from food

Estimates of the contribution from air and soil to the daily exposure of the general population to PCB were calculated based on the data as presented above.

Based on ambient air levels ranging from about 0.1-1 ng/m^3, a body weight of 15 kg and an inhalation rate of 7.5 m^3/day, the intake of PCB by children from inhalation was calculated to be 0.05-0.5 ng/kg b.w. per day. For adults with a body weight of 70 kg and an inhalation rate of 20 m^3/day, intake by inhalation is about 0.03-0.3 ng/kg b.w. per day. On average, the contribution from ambient air, amounts to only a low percentage of the intake via food.

The contribution from indoor air will generally be in the same order as that from ambient air and therefore will be low. Limited information from contaminated indoor environments indicate that the contribution of contaminated indoor air to the PCB body burden usually is small, however, specific situations exist in which this contribution to the overall exposure could be considerable for certain PCB congeners (see chapter 6.5.2.1).

The contribution from ingested soil or dust particles, particularly by children, is small. Based on soil concentrations of 10-100 ng PCB/g dry matter and assuming ingestion of 100 mg soil or dust per day, intake values of 0.06-0.6 ng/kg b.w. per day could be calculated for children.
It has been suggested that PCB entering the body from the airways and from the gastro-intestinal tract is readily absorbed. This is in contrast to dermal exposure where the absorption rate is low, and depends on the degree of chlorination of the PCB. Using an average dermal absorption rate of 14% (US-EPA, 2000), the dose which is absorbed from the skin following contact with highly contaminated soil (1,000 ng PCB/g dry matter) was calculated to be about 5 pg/kg b.w. per day for children, and 0.76 pg/kg b.w. per day for adults. These values are about three to four orders of magnitude lower than the average intake via food.

7. Toxicokinetics

The kinetic behaviour of the PCB congeners is influenced by their lipophilic nature and readiness to undergo metabolic transformation. The number and position of the chlorine atoms are major factors determining the rate and extent of metabolism and the overall fate of the different PCB congeners in the body.

7.1 Absorption

Absorption from the gastrointestinal tract

PCB are extensively absorbed from the gastrointestinal tract by passive diffusion (Kuratsune *et al*., 1987).

Studies in rats have shown that all PCB congeners are well absorbed, with >90% absorption of the lower chlorinated congeners (Albro and Fishbein, 1972; Safe, 1980; Bergman *et al*., 1982), and possibly lower absorption (about 75%) of the higher chlorinated congeners, such as octachlorobiphenyls (Tanabe *et al*., 1981). The reduced absorption of higher chlorinated PCB is consistent with the data on PCDD/PCDF, and probably arises from the inability of these compounds to form a molecular solution in the contents of the gut lumen. Factors such as dietary lipids and bile salts might enhance the extent of absorption, which probably involves incorporation into chylomicrons and uptake via the lymphatic system. The positive influence of bile has been shown by comparing normal and bile canulated rats treated with PCB (Bergman *et al*., 1982).

Absorption of NDL-PCB in a nursing infant was estimated to be 96-98% for the main congeners present in the mother's milk based on the difference between the amount ingested and the unabsorbed PCB fraction excreted in the faeces (McLachlan, 1993). Any variable that influences mobilisation of the PCB body burden, such as fasting, would alter the extent of elimination of the pre-existing body-burden.

Absorption from the airways

Inhalation is a major route of occupational exposure to PCB. It has been suggested that 80% of the levels commonly seen in adipose tissue of exposed capacitor workers may have been absorbed from the airways, with the remainder derived from dermal or oral exposure (Wolf, 1985; Wilson *et al*., 2001). The pattern of PCB congeners in the body following occupational exposure will be influenced both by the volatility of the congeners concerned and by the particle content of the working environment, since PCB are commonly adsorbed onto particles that will be inhaled. The PCB on particles could either be taken up via the respiratory system, or via the intestinal tract since particles may also be transported up the airways by mucociliary clearance and then swallowed.

Absorption from the skin

Transdermal absorption may be of relevance under occupational exposure situations. Absorption across the skin depends on a number of variables, with the formulation/vehicle being particularly important. Generally, dermal uptake of PCB is only a very minor pathway for their uptake.

7.2 Distribution

The distribution rate of PCB from blood lipids to tissue lipids depends on the blood flow to the organs. As indicated by studies on PCB transfer between the maternal and foetal compartments, transfer across cell membranes is by passive diffusion, and there is no evidence of specific transporters for PCB (Meironyté Guvenius *et al*., 2003; Soechitram *et al*., 2004). This distribution process results in lower body burdens in the foetus since the relative blood lipid content is lower in the foetal compartment than in the mother (approximately 0.3% and 0.6%, respectively). Also, the total lipid content influences the body burden of the foetus. Data on distribution between different types of lipids indicate that PCB seem to partition primarily to the triglycerides (Sandermann, 2003).

PCB have also been shown to be associated with the lipoprotein depleted fraction, the one mainly containing albumin (Norén *et al*., 1999). PCB and also PCB methyl sulfone metabolites are mainly transported via blood lipids, whereas the hydroxy metabolites, when retained in the body, are mainly bound to blood proteins. Hydroxy-PCB are more efficiently transferred to the foetus than the parent congeners (Meironyté Guvenius *et al*., 2003; Soechitram *et al*., 2004). On the other hand they are not transferred into mother's milk to any appreciable extent, i.e. the hydroxy-PCB concentrations are less than 1% of the PCB levels in the milk (Fängström *et al*., 2005). PCB methyl sulfones are distributed in a similar way as the PCB but the sulfones have generally strong tissue selectivity (see chapter 7.3).

Data on the concentrations in human tissues are available from occupational studies and therefore largely reflect inhalation exposure (Maroni *et al*., 1981; Takamatsu *et al*., 1985; Brown *et al*., 1994). Human tissue levels of PCB have also been reported from autopsy material (Schecter *et al*., 1989; Dewailly *et al*., 1999; Meironyté Guvenius *et al*., 2001). The pattern of distribution is what would be predicted for highly lipid soluble compounds, with high concentrations in adipose tissue, and levels in blood particularly associated with the lipid fraction. The pattern of different congeners present in the body depends on a number of variables such as the extent of recent intake, the long term intake, and most importantly the potential for metabolism.

7.3 Metabolism

The initial step in the biotransformation of PCB involves oxidation by cytochrome P-450 enzymes, including epoxide formation and an alternative route for direct insertion of a hydroxyl group to PCB congeners less easily forming arene oxides (Letcher *et al*., 2000; Safe, 2001; 2003). A general scheme for the metabolic transformation of PCB congeners is shown in Figure 8 with a description of enzymes involved in the transformation reactions given in Table 13 where relevant, non-enzymatic pathways are indicated. More than one arene oxide intermediate may be formed from PCB congeners with structural features susceptible for oxidation at more than one site, such as congeners with two unsubstituted *meta* and *para* carbon atoms (e.g. PCB 52, PCB 95 and PCB 136).

Arene oxides of PCB are reactive electrophilic intermediates that may form dihydrodiol-PCB, polychlorobiphenylols (hydroxy-PCB), glutathione conjugates or adducts to biomacromolecules (DNA and proteins) and to lipids. Dihydrodiol PCB can be aromatised and form catechol metabolites which are in equilibrium with their oxidized form, the corresponding hydroquinone and quinone. Both are reactive intermediates with the potential for adduct formation. It is not yet possible to assess human exposure to reactive intermediates of PCB, although the neutral, lipophilic methylsulfonyl-PCB ($MeSO_2$-PCB) metabolites could be used as a measure of arene oxide formation.

The major PCB metabolites formed are the hydroxy-PCB leading to a large number of different structures since hydroxy-PCB may be formed after 1,2-rearrangements of a chlorine atom as shown in Figure 8, and as has been described for PCB 105 and PCB 118, both of which produce the same metabolite, 2,3,3',4',5-pentachloro-4-biphenylol (4-OH-PCB107) (Sjödin *et al*., 1998). The majority of all hydroxy-PCB metabolites are excreted in a non-conjugated form or as glucuronide or sulfate conjugates. The hydroxy-PCB are excreted both in urine and faeces. Only five major hydroxy-PCB congeners of all potential hydroxy-PCB (approximately 50) are retained in the blood, bound to proteins such as transthyretin (Brouwer *et al*., 1998b; Purkey *et al*., 2004). Due to their physico-chemical properties the hydroxy-PCB do not partition to the lipid fraction very efficiently (Malmberg, 2004; Fängström *et al*., 2005). The major hydroxy-PCB congeners in blood are present in concentrations about 5-10 fold less than the most persistent PCB congeners (Letcher *et al*., 2000; Sjödin *et al*., 2000; Hovander *et al*., 2004; Soechitram *et al*., 2004).

PCB congeners with non-chlorinated meta-/para-positions and chlorinated neighbouring ortho-/meta-positions are rapidly metabolised. PCB congeners with free meta-/para-positions in at least one of the phenyl rings (Figure 8) may form PCB methylsulfone metabolites in a multi-step pathway involving GSH conjugation, mercapturic acid pathway degradation, enterohepatic circulation, methylation and oxidation (Bakke *et al*., 1982; Bakke and Gustafsson, 1984; Letcher *et al*., 2000). Methylsulfonyl-PCB are neutral PCB metabolites with a lipophilicity only slightly lower than that of the parent PCB compound. This leads to a general distribution to lipids but in humans the concentrations in blood are low (less than 1% the concentration of the most persistent PCB congeners) (Letcher *et al*., 2000; Hovander *et al*., 2004). The methylsulfonyl-PCB concentration is however relatively high in comparison to their parent PCB. It is notable that some of the methylsulfonyl-PCB accumulate in a highly tissue-specific manner, with liver and lung as target tissues. Four methylsulfonyl-PCB present in human tissues/fluids, form atropisomer pairs (optically active forms) that are retained with high enantiomeric selectivity. Some methylsulfonyl-PCB have strong tissue and cell specific retentions, leading to higher local (cellular) concentrations than general tissue levels. It is relevant to assess human levels of methlysulfonyl-PCB with the highest retention potential, since the corresponding maternal PCB congeners are only present in trace concentrations or are non-detectable due to their rapid metabolism.

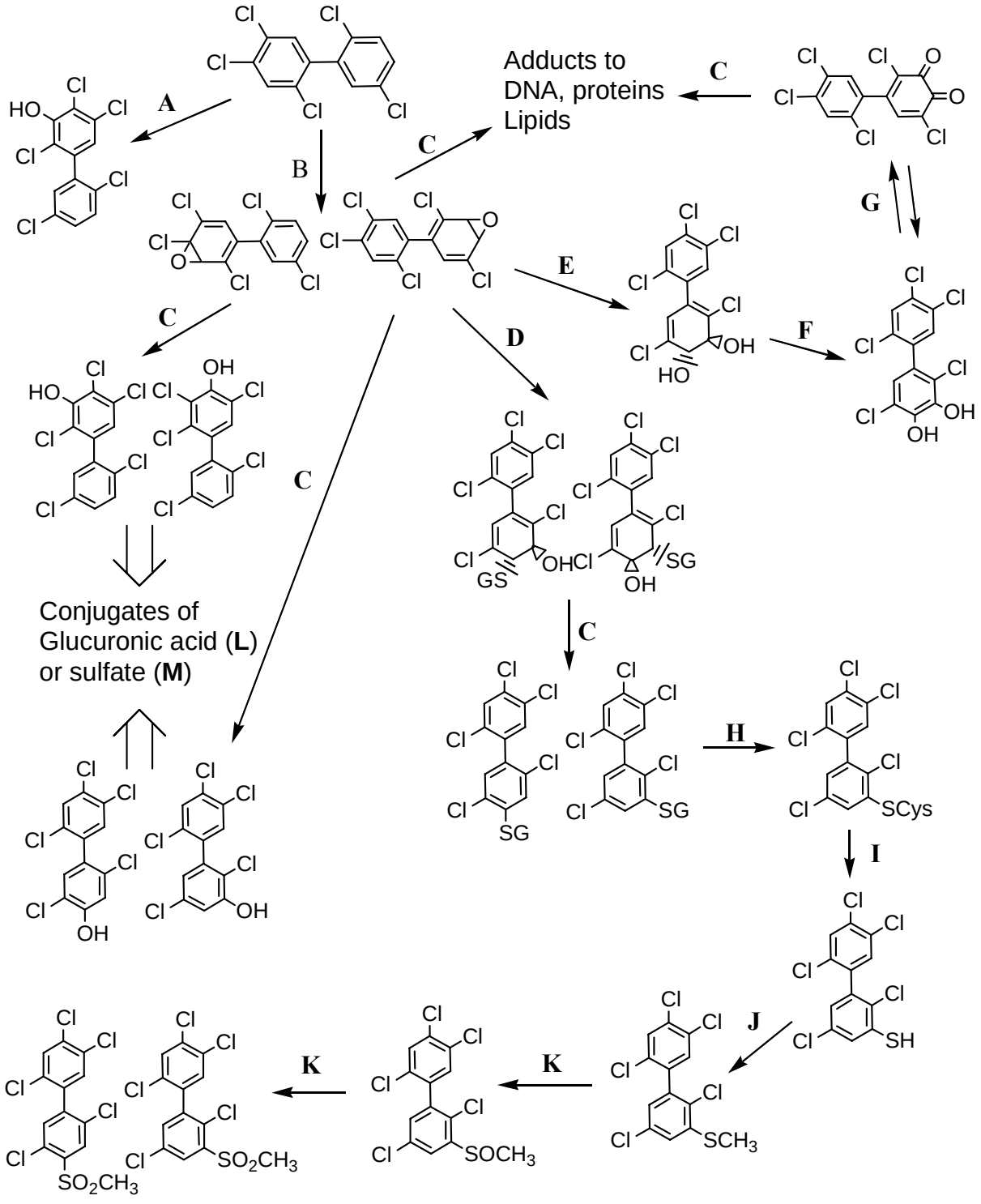


Figure 8. General metabolic scheme for a PCB congener, PCB 101. Enzymes involved in the metabolism are indicated by the letters A, B and D-M with the letter C indicating non-enzymatic transformations. Enzymes for these transformations are listed in Table 13.

Table 13. Enzymes involved in the metabolism of PCB. The letters given in the table correspond to those letters in Figure 8.

Enzyme "Letter"	Enzymes active in the metabolic process described
A	Cytochrome P450 enzyme system, Direct insertion in meta position; CYP2B (rodents)
B	Cytochrome P450 enzyme system CYP2B, CYP2C, CYP3A ; e.g. CYP2B1 (rodents); CYP3A4 (humans)
C	Non-enzymatic reaction
D	Glutathione -S-transferase
E	Epoxide hydrolase
F	Dihydrodiol dehydrogenase
G	Autooxidation and/or Peroxidases
H	Mercapturic acid pathway 1 glutamyltransferase 2 cysteinyl glycinase
I	C-S-lyase
J	S-adenosylmethionine S-Methyltransferase
K	CYP-mediated S-oxidation. P450 alt. FAD-containing mono-oxygenases
L	UDP-glucuronosyl transferase
M	Sulfotransferase

7.4 Elimination and bioaccumulation

Elimination of PCB largely depends on the excretion of the polar hydroxylated metabolites in urine and faeces. There is significant elimination of unchanged PCB and its neutral metabolites (methylsulfonyl-PCB) via breast milk, and as with other halogenated organic pollutants, this is source of exposure of breastfed infants.

The rates of elimination of PCB are dependent on the PCB structure and the degree of chlorination. Highly chlorinated PCB congeners with only isolated non-chlorinated carbons show the longest half-lives, and therefore the greatest accumulation (e.g. PCB 138, PCB 153, PCB 170, and PCB 180). On the other hand PCB with vicinal non-substituted carbons are readily eliminated via metabolism.

The half-lives reported in humans vary considerably and the different values have been scrutinised by Shirai and Kissel (1996). A set of half-lives in humans, as reported in the literature, is presented in Table 14, indicating half-lives ranging from one week up to several years. Half-lives as reported in rhesus monkeys and in rats are given for comparison (Table 14). In this case the lower chlorinated biphenyls have half-lives of a few days up to four months or more. For comparison it can be mentioned that the apparent half-life of the two main hydroxy-PCB metabolites, 4-OH-CB107 and 4-OH-CB187, in rats were reported to be 3.8 and 15 days, respectively (Malmberg *et al*., 2004).

Table 14: Reported half-lives of eight NDL-PCB congeners and PCB 118 in studies in humans, in rhesus monkeys and in rats.

PCB #	$T_{½}$ (Days - Years) Humans	Ref	$T_{½}$ (Months) Rhesus monkey	Ref	$T_{½}$ (Days) Rat	Ref
28	18/44 days[a)] 182 days 16.8 months 4.8 years 3.0 years	1 2 3 4 5			1.4/6 [b)]	11
52	5.5 years [c)]	4			0.9/3.4	11
101	7/14 days 5.7 years [d)]	1 4			2.6/35	11
105	186/212 days 3.9 years	1 3	4.8	I	98 5.6/>90	10 11
118	9.4/10 months 3.6-9.7 months 1.1 year 5.8 years 9.6 years	6 7 8 3 4	15.6	I	117 6.6/>90	10 11
138	10.7 months 3.4 years 6-7 years 16.3 years 16.7 years 20/32 years	7 8 3 5 4 5	9.6	I	101 >90	10 11
153	11.3 months 3.9 years 12.4 years 26/47 years 27 years	7 8 3 6 5	8.4	I	113 >90	10 11
170	4.5 years 47/71 years	8 6			83 >90	10 11
180	4.1 months 4.8 years 9.9 years	7 8 4	8.4	I	81 >90	10 11

[a)] Two values given in the study depending on sample selections
[b)] The two values presented represent first and second phase half-lives for compounds with biphasic eliminations.
[c)] Coelution between PCB 47, 49 and 52
[d)] Coelution between PCB 99 and 101

References 1-11:
1: Luotamo *et al.*, 1991; 2: Wolff and Schecter, 1991; 3: Brown, *et al*., 1989; 4: Wolff *et al*., 1992; 5: Yakushiji *et al*., 1984; 6: Chen *et al*., 1982; 7: Bühler *et al.,* 1988; 8: Ryan *et al*., 1993; 9: Mes *et al.,* 1995; 10: Öberg *et al,* 2002; 11: Tanabe *et al.,* 1981

7.5. Biomarkers of internal doses

Several biomarkers of exposure have been used as indicators of the internal dose or the body burden of PCB. These include concentrations of PCB congeners in plasma, adipose tissue, maternal or cord blood, human milk and hair. In principle, concentrations in blood lipids will reflect more recent exposures and also the full spectrum of PCB to which a person is exposed, while the pattern of PCB congeners in adipose tissue will reflect long-term intakes. PCB in milk largely reflects the concentrations of the congeners in adipose tissue.

A good correlation was obtained for PCB 74, 99, 118, 138, 146, 153, 156, 167, 170, 180, 183, and 187, in adipose tissue and serum from 293 women with non-occupational exposure (Stellman *et al.*, 1998) indicating that either serum or adipose tissue PCB levels may serve as useful biomarkers of the body burden. In principle the half-life for plasma and adipose tissue would be the same once tissue distribution is complete. However any recent elevated exposure, in particular to lower chlorinated congeners, could result in higher non-equilibrium levels in the circulation.

Koopman-Esseboom *et al.* (1994b) used the concentrations of four congeners (PCB 118, 138, 153, and 180) as measured in umbilical cord blood and in breast milk as indicators of PCB exposure of the developing foetus and breastfed infant. For these congeners the correlation coefficients between maternal plasma, cord plasma and human milk were highly significant.

7.6. Carry-over and residues of NDL-PCB, DL-PCB and PCDD/PCDF in food-producing animals

Due to differences in absorption, metabolism, distribution and excretion, the composition of PCB mixtures will change during transfer through the food chain.

Behaviour of PCB and PCDD/PCDF in farm animals

As for PCDD/PCDF, the carry-over of PCB from feed to edible products can be influenced by many factors. The absorption of the compounds depends on their physical chemical properties (e.g. lipophilicity), and on the source of contamination. Compounds bound to air particles, like fly ash, and deposited as such on feed or fodder, may be differently absorbed than compounds present in fatty feed components, and higher chlorinated PCB (8-10 chlorines), are absorbed less easily than the lower chlorinated congeners (McLachlan *et al.,* 1990, McLachlan, 1993, Thomas *et al.,* 1999a,b). In trout, PCB congeners with a log K_{ow} around 7, like PCB 138 and 153, showed the highest accumulation in the tissues (Fisk *et al.,* 1998, Buckman *et al.* 2004). In fish, factors like water temperature and season influence the absorption and distribution of PCB.

Many PCB are metabolised in food-producing animals, thus explaining their poor recoveries in mass-balance studies. This seems especially the case for some of the lower chlorinated congeners. However, very little information is available on metabolites of PCB in farm animals and their products.

Both in laying hens and dairy cows, PCB are distributed over the body fat and the fat in eggs and milk. During prolonged exposure, this results in a steady state situation where a balance is obtained between the input through the feed and the output into the milk or eggs. For some compounds this equilibrium is reached much earlier than for others. In the case of PCB, DL-PCB 126 and 169, but also the higher chlorinated indicator PCB 138, 153 and 180 show a

relatively high carry-over into the milk. Thomas *et al*. (1999a,b) studied the transfer of 53 PCB congeners into milk and showed that only 8% of the ingested amount appeared in the milk, as compared to 60% of the indicator PCB. The same was true for the body fat. Under steady state conditions, around 30% of the lower chlorinated compounds are transferred into milk, as compared to only 4% of the higher chlorinated congeners. Similar results were obtained in laying hens, showing carry-over rates of 53 and 59% for PCB 138 and 153, as compared to 49% for PCB 126 (Hoogenboom *et al.* 2005). For both PCB as for PCDD/PCDF, the higher chlorinated compounds tend to accumulate in the liver.

In the case of growing animals like calves, pigs, and broilers, but also in farmed fish like trout and salmon, the fat compartment will continuously increase and steady state conditions will not be obtained. Initially levels in well-perfused tissues will increase more rapidly than in poorly perfused tissues like fat. Results from a carry-over study of PCDD/PCDF in beef cattle (Thorpe *et al.,* 2001) showed that especially during the first days of exposure the levels in body fat are lower than the levels present in meat.

Following termination of exposure, the body burden of NDL-PCB is an important dose metric, being the sole source for transfer of contaminants to the milk or egg. In the case of an incidental episode, the duration of the exposure period is essential for the subsequent decrease of contaminant levels in milk and eggs following cessation of the exposure, since the storage of PCB in poorly perfused organs may cause a considerable delay in their mobilization. In general, levels in both milk and eggs decreased rapidly by about 50% during a first phase. In eggs this was preceded by a delay in the start of the elimination phase due to the fact that the production of an egg requires about 10 days. The first phase was followed by a much slower second phase, depending on the mobilization of PCB from the more poorly perfused fat tissues. Half-lives in laying hens for both PCB and PCDD/PCDF were determined to be around seven to eight weeks (Eijkeren *et al.,* 2005). These half-lives are likely to vary with the breed and productivity of the animals. In growing animals, like pigs, calves and broilers, dilution by increasing fat volumes is a major determinant in reducing the levels of lipophilic contaminants such as PCB, both during and after exposure.

Only a limited number of kinetic studies have included both PCB and PCDD/PCDF, allowing a direct comparison. In broiler and laying hens, it appears that indicator PCB and PCDD/PCDF show in general a similar pharmacokinetic behaviour. The same seems to be true for growing pigs, although PCDD/PCDF appear to show a slightly shorter half-life than the higher chlorinated indicator PCB.

Modelling of the behaviour of PCB

Several research groups have modelled the carry-over of persistent contaminants, particularly in the lactating cow. Approaches based on pharmacokinetic modelling (PB-PK-modelling) usually take into account the size of the different tissues and organs and parameters like blood flow and milk or egg production (Derks *et al.,* 1994, Eijkeren *et al.,* 2005). Usually the bioconcentration factor is expressed as the ratio of the concentrations in feed and milk, based on wet weight or lipid base. This factor is influenced however by the amount and type of feed consumed and by factors as water content and energy value. Therefore, the biotransfer factor, defined as the ratio of the concentration in the milk and the total ingested quantity of contaminant, seems to be a more appropriate parameter. The carry-over rate is defined as the percentage of the total amount ingested which is excreted into e.g. the milk or eggs. In most cases this is based on the daily intake and excretion when steady state conditions have been reached. Willett *et al.* (1990) evaluated the older studies with PCB, starting by standardization of the PCB-levels determined by gas chromatography and electron capture detection (GC-ECD). When focussing on cows exposed for 60 days or longer, the following ratios were obtained between daily dose (in mg) and milk or body fat levels (in mg/kg):

$$[PCB]_{milk\ fat} = 0.28 \times (\text{daily dose})^{0.82}$$
$$[PCB]_{body\ fat} = 0.16 \times (\text{daily dose})^{0.85}$$

It should be noted however, that as long as there is no equilibrium between intake and excretion e.g., during the first days or weeks of exposure, this will lead to an overestimation of the actual milk levels, due to the fact that during this period, part of the contaminants will be stored not only in the body fat, but also in the liver.

8. Toxicity data

8.1. Effects in laboratory animals

For the purpose of this assessment, the focus is on oral studies of subchronic and chronic duration with commercial PCB mixtures, individual NDL-PCB congeners, and reconstituted mixtures of PCB. For the evaluation of toxicity data on PCB the Panel used the information as reviewed in the ATSDR Toxicological Profile for Polychlorinated Biphenyls (update), November 2000. In addition, a working paper on Non Cancer Health Effects of PCB in Animals has been prepared (Annex II).

8.1.1. Commercial mixtures

For a number of the toxicological endpoints studied (e.g. haematological, cardiovascular, respiratory, muscular, renal, dermal) for technical PCB mixtures (Aroclor 1242, 1248, 1254, or 1260), no effect levels in rodents and monkeys have been found in the low mg/kg b.w. per day range. A number of other endpoints more relevant for the risk assessment of PCB are described below.

It is important to consider that very few of the commercial PCB mixtures were analysed with respect to their precise composition or even their content of PCDF and DL-PCB (see chapter 2). Consequently, the information derived from studies with commercial products does not have full relevance for the toxicological evaluation of NDL-PCB.

Gastrointestinal effects

Dietary administration of ≥1.3 mg/kg b.w. per day Aroclor 1248 or ≥0.12 mg/kg b.w. per day Aroclor 1242 for 2 months produced hypertrophy and hyperplasia of the gastric mucosa in monkeys (Allen, 1975; Allen and Norback, 1976; Allen *et al*., 1974; Becker *et al*., 1979). Moderate mucinous hypertrophic gastropathy was evident in three of four Cynomolgus monkeys treated with 0.2 mg/kg b.w. per day Aroclor 1254 in the diet for 12 or 13 months (Tryphonas *et al*., 1984, 1986a) and in two of four Rhesus monkeys treated similarly for 28 months (Tryphonas *et al*., 1986b). No effects on stomach tissue were observed in Rhesus monkeys receiving daily doses of ≤0.08 mg/kg b.w. per day Aroclor 1254 for 72 months (Arnold *et al*., 1997).

Hepatic effects

In rats fed 0.03 mg/kg b.w. per day (lowest dose tested) Aroclor 1242, 1248, 1254, or 1260 for 4 weeks, liver microsomal enzymes were induced (Bruckner *et al*., 1974, 1977; Litterst *et al*., 1972). These PCB mixtures also caused increased relative liver weight at a dose of 2.5 mg/kg b.w. per day and higher. Hepatic microsomal enzymes, liver weight, and lipid deposition in the liver were also increased in rats fed ≥0.25 mg/kg b.w. per day Aroclor 1242 for more than two months; no other hepatic histopathologic changes were observed.

A chronic toxicity study of PCB in rodents provided comparative clinical and histology data on four different mixtures: Aroclor 1016, 1242, 1254, or 1260 (Fish *et al*., 1997; General Electric Company 1997a,b; Mayes *et al*., 1998). The Aroclor 1254 batch used contained PCB 126 levels twice as high as normally found in Aroclor 1254 mixtures. Microscopic liver lesions (hypertrophy and vacuolisation) and increases in serum levels of liver enzymes were observed, mainly in female rats, in the dose range of 1-2 mg/kg b.w. per day and higher.

In Rhesus monkeys fed 0.2 mg/kg b.w. per day Aroclor 1254 for 12-28 months, liver enlargement, fatty degeneration, hepatocellular necrosis, and hypertrophic and hyperplasic changes in the bile duct were observed (Tryphonas *et al*., 1986a, 1986b). Rhesus monkeys that ingested capsules containing Aroclor 1254 for 72 months had increased liver weight attributed to hyperplasia (unspecified) at 0.08 mg/kg b.w. per day, as well as decreased serum levels of total bilirubin and cholesterol and increased serum triglycerides (Arnold *et al*., 1993b, 1997; Bell *et al*,. 1994). No such effects were seen at 0.04 mg/kg b.w. per day and lower.

Effects in monkeys that ingested Aroclor 1254 in capsules daily for 37 months, included normal plasma lipid profiles at doses ≤0.02 mg/kg b.w. per day, decreased total, very low and low density lipoprotein cholesterol at ≥0.04 mg/kg b.w. per day, and decreased high-density lipoprotein cholesterol and total carnitine at 0.08 mg/kg b.w. per day (Arnold *et al*., 1993b; Bell *et al*., 1994). Plasma triglycerides were significantly elevated at all tested doses (0.005-0.08 mg/kg b.w. per day) except at 0.04 mg/kg b.w. per day.

Endocrine effects

In rats administered Aroclor 1254 orally for one or five months, decreased serum levels of thyroxine (T4) and triiodothyronine (T3) and histological changes in the thyroid occurred at doses as low as 0.09 mg/kg b.w. per day (Byrne *et al*., 1987). In Sprague-Dawley rats, receiving daily doses of 0.1 mg/kg b.w. per day Aroclor 1254 by gavage for 15 weeks, serum levels of T4 were decreased. No histopathologic alterations were observed in the thyroid at doses up to 25 mg/kg b.w. per day Aroclor 1254 (Gray *et al*., 1993).

Enlarged thyroid glands and follicles with desquamated cells were observed in Rhesus monkeys exposed to 0.2 mg/kg b.w. per day Aroclor 1254 for 28 months (Tryphonas *et al*., 1986b).

Gestational exposure of rats to ≥1 mg/kg b.w. per day Aroclor 1254 (day six of gestation through weaning of pups), caused depressed serum T4 levels in the pups (Zoeller *et al*., 2000). In a study by Burgin *et al.* (2001) in male rats treated with two different Aroclor lots (124-191 and 6024) dose dependent decreases in total T4 in serum were found, which differed for the two lots. Aroclor 6024 contained a 10 times higher concentration (400 μg/g) of TEQ than Aroclor 124-191 (approximately 40 μg/g). While EROD induction was linearly related to the TEQ intake, the TEQ intake alone could not account for the decrease in T4, which was thought to be related to multiple mechanisms.

Serum corticosterone levels were increased by dietary exposure of 0.1 mg/kg b.w. per day Aroclor 1254 for 15 weeks (Miller *et al*., 1993).

Rats fed 0.05-2.5 mg/kg b.w. per day Aroclor 1242 or 1221 for five months had decreased serum levels of the adrenal cortex hormones, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHS) at ≥0.25 mg/kg b.w. per day Aroclor 1254. No effects were found at 0.05 mg/kg b.w. per day.

Reproductive and developmental effects

In two-generation studies with rats, exposed through the diet to Aroclor 1254 in doses of 0, 0.06, 0.32, 1.5, or 7.6 mg/kg b.w. per day or Aroclor 1260 in doses of 0, 0.39, 1.5, or 7.4 mg/kg/day, Aroclor 1254 caused significantly reduced litter sizes at 7.6 mg/kg b.w. per day in

the F1a generation and at 1.5 mg/kg b.w. per day in the F1b, F2a, and F2b generations. No effects were found for Aroclor 1260 (Linder *et al*., 1974).

Reproductive effects (reduction in conception rate) have been seen in female monkeys exposed to 0.8 mg/kg b.w. per day Aroclor 1248 for 2 months (Allen *et al*., 1974). In female Rhesus monkeys, exposed to 0.1 or 0.2 mg/kg b.w. per day Aroclor 1248 in the diet from seven months prior to breeding and throughout pregnancy, increased menstrual duration and bleeding occurred at $\geq$0.1 mg/kg b.w. per day, the conception rate was decreased at 0.2 mg/kg b.w. per day (Barsotti *et al*., 1976).

Rhesus monkeys ingested capsules providing 0, 0.005, 0.02, 0.04, or 0.08 mg/kg b.w. per day doses of Aroclor 1254 for up to 72 months (Arnold *et al*., 1993a,b, 1995, 1997). Comparisons between the treated and control groups showed that the conception rates were significantly ($p<0.05$) reduced at doses of 0.02 mg/kg b.w. per day and higher, and that foetal mortality was significantly ($p<0.05$) increased at 0.08 mg/kg b.w. per day, and marginally ($p=0.077$) increased at 0.02 mg/kg b.w. per day.

Of four male Rhesus monkeys that were fed 0.1 mg/kg b.w. per day Aroclor 1248 for 17 months, one developed decreased libido and dermal and ocular signs of PCB toxicity after the first year of exposure (Allen and Norback, 1976). A testicular biopsy on the affected animal showed marked hypo activity of the seminiferous tubules. The remaining three males remained healthy and sexually active. No effect on sperm morphology, viability or the ability to fertilize unexposed females was found for any of the four males.

Dose-related early abortions were reported in female monkeys fed a diet that provided 0.1 or 0.2 mg/kg b.w. per day Aroclor 1248 for 15 months (Allen and Barsotti, 1976). Mean birth weight in both groups was significantly lower than in controls and remained low for the next 12 weeks. Skeletal development was not affected by PCB treatment. At two months of age, the infants showed signs of PCB intoxication such as facial acne, swollen eyelids, loss of eyelashes, and hyper pigmentation of the skin. Three of the six young died of intoxication between days 44 and 329. Maternal toxicity, evidenced as facial acne, swollen eyelids, and lack of facial hair, was observed at weaning.

Arnold *et al*. (1995, 1997) treated female monkeys with Aroclor 1254 for 37 months (0, 0.005, 0.02, 0.04, or 0.08 mg/kg b.w. per day). After that time they were mated with untreated males, and dosing continued through mating and gestation. Treatment ceased when the infants were seven weeks old. There was a significant dose-related increased trend in foetal mortality, with 0.02 mg/kg b.w. per day identified as the LOAEL.

Immune effects

Dietary ingestion of Aroclor 1254 at doses of 0.1 mg/kg b.w. per day (2 Cynomolgus monkeys) or 0.4 mg/kg b.w. per day (one monkey) for 238 or 267 days, beginning at

approximately day 60 of gestation, caused a decreased antibody response to sheep red blood cells (SRBC) in all treated animals compared to one control monkey (Truelove *et al*., 1982). Both monkeys exposed to 0.1 mg/kg b.w. per day delivered stillborn infants, and the 0.4 mg/kg b.w. per day monkey delivered a live infant which was nursed, but failed to respond to SRBC and died at 139 days postpartum with acute confluent bronchopneumonia.

Cynomolgus and Rhesus monkeys exposed to 280 µg/kg b.w. per day Aroclor 1254 (5 days/week for 12 to 28 months), showed reduction of total serum IgM levels and anti-SRBC (IgM) titres (Tryphonas *et al*., 1986a).

In Rhesus monkeys administered Aroclor 1254 in capsules, significant dose-related decreases in IgM and IgG antibody titres to sheep red blood cells were found at dose levels of 5 µg/kg b.w. per day and higher (Tryphonas *et al*., 1989, 1991).

Following dietary exposure of two monkeys to approximately 0.1-0.2 mg/kg b.w. per day Aroclor 1248, increased susceptibility to bacterial infections was reported. The monkeys developed severe enteritis, and died after 173 and 310 days of treatment (Barsotti *et al*., 1976).

Rhesus monkeys exposed to 0.2 mg/kg b.w. per day Aroclor 1248 for 11 months, showed reduced anti-SRBC antibody titres at weeks 1 and 12 after primary immunization and decreased percent gamma-globulin after 20 weeks. Antibody responses to SRBC were not significantly affected at 0.1 mg/kg b.w. per day (Thomas and Hinsdill, 1978).

Pathological changes in lymphoid tissues occurred in offspring of Rhesus monkeys that were fed 0.1 or 0.2 mg/kg b.w. per day Aroclor 1248 for a 15-month period that included breeding, gestation, and lactation (Allen and Barsotti, 1976). Early infant mortality was observed in both groups.

Neurobehavioral effects

Neurobehavioral deficits, reflected as impaired performance on a spatial learning and memory task, were seen in the progeny of monkeys fed 0.08 mg/kg b.w. per day Aroclor 1248 for 18 months and allowed to breed 32 months post exposure (Levin *et al*., 1988). Aroclor 1016, tested at a dose level of 0.008 mg/kg b.w. per day, did not significantly alter performance on the learning and memory task (Levin *et al*., 1988), but impaired the monkeys' ability to learn a simple spatial discrimination problem at 0.03 mg/kg b.w. per day (Schantz *et al*., 1989).

Dermal effects

Dermal effects (facial oedema, acne, folliculitis, and alopecia) were reported in Rhesus monkeys at estimated doses of 0.1 mg/kg b.w. per day Aroclor 1248 (Allen and Norback, 1976, Barsotti *et al*., 1976). Tryphonas *et al*. (1986a,b) reported fingernail and toenail changes

in monkeys during treatment with a dose of 0.005 mg/kg b.w. per day Aroclor 1254 over a 37-month period. Offspring from Rhesus monkeys treated before mating and during gestation with 0.03 mg/kg b.w. per day Aroclor 1016 showed hyper pigmentation (Barsotti and Van Miller, 1984). Small doses of Aroclor 1254 (0.005 mg/kg b.w. per day) produced clear signs of PCB intoxication manifested as inflammation and/or enlargement of the tarsal glands, and nail and gum lesions in monkeys exposed during gestation and via breast milk for 22 weeks (Arnold *et al*., 1995, 1997).

Ocular effects

Reversible ocular effects were observed in Rhesus monkeys (particularly in females) exposed for two months to estimated dietary doses of 0.1 mg/kg b.w. per day Aroclor 1248 and Aroclor 1242 (Barsotti *et al*., 1976; Becker *et al*., 1979). Monkeys exposed to 0.005-0.08 mg/kg b.w. per day Aroclor 1254 for 37 months, showed dose-related ocular and dermal effects (Arnold *et al*., 1993a). Conjunctivitis was observed in Rhesus monkeys treated in the diet with 0.2 mg/kg b.w. per day Aroclor 1254 for 12 months (Tryphonas *et al*., 1986a).

8.1.2. Reconstituted mixtures

Female Long-Evans rats were administered a diet containing 40 mg/kg (approximately 4 mg/kg b.w. per day) of either a reconstituted PCB mixture (RM) composed according to an idendified congener-pattern in human breast milk (PCB 28 – 5.9%; PCB 77 – 0.00179%; PCB 101 – 1.4%; PCB 105 – 2.5%; PCB 118 – 7.3%; PCB 126 – 0.00828%; PCB 138 – 22.1%; PCB 146 – 3.13%; PCB 153 – 27.6%; PCB 156 – 3.82%; PCB 169 – 0.00373%; PCB 170 – 7.4%; PCB 180 – 14.03%; PCB 187 – 4.77%), or Aroclor 1254. The exposure period started 50 days prior to mating and was terminated at delivery. Female RM-weanlings exhibited significantly elevated uterine weights on post natal day (PND) 21. At PND 170, adult male offspring exposed prenatally to either PCB mixture showed markedly reduced testes weights and serum testosterone levels. On PND 180, male RM-rats exhibited a behavioural feminisation in a sweet preference test, indicating long-lasting changes in neuronal brain organization. The results suggest that maternal exposure to the RM resulted in more distinct effects on sex steroid-dependent processes and behaviour than the technical PCB mixture Aroclor 1254. PCB levels in brain and adipose tissue in the offspring exposed to both PCB mixtures were about one to two orders of magnitude higher than concentrations in humans (Hany *et al*., 1999).

Female rats were fed diets containing the above-mentioned reconstituted mixture at levels of 0, 5, 20, or 40 mg PCB/kg diet (corresponding to 0, 0.5, 2, or 4 mg/kg b.w) following the same dose regimen. Behavioural effects (e.g. sweet preference) were observed in adult male offspring. In weanling female offspring, dose-dependent reductions in sex hormones were detected. In addition, testosterone concentrations were reduced in a dose-dependent manner in adult male offspring, long after cessation of exposure. The NOAEL was 0.5 mg PCB/kg b.w. per day. Concentrations of total PCB in adipose tissue of the dams at postnatal day 0 were

26.8, 155.8, and 300.2 µg/g fat in the 0.5, 2, and 4 mg/kg b.w. per day groups, respectively (Kaya *et al.*, 2002). Assuming a content of 10% fat in the dams (Geyer *et al.*, 1990), this would correspond to body burdens of 2,700, 15,500, and 30,000 µg/kg b.w.
Groups of one day-old Rhesus (*Macaca mulatta*) and cynomolgus (*M. fascicularis*) monkeys were dosed from birth to 20 weeks of age with 7.5 µg/kg b.w. per day of a reconstituted PCB mixture with a composition analogous to that found in breast milk from Canadian women (PCB 52 – 1.5%; PCB 66 – 2.9%; PCB 74 –10.4%; PCB 105 – 4.4%; PCB 118 –12.8%; PCB 138 – 17.5%; PCB 153 – 18.6%; PCB 156 –4.7%; PCB 157 – 1.5%; PCB 180 –12. 8%; PCB 183 – 2.3%; PCB 187 – 4.7%; PCB 189 – 0.5%; PCB 194 – 2.9%; PCB 203 – 2.3%). The only significant differences found were a reduction over time for immunoglobulins M and G antibodies to sheep red blood cells and a treatment-related reduction in the levels of the lymphocyte cell surface antigen human leukocyte antigen DR (HLA-DR) (Arnold *et al.*, 1999).

In male cynomolgus monkeys dosed according to the above mentioned regimen, blood and fat levels at the end of the dosing period were 1.7-3.6 mg/kg fat, which is 6-12 times higher than the median concentration of approximate 0.3 mg PCB/kg fat found in European human milk. The levels in control monkeys were 0.05-0.2 mg/kg fat, which are in the lower end of the range observed in humans in Europe. Behavioural deficits were apparent on spatial delayed alternation, fixed interval, and differential reinforcement of low rate performance when the monkeys were between 2.5 and 5.0 years of age. The effects included retarded learning, preservative behaviour, and inability to inhibit inappropriate responding (Rice, 1999).

8.1.3 Individual congeners

Adverse effects reported in laboratory animals following exposure to individual NDL-PCB (PCB 18, 28, 47, 52, 95, 101, 110, 128, 132, 149, 153, 170, 180, 206, 209, see Annex II) were effects on the thyroid, liver, brain biochemistry, immunotoxicity, oestrogenicity, reproductive and neurodevelopmental effects, in particular in the offspring of rodents following *in utero* exposure.

In acute and subacute rodent studies (single dose or a few days of dosing) the NOAELs for these effects for the individual NDL-PCB generally exceeded 1 mg/kg b.w. per day (Table 18). For the NDL-PCB tested for reproductive and developmental effects in rodents, including oestrogenic effects and effects on the thyroids as well as on the developing nervous system (PCB 18, 28, 47, 52, 101, 110, 153), the NOAELs ranged from 1 mg to >50 mg/kg b.w. per day. In most studies, the dams were treated on gestational days (GDs) 10-16, and the test compounds administered by either gavage or intraperitoneal injection.

The Panel also considered neurobehavioral studies where newborn mice were given a single oral dose by gavage at 10 days of age. NOAELs of 360-4100 µg/kg b.w. were reported for PCB 28, 47, 52, and 153 (Eriksson and Fredriksson, 1996a,b; Eriksson, 1998). Dosing at 10 days after birth is in the critical period for exerting effects on brain development in the mouse.

The corresponding critical period for exerting effects on brain development in humans, however, is during fetal life in the last trimester of pregnancy and shortly after birth. Thus, if the NOAELs of 360-4100 µg/kg b.w. obtained in these studies have to be converted to the human situation, fetal body burdens of 360-4100 µg/kg b.w. have to be assumed. Studies on the relationship between maternal and fetal levels of PCB are not available in mice or rats. Studies on TCDD in rats (Hurst *et al.,* 2000a,b) however, indicate that at long term exposure the body burden of the dams is about 10 times higher than that of the foetus. Assuming a similar kinetics for persistent PCB in humans would indicate that to obtain a similar situation in fetal life of humans as that of the neonatal exposure in mice would require much higher exposure levels than those of the 90 days studies mentioned above. Furthermore the relevance of high bolus dosing of postnatal pups to exposure of newborn infants via breastmilk is uncertain. Therefore the results of these neurobehavioral studies were not further considered in the risk characterization of NDL-PCB.

Significantly lower NOAELs for effects on liver and thyroid have been reported for the few individual NDL-PCB (PCB 28, 128, and 153) that have been tested in 90-day rat studies of an acceptable quality. These NOAELs were in the range of 30-40 µg/kg b.w. per day (PCB 28: 36 µg/kg b.w. per day; PCB 128: 43 µg/kg b.w. per day; PCB 153: 34 µg/kg b.w. per day). The corresponding LOAELs were 10 times higher. In all three studies, significantly increased liver EROD activities were reported, indicative of the expression of dioxin-like activity. From the reported accumulated concentrations of the NDL-PCB in the fat tissue of the rats at the NOAELs, the body burdens were estimated at 0.4, 0.8, and 1.2 mg/kg b.w. for PCB 28, 128, and 153, respectively.

Differences in potency between NDL-PCB and DL-PCB congeners on female reproduction and neurobehavioral development of the offspring have been shown in studies performed in rats in the same laboratory, using the same dosing protocol (gavage dosing from GD 10-16) and measuring the same endpoints (Schantz *et al*., 1995, 1996). The LOAEL for PCB 126 was <0.001 mg/kg b.w. per day, for PCB 118 the LOAEL was 4 mg/kg b.w. per day; for PCB 77 the NOAEL was at 2 mg/kg b.w. per day. For NDL-PCB 28 and 153 the NOAEL was 8 and 16 mg/kg b.w. per day, respectively. For all endpoints examined, the dioxin-like congener PCB-126 was by far the most potent, whereas the potencies of the other DL-PCB tested were more similar or slightly higher than the potencies of the NDL-PCB.

No studies on chronic toxicity and carcinogenicity have so far been published for any individual NDL-PCB. However, a draft abstract of the results from a two year toxicology and carcinogenicity study of PCB 153 in female Harlan Sprague-Dawley rats is available from the U.S. National Toxicology Program (NTP, 2005) In this study, groups of female rats received PCB 153 (stated purity >99%) by gavage at doses of 0, 10, 100, 300, 1,000 or 3,000 µg/kg b.w. five day per week for up to 105 weeks. Hepatocyte hypertrophy, diffuse fatty changes in the liver, and minimal to mild follicular cell hypertrophy of the thyroid gland were increased in the groups given 300 µg/kg b.w. or greater. Two liver cholangiomas were seen in the group administered 1,000 µg/kg b.w. The NOAEL for effects on liver and thyroid thus appeared to

be approximately 70 µg/kg b.w. per day. At all dose levels tested an increased liver EROD activity was found, which may indicate that the effects observed might have been due to, or influenced by, some dioxin-like contamination.

8.1.4 Metabolites

A number of studies have assessed the effects of hydroxy (OH) or methylsulfone metabolites, mostly following systemic administration.

Immature female Sprague Dawley rats (20-day old), treated intraperitoneally with 5.6 mg 4'-OH-PCB 30/kg b.w./day for two consecutive days, showed a significant increase in uterine weight (Jansen *et al*, 1993).

In an uterotropic assay, immature female Sprague-Dawley rats and immature female B6C3F1 mice received i.p. injections of 25, 50, or 100 mg/kg b.w. per day of several 4'-OH-PCB metabolites, for three days. The 4'-OH-metabolites of PCB 69, PCB 93, PCB 109, and PCB 112 exhibited effects in both rats and mice at the lowest dose tested. For 4'-OH-PCB 88, increased uterine weights were found in rats at the lowest dose, and the NOAEL in mice was 25 mg/kg b.w. per day. The 4'-OH metabolites of PCB 50, PCB 86 and PCB 106 had effects at 25 mg/kg b.w. per day in the rat, but in the mouse NOAELs of 50, 100 and 100 mg/kg b.w. per day were found (Connor *et al*., 1997).

Immature female B6C3F1 mice were treated intraperitoneally for three days with 50 or 100 mg/kg b.w. per day of 4'-OH-PCB 30 or 5.6, 22.5, 56.3, 113 mg/kg b.w. per day of 4'-OH-PCB 61, or an equimolar mixture of the two. 4-OH-PCB 30 caused inceased uterine weight and peroxidase activity at the highest dose level (NOAEL 50 mg/kg b.w. per day), whereas 4'-OH-PCB 61 increased uterine peroxidase activity at all dose levels and progesterone content at the highest dose only (LOAEL 5.6 mg/kg b.w. per day). Uterine peroxidase activity and progesterone content were increased at all doses following administration of the mixture. The activity of the mixture was additive (Ramamoorthy *et al*., 1997).

Pregnant Wistar WU rats were administered 4'-OH-PCB 107 by gavage at a dose level of 5 mg/kg b.w. per day from gestation days (GD) 10 to 16. Fetal plasma total and free T4 levels were significantly decreased at GD 17 and GD 20 (89% and 41% respectively). Fetal thyroid stimulating hormone levels were increased by 124% at GD 20. The deiodination of thyroxine (T4) to triiodothyronine (T3) was significantly increased in fetal forebrain homogenates at GD 17 (Meerts *et al*., 2002). Administration of 4'-OH-PCB 107 to pregnant rats from gestational days 10-16 showed a significant dose dependent prolongation of the oestrous cycle in 75% and 82% of female offspring exposed to 0.5 and 5 mg 4'-OH-PCB 107/kg b.w. per day, respectively. Plasma estradiol concentrations were significantly increased (50%) in the pro-estrous stage after exposure to 5 mg/kg b.w. per day of 4'-OH-PCB 107. Male and female

offspring of both groups showed long term (>PND100) impaired performance and decreased brain neurotransmitter levels (Meerts *et al.,* 2004).

Male Sprague-Dawley rats received four consecutive intraperitoneal (i.p.) doses of 20 micromoles/kg b.w. per day of nine methylsulfonyl metabolites of tetra-, penta- and hexachlorinated biphenyls to determine their effects on thyroid hormone levels. These metabolites are the major PCB methylsulfones detected in human milk, liver and adipose tissue. All nine methylsulfonyl metabolites reduced serum total T4 levels (16-44%). Total T3 level was significantly reduced by 3-MeSO2-PCB 49 and 3-$MeSO_2$-PCB 149, but increased by 3-$MeSO_2$-PCB 70 and 4-$MeSO_2$-PCB 101. For nearly all metabolites reductions in T4 levels led to an increase in the level of thyroid-stimulating hormone. A 30% increase in thyroid weight was found after treatment with 3-$MeSO_2$-PCB 101 and 3-$MeSO_2$-PCB 141 (Kato *et al*., 1998, 1999, 2000a).

Each of the seven 3-$MeSO_2$-PCB and 4-$MeSO_2$-PCB 101 congeners significantly increased the activities of UDP-glucuronosyltransferase (UDP-GT) toward T4. A significant correlation was found between the activity of UDP-GT toward T4 and serum total T4 concentration after the administration of each of these methylsulfonyl metabolites, indicating that the reduction of serum T4 levels was caused by an increase in the hepatic T4 glucuronidation (Kato *et al*., 2000b).

8.1.5 Interaction of DL- and NDL-PCB

Analysis of the effects of technical PCB mixtures on non-cancer endpoints in experimental animals revealed that in most toxicological studies, only one individual mixture with a fixed ratio between DL- and NDL-PCB was used. Thus it is not possible from these data to calculate the relative contributions of NDL- vs. DL-PCB to the effects observed. In a number of other studies, certain lots of technical PCB mixtures were used but no data on the composition of those lots were provided or were available from the literature.

Only two studies were identified which used at least two different technical mixtures with documented composition.

In the first study (Mayes *et al.*, 1998) it was found that various parameters for hepatotoxicity in female rats were strongly correlated with the TEQ portion and not with the dose of total PCB applied to the animals. The increase in relative liver weight observed in female animals was also dependent, at least in part, on the TEQ portion of the dose. In male rats some relationship between the TEQ dose and the increase in relative thyroid weight was found.

In the second study (Burgin *et al.,* 2001), consistent dose-response relationships were found for the suppressing effects of two different technical mixtures on thyroid hormone (T4) levels in rats when the dose was expressed as total PCB rather than as TEQ.

This analysis suggests that the TEQ portion can play a predominant role in the hepatotoxicity of technical PCB mixtures in female rats, and contributes to the increase in relative thyroid weight in male rats. The decrease in serum T4 observed in male rats mainly depends on the total PCB dose and, to a lesser extent, on the TEQ portion of the mixtures.

Only a few *in vivo* studies looked at interactions of specific congeners (see Annex II). PCB 153 can antagonise the effects of PCB 126 on immune function or production of cleft palate. PCB 47 in combination with PCB 77 failed to produce reproductive and developmental effects, but did produce at least an additive effect on behaviour. The effects of PCB 153 and PCB 77 on thyroid function following in utero exposure were additive. Also PCB 52 and PCB 77 produced an additive effect on immune parameters in a chronic study.

8.2 Effects in domestic animals

8.2.1 Case reports

Technical mixtures and biologically weathered[14] mixtures of PCB show low acute toxicity, and only a few cases are reported where accidental PCB poisoning has produced adverse effects in domestic animals. Single lethal doses of technical mixtures of PCB are approximately 1-10 g/kg b.w. in mammals, birds and fish (WHO, 1976; Osweiler, 1996). Sources of PCB exposure in domestic animals have been feedstuff of marine origin, and feedstuff contaminated during manufacture or storage, or by accidental use of PCB oil (Humphreys, 1988).

During the 1960s, reproductive failures and mortality were observed in the USA and Canada in mink fed fish from the Great Lakes. These effects were attributed primarily to PCB contamination of the fish (Aulerich *et al.*, 1973). The PCB level in the feed was approximately 30 mg/kg, and the average PCB residue levels in brain, liver and muscle of minks that died were 11, 5 and 5 mg/kg wet weight (PCB were quantified with Aroclor 1254 as a standard).

In the USA in 1971, contamination of broiler feed with Aroclor 1242 from a heat-exchange unit caused clinical signs and death in herds of broiler chicken. Pathological lesions were noted in the kidneys, spleen, liver and muscle tissue (Harris and Rose, 1972). Analysis of the feed revealed a PCB level of 148 mg/kg. In Japan, in 1968 PCB (Kanechlor 400) contaminated rice oil caused a "Yusho-like" incident in chicken. The acute toxic concentration for chicken was between 100 and 300 mg/kg feed (Kohanawa *et al.*, 1969). In Belgium, in 1999, problems with the hatching of hen eggs, reduced viability of young chicken and oedema in older chicken were associated with PCB contaminated animal feed at 32 mg/kg and above, quantified with the use of seven indicator PCB congeners (van Larebeke *et al.*, 2001; Hoogenboom *et al.*, 2004).

[14] Weathered: refers to alterations in the composition of a mixture that have occurred e.g. as a result of bacterial action, exposure to ultraviolet radiation, heat, extreme cold, through metabolic processes in higher biological organisms.

Toxic symptoms due to exposure of feedlot cattle to PCB contaminated feed for about four months were reported in the USA. The animals showed anorexia, dyspnoea, thirst, diarrhoea, abdominal pain and recumbence and gastrointestinal hyperaemia and intestinal haemorrhage. Reported PCB level in liver and fat were 80 mg/kg wet weight and 170-1100 mg/kg, respectively (Robens and Anthony, 1980). These effects became apparent after the animals were transported and placed in another feedlot, indicating that transportation stress could have played a role in the initiation of the effects.

8.2.2 Experimental studies with technical or weathered PCB mixtures

Sheep

In lambs fed diets containing 20 mg PCB/kg (42 or 54% chlorine, 0.6-1.0 mg PCB/kg b.w. per day) from weaning to market weight, reduced feed efficiency and rate of weight gain were found. The only other effect seen was a higher prevalence of chronic pneumonia among PCB treated animals (Hansen *et al.*, 1976b).

Pigs

Sows fed Aroclor 1242 at a level of 20 mg/kg (0.4-0.6 mg/kg b.w. per day) feed throughout gestation and nursing, produced a lower number of live piglets and an increased number of mummified foetuses. Slight atrophy of the spleen and thyroid gland was observed in piglets from PCB exposed sows, and the exposed sows had hypertrophy of the liver and some of them had erosions of the stomach (Hansen *et al.*, 1975).

In growing pigs fed diets containing 20 mg PCB/kg (42 or 54% chlorine, 0.6-2 mg/kg b.w. per day) from weaning time to market weight, reduced feed efficiency and weight gain, and increased incidences of gastric erosions were found (Hansen *et al.*, 1976b).

Rabbits

Rabbits of about 2 kg b.w. were administered approximately 150 mg/kg b.w. Aroclor 1221, 1242 or 1254, once a week for 14 weeks by gavage. During the last weeks of exposure, the animals were inoculated with pseudo rabies virus. Virus antibody titres were reduced in rabbits exposed to the various technical PCB mixtures. Pathological findings were hepatomegaly with necrosis and fibrosis, particularly in rabbits given Aroclor 1254 and to a lesser extent in those given Aroclor 1242 (Koller and Thigpen, 1973; Koller and Zinkl, 1973).

Rabbits of about 2 kg b.w. were fed Aroclor 1254 for one month at 4, 20, 45 and 170 mg/kg diet (0.2, 0.9, 2.1 or 6.5 mg/kg b.w. per day) before challenging with sheep red blood cells and continued PCB feeding for another month. Significant liver and spleen enlargements compared to controls were found at the two highest dose levels. Dose related decreases in

count of lymphnodal plasma cells, and germinal centres in the spleen were seen, as well as thymus atrophy at all dose levels (Street and Sharma, 1975).

In offspring of female rabbits fed diets containing 10, 100 and 250 mg/kg Aroclor 1248 (0.5, 5 and 13 mg/kg b.w. per day) from four weeks before mating to four weeks after delivery, depressed immune function was seen at the highest dose level (Thomas and Hinsdill, 1980). The NOAEL in this study was 5 mg/kg b.w.

Mink

Mink is a particularly susceptible species for PCB toxicity, and effects on reproduction seem to be the most sensitive endpoint. Administration of a diet with 30 mg/kg technical PCB (mixed Aroclors 1242, 1248 and 1254 approximately 1.5 mg/kg b.w. per day) to adult female and male mink resulted in complete reproductive failure, fatty liver, kidney degeneration, haemorrhagic gastric ulcers, and finally death after three to six months (Aulerich *et al.,* 1973). Administration of 2 mg/kg Aroclor 1254 in the diet (approximately 0.1 mg/kg b.w. per day) for eight months, exerted effects on reproduction (Aulerich & Ringer, 1977). No effects were induced by similar administration of Aroclor 1242, 1221, or 1016.

Platonow and Karstad (1973) fed a ration containing meat from cows fed Aroclor 1254, to adult male and female mink. The PCB concentrations in the meat (wet weight) were 3.6 mg/kg (approximately 0.6 mg/kg b.w. per day) and 0.64 mg/kg (approximately 0.1 mg/kg b.w. per day). At the high dose no live offspring were produced and all adult female and male mink died during a 105 days period of feeding. At the low dose only one out of 12 females produced offspring, but they died within one day. Two out of 12 females died within 160 days of exposure. Histological lesions comprised fatty degeneration and necrosis of the liver, nephrosis, brain oedema and disseminated intravascular coagulation. The mean liver PCB concentrations (expressed as Aroclor 1254) in adult mink fed meat containing 3.6 and 0.64 mg/kg PCB were 12 and 1.2 mg/kg wet weight, respectively.

The results from the studies of Aulerich and Ringer (1977) and Platonow and Karstad (1973) indicate a more pronounced effect from weathered PCB based on Aroclor 1254 than from Aroclor 1254 itself. This is supported by studies in mink comparing the effect of technical PCB mixtures with weathered PCB mixtures, consisting of either meat from rabbits treated with Aroclor 1254 (Aulerich *et al.*, 1986), or meat from fish treated with technical PCB mixtures (Giesy *et al.*, 1994; Giesy and Kannan, 1998). In the study of Aulerich *et al*. (1986), the 28-days LC_{50} of Aroclor 1254 was 79 mg/kg feed and the corresponding LC_{50} based on meat from rabbits administered Aroclor 1254, was 47 mg/kg feed.

Effects of various fractions of technical PCB (Clophen A50) on reproductive impairment in mink were found to be caused primarily by mono- and non-ortho PCB, but also the fraction of 2-4-ortho chlorinated PCB contributed to the total effect of the technical PCB (Kihlström *et al.*, 1992).

Birds

In studies on reproduction in hens, reduced hatchability of eggs has been found at dietary concentrations of 10 mg/kg and higher of PCB (Aroclors 1232, 1242 or 1248) when fed for six-eight weeks (Britton and Huston, 1973; Harris *et al.*, 1976). After replacement of the PCB diet with uncontaminated feed, the reduced hatchability gradually disappeared. No effects were found at 5 mg/kg diet (0.3 mg/kg b.w. per day).

White Leghorn hens were fed a weathered mixture of organochlorines containing primarily PCB in the diet as contaminated fish (carp from Lake Huron or less contaminated ocean fish) for eight weeks. Total PCB level in the diets were 0.3 (control), 0.8 and 6.6 mg/kg (measured as the sum of Aroclors 1242, 1248, 1254 or 1260, 0.02, 0.05 and 0.40 mg/kg b.w. per day). No significant effects were found on egg production, egg weight or fertility, but embryo mortality was increased and the hatching rate decreased in the highest dose group. In addition, in the high dose group, increased liver weight was found in embryos and chicks, and deformities (e.g. oedema and haemorrhage in the head, neck, abdomen and deformed legs, skull, brain and yolk-sac) were observed at both dose levels (Summer *et al.*, 1996a, b). The NOAEL of this study is 0.02 mg/kg b.w.

In broiler chicken fed Aroclor 1254 at concentrations of 0.1, 1, 5, 10 or 20 mg/kg in the diet from hatching to eight weeks of age, a dose-dependent reduction in growth was found being significant at 10 and 20 mg/kg diet. Increased mortality (10 and 30% of the animals) was found at 10 and 20 mg/kg diet levels (Bird *et al.*, 1978). These results indicate that the NOAEL for chick mortality was 5 mg/kg diet, corresponding to 0.5 mg/kg b.w. per day.

Moderate liver weight increment and spleen weight decrement were observed in a study in broiler chicken fed a diet containing 20 mg/kg of PCB (Aroclor 1242 or 1254) between one and nine weeks of age (Hansen *et al.*,, 1976a).

Fish

In rainbow trout fed Aroclor 1254 at 1, 10 or 100 mg/kg of diet for up to 330 days, occasional behavioural changes (increased aggression and hyper excitability) and pathological changes in the kidney, liver and spleen were found in fish fed the two highest PCB concentrations (Nestel and Budd, 1975). The NOAEL was 1 mg/kg diet, corresponding to 0.002-0.02 mg/kg b.w. based on a daily feed intake for farmed trout of 0.2-2% relative to the body weight.

Diets containing 5, 50 or 500 mg/kg of Aroclor 1254 were fed to rainbow trout fry for 30 days. Mortality or mean time to death following challenge with infectious haematopoietic necrosis virus (IHNV) was not affected in fry. However, histopathologic lesions due to virus disease were more severe and occurred more frequently in all PCB exposed fish than in control fish. Fish fed PCB in the diet at 5 and 50 mg/kg and not exposed to this virus, remained clinically normal throughout the 75-days examination, but fish fed 500 mg/kg for 50

days consumed feed less quickly and less completely and exhibited fin necrosis and melanosis (Spitsbergen *et al.*, 1988).

Diets with 3, 30 or 300 mg/kg of Aroclor 1254 were fed to juvenile rainbow trout for 12 months. Weight loss and hepatomegaly occurred at the highest dose level. Assessment of humoral immunomodulation by plaque forming cell response to sheep red blood cells was negative (Cleland *et al.*, 1988). The NOAEL was between 0.06-0.6 mg/kg b.w. based on feed intake of 0.2-2% relative to b.w.

8.2.3. Studies with individual NDL-PCB congeners

Goats

Pregnant goats were orally administered NDL-PCB 153 or DL-PCB 126 three times a week from day 60 of gestation until delivery (13 weeks), at doses corresponding to 98 and 0.049 µg/kg b.w. respectively, per day. The pre-pubertal concentration of luteinizing hormone (LH) was lower, puberty was delayed and progesterone level during the luteal phase of the oestrous cycle was higher in the female kids exposed to PCB 153. Kids exposed to PCB 153 had a significantly higher number of white blood cells, neutrophils and lymphocytes at two weeks of age compared to controls. Kids exposed to PCB 126 had a significantly lower level of monocytes at eight weeks of age and no effect on lymphocyte proliferation (Lyche *et al.*, 2004a; b).

Mink

In mink, no adverse reproductive effects were observed when NDL-PCB 136 or 153 were fed at 5.0 mg/kg feed for three months (approximately 0.25 mg/kg b.w. per day). However, these diets slightly altered the brain dopamine concentrations. However, when mink were fed the planar PCB 169 at 0.10 mg/kg feed (approximately 0.005 mg/kg b.w. per day) for three months, 50% mortality was seen as well as reproductive failure, hormonal and metabolic changes (Aulerich *et al.*, 1985).

Fish

In rainbow trout fed PCB 153 in the diet at 5 or 20 mg/kg for 12 weeks, no effect on growth rate or relative liver weight was found. The hepatic arylhydrocarbon hydroxylase (AHH) and ethoxyresorufin-O-deethylase (EROD) activities were slightly increased (Da Costa and Curtis, 1995). The results indicate a NOAEL for PCB 153 in rainbow trout between 0.04-0.4 mg/kg b.w. based on a feed intake of 0.2-2% relative to b.w.

8.3. Effects in wild animals

8.3.1 Observational studies

One of the first cases investigated was the incidence of premature parturition and abortions in colonies of California sea lions (DeLong *et al.*, 1973). Females that aborted had mean PCB levels in blubber, quantified with Aroclor 1254 as a standard, of 110 mg/kg wet weight, compared with 17 mg/kg in females that carried full term. The case was, however, inconclusive because bacterial and viral agents associated with abortions were also present (Gilmartin *et al.*, 1976).

Declining populations of harbour, ringed and grey seals in the Baltic and harbour seals in the Wadden Sea were also believed to be due to environmental PCB exposure (Helle *et al.*, 1976). A high incidence of uterine occlusions and stenoses were found, possibly related to foetal death and resorption. Blubber levels of PCB (quantified with Clophen A50 as a standard) in ringed seals with and without uterine occlusions were on average 110 and 89 mg/kg, respectively. Based on the results of analyses of organochlorine compounds, Reijnders (1980) concluded that the dramatic decrease in reproductive success of the Dutch harbour seal population was correlated strongly with elevated PCB concentrations.

Environmental PCB exposure has also been suspected of involvement in the decline of other populations of seals and sea lions, and to be the main cause of the decline in various populations of whales such as harbour porpoises, killer whales, pilot whales, beluga whales, and bottlenose dolphins. Reported average residue levels in these cetacean populations were 88-250 mg PCB/kg blubber wet weight (reviewed by Gilbertson, 1989). More recently, the PCB levels in these species have declined (AMAP, 2004).

Dramatic regional decline in populations of wild mink and otter in the USA and Europe are suspected to be caused by environmental PCB exposure. Average liver PCB levels in mink and otter populations were approximately 20 and 50 mg/kg lipid weight respectively (Gilbertson, 1989).

Kannan *et al.* (2000) have reviewed field and semi-field studies on seals, mink and otter to establish mean threshold tissue concentrations of PCB linked to subtle effects on the immune system, vitamin A storage and thyroid hormone level. The threshold concentrations in liver or blood for these effects were found to be 6.6-11 mg/kg lipid weight. The reported dietary threshold concentrations were 10-150 μg/kg wet weight.

In Svalbard polar bears, an inverse correlation between IgG and the PCB level in the animals has been found (Bernhoft *et al.*, 2000). The di-ortho chlorinated NDL-PCB 99 was found to have stronger influence on IgG than mono-ortho chlorinated DL-PCB. The concentration range for the sum of fourteen individual congeners was 21-228 μg/kg blood plasma based on wet weight (approximately 1.9-21 mg/kg plasma lipids). Furthermore, following immunization of the polar bears, their ability to produce protective antibodies was impaired, and the *in vitro* proliferation of lymphocytes decreased in polar bears with high PCB levels

(Lie *et al*., 2004; 2005). Testosterone levels in male Svalbard polar bears were found to be inversely correlated to plasma levels of PCB (Oskam *et al.*, 2003). A significant negative correlation has also been found between plasma retinol and PCB levels, and between the ratio total free T4 and PCB in plasma (Skaare *et al.*, 2001).

For reproductive success in fish-eating and predatory birds, a NOEL range for total PCB (using different quantification methods) of 1.3-11 mg/kg egg wet weight was reported (AMAP, 2004). Dietary LOECs for total PCB range from 2-50 mg/kg wet weight feed for reproductive endpoints in a number of wild bird species. In glaucous gulls from Bear Island, Norway, a positive correlation has been found between PCB level and nematode density (Sagerup *et al*., 2000). In black guillemots at Saglek Bay, Canada, a negative correlation was found between liver PCB and liver retinol (Kuzyk *et al*., 2003).

There are outbreaks of disease in fish populations that are believed to be related directly or indirectly to PCB (Gilbertson *et al*., 1989).

8.3.2 Experimental studies with technical or weathered PCB mixtures

Seals

Captive harbour seals from the Dutch Wadden Sea, exposed to PCB via different fish diets, had reduced reproductive success at PCB levels of 25 mg/kg lipid weight in blood (quantified as sum of 22 individual congeners) (Reijnders, 1986; Boon *et al*., 1987).

In captive harbour seals fed herring from the Baltic Sea (mean PCB level 4.4 mg/kg lipid quantified as sum of 22 individual congeners) for 2.5 years, reduction of immune parameters and functions as well as disrupted vitamin A physiology were found when compared to seals fed less contaminated Atlantic herring (mean PCB 0.9 mg/kg lipid) (Ross *et al.*, 1995; De Swart *et al.*, 1996; Vos *et al.*, 2003). The accumulated PCB concentration in the blubber of the seals fed Baltic and Atlantic fish were 16.5 and 6.9 mg/kg lipid, respectively.

Birds

Mallard ducklings were fed a diet containing PCB (Aroclor 1254) at 25, 50 or 100 mg/kg feed from 10 to 20 days of age and then challenged with duck hepatitis virus. The birds showed no apparent clinical intoxication during PCB exposure but all groups of exposed birds showed significantly higher mortality after the challenge with duck hepatitis virus than birds not given PCB (Friend and Trainer, 1970). Using a daily feed intake at approximately 6% relative to body weight, the lowest dose still showing immunological effects corresponds to 1.5 mg/kg b.w. per day.

In ring doves fed on a diet containing 10 mg Aroclor 1254/kg (corresponding to 0.6 mg/kg b.w. per day) for three months, reduced hatchability of eggs was found (Peakall *et al.*, 1972).

Adult ring doves fed diets with Aroclor 1254 at 1, 10 and 100 mg/kg b.w. per day for eight weeks showed a significant reduction in the the levels of dopamine and norepinephrine in the brain at 10 and 100 mg/kg b.w. per day compared to controls. (Heinz *et al.*, 1980).

American kestrels were fed a mixture of Aroclors 1248, 1254 and 1260 (1:1:1) in their diet at approximately 10 mg/kg (corresponding to 0.6 mg/kg b.w. per day) for 120 days, followed by a year on control diet, before they were subjected to a standardized capture, handling and restraint protocol designed to produce an increase in circulating corticosterone. Both baseline and stress-induced corticosterone levels were significantly lower in PCB exposed birds compared to controls (Love *et al.*, 2003).

Fish

Juvenile Chinook salmon were fed Aroclor 1254 for four weeks at levels 0.3, 1, 3.2, or 10 mg/kg diet before vaccination against *Listonella anguillarum* and subsequently challenge with this bacterium (Powell *et al.*, 2003). No effect on growth, innate disease resistance or acquired immunity to *L. anguillarum* was detected. The NOAEL was 10 mg/kg feed, corresponding to 0.02-0.2 mg/kg b.w. per day, based on a daily feed intake at 0.2-2% relative to b.w.

Male Atlantic croaker (*Micropogonias udulatus* L.) were fed Aroclor 1254 for 30 days at 1 mg/kg b.w. per day (approximately 100 mg/kg diet) during gonadal maturation. Hypothalamic tryptophan hydrolase (TPH), a rate-limiting enzyme in serotonin synthesis as well as the growth of gonads were reduced compared to controls. Co-treatment with vitamin E reduced the PCB effect on TPH activity and gonadal growth (Khan and Thomas, 2004).

8.4 Carcinogenicity

Available data from animal experiments indicate that complex mixtures of polychlorinated biphenyls cause liver and thyroid neoplasms in rats. The results of a comprehensive comparative carcinogenicity study conducted in rats with Aroclor 1016, 1242, 1254 and 1260 were described by Mayes *et al.* (1998). Each mixture was assessed at multiple dietary concentrations ranging from 25 to 200 ppm for two years in male and female Sprague-Dawley rats. For females, increased survival was observed for all Aroclor treatment groups. Liver toxicity was distinctly more severe in females than in males. The incidence of hepatocellular neoplasms (primarily adenomas) was highly sex-dependent (females much more susceptible than males), differed among mixtures and, for females, was dependent on the level of chlorination (highest with Aroclor 1254 and lowest with Aroclor 1016). A significant response in males was observed only for the high dose of Aroclor 1260. For males, a small increase in the incidence of thyroid gland follicular cell adenomas was noted for Aroclors 1242, 1254 and 1260, with similar incidences across dose groups and mixtures. For females

receiving Aroclors 1242, 1254 or 1260, a significantly decreased trend in the incidence of mammary gland tumours was observed.

PCB without distinction in dioxin-like or non dioxin-like congeners, were classified by IARC (1987) in Group 2A (probably carcinogenic to humans), based on limited evidence in humans and sufficient in animals.

No published peer reviewed data are available on the carcinogenic potency of single congeners. In the draft abstract of the NTP long-term and carcinogenicity study with PCB 153 in female rats cited in Section 8.1.3, it was concluded that the evidence of carcinogenicity of PCB 153 was equivocal.

The interpretation of carcinogenicity studies with technical mixtures is however hampered by the fact that these mixtures contain both dioxin-like and non dioxin-like congeners. Since liver carcinogenicity has been shown in female rats for the prototype dioxin 2,3,7,8-TCDD, but also for 2,3,4,7,8-PCDD and for the most potent DL-PCB congener PCB 126, the possibility has to be considered that the liver carcinogenicity of technical PCB mixtures is due to the dioxin-like compounds present in these mixtures.

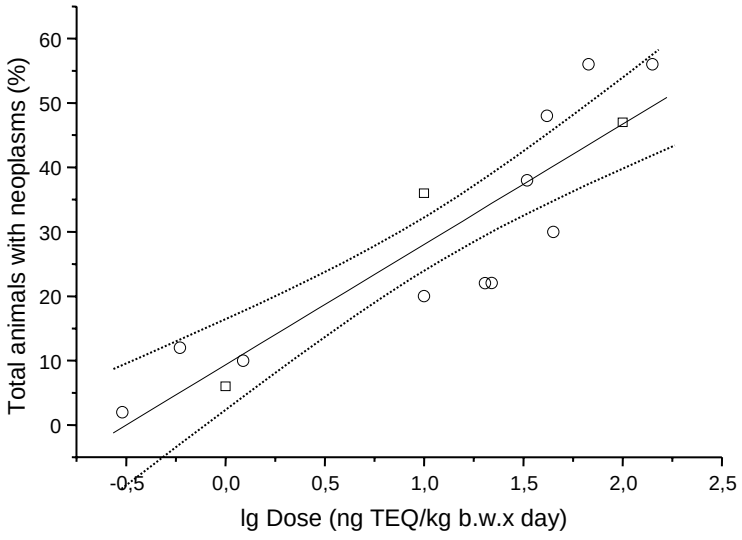


Figure 9. Linear regression including 95% confidence intervals of the relationship between the total number of female rats with liver neoplasms and the dose of TEQ derived from TCDD or Arochlors, respectively, according to Mayes *et al*., 1998 (circles) or Kociba *et al*., 1978 (squares).

Evaluation of the results from the chronic carcinogenicity study in rats described above (Mayes *et al*., 1998) indicates that the total TEQ-doses, associated with dioxin-like constituents within the technical mixtures, but not the doses of total PCB, are mainly, if not exclusively, responsible for the development of liver neoplasms. A quantitative comparison

with a chronic carcinogenicity study with TCDD in female rats (Kociba *et al*., 1978) as presented in Figure 9, reveals similar dose-response curves for the total TEQs in the various technical PCB mixtures as for TCDD as inducers of hepatic neoplasms in female rats. These findings suggest that in rats, NDL-PCB administered together with DL-PCB in technical mixtures play a minor - if any - role as carcinogens.

Tumour promotion experiments have shown that after initiation with a genotoxic carcinogen, technical PCB mixtures and individual dioxin-like and non dioxin-like congeners as well as TCDD act as liver tumour promoters in rats (Anderson *et al.*, 1986; Buchmann *et al.*, 1986; 1990; Hemming *et al.*, 1993; Haag-Grönlund *et al.*, 1997; Dean *et al*., 2002). The promoting activity of di-*ortho* PCB such as PCB 47, 52, 49, and 153 has been demonstrated in short-term assays in which orally administered congeners promoted development of preneoplastic lesions in rat liver following induction by various initiators (Hemming *et al*., 1993; Preston *et al*., 1985). In this respect NDL-PCB appear to be less effective than DL-PCB (Buchmann, 1991). Based on the determination of the number and volume of γ-glutamyltranspeptidase (GGT)-positive foci (preneoplastic lesions) it was shown that PCB 3, PCB 15, PCB 52 and PCB 77 significantly increased the number of the GGT-positive foci per cm^3 of liver and per liver in male rats. Only PCB 3 and PCB 15 in particular, also increased the volume of the GGT-positive foci.

Knowledge of the mechanisms of action underlying the tumour-promoting capacity of NDL-PCB is limited to data obtained from *in vitro* studies (Bohnenberger *et al*., 2001; Machala *et al.*, 2003). Many tumour promoters such as TCDD have been shown to suppress apoptosis of preneoplastic cells (Stinchcombe *et al.*, 1995) and/or inhibit intercellular gap junctional communication (Machala *et al*., 2003). This cellular function is thought to prevent uncontrolled growth of cells bearing an intrinsic deficiency in single-cell growth regulation. Induction of oxidative stress, inhibition of cellular communication, and inhibition of apoptosis are mechanisms which have also been observed after PCB exposure, and which may be of relevance for PCB-related tumour promotion (Bager *et al*., 1997; Worner and Schrenk, 1996; Bohnenberger *et al.,* 2001). In addition, sulphonated and hydroxylated PCB metabolites have also been shown to inhibit gap junction intracellular communication *in vitro* (Kato 1998; Machala, 2004).

The development of thyroid tumours in rats was attributed to the ability of Aroclor treatment to decrease the thyroid hormone levels in peripheral blood. As a result the release of thyroid-stimulating hormone (TSH) from the pituitary gland is enhanced (Vansell *et al*., 2004). This effect is considered a risk factor in the development of thyroid cancer in rodents, but not in humans. This is based on the fact that the transport of thyroid hormones in the blood follows a different mechanism in humans than in rodents.

8.5. Genotoxicity

In vitro studies

Table 15 shows the results of *in vitro* studies on gene mutations, chromosome abnormalities and DNA damage and repair. Aroclor 1254 and PCB 52 did not induce gene mutations in *S. typhimurium* with or without exogenous metabolic activation. Aroclor 1254 was not clastogenic in an *in vitro* chromosome aberration test carried out with human lymphocytes (Hoopingarner *et al.*, 1972). No clastogenicity was observed in human peripheral lymphocytes exposed *in vitro* to Delor 103 (Kalina *et al.*, 1986). PCB 52 did not induce chromosome damage. Sargent *et al*. (1989) showed that PCB 77 caused dose-related chromosome breakage in human lymphocytes in a range of non toxic concentrations (10^{-1}-10^{-4} μg/mL), and they reported an interactive effect of PCB 77 with PCB 52. However, Belpaeme *et al.* (1996) did not find any increase in micronucleus frequencies or DNA single strand breaks in human lymphocytes treated with PCB 77.

Aroclor 1254, in contrast to TCDD, was able to induce unscheduled DNA synthesis (UDS) in cultured rat hepatocytes (Althaus *et al*., 1982). Aroclor 1242 and Clophen A60 were found to be negative in a gene mutation assay carried out in Chinese hamster V79 cells in the absence of metabolic activation.

In vitro covalent binding of radiolabelled PCB 153 to calf thymus DNA and to proteins, measured by liquid scintillation spectrometry, was reported by Narbonne and Daubeze (1980). By using ^{32}P-postlabelling Oakley *et al.* (1996) showed that some lower chlorinated PCB produced modified DNA bases, revealed as "spots" on the TLC plate, and that guanine was the preferential site of attack.

Robertson and Gupta (2000) showed that metabolism of PCB, generates electrophilic metabolites and reactive oxygen species that can damage DNA. Srinivasan *et al*. (2001) showed that dihydroxylated PCBs and PCB quinones, after reaction with glutathione, produced reactive oxygen species in HL-60 human cell lines and oxidative DNA damage in the form of DNA strand breaks in a supercoiled plasmid DNA from *E. coli*. A study by Pereg *et al*. (2001) compared, by the ^{32}P-postlabeling assay, modified DNA bases formed after bioactivation of PCB with rat, mouse and human hepatic microsomes, and investigated the role of synthetic quinoid metabolites of 4-monochloro-biphenyl (4-CB). Eight congeners ranging from mono- to hexachlorinated biphenyls were tested. Modified DNA bases were formed with mono-, di- and tri-chlorinated congeners, but not with higher chlorinated congeners. Similar adduct patterns were observed for 2-monochlorobiphenyl (2-CB) activated with all microsomal systems, while 4-CB, 3,4-CB and 3,4,5-CB showed similar patterns for two out of the three microsomal systems used. 4,4'-CB showed different adduct patterns in all microsomal systems. Higher adduct levels were obtained with the rodent microsomes compared with human microsomes. Using the same technique, low levels of DNA damage were also observed in human hepatocytes exposed to Aroclors 1016 and 1254 (Borlak *et al.*, 2003). Recently, Zhao *et al*. (2004) reported the formation of a guanine-adduct after

incubation of calf thymus DNA with quinones of lower chlorinated PCB. These studies have shown that liver enzymes metabolise lower chlorinated PCB congeners to reactive intermediates that can produce DNA damage *in vitro* and that para-quinone metabolites of PCB may in part be involved.

By using a modified ^{32}P-postlabeling technique Schilderman *et al.* (2000) showed that the incubation of PCB 1, PCB 12, PCB 28, PCB 38 and PCB 52 with calf thymus DNA and liver microsomes from rats treated with Phenobarbital produced five to eight different spots. For some higher chlorinated congeners (PCB 138, PCB 153 and PCB 180) a single dominant spot was detected after butanol enrichment. Both higher and lower chlorinated PCB congeners were unable to significantly increase oxidative DNA damage in calf thymus DNA measured as 8-oxo-7,8-dihydro-2'-deoxyguanosine.

Table 15. *In vitro* studies with PCB (mixtures or congeners)

Test system	Genetic endpoint	Results	Mixture or Congener	Reference
Salmonella typhimurium (reverse mutation)	Gene mutations	—	Aroclor 1254	Schoeny *et al.*, 1979
S. typhimurium (reverse mutation)	Gene mutations	—	Aroclor 1254	Bruce and Heddle, 1979
S. typhimurium (reverse mutation)	Gene mutations	—	Aroclor 1254	Zeiger *et al*., 1988
S. typhimurium (reverse mutation)	Gene mutations	—	Mixture	Silberhorn *et al*., 1990
S. typhimurium (reverse mutation)	Gene mutations	+	4-chlorobiphenyl	Wyndham *et al*., 1976
S. typhimurium (reverse mutation)	Gene mutations	—	PCB 52	Hsia *et al*., 1978
Escherichia coli	Gene mutations	—	Mixture	Dunkel *et al*., 1984
Chinese hamster V79 cells (HPRT)	Gene mutations	—	Aroclor 1242 and Clophen A60	Hattula, 1985
Human lymphocytes	Chromosome aberrations	—	Aroclor 1254	Hoopingarner *et al*., 1972
Human lymphocytes	Chromosome aberrations	+	PCB 77	Sargent *et al*. 1989
Human lymphocytes	Chromosome aberrations	—	PCB 52	Sargent *et al*. 1989
Human lymphocytes	Chromosome aberrations	—	Delor 103	Kalina *et al*., 1986
Human lymphocytes	Micronuclei	—	PCB 77	Belpaeme *et al*., 1996
Human lymphocytes	Single Strand Breaks (Comet assay)	—	PCB 77	Belpaeme *et al*., 1996
Mammalian cells	Single Strand Breaks	+	PCB 52	Stadnicki *et al*., 1979
Chinese hamster ovary cells	UDS DNA repair	+	PCB 3	Wong *et al*., 1979
Rat hepatocytes	UDS DNA repair system	+	Aroclor 1254	Althaus *et al*., 1982

In vivo studies

Table 16 summarises the results of *in vivo* studies on effects of PCB on chromosomal abnormalities, micronuclei and dominant lethal mutations.

Table 16. *In vivo* studies with PCB (mixtures or congeners)

Test system	Genetic endpoint	Results	Mixture or Congener	Reference
Mammalian cells				
Mouse bone marrow cells	Micronuclei	—	Aroclor 1254	Bruce and Heddle, 1979
Mouse sperm cells	Chromosome aberrations	—	Aroclor 1254	Bruce and Heddle, 1979
Rat spermatogonia	Chromosome aberrations	—	Aroclor 1254	Dikshith *et al*., 1975
Rat sperm and bone marrow cells	Chromosome abnormalities	—	Aroclor 1254 and Firemaster BP6	Garthoff *et al*., 1977
Rat hepatocytes	DNA fragmentation	+	Aroclor 1254	Robbiano and Pino, 1981
Mouse bone marrow cells	Micronuclei	—	Mixture	Watanabe *et al*., 1982
Rat spermatogonia and bone marrow cells	Chromosome aberrations	—	Aroclor 1242	Green *et al*., 1975a
Rat sperm cells	Dominant lethal mutations	—	Aroclor 1242	Green *et al*., 1975b
Rat bone marrow cells	Chromosome aberrations	+	PCB 52 and 77 (in combination)	Meisner *et al*., 1992
Non-mammalian cells				
Drosophila	Chromosome non-disjunction	—	Clophen 30 and Clophen 50	Nilsson and Ramel, 1974
Chicken embryos	Chromosome aberrations	—	Aroclor 1242	Blazak and Marcum, 1975
Ring doves	Chromosome aberrations	+	Aroclor 1254	Peakall *et al*., 1972
Fish erythrocytes	Chromosome aberrations	+	Aroclor 1254	Al-Sabti, 1986

Clophen 30 and Clophen 50 did not induce chromosomal non-disjuction in *Drosophila melanogaster* (Nilsson and Ramel, 1974). Aroclor 1254 produced chromosome aberrations in embryos (Peakall *et al*., 1972) and in fish erythrocytes (Al-Sabti, 1986). It also induced DNA fragmentation in rat hepatocytes (Robbiano and Pino, 1981), but was unable to induce micronuclei in mouse bone marrow cells or chromosomal abnormalities in mouse sperm cells

(Bruce and Heddle, 1979). It was not able to induce chromosomal abnormalities in rat sperm cells and bone marrow cells either (Dikshith *et al*., 1975; Garthoff *et al*., 1977). Aroclor 1242 did not induce chromosomal abnormalities in rat bone marrow cells and rat spermatogonia (Green *et al*., 1975a), nor dominant lethal mutations in rat sperm cells (Green *et al*., 1975b). A mixture of PCB was found to be unable to induce micronuclei in mouse bone marrow cells (Watanabe *et al*., 1982). PCB 52 and 77 given individually in the feed were unable to produce chromosome aberrations in the bone marrow cells of rats (Meisner *et al*., 1992). However, there was a significant increase in chromosomal damage in rats fed both PCB 52 and PCB 77 in combination.

An early *in vivo* study in mice showed covalent binding of PCB 136 to DNA, RNA and proteins in liver, muscle and kidneys and of PCB 153 to RNA and proteins in the liver (Morales and Mattews, 1979). Another study showed binding of PCB 153 to nuclear proteins and DNA in the livers of treated rats (Daubeze and Narbonne, 1984). In rats orally treated with Aroclor 1242 no DNA adducts nor oxidative DNA damage were detected in any of several organs (Schilderman *et al.,* 2000).

Human data

Available information on *in vivo* genotoxic effects of PCB in humans is limited by confounding exposures that involved mixtures of chemicals. Workers exposed for 2-25 years during the production of PCB-based products named Delor 103 and Delor 106 showed increased chromosome aberrations and sister chromatid exchanges (SCE) in their lymphocytes, compared to controls matched for alcohol consumption and smoking. The length of exposure over 10 years was associated with increased frequencies of aberrant cells with chromosome aberrations and SCE (Kalina *et al*., 1991).

Conclusion on genotoxicity

In conclusion it can be said that the overall negative results of *in vitro* and *in vivo* genotoxicity studies indicate that technical PCB mixtures are not mutagenic at gene or chromosome level. Some lower chlorinated PCB formed modified DNA bases revealed as spots by the ^{32}P-postlabeling assay. By using the same technique it was shown that PCB 153 also produced modified DNA bases, *in vitro* as well as *in vivo*. Furthermore it has been shown that PCB-derived paraquinones can bind to DNA *in vitro* to form specific adducts at the N2-position.

The results obtained by ^{32}P-postlabeling are difficult to interpret, because this technique does not provide structural information on the analytes, but only detects unidentified spots. Reactive oxygen species might be responsible for their formation. Although it is difficult to draw a general conclusion from the present data, they raise the possibility that oxidative DNA damage may be involved in the carcinogenicity of PCB in rodents.

9. Mechanistic considerations

Enzyme induction

DL-PCB bind to the aryl hydrocarbon receptor (Ah receptor) and induce CYP1 drug metabolising enzymes as measured for example as an increase in EROD activity. Binding to the Ah receptor is considered as crucial for the toxic action of DL-PCB (Safe, 1990). NDL-PCB do not bind to the Ah receptor and display no CYP1A induction, except for a few mono-*ortho* and multiple-*ortho* congeners that were about 1,000- and 10,000-fold less potent *in vitro* than the most potent DL-PCB (van der Burght *et al*., 1999). DL-PCB are dioxin-type inducers of CYPs which may activate compounds into carcinogenic, mutagenic or teratogenic metabolites. NDL-PCB are phenobarbital-type inducers and induce CYP2 and /or CYP3 enzymes independent of the Ah receptor (Sueyoshi *et al*., 1999, Kliewer *et al*., 2002). However, the relationships between potency in inducing CYPs 2B1/2B2/3A, PCB structural properties, and toxic effects have not been completely elucidated yet (Connor *et al*., 1995).

Among the sulphonate PCB metabolites, 3-$MeSO_2$ metabolites were strong phenobarbital type inducers of hepatic drug-metabolising enzymes, while 4-$MeSO_2$ derivatives had almost no effect on both cytochrome content and enzyme activities (Kato *et al.*, 1995).

Neurotoxicity

Mechanistic studies *in vivo* and *in vitro* have shown that NDL-PCB can affect components of the nervous system in at least four different ways: i) by interference with intracellular sequestration of calcium and increased activation of protein kinase C (PKC), thereby altering intracellular signal transduction pathways (Tilson, 1998; Kodavanti and Tilson, 1997), ii) through induction of apoptosis subsequent to activation of the ryanodine receptor and increased production of reactive oxygen species (Howard *et al.*, 2003), iii) by changing the levels of neurotransmitters such as dopamine and acetylcholine (Seegal, 1989; Shain, 1991), the latter may be due to interference with PCB on thyroid hormone levels because cholinergic fibres are particularly sensitive to thyroid hormone deficiency (Juárez de Ku, 1994), and iiii) by increasing the release of arachidonic acid (Kodavanti and Derr-Yellin, 2002).

In vivo observations have confirmed changes in the PKC signalling pathway and calcium homeostasis (Yang, 2003) and reduced dopamine levels were observed in brain tissue from adult non-human primates (*Macaca nemestrina*) (Seegal *et al.*, 1991). For these endpoints NDL-PCB were more potent than DL-PCB. These endpoints are thought to be related to modulation of motor activity, learning and memory, neural damage and abnormal brain development.

Endocrine effects

Both estrogenic activity and anti-estrogenic activity have been observed for NDL-PCB and hydroxylated metabolites of lower chlorinated NDL-PCB. Structure activity relationships were complex and differed from one *in vitro* assay to another (Connor, 1997). *In vivo* animal studies, using single congeners, showed estrogenic effects such as increases in uterine weight, and changes in oestrogen and progesterone receptors. DL-PCB however showed similar changes and were more potent: LOAEL in rats of 0.016 mg PCB126 /kg b.w per day versus a LOAEL of 8 mg PCB18 /kg b.w. per day for the same endpoint (Fisher *et al.,* 1998; Li and Hansen, 1995). NDL-PCB may also interfere with the binding of testosterone with the androgen receptor (Schrader and Cooke, 2003).

NDL- and DL-PCB interfere with thyroid hormone status through both distinct and similar mechanisms. NDL-PCB and hydroxy-PCB may bind to the hormone receptor and affect thyroid hormone status by inhibiting the binding of T4 to transthyretin, which is an important transport protein for both T4 and T3 in rats (Chauhan, 2000). Some hydroxy-PCB are potent inhibitors of thyroid hormone sulfation (Schuur, 1998). Furthermore, NDL-PCB can induce a UDP-glucuronosyltransferase which can enhance the elimination of T4 from the circulation via glucuronidation (Hood and Klaassen, 2000).

Immune effects

Immunological effects of PCDD/PCDF and PCB include morphological changes in organs related to the immune system, as well as functional impairment of humoral- and cell-mediated immune responses. *In vitro* results indicate the existence of mechanisms of immunotoxic actions of PCB that are independent of the Ah receptor: reduced lipopolysaccharide induced proliferative response in splenocytes, reduced antibody secretion (Smithwick *et al.*, 2003) and impaired neutrophil function (Brown and Ganey, 1995). DL-PCB may disrupt the immune system also, but by different modes of action: disruption of the endothelial barrier function, activation of oxidative stress-sensitive signalling pathways, and induction of subsequent pro-inflammatory events (interleukin-6) (Hennig, 2002), indicating a possible role in the pathology of atherosclerosis and cardiovascular disease. *In vivo* immune defects included decreases in thymic weight, reduced B cell numbers, reduced cytotoxic T-lymphocyte response, and reductions in plaque forming cell response and IgM (Sargent *et al.,* 1991; Kerkvliet *et al.,* 1990, Harper *et al.,* 1995; Arnold *et al.,* 1999). From the data following systemic administration by Leece et a. (1987), Biegel et al. (1989) and Harper et al. (1995) as presented in Annex 2, it can be concluded that the NDL-PCB tested (PCB 153, 170, 180) are less potent *in vivo* than DL-PCB.

10. Human data

Current epidemiological evidence provides observational data on the adverse health effects of exposure to technical or environmental PCB mixtures in occupational settings, due to

accidents, or caused by food contamination. Most of the epidemiological studies do not differentiate between DL- and NDL-PCB, and when they do, congener exposures are highly correlated, thereby complicating causal inferences.

10.1 Observations in adults

Cancer

Mortality studies of occupational cohorts have in some cases reported excess rates from cancers of the liver, gall bladder, biliary tract and gastrointestinal tract and malignant melanoma in capacitor manufacturing workers and electrical utility workers exposed to various technical PCB mixtures (Brown, 1987; Sinks *et al.*, 1992; Tironi *et al.*, 1996; Loomis *et al.*, 1997; Gustavsson and Hogstedt, 1997). Some studies included a fairly large number of subjects, but relatively few of them were employed for periods longer than 10 years, and the duration of follow-up was limited. Overall these epidemiological studies provided only limited support for human carcinogenicity as was also concluded by ATSDR (2000).

Many studies have focused on breast cancer, but most did not reveal any significant association with PCB concentrations in blood (Moysich *et al.,* 2002). One case-control study suggested that a PCB-associated breast cancer risk was limited to women with a mutation in a metabolising enzyme (Moysich *et al.,* 1998). A significant association between PCB concentrations in adipose tissue and non-Hodgkin's lymphoma was reported in another study (Hardell *et al.*, 1996). Most studies used samples obtained at the time of diagnosis for PCB analysis. However, one study on testicular cancer found that mothers of the patients had an increased PCB body burden (Hardell *et al.,* 2003).

Reproductive system

Information is available on the effects of PCB-containing mixtures on human reproduction from studies of people exposed via the general environment: consumption of contaminated rice oil in the Yusho and Yu-Cheng poisoning incidents, consumption of contaminated fish, and occupational exposures. Menstrual irregularities (Kusuda, 1971), miscarriages (Gerhard *et al*., 1988), shorter length in menstrual cycle (Mendola *et al.*, 1997) and spontaneous foetal death (Mendola *et al.*, 1995), were all reported to be associated with elevated exposure.

In regard to male reproductive functions, some studies reported a PCB-associated risk of infertility (Pines *et al.*, 1987) or decrease in sperm motility in infertile men (Bush *et al*., 1986), whereas sperm counts, fertility and testicular examinations were considered normal following occupational exposure to technical PCB mixtures (Emmett *et al*., 1988a, 1988b).

Decreased numbers of male births relative to all births were documented in couples exposed to TCDD in Seveso (Mocarelli *et al.*, 2000) whereas the findings of most studies of human populations exposed to PCB in different settings are equivocal. A recent study of subjects

exposed to environmental PCB from eating Great Lakes fish may indicate that maternal exposure to PCB may decrease the sex ratio (number of boys/number of girls) of offspring, but that paternal exposure to PCB could possibly have the opposite effect (Weisskopf *et al.*, 2003).

Nervous system function

Workers exposed to technical PCB mixtures reported a variety of neurological symptoms, but routine medical examination of these workers did not document any obvious dysfunction (Emmett *et al.*, 1988a; Fischbein *et al.*, 1979; Smith *et al.*, 1982). Neurological examination of Yusho and Yu-Cheng victims showed both reduced motor and sensory nerve conduction velocities (Chen *et al.*, 1985; Chia and Chu 1984, 1985; Kuroiwa *et al.*, 1969), but it is unclear if this can be attributed to PCB.

In 180 Michigan residents, 101 of whom had eaten contaminated Great Lakes fish in the past, limited evidence was found for deficits in learning and memory associated with dietary exposure to environmental PCB and/or DDE (Schantz *et al.*, 2001).

Chemical analyses of brain tissue from deceased patients with Parkinson's disease, and from controls, showed that NDL-PCB congeners reached higher concentrations in affected brain tissue of patients than in age-matched controls (Corrigan *et al.,* 1998). One preliminary report (Seegal, 2004) suggested an excess occurrence of Parkinson's disease in former capacitor production workers.

Thyroid gland

Exposure to technical PCB mixtures was reported to be associated with an increased thyroid gland volume as reported in workers at a PCB production facility and nearby residents as compared to subjects from less polluted areas (Langer *et al.*, 1998; 2003). An elevated odds ratio for goitre has also been found among the Yu-Cheng cohort (Guo *et al.*, 1999). Although serum concentrations of thyroid hormones were mostly within normal ranges, exposed workers and nearby residents had an elevated prevalence of antibodies against thyroid peroxidase (Langer *et al.,* 2003, 2005).

Cardiovascular system

Occupational cohort studies suggest no obvious effects of PCB on cardiovascular function (ATSDR, 2000). Increased systolic and diastolic blood pressures in a general population showed significant associations with serum PCB concentrations (Kreiss *et al.*, 1981) but the causative role of PCB remains uncertain.

PCB may interfere with lipid metabolism (Tokunaga & Kataoka, 2003; Grandjean & Weihe, 2003), thereby changing lipid and lipoprotein patterns toward a higher cardiovascular risk profile (Bell *et al.*, 1994; Lind *et al.*, 2004).

10.2 Observations in infants and children

Perinatal growth and early postnatal development

Several environmental studies have indicated decreased birth weight and early postnatal growth as possible indicators of adverse developmental effects of mixtures containing PCB. Some studies reported significant negative associations between anthropometric measures at birth (and at early ages) and exposure to PCB (Fein *et al*., 1984; Jacobson *et al*., 1990a b; Rylander *et al*., 1998; Hertz-Picciotto *et al.*, 2005), others found equivocal or no-significant results (Sauer *et al*., 1994; Patandin *et al*., 1998; Vartiainen *et al*., 1998; Grandjean *et al*., 2001a; Longnecker *et al.*, 2005). The wide range of results may reflect the different degree of controlling for confounders and/or different ways of measuring exposure.

In women occupationally exposed to technical PCB mixtures through the manufacture of capacitors, Taylor *et al.* (1989) found a significant association between the increased PCB exposure and decreased birth weight and gestational age. Similar findings were reported following high-level exposure to PCB and related chemicals during the Yusho and Yu-Cheng poisoning incidents (Funatsu *et al.*, 1971; Lan *et al.*, 1987; Rogan 1989; Yamaguchi *et al.*, 1971).

In regard to postnatal growth, the Dutch study (Patandin *et al.,* 1998) found no significant association with PCB exposure with growth up to age 42 months. In a US study, prenatal PCB exposure was associated with increased height and weight at age five years in girls (Hertz-Picciotto *et al.,* 2005). However, several confounders may have affected these associations. The tendency towards lower body weight when a child had been breastfed for a longer time (Dewey *et al.,* 1995) was replicated in a prospective cohort study in the Faroe Islands, but the duration of breastfeeding as such was found to be an unimportant predictor of growth. Reduced body size was primarily associated with the calculated transfer of contaminants via human milk (Grandjean *et al*., 2003).

Nervous system development

Two mass poisoning events in Japan in 1968 (Yusho) and Taiwan in 1979 (Yu-Cheng) led to the accidental exposure of between one and two thousand adults to high levels of PCB (and other halogenated organic pollutants) from contaminated rice oil. Lower IQ scores, increased behavioural disorders and activity levels, and more frequent behavioural disorders were reported in children of exposed mothers, but there was no correlation between the degree of deficit and the PCB-levels of the mothers (Schantz, 1996).

Subsequent epidemiological studies on developmental adversity were conducted in the US and in Europe (Table 17). In the North Carolina study (Rogan *et al*., 1986) mother and infant pairs were recruited from the general population. Hyporeflexia, hypotonicity and delayed motor development up to 24 months postnatally were related to the prenatal PCB body burden of the mothers as indexed by total PCB in early milk samples. Mental or psychomotor development was not affected at any age.

In the Michigan study, total PCB concentrations were measured in maternal and umbilical cord serum and in maternal milk from breastfeeding mothers. Visual Recognition Memory at seven months was negatively related to total PCB levels, and at four years of age this was also true for memory performance. At 11 years of age the IQ score exhibited a negative association with a PCB exposure index based on all analyses performed (Jacobson and Jacobson, 1996).

In the ongoing Oswego-study[15] (Darvill *et al*., 2000; Stewart *et al*., 2000; 2003) infants and children were studied from birth to 54 months of age. At 6, 12 and 38 months of age negative associations with perinatal PCB were found for different neurodevelopmental outcomes although these were no longer evident at 54 months.

Table 17: Measured or estimated serum levels of PCB 153 in studies of PCB-associated effects on neurodevelopment in children (modified from Longnecker *et al*., 2003)

Reference	**Study area**	**Years of sample collection**	**PCB 153 (ng/g lipid) median (5^{th} and 95^{th} percentiles)**
Rogan *et al*., 1986	US North Carolina	1978-1982	80 (40, 170)
Jacobson & Jacobson, 1996	US Michigan	1980-1981	120 (30, 280)
Patandin *et al*., 1999	Netherlands (Rotter-dam/Groningen	1990-1992	100 (50, 200)
Darvill *et al*., 2000	US New York (Oswego)	1991-1994	40 (10, 120)
Walkowiak *et al*., 2001	Germany (Düsseldorf)	1993-1995	140 (50, 220)
Steuerwald *et al*., 2000	Denmark (Faroe Islands)	1994-1995	450* (140, 1430)

*) level influenced by the high proportion of traditional marine food in the diet

In the Dutch study (Huisman *et al*., 1995; Koopman-Esseboom *et al*., 1994b) 200 healthy mother-infant pairs were recruited both in Groningen and Rotterdam. Half of them were breastfeeding, the other half used formula feeding. Four PCB-congeners (118, 138, 153, and 180) were measured in maternal and cord plasma, as well as additional PCB congeners and a number of PCDD/PCDF in early breast milk samples. Negative associations were reported

[15] US New York

between milk levels of PCDD/PCDF and PCB (NDL- as well as DL-PCB) and neurological status (two weeks, seven and 18 months), and psychomotor development (three and seven months).

In the joint European study, which also included the Dutch cohort at 42 and 72 months of age, two additional cohorts each comprising about 170 healthy mother-infant pairs were formed, namely a Danish cohort from the Faroe Islands (Steuerwald *et al*., 2000) and a German cohort from Düsseldorf (Winneke *et al*., 1998; Walkowiak *et al*., 2001). An association was found between PCB concentrations and mental development at 30 months for the German and at 42 months in both the Dutch (Patandin *et al*., 1999) and German cohorts. Upon reassessment between 72 and 77 months of most of the participants, no statistically significant developmental delay was observed in either the Dutch or German cohort (Vreugdenhil *et al*., 2002; Winneke *et al*., 2005). However, in the Dutch study negative PCB-associations were still reported for socially disadvantaged mothers.

Re-examination of the Rotterdam part of the Dutch cohort at age nine years, revealed that prenatal PCB exposure was associated with longer response times, greater variability, and lower scores on an executive function test (Vreugdenhil *et al.*, 2004a). The latter also appeared negatively affected by lactational exposure to PCBs, while breastfeeding was associated with better scores. Likewise, the latencies on event-related potentials of the brain were longer at higher PCB exposure levels, but breastfeeding was associated with a decrease (Vreugdenhil *et al.*, 2004b). These results suggest that the neurobehavioural manifestations reported to be associated with PCB exposure are likely to be permanent, but that the appearance may change during development.

Thyroid gland

In the Dutch study, increased PCB exposures were associated with reduced T3 and T4 in the infants at age two weeks and three months, while TSH was increased (Koopman-Esseboom *et al.*, 1994a). These findings are in agreement with PCB-mediated toxicity to thyroid function, although the outcome of several other studies has not produced unequivocal support (Fiolet *et al.*, 1997; Longnecker *et al.*, 2000; Nagayama *et al.*, 1998; Osius *et al.*, 1999; Steuerwald *et al.*, 2000; Pluim *et al.*, 1993; Weipert, 1999).

Immune functions

In children whose mothers had consumed contaminated Great Lakes fish, the number of infectious illnesses (colds, earaches, and/or flu symptoms) during the first four months of life was positively correlated with maternal serum PCB levels (Smith, 1984). Likewise, associations were reported between risk of acute otitis media and increasing exposure to PCB and other organochlorine compounds during the first year of life in infants of Inuit women (Dewailly *et al*., 2000).

In a Dutch study (Weisglas-Kuperus *et al.*, 1995) changes were found in lymphocyte T cell subpopulations in infants, but no increased incidence of infections (otitis media, rhinitis, bronchitis, or tonsillitis) or decreased concentrations of antibodies to childhood vaccines (mumps, measles, or rubella), during the first 18 months of life. However, at 42 months of age, the current PCB body burden was associated with a higher prevalence of recurrent middle-ear infections and of chicken pox, and a lower prevalence of allergic reactions (Weisglas-Kuperus *et al.*, 2000). In further follow-up studies at school age, a higher postnatal PCB exposure through lactation was significantly associated with a greater prevalence of recurrent middle ear infections (Weisglas-Kuperus *et al.*, 2004).

In a Faroese birth cohort (Heilmann *et al.*, 2003) antibody responses to childhood vaccination were measured. The anti-diphtheria toxoid antibody showed a significant decrease at higher levels of PCB exposure, whereas the correlation between PCB exposure and anti-tetanus toxoid antibody concentrations tended to be weaker.

In utero exposure to PCB from heat-degraded transformer oil in the Yu-Cheng incident was associated with increased frequencies of childhood infections, such as middle ear and respiratory tract infections. These observations were linked to reduced immune functions as indicated by decreased concentrations of immunoglobulin and by lymphocyte subset aberrations in exposed infants (Chang *et al.*, 1981).

Benchmark dose calculations

Two sets of benchmark dose (BMD) calculations are available. One on neurobehavioural effects, the other on immunotoxic effects, both in regard to children exposed perinatally. In both cases, the dose was expressed in terms of lipid-based PCB concentrations in biological samples (serum and milk). The Michigan data included four cognitive outcomes. The BMDs (5%) were similar for these four outcomes and varied between 0.94 and 1.05 µg total PCB/g lipid. The lower 95% confidence limit of the BMDs (BMDLs) were between 0.63 and 0.71 µg/g lipid (Jacobson *et al*., 2002).

In the Faroes study, PCB measurements were available from three sets of samples. Outcome variables were the concentrations of specific antibodies to diphtheria and tetanus as indicators of immunotoxic effects. The BMD (5%) for the various dose-response relationships varied between 2.3 and 9.0 µg total PCB/g lipid, and the BMDLs, were between 1.2 and 3.0 µg/g lipid (Grandjean, 2003).

11. Risk Characterisation

Exposure to NDL-PCB

It is estimated that more than 90% of the NDL-PCB exposure in the general population is via food. Average daily dietary intakes of total NDL-PCB by adults in most European countries where recent intake studies are available are estimated to be in the range of 10-45 ng/kg b.w. per day. Limited data on young children (birth to six years of age) indicated an average intake, breastfeeding excluded, of indicator NDL-PCB of 13.5-25 ng/kg b.w. per day. This corresponds to 27-50 ng/kg b.w. per day for total NDL-PCB, based on the finding that the six indicator PCB represent approximately 50% of total NDL-PCB in food. The Panel noted that, because of the higher food consumption in relation to their body weight, intake by young children expressed on a bodyweight basis is usually higher than for adults.

In specific subpopulations with high dietary exposure such as fisherman from the Baltic (east cost of Sweden), the average daily intake from fish of the sum of the six NDL-PCB could be around 40 ng/kg b.w., corresponding to an intake of total NDL-PCB of 80-100 ng/kg b.w. per day. High NDL-PCB exposure is also observed in specific populations of humans such as at the Faroe Islands representing individuals with high intake of pilot whale blubber and people in eastern Slovakia being exposed via food originating from a PCB contaminated area.

Breastfed infants are a special group with high intake of NDL-PCB. From the results of the most recent WHO exposure study (see 6.5.1.2), a mean intake of about 1,600 ng/kg b.w. per day (range: 230-7,300 ng/kg b.w. per day) can be calculated for total NDL-PCB. Thus, the exposure of infants to NDL-PCB (and DL-PCB) through human milk is about two orders of magnitude higher than the average daily intake by adults. The Panel noted, however, that levels of PCB in food and consequently also in human milk have been declining over the last decades.

Additional direct exposure to NDL-PCB might come from air, dust and soil. In contrast to food, the more volatile lower chlorinated congeners, such as PCB 28, 31, 44, 49, and 52 dominate the PCB composition of air. Many of these congeners are more rapidly metabolised and accumulate to a lesser extent than the congeners more commonly found in food. The PCB composition in soil often resembles more the commercial mixtures deposited or spilled.

Usually NDL-PCB from air (ambient, indoor), dust and soil contribute only a few percent to the body burden of NDL-PCB. However, depending on the source of contamination, situations exist where a contribution from indoor air, particularly of the lower chlorinated congeners, could be considerable. Therefore, the health impact of the potential combined exposures from food, air, dust and soil should not only take into account the different exposure scenarios, but also the potential different compositions of the PCB mixtures concerned.

Effects in animals of technical PCB mixtures

A large amount of data is available on the toxic effects of technical PCB mixtures in laboratory animals. These data are not considered suitable to derive a toxicological health based guidance value for NDL-PCB, as information is lacking on the exact chemical composition of the mixtures used, especially with respect to the levels of dioxin-like constituents and contaminants. A detailed analysis of non-cancer endpoints was limited to those studies, which reported parallel experiments with mixtures containing clearly different portions of dioxin-like constituents. It was found that most, if not all, of the hepatotoxic effects seen mainly in female rats with technical PCB mixtures could be explained by the dioxin-like compounds in the mixtures. For effects on thyroid hormone homeostasis, a similar analysis revealed that part, but not all, of the decline in blood thyroxine levels observed after treatment of rats with technical PCB mixtures was due to the dioxin-like part of the mixtures.

Carcinogenicity studies in rats with technical PCB mixtures revealed a strong correlation between the number of animals with neoplasms and the doses of dioxin-like constituents of the mixture, expressed as 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents (WHO-TEQ). This was true both for liver neoplasms observed in female rats and for thyroid neoplasms in male rats. A comparison with cancer data obtained from chronic exposure of rats to TCDD showed a very similar dose-response relationship for liver neoplasms. These results indicate that it is mainly the portion of dioxin-like components in technical PCB mixtures that is responsible for the carcinogenicity of these mixtures in rats.

Overall, these analyses indicate that effects in both chronic toxicity and carcinogenicity studies of technical mixtures in experimental animals were mainly due to dioxin-like constituents in these mixtures. Therefore, the Panel concluded that the studies with commercial mixtures should not be used in the evaluation of NDL-PCB.

Effects in animals of individual NDL-PCB congeners

The results of the available toxicological studies that have used administration of individual NDL-PCB congeners, and the respective NOAELs and/or LOAELs are summarised in Table 18. The main adverse effects reported in laboratory animals following exposure to individual NDL-PCB were effects on the thyroid, liver, brain biochemistry, immunotoxicity, oestrogenicity, and reproductive and neurodevelopmental effects. The latter effects are particularly found in the offspring of rodents following *in utero* exposure.

In acute and subacute rodent studies the NOAELs for the individual NDL-PCB tested (PCB 18, 28, 47, 52, 101, 110, 153) for reproductive and developmental effects, and effects on oestrogenicity, the thyroids, the immune system and the developing nervous system in rats, ranged from 1,000 to >50,000 µg/kg b.w.

Significantly lower NOAELs for effects on liver and thyroid have been reported for the few individual NDL-PCB (PCB 28, 128, and 153) that have been tested in 90-day rat studies. These NOAELs were in the range of 30-40 µg/kg b.w. per day (PCB 28: 36 µg/kg b.w. per day; PCB 128: 43 µg/kg b.w. per day; PCB 153: 34 µg/kg b.w. per day). The corresponding LOAELs were 10 times higher.

No long-term studies on chronic toxicity and carcinogenicity have been performed so far for any individual NDL-PCB with the exception of a two-year toxicity and carcinogenicity study with PCB 153 in female Harlan Sprague-Dawley rats (draft abstract from the National Toxicology Program (NTP, 2005)). No compound-related increase in tumour incidence was reported. The NOAEL for hepatocyte hypertrophy, diffuse fatty changes in the liver, and minimal to mild follicular cell hypertrophy of the thyroid gland was approximately 70 µg/kg b.w. per day. The LOAEL was approximately 210 µg/kg b.w. per day. Thus, the NOAEL for PCB 153 that can be extracted from this draft report is higher than the NOAEL from the 90-day study.

The Panel noted that effects such as oestrogenicity and effects on the thyroid could partly be due to the formation of hydroxy-PCB or methylsulfonyl-PCB metabolites. However, such metabolites are not specific for NDL-PCB, but could also be formed from DL-PCB.

Impact of impurities of the NDL-PCB tested on the outcome of the experimental studies

The effects of individual NDL-PCB on liver and thyroid in the rat are similar to those seen after administration of PCDD, PCDF and DL-PCB. Induction of liver microsomal EROD activity was seen in groups of rats treated with PCB 28, PCB 128, and PCB 153 and a reduction in liver vitamin A was seen with high doses of PCB 128 and 153, but not PCB 28. These observations and the slightly higher sensitivity of females than males for liver toxicity in all three 90 day studies with NDL-PCB, raise concern with respect to a possible contamination of the test preparations, especially for PCB 128 and 153, with dioxin-like compounds. It is known that PCB 153 can be contaminated with 1,2,3,7,8-PeCDF (Moron *et al*. 1973; Hemming *et al*., 1993). Therefore, the effects on liver and thyroid may be in part or even mainly due to dioxin-like compounds. For the DL-PCB tested (PCB 77, 105, and 118, and 126) in comparable 90-day rat toxicity studies, NOAELs of 8.7, 3.9, 17, and 0.01 µg/kg b.w. per day respectively, were established for effects on the liver and thyroid (see Annex II). Analysis of the toxicological data performed by the Panel suggests that liver toxicity of Aroclors was mainly due to the dioxin-like constituents of the mixtures, such as DL-PCB and PCDF. For changes in serum thyroxine in mice and increases in relative thyroid weight in rats, a contribution of dioxin-like components was also evident.

Since several PCDD, PCDF, and PCB 126 were shown to be about three orders of magnitude more potent as liver or thyroid toxicants than the NDL-PCB tested, contamination of NDL-

PCB with 0.1% or less of potent dioxin-like contaminants would be sufficient to explain the observed adverse effects.

Effects in humans of exposure to technical or environmental PCB mixtures

Current epidemiological data indicate that adverse health effects might be associated with PCB resulting from occupational exposure, accidental or environmental food contamination.

There have been reports that occupational exposure to technical PCB mixtures are associated with an increased risk of cancer of the digestive system and possibly other sites. Some studies have suggested that environmental PCB exposure may play a role in the development of breast cancer, although perhaps only in certain vulnerable subgroups. Among non-cancer effects reported to be associated with environmental PCB exposure, adverse reproductive outcomes, delayed neurodevelopment and impairment of the developing immune system are considered to be the most important. The epidemiological studies however do not allow differentiation between the effects caused by NDL-PCB and DL-PCB, and PCDD/PCDF.

Substantial amounts of PCB are transferred to the infant from human milk, and limited evidence suggests that such postnatal transfer may be associated with neurodevelopmental deficit in young children. The existing epidemiological studies however do not allow an estimation of the toxicity, whether prenatal or postnatal, that can specifically be attributed to the NDL-PCB.

Two sets of benchmark dose (BMD) calculations have been reported, for the hazard characterisation of environmental mixtures containing NDL-PCB and DL-PCB, one on neurobehavioural effects, and one on immunotoxic effects. Both relate to adverse outcomes in children exposed perinatally. In both cases, the dose was expressed in terms of lipid-based PCB concentrations in biological samples from the mothers (serum and milk). The BMDL values were about 1 μg total PCB/g lipid.

11.1 Human health risk characterisation of NDL-PCB exposure

The Panel noted that the comprehensive toxicological database on health effects of technical PCB mixtures was not suitable for the separate assessment of NDL-PCB, and that the human data on exposure to environmental mixtures containing PCB did also not allow for distinguishing between effects of NDL- and DL-PCB and PCDD/PCDF either. Therefore, in its assessment the Panel concentrated on the toxicological information available for individual NDL-PCB congeners. Although the absence of mutagenicity indicates that a threshold approach is appropriate for the hazard characterisation, the toxicological database was considered to be too limited to allow the establishment of a health based guidance value for NDL-PCB. The Panel therefore decided to perform its health risk characterisation on the basis of a margin of exposure approach. The Panel also conducted the calculations based on lipid concentrations.

As a provisional approach to the assessment of the effects of exposure to NDL-PCB, it may be assumed that all the NDL-PCB in food have toxicological potencies similar to PCB 28, 128, and 153, and that the effects for the individual PCB congeners are additive. An overall NOAEL for NDL-PCB of 30-40 µg/kg b.w. per day as found in the 90-day rat studies, would provide a margin of exposure ranging from 800 to 4,000 when compared with the estimated daily intake of total NDL-PCB by humans (10-45 ng/kg b.w. per day). Such a margin of exposure would appear to be comfortable for most compounds, even when based on a 90-day study. However, for compounds that accumulate in the body, such as the NDL-PCB, the Panel considered that, by analogy to the risk assessments of PCDD, PCDF and DL-PCB performed by the SCF in 2000 and 2001 (EC, 2000, 2001), the body burden (BB) in experimental animals and humans would be more appropriate dose metrics for the assessment of NDL-PCB. However, the Panel also conduced calculations on the basis of lipid concentrations.

The Panel noted that the NDL-PCB found in human milk (Table 8 in chapter 6.3) are the congeners that accumulate in the human body: PCB 18, 28, 33, 37, 52, 60, 66, 74, 99, 101, 110, 128, 138, 141, 153, 170, 180, 183, 187, 194, 206, and 209. The median total concentration of all the NDL-PCB measured in human milk was about 240 ng/g fat, which would correspond to an estimated median human body burden of about 48 µg/kg b.w., assuming 20% fat content in the human body. The median total concentration of all the DL-PCB measured in human milk was about 27 ng/g fat, which would correspond to an estimated median human body burden of about 5.4 µg/kg b.w., assuming 20% fat content in the human body.

The estimated median human BB was also calculated for each congener from the median lipid-based contents reported for human milk (see Table 18). Table 18 also includes the NOAELs and/or LOAELs for various toxicological effects, derived from the experimental studies on individual NDL-PCB as well as the corresponding estimated animal body burdens, NOAEL BB and/or LOAEL BB. These body burdens were estimated as follows: In the case of the 90-day feeding studies on PCB 28, 128, and 153 the body burdens were calculated from the reported measured accumulated concentrations of the respective NDL-PCB in the fat tissue of the rats, assuming that rats contained 10% fat as reported by Geyer *et al.* (1990). From the studies where only a single dose was administered, this dose was considered equal to the body burden, assuming 100% bioavailability, irrespective of the route of administration. In the studies using more than one day of administration, the body burden at study termination was estimated assuming 100% bioavailability and one compartment, first order kinetics, using the half-lives in rats reported for individual NDL-PCB congeners by Tanabe *et al.* (1981).

Finally, a comparison is given of the estimated body burden at the NOAEL or LOAEL in animals with the estimated median human body burden, expressed as the margin of body burden (MoBB) by dividing the estimated animal body burdens with the estimated median human body burden.

Table 18. Comparison of animal NOAEL/LOAEL body burden (BB) for NDL-PCB tested *in vivo* with estimated human body burdens of NDL-PCB, expressed as margin of body burden (MoBB).

PCB No	Human BB[a)] (µg/kg)	Effect/Reference	NOAEL (µg/kg/day)	NOAEL BB (µg/kg)	LOAEL (µg/kg/day)	LOAEL BB (µg/kg)	MoBB[b)] NOAEL	MoBB[b)] LOAEL
18	0.018	Increased uterus weight in immature rats (1)	–	–	8,000 i.p.	12,000[c)]	–	670,000
		Serum thyroxine in weanling rats (1)	128,000 i.p.	190,000[c)]	–	–	$>10^7$	–
28	0.44	90-day toxicity, rat (2)	36 p.o.	400[d)]	360 p.o.	4,000[d)]	900	9,000
		Repro rat, decreased body weight and spatial learning in female offspring (3)	8,000 p.o	14,000[c)]	32,000 p.o	56,000[c)]	32,000	127,000
33	0.012	–						
37	0.0025	–						
47	No representative data for human milk	Repro, rat, decreased dopamine in offspring (4)	1,000 p.o.	4,200[c)]	10,000 p.o.	42,000[c)]	–	–
		Repro rat, sexual behaviour (5)	1,000 i.p.	4,200[c)]	20,000	84,000[c)]	–	–
		Thyroid, weanling rat (6)	–	–	30,000 i.p.	48,000[c)]	–	–
52	0.064	Increased uterus weight in immature rats (7)	–	–	14,000 i.p.	20,000[c)]	–	310,000
		Immunotoxicity, rat (8)	1,000 p.o	5,000[c)]	–	–	78,000	–
60	0.082	–						
66	0.24	–						
74	1.36	–						
95	No representative data for human milk	Reproduction, rat (9)	32,000 p.o.	64,000[c)]	–	–	–	–
		Reproduction, behaviour in offspring, rat (10)	–	–	8,000 p.o.	16,000[c)]	–	–
		Thyroid, rat (14)	4,000 i.p.	7,000[c)]	8,000 i.p.	14,000[c)]	–	–
99	1.24	–						
101	0.138	Thyroid, rat (11, 12)	–	–	16,000 i.p.	30,000[c)]	–	217,000
110	0.042	Oestrogenicity and thyroid hormones, rat (13)	4,000 i.p.	8,000[c)]	16,000 i.p.	32,000[c)]	190,000	762,000
114	0.106	–						
128	0.126	90 day toxicity, rat (14)	42 p.o.	800[d)]	420 p.o.	7,000[d)]	6,300	50,000
138	11.1	–						
141	0.034	–						

PCB No	Human BB[a] (µg/kg)	Effect/Reference	NOAEL (µg/kg/day)	NOAEL BB (µg/kg)	LOAEL (µg/kg/day)	LOAEL BB (µg/kg)	MoBB[b] NOAEL	MoBB[b] LOAEL
153	13.56	90 day toxicity, rat (15)	34 p.o.	1,200 [d]	340	9,000 [d]	85	660
		Reproduction, mouse (16)	125,000	125,000 [c]	250,000	250,000 [c]	9,200	18,000
		Oestrogenicity, rat (17)	11,000 i.p.	22,000 [c]	25,000 i.p.	50,000 [c]	1,600	3,700
		Thyroid, rat offspring (3)	–	–	16,000 p.o.	32,000 [c]	–	2,300
		Learning, rat offspring (18)	16,000 po.	32,000 [c]	32,000	64,000 [c]	2,300	4,700
		Hyperactivity, rat offspring (19)	–	–	5,000	50,000 [c]	–	3,700
		Immunotoxicity, mouse (20)	100,000	100,000 [e]	–	–	7,400	–
170	3.58	Immunotoxicity, mice (21)	50,000 i.p.	50,000 [e]	100,000 i.p	100,000 [e]	14,000	28,000
180	9.16	Immunotoxicity, mice (21)	50,000 i.p	50,000 [e]	100,000 i.p	100,000 [e]	5,500	11,000
183	1.2	–						
187	1.92	–						
194	0.64	–						
206	0.06	Immunotox, mice (22)	4,600 i.p.	4,600 [e]	11,500 i.p.	11,500 [e]	77,000	192,000
209	0.028	Immunotox, mice (22)	11,500 i.p.	11,500 [e]	46,000 i.p.	46,000 [e]	410,000	1,640,000

[a] Human body burdens calculated from the median PCB concentrations found in human milk (Table 8 in chapter 6.3) assuming 20% lipid in the human body.

[b] MoBB (Margin of body burdens) is calculated by dividing the estimated body burden in animals at the NOAEL or LOAEL with the calculated median human body burden

[c] The body burden at study termination was estimated assuming 100% bioavailability and one compartment, first order elimination kinetics, using the half-lives in rats reported for individual PCB by Tanabe *et al.* (1981).

[d] The body burdens were calculated from the reported measured accumulated concentrations of the respective NDL-PCB in the fat tissue of the rats. It was assumed that the rats contained 10% fat as reported by Geyer *et al.*, (1990).

[e] Single dose study. The dose was considered equal to the body burden, assuming 100% bioavailability, irrespective of the route of administration.

References 1-22: 1: Li and Hansen, 1995; 2: Chu *et al.*, 1996a; 3: Ness *et al.*, 1993 ; 4: Seegal *et al.*, 1997; 5: Wang *et al.*, 2002; 6: Saeed and Hansen, 1997; 7: Ecobichon and MacKenzie, 1974, 8: Sargent *et al.* 1991; 9: Schantz *et al.*, 1996; 10: Schantz *et al.*, 1997; 11: Khan *et al.*, 2002; 12: Khan and Hansen, 2003; 13: Li *et al.*, 1998; 14: Lecavalier *et al.*, 1997; 15: Chu *et al.*, 1996b; 16: Morrissey *et al.*, 1992; 17: Li *et al.*, 1994; 18: Schantz *et al.*, 1995; 19: Holene *et al.*, 1998; 20: Kerkvliet *et al.*, 1990; 21: Harper *et al.*, 1995; 22: Harper *et al.*, 1993.

For the NOAELs in the 90-day subchronic rat studies for PCB 28 (36 µg/kg b.w. per day), PCB 128 (43 µg/kg b.w. per day) and PCB 153 (34 µg/kg b.w. per day) for effects on liver and/or thyroid, and using the reported accumulated concentrations of the respective NDL-PCB in the fat tissue, corresponding BB of 400, 800 and 1200 µg/kg b.w. respectively, were calculated. Comparison of these BB with the estimated human BB for these congeners results in NOAEL MoBBs of 900, 6,300, and 85 for PCB 28, 128, and 153 respectively (Table 18). Although PCB 28, 128, and 153 showed similar potencies in the 90-day toxicity studies, PCB 153 has by far the lowest MoBB due to its higher abundance in human tissues.

For the NDL-PCB tested (PCB 18, 28, 52, 101, 110, 153) for reproductive and developmental effects, oestrogenicity, thyroid effects and effects on the immune system and the developing nervous system in rats, the NOAEL-MoBBs were in most cases higher than 1,000.

The Panel also considered neurobehavioral studies in newborn mice by Eriksson (see 8.1.3). In these studies a single oral dose was given to the pups by gavage at 10 days of age, because this day is within the critical period for exerting effects on brain development in the mouse. The corresponding critical period for exerting effects on brain development in humans however, is during fetal life in the last trimester of pregnancy and shortly after birth. Thus, if the NOAELs of 360-4100 µg/kg b.w. obtained in these studies have to be converted to the human situation, fetal body burdens of 360-4100 µg/kg b.w. have to be assumed. Studies on the relationship between maternal and fetal levels of PCB are not available in mice or rats. Studies on TCDD in rats (Hurst *et. al.* (2000a,b), however, indicate that at long term exposure the body burden of the dams is about 10 times higher than that of the foetus. Assuming similar kinetics for persistent PCB in humans would indicate that to obtain a similar situation in fetal life of humans as that of the neonatal exposure in mice would require much higher exposure levels than those of the 90 days studies mentioned above. Furthermore the relevance of high bolus dosing of postnatal pups to exposure of newborn infants via breastmilk is uncertain. Therefore the results of these neurobehavioral studies were not further considered in the risk characterization of NDL-PCB.

Evaluation based on animal studies on NDL-PCB

The most sensitive effects seen in studies with NDL-PCB in experimental animals are liver and thyroid toxicity. The NOAELs in 90-day rat studies were in the range of 30-40 µg/kg b.w. per day. The effects seen in these studies occurred at considerably lower dose levels than many other effects observed in studies of shorter duration with different NDL-PCB. However, when a comparison is made on the basis of estimated body burdens it appears that the NOAELs for all these effects are found at rather similar body burdens, ranging from about 400-1200 µg/kg b.w. or higher.

The Panel noted that the available toxicological database on NDL-PCB covered a wide range of the possible congeners present in food, and, considering that the LOAELs for the most sensitive effects were 10 times higher than the NOAELs, as a conservative approach the Panel chose an overall body burden of 500 µg/kg b.w. as a representative NOAEL BB (body burden at the NOAEL) for all individual NDL-PCB and for the sum of NDL-PCB occurring in human tissues. The median total concentration of all NDL-PCB measured in human milk was about 240 ng/g fat, which would, assuming 20% fat content in the human body, correspond to an estimated median human body burden of about 48 µg/kg b.w. Consequently a MoBB of about 10 can be calculated. The Panel noted that if this comparison had been based on lipid concentrations, this would have resulted in a margin of 20 between animals and humans.

It should be stressed that thyroid and liver toxicity in rats can also be observed after treatment with PCDD/F or DL-PCB. Since a number of these compounds exhibit relatively high potencies for these effects in rats (LOAEL in the range of 300 ng TEQ/kg b.w. per day), minor levels of potent dioxin-like contaminants (in the range of 0.1%) in the NDL-PCB test preparations might be sufficient to explain the effects observed. Thus, any estimate of a NOAEL for NDL-PCB is hampered by the uncertainty as to what extent the individual congeners were contaminated with PCDF and/or DL-PCB.

Evaluation based on human studies on environmental exposures

Benchmark dose (BMD) tissue concentrations in human milk or serum in the order of 1.0 µg PCB/g lipid (95% lower confidence limit) are reported to be associated with a 5% incidence in neurological and immune effects following perinatal exposure to PCB. This level is about four times higher than the median lipid based concentration of about 240 ng/g fat for all NDL-PCB measured in human milk. Assuming 20% fat in the human body this would correspond to a body burden of 200 µg/kg b.w., which is about four times higher than an estimated median human body burden in the general population of about 48 µg/kg b.w. for the measured NDL-PCB.

To convert the median human body burden of about 48 µg/kg NDL-PCB/kg b.w. at steady state into a daily intake[16], the Panel considered the limited data on bioavailability (chapter 7.1) and the reported half-lives for the most persistent congeners (Table 14) and assumed a bioavailability from food of 90% and an overall biological half-life of 10 years. Using these assumptions, an estimated intake of about 10 ng/kg b.w. per day of total NDL-PCB would be needed to achieve steady state at 48 µg/kg b.w. This median estimate is in the same order of magnitude as the current estimated intakes of 10-45 ng/kg b.w. per day and of the median intakes reported for adults by several European countries (Table 10).

[16] body burden (µg/kg b.w.) = intake (µg/kg b.w.) x (half life / ln2) x f (where f is the bioavailability factor)

It is possible that part or all of the effects that form the basis for the reported lower confidence limit of benchmark dose (BMDL), could be due to simultaneous exposure to dioxin-like compounds as well as other persistent organic compounds transferred to the child along with the NDL-PCB. According to the third WHO human milk study, see Tables 8 and 9, the total PCB concentration (all congeners, measured in ng/g fat) should be multiplied by 0.065 to calculate the total PCDD/F/PCB-TEQ concentration (in pg/g lipid). Assuming that the relative concentrations of all of these compounds are the same as in the epidemiological studies for which the PCB-based BMDL was calculated, then the above mentioned BMDL value of about 1 µg/g fat (total-PCB) would correspond to an approximate BMDL of 65 pg TEQ/g fat, corresponding to a steady state body burden at 13 ng TEQ/kg b.w. In comparison, the study from The Netherlands examining early neurodevelopmental effects and thyroid hormone status in infants after *in utero* exposure to PCDD/PCDF, DL-PCB, and NDL-PCB, used a similar figure for the classification into either a 'high exposure group' (above 63 ng total TEQ/kg fat in human milk) or a 'low exposure group (below 63 ng total TEQ/kg fat in human milk) (EC, 2000).

During the nursing period breastfed infants on a body weight basis may have daily intakes of NDL-PCB estimated to be about two orders of magnitude higher than the average adult intake. This elevated intake by the infants is related to the mother's long-term intake of NDL-PCB with food. The subtle effects that were reported in some studies of human infants were mainly associated with exposure to a mixture of NDL-PCB, DL-PCB, and PCDD/PCDF, and any causal role of NDL-PCB is unclear. The Panel noted that in many other studies of infants, breastfeeding was associated with beneficial effects, in spite of the contaminants present.

The Panel also took cognisance of the SCF Opinion on the Risk Assessment of Dioxins and Dioxin-like PCBs in Food (EC, 2000) and noted that the WHO Regional Office for Europe (WHO-EURO) has co-ordinated a comprehensive program on PCDD, PCDF and PCB since 1985. The efforts have been directed towards risk assessment of these compounds, in particular with respect to their presence in human milk. In 1987, WHO assessed the health risks for infants due to the presence of PCDD, PCDF, and PCB in human milk (WHO-EURO, 1988). Although only limited research had been carried out at that time, WHO concluded that there was no evidence that breastfeeding should not be recommended and it even promoted breastfeeding. In 1995, WHO reassessed the health risks to infants associated with perinatal exposure to PCDD, PCDF and PCB, because exposure assessments had revealed that concentrations of these compounds in human milk had shown a continuous decline, in some countries by up to 50%. The provisional conclusions were that the available evidence did not warrant altering the previous WHO recommendation for promotion/support of breastfeeding. However, because new clinical data had indicated subtle effects in offspring following perinatal exposure (Brouwer *et al.*, 1998a), continued and enhanced effort should be directed towards identifying and controlling sources of environmental input for these contaminants.

11.2 Health risk assessment for domestic animals

Only a few studies have been conducted with individual NDL-PCB congeners. In offspring of goats given PCB 153 in the diet (0.1 mg/kg b.w. per day), effects on sex hormones and on white blood cells were found. In mink fed PCB 136 and 153 (0.25 mg/kg b.w. per day) no reproductive effects were seen, but a slight decrease of brain dopamine levels was apparent. In rainbow trout the NOAEL for PCB 153 was between 0.04 and 0.4 mg/kg b.w. day.

In experimental studies of domestic animals with oral administration of technical PCB mixtures, reduced weight gain, effect on reproduction (particularly foetal mortality), immunological effects (immune function, histological effects on lymphoid tissues), liver and kidney toxicity, and behavioural effects dominate. Dietary PCB concentrations associated with observed effects range from 2-100 mg/kg (corresponding to 0.1-5 mg/kg b.w.). In most species the lowest observed adverse effect level of technical PCB is around 10 mg/kg diet. Mink is the most susceptible species and a 2 mg/kg diet of Aroclor 1254 (0.1 mg/kg b.w. per day) exerted pronounced effect on reproduction. No reproductive effects were induced by similar exposure to Aroclor 1242, 1221 or 1016, as well as PCB 136 and 153, suggesting that the dioxin-like compounds present in Aroclor 1254 might play an important role in the toxicity. In general no distinction could be made between effects caused by NDL-PCB or DL-PCB or PCDD/PCDF.

Results from studies in mink indicate that weathered mixtures of PCB are more toxic than the original technical mixtures.

To assess the risk for domestic animals, the Panel compared the effect concentrations in the experimental diet with the NDL-PCB concentration in animal feed. Following a conservative approach, the 90th percentile of the sum of six NDL-PCB in compound feed, 0.02 mg/kg feed was taken as the point of comparison. This figure corresponds to about 0.04 mg total NDL-PCB, which is more than two orders of magnitude below the concentrations causing effects in most domestic animals studied. Mink are usually given feed based on fish. The 90th percentile of the sum of the six NDL-PCB in fish and fish products is 0.067 mg/kg corresponding to 0.13 mg/kg total NDL-PCB. This is only about five times below the concentration of PCB in feed that produced pronounced effects on reproduction in mink.

11.3. Conclusion on the risk characterisation of NDL-PCB

The Panel noted that the comprehensive toxicological database on health effects of technical PCB mixtures and the human data on exposure to environmental mixtures containing PCB did not prove to be suitable for the assessment of NDL-PCB, because they were unable to distinguish between the effects of NDL-PCB, and DL-PCB and PCDD/PCDF.

As the toxicological database on effects of exposure to individual NDL-PCB was considered to be too limited to allow the establishment of a health based guidance value for NDL-PCB,

the Panel decided to perform its health risk characterisation on the basis of a margin of exposure approach

For compounds that accumulate in the body, such as the NDL-PCB, the Panel considered evaluations based on body burden (BB) calculations that are more appropriate than evaluations based on the external dose. The Panel therefore compared estimated body burdens at the NOAEL (or LOAEL) for different effects in animals with the estimated median human body burden derived from the most recent analyses of human milk. NOAEL or LOAEL "margin of body burdens" (MoBB) were calculated by dividing the estimated animal body burdens with the estimated median human body burden.

Based on the most sensitive effects (e.g. effects on liver and/or thyroid) in the rats the Panel chose an overall body burden of 500 µg /kg b.w. as a representative, conservative NOAEL BB (body burden at the NOAEL) for all individual NDL-PCB and for the sum of NDL-PCB that occurred in human tissue. Comparison with an estimated median human body burden for NDL-PCB of about 48 µg/kg b.w. resulted in a NOAEL MoBB of about 10.

The Panel noted that thyroid and liver toxicity in rats can also be observed after treatment with PCDD, PCDF, or DL-PCB. Thus, estimateing of a NOAEL for NDL-PCB is hampered by the uncertainty to what extent NDL-congeners were contaminated with potent PCDF and/or DL-PCB exhibiting the same effect. Therefore, the "true" NOAEL MoBB for NDL-PCB might be larger.

On the other hand it was recognized that the MoBB was calculated on the basis of the median concentrations of NDL-PCB in human milk, and that some populations in Europe may have considerably higher body burdens. The Panel therefore concluded that a continuing effort to lower the levels of NDL-PCB in food is warranted.

The Panel concluded that current background levels of NDL-PCB in animal feed are of no concern with respect to health effects in most domestic animals, with the possible exception of mink.

CONCLUSIONS

Due to their lipophilic properties and their long half-lives, PCB 138, 153 and 180 are the NDL-PCB congeners that accumulate most during transfer along the ecological food chains. Consequently, concentrations of these NDL-PCB congeners in feed and food samples of animal origin, particularly from carnivores and predatory fish, are higher than those in products of plant origin.

Regarding feed and feed components, fish oil, feeding stuffs for fish as well as fish and fishery products were identified as the products with the highest contamination.

In food samples the highest levels were found in fish oil, followed by eggs, meat and meat products, and milk and dairy products, which all show similar average levels. Depending on the fat content, certain fish species from specific fishing grounds contain high levels of NDL-PCB.

The sum of the six indicator PCB (PCB 28, 52, 101, 138, 153 and 180) comprises about half of the amount of total NDL-PCB present in feed and food. Therefore this sum of the six indicator PCB is considered an appropriate indicator for occurrence and human exposure to NDL-PCB.

Special analytical attention has to be paid to the determination of PCB 138, because this congener may co-elute with PCB 163 on non-polar GC columns. This might lead to significant overestimation of the true PCB 138 level.

The main route of human exposure to NDL-PCB is via food. Recent dietary intake studies indicate that for adults in most European countries the average daily intake of total NDL-PCB is in the range of 10-45 ng/kg b.w. For young children up to six years of age (breastfeeding excluded), daily intake values for total NDL-PCB are approximately 27-50 ng/kg b.w.

Based on data on levels of PCB in human milk samples from European countries a mean daily intake of the total NDL-PCB of approximately 1,600 ng/kg b.w. was estimated for exclusively breastfed infants. This exposure to NDL-PCB is about two orders of magnitude higher than that of adults.

In specific subpopulations such as Baltic Sea fishermen the daily intake of the sum of the six NDL-PCB from fish could be about 40 ng/kg b.w., corresponding to an intake of total NDL-PCB of about 80 ng/kg b.w. per day.

Exposure to NDL-PCB from air (ambient, indoor), dust and soil generally only contributes a few percent to the body burden of NDL-PCB. In buildings where PCB have been used indoor air PCB concentrations are often found to be considerably elevated. This results in increased exposure particularly to low-chlorinated PCB. It is however not always possible to detect significant increase in body burden of NDL-PCB as a result of this additional exposure.

Following exposure of farm animals, NDL-PCB will accumulate in meat, liver and particularly in fat tissues. NDL-PCB will be transferred into milk and eggs, and will reach a steady state following exposure for a period of several weeks. Current background levels of NDL-PCB in animal feed are of no concern with respect to health effects in most domestic animals, with the possible exception of mink.

PCB 138 and 153 show the highest carry-over into milk and eggs, in the order of 50-60%. In growing animals such as pigs, calves, and broilers but also in farmed fish, steady state is not reached before slaughter.

Due to the different sources of contamination, different places of origin of the feed and food commodities, as well as different production methods and circumstances, definite relationships between NDL-PCB and total TEQ are only found occasionally in specific well-defined contamination cases or in geographically defined sampling areas.

Usually, samples containing high levels of NDL-PCB will also contain high levels of DL-PCB and PCDD and PCDF. In these circumstances risk management measures to reduce DL-PCB TEQ and total TEQ levels, will probably also protect consumers from elevated NDL-PCB exposure. In specific situations, such as contamination with lower chlorinated technical PCB mixtures, where levels of NDL-PCB could be high, but TEQ levels could be low, measures to reduce total TEQ will not guarantee protection of the population against products with high levels of NDL-PCB.

Both NDL- and DL-PCB are metabolised to hydroxy-PCB, most of which are rapidly excreted, but a limited number of hydroxy-PCB congeners are retained in the blood bound to proteins. Hydroxy-PCB congeners are not transferred via the food, but are products of metabolism of the parent PCB congeners.

Some PCB with short half-lives form methylsulfonyl-PCB metabolites. Compared to hydroxy-PCB they are more lipophilic and are primarily found in liver and lung tissue. Metabolism in mammals (including humans), seems to be the most important origin of methylsulfonyl-PCB metabolites.

Experimental studies in domestic animals with technical PCB mixtures indicate that mink is the most susceptible domestic species, showing pronounced reproductive effects at 2 mg/kg diet of Aroclor 1254 (0.1 mg/kg b.w. per day). Studies in this species also indicate that weathered PCB mixtures are more toxic than technical PCB mixtures.

Studies using technical or reconstituted mixtures were not suitable for the evaluation of effects of NDL-PCB in laboratory animals, because in most instances no distinction could be made between effects caused by NDL-PCB and those caused by DL-PCB or PCDD/PCDF.

No data are available on the oral toxicity of the abundant NDL-PCB congeners PCB 138 and PCB 180.

Adverse effects, such as effects on the thyroid, liver, and immune and reproductive systems reported in laboratory animals following exposure to individual NDL-PCB congeners, are not specific for NDL-PCB but are also seen after exposure to PCDD, PCDF, and DL-PCB.

Results of *in vitro* and *in vivo* genotoxicity studies indicate that technical NDL-PCB mixtures are not mutagenic at gene or chromosome level. Some NDL-PCB congeners, in particular the lower chlorinated ones, caused DNA damage, probably resulting from the formation of reactive oxygen species.

Evaluation of cancer studies in rats with technical PCB mixtures, and comparison with data obtained with TCDD, indicate that the portion of dioxin-like components in technical PCB mixtures is mainly responsible for the carcinogenicity of these mixtures in rats.

Benchmark dose calculations have been based on human studies on developmental neurotoxicity and immunotoxicity after perinatal exposure to total DL and NDL-PCB. The 95% lower confidence limit (BMDL) of approximately 1 µg PCB/g lipid is only about four times higher than the current median concentration in human milk. However the existing epidemiological studies do not allow an estimation of the toxicity that may specifically be attributed to the NDL-PCB.

By comparing an overall body burden of 500 µg/kg b.w. at the NOAEL for the most sensitive effects in liver and thyroid in rats with an estimated median human body burden for total NDL-PCB of about 48 µg/kg b.w., a margin of body burdens (MoBB) was about 10. The MoBB was calculated on the basis of the median concentrations of NDL-PCB in human milk, and some populations in Europe may have considerably higher body burdens.

RECOMMENDATIONS

Most monitoring data on PCB required by the European Commission from the Member States are reported as compliant and non-compliant. In order to use these data for future risk assessment purposes, it would be valuable if actual levels were to be reported both on fat basis and also on a fresh weight basis.

Despite the large amount of PCB occurrence data originally submitted to the Comission as part of the EU recommended monitoring programme only a minor fraction could be used for this assessment. The shortcomings in the occurrence data demonstrate the need for improvement of the analytical methodologies for determination of NDL-PCB in feed, food and human samples. This particularly concerns harmonization of analytical requirements and performance criteria.

Availability of certified reference materials for relevant matrices, such as fish oil, dairy products or human serum is a valuable means for laboratories to optimise their analytical methodologies. Because such certified reference materials are sparse, it is recommended that such materials are prepared and made available to analytical laboratories.
Human samples from epidemiological studies should be collected and analysed by comparable techniques to facilitate comparison between similar outcomes assessed in

populations with different congener profiles. Emphasis should be placed on outcomes associated with NDL-PCB exposure during early life stages.

There is a need to study the contribution of exposure to NDL-PCB especially during early life stage to adverse health effects. Further studies on individual NDL-PCB should take into account contamination by dioxin-like compounds.

A continuing effort to lower the levels of NDL-PCB in food is warranted.

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