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Chlorinated biphenyls – Addendum for evaluation of a concentration corresponding to an assignment of Pregnancy Risk Group C

Assessment Values in Biological Material – Translation of the German version from 2019

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Keywords

Chlorinated biphenyls, chlorobiphenyls, chlordiphenyls, PCB, polychlorobiphenyls, polychlorodiphenyls, biological tolerance value, BAT value, pregnancy risk group

Abstract

In 2018 the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated the possibility to add the indication "prerequisite for Pregnancy Risk Group C" for chlorinated biphenyls [1336-36-3]. Chlorinated biphenyls are classified in Pregnancy Risk Group B because adhering to the biological tolerance value (BAT value) of 15 µg/l plasma for the sum of the indicator congeners PCB 28, PCB 52, PCB 101, PCB 138, PCB 153, PCB 180 cannot exclude a risk to the developing foetus. This classification was mainly based on developmental neurotoxicity and reduced birth weight in monkeys exposed to mixtures of chlorinated biphenyls. In this re-evaluation, numerous environmental epidemiological studies on developmental effects and birth weight and extensive reviews of these studies are taken into account. These studies show that the critical effect in humans is developmental neurotoxicity, for which a NOAEL of 3.5 µg/l plasma for the sum of the 6 indicator congeners can be derived.

Therefore, an internal exposure not higher than this concentration would be the prerequisite for an assignment to Pregnancy Risk Group C, which means that damage to the embryo or foetus is unlikely at this concentration.

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BAT (2015)	**ΣPCB 28, PCB 52, PCB 101, PCB 138, PCB 153, PCB 180**	**15 µg/l plasma**
	Sampling time: not fixed	
BAR (2011)	**PCB 28**	**0.02 µg/l plasma**
	PCB 52	**< 0.01 µg/l plasma**
	PCB 101	**< 0.01 µg/l plasma**
	Sampling time: not fixed	
MAK value (2015)	**0.003 mg/m³ I**[a)]	
Peak limitation (2015)	Category II, excursion factor 8	
Absorption through the skin (1969)	H	
Sensitization	–	
Carcinogenicity (2015)	Category 4	
Prenatal toxicity (2015)	Pregnancy Risk Group B[b)]	
Germ cell mutagenicity (2015)	Category 5	

[a)] (PCB 28 + PCB 52 + PCB 101 + PCB 138 + PCB 153 + PCB 180) × 5

[b)] For information on the prerequisite for Pregnancy Risk Group C, see "Evaluation"

1 Re-evaluation

Chlorinated biphenyls (PCBs) have been classified in Pregnancy Risk Group B since 2012/15 described in supplements of 2013 and 2016 (translated 2016, Hartwig and MAK Commission 2016 a), as the margin to the NOAEL (no observed adverse effect level) for developmental toxicity in monkeys is not sufficiently large with exposure at the MAK value. A BAT value of 15 µg/l plasma was derived for PCB indicator congeners (Rettenmeier et al. 2017).

The PCB body burden increases with each decade of life; over the last decades, however, the environmental burden has decreased. Dietary exposure is the main source of background exposure. As higher chlorinated biphenyls have significantly longer half-lives, these accumulate in the adipose tissue and can still be detected in the blood even after many years. The more volatile PCBs with a lower degree of chlorination are indicators for exposure via the air. In view of the additional dietary exposure and accumulation with age, the concentration in blood is better suited for determining the exposure than the concentration in air. If data for the body burden are available, it is important when advising pregnant women to know up to which plasma concentration damage to the foetus is not to be expected. This addendum assesses which plasma concentration would correspond to an assignment of Pregnancy Risk Group C, that is, up to which plasma concentration prenatal toxicity is unlikely.

Conversion factors

The PCB concentration in serum is equivalent to that in plasma. The concentration of total PCBs in plasma is about twice as high as the concentration in whole blood.

A mean plasma lipid content of 6.36 g/l (± 1.28 g/l) was determined by applying various calculation methods of the United States Centers for Disease Control and Prevention. The 95th percentile was 8.67 g/l or 8.61 g/l. The Institut National de Santé Publique du Quebec (Carrier et al. 2007) calculated PCBs in lipids from PCBs in plasma using a lipid content of 7.35 g/l plasma as the basis for conversion. A value of 5 to 9.2 g/l was determined for the total lipid content in Germany. A lipid content of 7 g per litre of plasma is used to convert the lipid-based burden of the total PCB concentration of 1 µg/g blood lipids to a serum-based or plasma-based value. Assuming a mass-to-volume ratio of 1:1, this would be equivalent to a total PCB content of 7 µg/l plasma.

Data for the blood lipid levels of pregnant women and in the cord blood were published by El Majidi et al. (2012), Needham et al. (2011) and Govarts et al. (2012).

An overview of the conversion factors that were applied can be found in Table 1.

Tab. 1 Conversion factors

General information		
Total PCBs in plasma/blood	Sum of the 6 indicator congeners × 2 Sum of PCB 138 + 153 + 180 × 2, as the low chlorinated indicator congeners are not relevant for control collectives PCB 153 × 5	
Total PCBs in air	Sum of the 6 indicator congeners × 5	
Men and non-pregnant women		
1 µg total PCBs/g blood lipids	7 µg total PCBs/l plasma	HBM-Kommission 2012
1 µg total PCBs/g blood lipids	7.35 µg total PCBs/l plasma	El Majidi et al. 2012
1 µg total PCBs/g blood lipids	8.90 µg total PCBs/l plasma	Needham et al. 2011
1 µg total PCBs/g blood lipids	4.48 µg total PCBs/l whole blood	El Majidi et al. 2012
Pregnant women		
1 µg total PCBs/g blood lipids	9.30 µg total PCBs/l plasma	El Majidi et al. 2012
1 µg total PCBs/g blood lipids	5.68 µg total PCBs/l whole blood	El Majidi et al. 2012
Cord blood		
1 µg total PCBs/g blood lipids	2.8 µg total PCBs/l plasma	El Majidi et al. 2012
1 µg total PCBs/g blood lipids	1.7 µg total PCBs/l whole blood	El Majidi et al. 2012
1 µg total PCBs/g blood lipids	3.0 µg total PCBs/l plasma	Needham et al. 2011
1 µg total PCBs/l maternal plasma	0.2 µg total PCBs/l cord blood plasma	Needham et al. 2011; Govarts et al. 2012
	0.2–0.4 µg total PCBs/l cord blood plasma	Casas et al. 2015

1.1 Developmental toxicity in humans

Summary (Hartwig and MAK Commission 2016 a): Effects on sperm morphology and sperm motility were described among male offspring of Yucheng patients (consumption of rice oil contaminated with chlorinated biphenyls). Sperm damage among exposed workers has not been reported to date.

Toxic effects on development after oral intoxication were reduced birth weights and sizes, and hyperpigmentation of the skin, gingivae and nails. There is evidence of delayed cognitive development in the children. Overall, the data indicate that developmental toxicity is induced by PCB exposure (Table 2). However, in these cases, it is likely that the effects were also caused by the PDCFs (polychlorinated dibenzofurans) present in the contaminated rice oil.

Tab. 2 Effects in humans after ingestion of contaminated rice oil

	Total PCB in maternal serum [µg/l]	Effects
Yucheng patients	49.3 (arithmetic mean) end of pregnancy 26.8 (median) (Guo et al. 2004)	Reduced birth weight (500 g), hyperpigmentation of the skin, nails and oral mucosa, acne and deformed nails, tooth effects (Hartwig and MAK Commission 2016 a)

Reduced birth weights were reported in the offspring of women occupationally exposed to PCBs. The geometric mean for exposure to total PCBs was 300 µg/l serum in the high exposure group, 61 µg/l serum in the low exposure group and 16 µg/l serum in the control group (Taylor et al. 1984, 1989).

A comprehensive evaluation was made of animal studies and (environmental) epidemiological studies that investigated PCBs (HBM-Kommission 2012). The HBM Commission identified developmental neurotoxicity as the most sensitive end point. The HBM Commission's evaluation forms the basis for this addendum, together with relevant literature published since 2011.

1.1.1 Developmental neurotoxicity

Findings on developmental neurotoxicity from a total of 15 birth cohorts from 8 different countries had been published by the end of 2011 (HBM-Kommission 2012). All of the studies determined PCB exposure via the cord blood or maternal blood and some also reported postnatal exposure via breast milk. The studies applied different neuropsychological and neuromotor test systems to investigate age-related developmental deficits in newborn babies and toddlers. However, it is difficult to compare the findings of the studies because of the different neurological and neuropsychological end points investigated with the different test systems. Nine cohort studies found a significant association between at least one specific effect parameter and the PCB burden. Two other studies initially reported (in some cases weak) associations; however, these were no longer significant after adjusting for confounders (in particular methylmercury). Four studies found no associations. Overall, the HBM Commission concluded that there is sufficient epidemiological evidence that PCBs induce neurotoxic effects in the developing nervous system. In addition, in spite of their heterogeneity, the studies did identify a concentration below which no neurotoxic effects were observed. This concentration was derived from the study of Jacobson et al. (2002), which carried out a benchmark analysis of the so-called Michigan cohort. This cohort had a relatively high body burden from PCBs in the 1980s resulting from the consumption of fish. On the basis of these data, the following HBM values were derived for infants, toddlers and women of child-bearing age:

HBM I value: 3.5 µg total PCB/l serum (derived from 0.5 µg total PCB/g blood lipids)

HBM II value: 7 µg total PCB/l serum (derived von 1.0 µg total PCB/g blood lipids; ≙ 3.5 µg indicator congeners/l serum)

(Total PCB: sum of PCB 138 + PCB 153 + PCB 180 in serum × 2) (HBM-Kommission 2012).

The HBM I value represents the concentration of a substance in human biological material, below which—according to the knowledge and judgement of the HBM Commission—there is no risk of adverse health effects.

The HBM II value represents the concentration of a substance in human biological material above which there is a risk of adverse health effects that are considered relevant for the respective subjects.

The HBM II value can be derived even without conducting a benchmark analysis based on the figures published by Jacobsen et al. (2002). These suggest a NOAEL for total PCBs of 1.0 µg/g blood lipids.

A comparative review of the end points investigated in the cohorts was carried out to re-evaluate the toxicological risk of PCBs. In order to improve comparability, the exposure concentrations of the birth cohorts were converted to

total PCB burdens. The authors concluded that none of the studies observed effects below a total PCB concentration of 0.9 µg/g blood lipids (equivalent to 6.3 µg total PCB/l plasma) (Carrier et al. 2007).

In 2013, the same research group re-assessed the data available for the developmental neurotoxicity of PCBs. The cognitive and motor development of the children in 9 birth cohorts were analysed according to the Bradford-Hill criteria and with regard to the PCB burden. Cognitive development was impaired in 3 cohorts at a median total PCB concentration of 0.5 µg/g lipids in maternal plasma. However, these effects were not consistent over time (temporary effects). For this reason, these 3 cohorts were excluded from further analysis. No significant developmental impairment was found in 4 of the cohorts. The median content of total PCBs was between 0.48 and 1.53 µg/g lipids in maternal plasma. Significant and consistent impairment was found in 2 cohorts. The median total PCB concentrations in the two studies were 0.25 and 1.6 µg/g lipids in maternal plasma, respectively. The results of the 6 cohort studies used for evaluation were therefore inconsistent in spite of overlapping exposure ranges. The authors were not able to establish an exposure–effect relationship. An assessment of the methodological quality of the studies found that the North Carolina and CPP (Collaborative Perinatal Project) cohorts yielded the most reliable results. These studies found no significant effects and the 95th percentile of the maternal PCB concentration was about 1 µg/g blood lipids for total PCBs, which is equivalent to a total PCB concentration of 7 µg/l plasma (El Majidi et al. 2013).

A study with Inuit children (255 participants) investigated the relationship between the concentrations of PCBs, mercury and lead in the cord blood and in the blood of 11-year-old children and performance in three tests of fine motor skills (Santa Ana Form Board, NES-3 Finger-Tapping-Test, Stanford-Binet Copying subtest). The measurements in cord blood (see Table 3) were carried out between 1996 and 1998. The authors reported that the population had a very high burden from PCBs and mercury because of their high consumption of fish.

Tab. 3 Concentrations in the cord blood of four different congeners (Boucher et al. 2016)

PCB congeners	Number	Mean [µg/kg lipids]	SD [µg/kg lipids]	Median [µg/kg lipids]	Range [µg/kg lipids]	Mean [µg/l plasma][a)]
PCB 118	255	22.4	17.8	18.0	3.4–121	0.063
PCB 138	255	81.6	63.1	63.4	6.8–435.1	0.228
PCB 153	255	124.3	101.9	93.8	9.7–653.6	0.348
PCB 180	255	50.2	44.1	35.1	3.4–85.6	0.140
Σ PCB 138, PCB 153, PCB 180		256.1				0.716
Total PCBs[b)]		512.2				1.432

[a)] retrospectively calculated according to El Majidi et al. (2012)
[b)] Total PCBs = 2 × Σ PCB 138, PCB 153, PCB 180
Abbreviation: SD = standard deviation

A significant association ($p < 0.05$) was established between poorer performance in the Finger-Tapping-Test and the concentration of PCB 153 in the cord blood. In addition, there was a significant association between poorer performance in the Santa Ana Form Board and the Finger-Tapping-Test and concentrations of lead, mercury and PCB 153 in the blood of the children. Whether the observed effects can be attributed to the PCB body burden (converted to 1.4 µg total PCBs/l plasma) cannot be determined from this study because of the associations also with lead and mercury (Boucher et al. 2016).

Summary: In a number of studies, a maternal concentration of total PCBs of 1 µg/g blood lipids was found to be the NOAEL for developmental neurotoxicity. This is equivalent to concentrations of total PCBs of 7 µg/l plasma and of PCB indicator congeners of 3.5 µg/l plasma.

1.1.2 Birth weight

As birth weight was found to be a sensitive parameter for PCB exposure also in studies with monkeys (see 1.2.1.1) and numerous environmental epidemiological studies have investigated the association between birth weights and PCB exposure (and other environmentally relevant substances), these studies are discussed in the following on the basis of recent reviews.

A review evaluated 20 relevant epidemiological studies that were published up until 2011. The means or medians of the total PCB concentrations ranged from 0.044 to 1.6 µg/g blood lipids (about 0.22 to 8 µg PCB indicator congeners/l plasma, converted as given in the publication for the blood lipid content of pregnant women). In 10 of the 20 studies, the maternal PCB concentration was not related to a significant reduction in birth weights, even though the PCB burden overlapped with that of the other studies. The remaining 10 studies found significant negative associations. In these studies, a reduction in birth weight was observed at total PCB concentrations between 0.212 and 2.746 µg/g blood lipids (about 1 to 13 µg PCB indicator congeners/l plasma). The authors were not able to derive a dose–response relationship from these data. An association between the PCB burden and abnormal birth weights (< 2500 g) could also not be established (El Majidi et al. 2012).

A meta-analysis that evaluated data from more than 7000 births determined a reduction in birth weight by 150 g for every µg of PCB 153 per litre of cord serum (Govarts et al. 2012). This study was criticized for not adjusting for the confounder gestational weight gain. Maternal weight gain is positively associated with birth weight, but negatively associated with PCB plasma levels (Verner et al. 2013).

The study of Govarts et al. (2012) was extended in 2015 to include 9000 births from 11 European cohorts. Gestational weight gain was taken into consideration and the following confounders were adjusted for: cohort, maternal age at birth, parity, sex of child, body mass index before pregnancy, maternal body size, smoking during pregnancy, maternal educational level, time of PCB sampling, length of gestation and length of gestation squared (thereby placing greater weight on the length of pregnancy). From the meta-analysis of all studies, a reduction in birth weight of 171 g was calculated for every µg of PCB 153 per litre of cord serum. The regression coefficient β decreased by 48% after adjusting for gestational weight gain. The negative association between PCB concentration and birth weight was considerably higher in girls than in boys born to non-smoking mothers, which is not consistent with the data available from other publications. In the daughters of non-smoking mothers, a PCB 153 concentration of 1 µg/l cord serum corresponded to a reduction in birth weight by 141 g, however, the effect of gestational weight gain was not considered (Casas et al. 2015).

Assuming that gestational weight gain decreases the β coefficient by 48% also in this subgroup, then a PCB 153 concentration of 1 µg/l cord blood serum would reduce the birth weight by about 70 g. An interesting finding of this study was that the highest mean birth weights were found in the 2 cohorts with the highest PCB body burdens; this actually contradicts the study results. The mean birth weights of the cohorts ranged from 3181 to 3729 g.

In view of such a high degree of variability, it is questionable whether all confounders can even be taken into consideration to ensure that the negative association found between PCB content and birth weight is correct. Furthermore, the authors assume a linear relationship, this means that there is no exposure without effect. In view of the great variation in values, this can neither be proven nor disproven. Regarding the above-derived relationship, namely that a PCB 153 concentration of 1 µg/l cord serum leads to a reduction in birth weight of about 70 g, as a worst-case, a PCB 153 concentration of 1 µg/l cord serum would be equivalent to a PCB 153 concentration of about 2.5 to 5 µg/l maternal serum (Casas et al. 2015) and this, in turn, would correspond to a concentration of PCB indicator congeners of about 6.25 to 12.5 µg/l plasma (calculated from the share of median PCB 153 concentrations in the sum of indicator congeners in the age groups up to 50 years = 40%, see Table 5). On the basis of the above relationship, at a concentration of PCB indicator congeners of 3 µg/l plasma, the birth weights of girls born to non-smoking mothers would be reduced by 17.5 to 35 g or by 0.5% to 1% at an average weight of about 3400 g.

A study from Sweden found the sum of PCB 138, PCB 153 and PCB 180 in the breast milk to be **positively** associated with birth weight in 413 pregnancies. An increase of 64 µg/kg milk lipids corresponded with an increase in birth weight by about 100 g. The results were adjusted for gestational weight gain (Lignell et al. 2013).

The relationship between PCB 153 concentrations in serum, breast milk or cord blood and the postnatal growth of children was investigated in 7 European birth cohorts comprising about 2500 births. Postnatal, but not prenatal, exposure of the children to PCB 153 was associated with significantly reduced weights at the age of 24 months. According to these calculations, the weight of children with an increase in the postnatal PCB 153 burden of 183 µg/kg blood lipids (which is equivalent to the difference between the 75th and 25th percentiles) would be reduced by 140 g at the age of 24 months (Iszatt et al. 2015). A 24-month-old child weighs about 12 kg (WHO 2018). This calculated reduction in weight gain corresponds to 1% for an increase in the levels of PCB indicator congeners by 3.3 µg/l plasma (assumption: the ratio of PCB in blood lipids to PCB in plasma in children is the same as that in adults according to El Majidi et al. (2012) and the ratio of PCB 153 to the sum of the indicator congeners in the age groups up to 50 years = 40% as shown in Table 5).

Summary: The results of the birth weight studies are inconsistent. Birth weights are highly variable and dependent upon many factors. It is therefore questionable whether the negative association found in some studies between PCBs and birth weights or postnatal weight development can be causally related to PCBs. Even if the dose–response relationships established by the two recent and most comprehensive meta-analyses (Casas et al. 2015; Iszatt et al. 2015) could be causally related to PCBs, the birth weights would be reduced only by 1% at a concentration of PCB indicator congeners of around 3.5 µg/l maternal plasma. In an international subcohort with a low risk for reduced birth weights, the average birth weight of 20 486 newborn babies was 3.3 ± 0.5 kg (Villar et al. 2014). Thus, the range of variation for lower than average birth weights is 15 times higher than the 1% decrease in birth weight caused by a concentration of PCB indicator congeners of about 3.5 µg/l maternal plasma.

1.1.3 Thyroid hormones

Using a method similar to that described in El Majidi et al. (2012) and El Majidi et al. (2013), the same research group also reviewed 19 cohort studies to analyse the relationships between PCB burden and thyroid hormones (total T3 and T4, free T3 and T4 and TSH) in pregnant women and newborn babies. PCB concentrations were associated with total T3 in only 1 of 10 studies with pregnant women that were assigned a high confidence. In the studies assigned a high confidence, no association was found between PCB concentrations and thyroid hormones in newborn babies. This led the authors to conclude that a total PCB concentration of 1 µg/g lipids in maternal plasma, which corresponds to a total PCB concentration of 7 µg/l plasma and a concentration of PCB indicator congeners of 3.5 µg/l plasma, has no significant effect on the thyroid hormones of mothers and their newborn babies (El Majidi et al. 2014).

1.2 Animal experiments and in vitro studies

1.2.1 Reproductive and developmental toxicity

1.2.1.1 Developmental toxicity

An extensive evaluation of the developmental toxicity studies was carried out in Hartwig and MAK Commission (2016 a).

The presence of biphenyls with a lower degree of chlorination indicates workplace exposure, while those with a higher degree of chlorination are mainly found in food. The following provides a brief overview of relevant studies that investigated low and higher chlorinated biphenyls in monkeys and included data for the body burden.

Groups of 7 rhesus monkeys were given Aroclor 1016 via the diet in doses of 0, 0.25 and 1 mg/kg (0, 8 and 30 µg Aroclor 1016/kg body weight and day, for 21.8 months) for 7 months before mating, during mating and gestation

and for 4 months after birth. The birth weights were reduced at an Aroclor 1016 dose of 30 µg/kg body weight and day. Hyperpigmentation at the hairline was found postnatally in the offspring until weaning, which had regressed by the age of 14 months, and behavioural and learning deficits were recorded at 14 months and from 4 to 6 years of age. The concentration of chlorinated biphenyls found in the maternal blood was 12 ± 6 and 27 ± 8 µg/l serum, respectively, at the Aroclor 1016 dose of 8 and 30 µg/kg body weight and day (Barsotti and Van Miller 1984; Schantz et al. 1989, 1991).

The lowest dose of tetrachlorinated and higher chlorinated biphenyls and their mixtures, which was administered to rhesus monkeys as Aroclor 1254, was 5 µg/kg body weight. It caused only mild effects in the offspring in the form of nail changes on the day of birth and in the following weeks, and an increase in foetal mortality that was not significant (Arnold et al. 1995). This dose corresponds to a total PCB concentration of about 10 µg/l blood or 20 µg/l plasma (Arnold et al. 1993 a, b). A dose-dependent trend for foetal mortality was found in the offspring of the monkeys; at the dose of 80 µg/kg body weight and day, the incidence of foetal mortality was statistically significant compared with the mortality data for the controls (Arnold et al. 1995).

Findings on the skin and nails of humans would certainly have been observed in the past in view of the ubiquitous, higher levels of background exposure (for example, in Japan the PCB concentrations in the blood of the general population were 0.5 to 23 µg/l in the 1970s (Hara 1985) and in the United States the geometric mean background concentration of highly chlorinated congeners was found to be 9 µg/l plasma (Taylor et al. 1989)). It is therefore assumed that rhesus monkeys are more sensitive to these effects than humans, or that the Aroclor mixture used contained PCB components that do not correspond to the congener pattern found in human exposure via the diet. Therefore, the findings obtained on the skin and nails of monkeys are not included in the evaluation of prenatal toxicity for humans.

In another study in monkeys, the birth weights and body weight gains of the offspring were reduced after treatment with Aroclor 1254 for 14 months at 25 µg/kg body weight and above; the NOAEL was 5 µg Aroclor 1254/kg body weight and day (US EPA 1996). However, no changes were observed for this parameter after treatment with Aroclor 1254 for 76 months at doses of up to 80 µg/kg body weight and day (Arnold et al. 1995). The US EPA likewise derived a NOAEL of 5 µg/kg body weight and day for the developmental toxicity of Aroclor 1254 (US EPA 1996).

Summary: Monkeys were the most sensitive species for developmental toxicity after oral treatment with PCBs. The NOAEL for the prenatal developmental toxicity of monochlorinated, dichlorinated and trichlorinated biphenyls and low chlorinated mixtures was 8 µg/kg body weight and day for Aroclor 1016, which corresponds to a total PCB burden of 12 µg/l plasma (see Table 4). Developmental neurotoxicity was observed at an Aroclor 1016 dose of 30 µg/kg body weight and day, or a total PCB concentration of 27 µg/l plasma. The NOAEL for the developmental toxicity of tetrachlorinated and higher chlorinated biphenyls and their mixtures was 5 µg/kg body weight and day for Aroclor 1254, which corresponds to a total PCB concentration of 20 µg/l plasma (see Table 4).

Tab. 4 NOAEL and LOAEL for developmental toxicity and body burden in monkeys

PCB mixture	NOAEL	LOAEL	References
Aroclor 1016	8 µg/kg body weight and day	30 µg/kg body weight and day: birth weight ↓, behavioural and learning deficits	Barsotti and Van Miller 1984; Schantz et al. 1989, 1991
	PCB burden: 12 ± 6 µg total PCB/l serum	PCB burden: 27 ± 8 µg total PCB/l serum	Barsotti and Van Miller 1984
Aroclor 1254	5 µg/kg body weight and day	25 µg/kg body weight and day: birth weight ↓	US EPA 1996
	PCB burden: 10 µg/l whole blood ≙ 20 µg total PCB/l plasma	PCB burden: about 40 µg/l whole blood (extrapolated) ≙ 80 µg total PCB/l plasma	Arnold et al. 1993 a, b

LOAEL: lowest observed adverse effect level; NOAEL: no observed adverse effect level

1.3 Background exposure and exposure data

Determination in blood

The concentrations of the 6 indicator congeners and the 12 dioxin-like congeners were determined in blood samples taken from a group of 105 non-smokers. The limit of detection was 0.01 µg/l plasma. As all values determined for PCB 52 were below the limit of detection, this congener is not included in Table 5. The concentrations of the 12 individual dioxin-like congeners were in the range of the limit of detection; among persons older than 60 years, a maximum of 0.34 µg/l plasma was determined for the congener PCB 156 and 0.295 µg/l for the congener PCB 118. The 95th percentile of the total PCB concentrations was in a range from 1.57 to 4.56 µg/l plasma in the age group of 21 to 50-year-olds (see Table 5) (Schettgen et al. 2011).

Tab. 5 PCB concentrations in the blood of non-smokers of the general population (modified according to Schettgen et al. 2011)

	Concentration [µg/l plasma]					
	PCB 28	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**	**Σ PCBs**
21–30 years[a)] (number)	**8**	**6**	**15**	**15**	**15**	
median	0.011	< 0.01	0.21	0.271	0.173	0.668
95th percentile	0.028	0.021	0.468	0.597	0.476	1.571
maximum level	0.029	0.034	0.564	0.705	0.561	1.898
31–40 years[a)] (number)	**10**	**9**	**15**	**15**	**15**	
median	0.012	0.011	0.358	0.527	0.417	1.355
95th percentile	0.025	0.018	0.775	1.035	0.699	2.535
maximum level	0.026	0.02	0.914	1.206	0.896	3.071
41–50 years[a)] (number)	**10**	**6**	**15**	**15**	**15**	
median	0.016	< 0.01	0.347	0.528	0.531	1.34
95th percentile	0.029	0.019	1.235	1.669	1.616	4.562
maximum level	0.029	0.027	1.458	1.889	2.588	5.984
51–60 years[a)] (number)	**10**	**6**	**15**	**15**	**15**	
median	0.014	< 0.01	0.613	0.903	0.892	2.432
95th percentile	0.033	0.02	1.655	2.005	1.678	5.291
maximum level	0.046	0.027	1.794	2.514	2.312	6.643
> 60 years[a)] (number)	**9**	**7**	**15**	**15**	**15**	
median	0.016	< 0.01	0.874	1.338	1.292	3.608
95th percentile	0.037	0.017	1.542	2.223	1.876	5.53
maximum level	0.048	0.021	1.544	2.3	1.969	5.724

[a)] age

PCB concentrations were determined in the plasma of 209 persons exposed to PCBs via indoor air (median age: 35 years) and 98 control persons (median age: 42 years) (see Table 6). In the control persons, the median concentrations of PCB 28, 52 and 101 in plasma were below the limit of quantification. Maximum values of 0.059 for PCB 28, 0.029 for PCB 52 and 0.015 µg/l plasma for PCB 138 were reported. Accordingly, the plasma concentrations of the control persons were in the same range as the values published by Schettgen et al. (2011). The concentrations of these 3 indicator congeners were significantly increased in the plasma of persons exposed via the air, but not the concentrations of the higher chlorinated indicator congeners PCB 138, PCB 153 and PCB 180. This is due to the higher concentration of the more volatile trichlorobiphenyls and tetrachlorobiphenyls in the air. A significant

increase in the concentration in plasma was observed also for the dioxin-like congeners PCB 105 and PCB 118. The plasma concentrations were not significantly increased for the sum of the dioxin-like PCB congeners (Schettgen et al. 2012).

Tab. 6 PCB concentrations in indoor air and in plasma after exposure via indoor air (Schettgen et al. 2012)

	Indoor air [ng/m³ air]						
PCB congener	**28**	**52**	**101**	**138**	**153**	**180**	**Σ 6 PCBs × 5**
median	140	160	29	3	2	< 1	1740
95th percentile	320	348	86	22	13	2	3740
maximum	450	470	150	31	21	3	4280
	Exposed persons [µg/l plasma]						
PCB congener	**28**	**52**	**101**	**138**	**153**	**180**	**Σ**
median	0.087	0.024	0.012	0.253	0.380	0.279	1.035
95th percentile	0.352*	0.091*	0.046*	0.846	1.256	1.085	3.676
maximum	0.878	0.426	0.123	2.226	3.360	3.179	10.2
	Control persons [µg/l plasma]						
PCB congener	**28**	**52**	**101**	**138**	**153**	**180**	**Σ**
median	< 0.01	< 0.01	< 0.01	0.263	0.392	0.301	0.971
95th percentile	0.021	< 0.01	< 0.01	0.92	1.492	1.148	3.591
maximum	0.059	0.029	0.015	2.437	3.523	3.186	9.25

* $p < 0.001$ compared to control persons

From September 2010 to March 2014, PCB concentrations were determined in the plasma of persons living in North-Rhine Westphalia and Hesse. Only the data for PCB 138, PCB 153 and PCB 180 were reported, as the remaining three indicator congeners were not relevant for the body burden (Schettgen et al. 2015) (see Table 7). Assuming that the PCB burden was about the same for the women and men of each age group, the concentration of PCB indicator congeners in the blood of 0.5% of women up to the age of 45 would exceed 3.5 µg/l plasma.

Tab. 7 Background burden of chlorinated biphenyls in the blood plasma of different age groups (Schettgen et al. 2015)

	Concentration [µg/l plasma]			
	PCB 138	**PCB 153**	**PCB 180**	**Σ PCBs**
18–25 years[a] (n = 157)[b]				
median	0.12	0.17	0.10	0.38
95th percentile	0.25	0.38	0.29	0.88
maximum value	0.58	0.84	0.40	1.80
26–35 years[a] (n = 710)[b]				
median	0.15	0.21	0.14	0.5
95th percentile	0.33	0.49	0.34	1.14
maximum value	0.71	0.89	0.77	2.37
36–45 years[a] (n = 400)[b]				
median	0.24	0.37	0.29	0.92
95th percentile	0.53	0.79	0.65	1.95
maximum value	1.08	1.55	1.43	3.57
46–55 years[a] (n = 525)[b]				
median	0.39	0.63	0.57	1.58
95th percentile	0.93	1.41	1.23	3.54
maximum value	1.70	2.65	4.59	8.19
56–65 years[a] (n = 357)[b]				
median	0.56	0.92	0.87	2.41
95th percentile	1.26	1.94	1.87	4.82
maximum value	3.98	5.45	9.08	18.50

[a] age
[b] number of persons examined

A blood sample was taken in 2013 from 37 female persons and 33 male persons aged 4 to 76 years (median age: 42 years) who lived within a 100 to 1000-metre radius of a recycling company and the PCB levels were determined. Ten of the participants were smokers. The PCB concentrations in the blood of all of the participants were below the reference value of 1–7.8 µg/l for the sum of PCB 138, PCB 153 and PCB 180 (HBM-Commission 2003). Thus, no evidence was found for the suspected increased burden resulting from PCB emissions from this factory (Fromme et al. 2015). The findings are shown in Table 8. However, it must be kept in mind that the decreasing background burden in the younger age groups up to 49 years has greatly reduced the reference values over the course of the last 10 years (HBM-Kommission 2016).

Tab. 8 PCB burden of residents living next to a recycling company (Fromme et al. 2015)

	Concentration [µg/l whole blood]						
PCB congeners	**PCB 28**	**PCB 52**	**PCB 101**	**PCB 138**	**PCB 153**	**PCB 180**	**Σ PCBs[a]**
median	0.003	0.001	0.001	0.082	0.152	0.153	0.773
95th percentile	0.008	0.002	0.003	0.552	0.995	1.022	4.895
maximum	0.02	0.005	0.004	0.621	1.138	1.079	5.617

[a] sum of the congeners PCB 138, PCB 153 and PCB 180 multiplied by 2

A study analysed all 209 congeners in the whole blood and plasma of 27 women and 16 men (median age: 57 years) who were exposed to indoor air contaminated with PCBs for more than 2 years. A group of 21 men and 21 women who were not exposed to PCB via the air were used as the control collective (median age: 46 years). In exposed persons, PCB concentrations of 99 to 2152 ng/g blood lipids (median: 454 ng/g blood lipids; 95th percentile: 1404 ng/g blood lipids) were determined in the whole blood for the sum of all PCB congeners. PCB concentrations of 52 to 933 ng/g blood lipids (median: 226 ng/g blood lipids; 95th percentile: 642 ng/g blood lipids) were found in the plasma of the control group. The predominant congeners found in the whole blood or plasma samples were PCB 153 (24% and 26%, respectively), PCB 180/193 (17% and 18%, respectively) and PCB 138/160 (8% and 11%, respectively). PCB 28 was found only in exposed persons. The sum of the 3 indicator congeners PCB 138, 153 and 180 was equal to 49% of the total PCB content in the whole blood and to 55% in the plasma. The data from this study show that the factor of 2 that was used to convert the standard 6 indicator congeners to the total PCB burden was in the correct order of magnitude (Kraft et al. 2017). An earlier publication reported the concentrations of the 6 indicator congeners that were found in the blood of the control group not exposed to PCB via contaminated indoor air (age: 20 to 68 years) (Fromme et al. 2016). Data for the concentrations of individual congeners in the air and plasma were determined from a sub-collective of 35 persons (median age: 58 years) who were exposed via the indoor air for 40 hours a week over a period of 2 to 44 years (see Table 9) (Kraft et al. 2018).

Tab. 9 PCB concentrations in indoor air and in the blood/plasma of persons exposed via indoor air and in control persons (Fromme et al. 2016; Kraft et al. 2017, 2018)

	Indoor air [ng/m^3 air] (Kraft et al. 2018)						
PCB congener	**28**	**52**	**101**	**138**	**153**	**180**	**Σ 6 PCBs × 5**
median	25	57	13	2.8	1.8	0.28	479
95th percentile	123	250	49	9.7	5.8	1.2	2297
maximum	214	305	78	11	7.8	1.4	2797
	Control persons [µg/l plasma] (Fromme et al. 2016)						
PCB congener	**28**	**52**	**101**	**138**	**153**	**180**	**Σ 6 PCBs**
median	0.002	not specified	0.001	0.15	0.32	0.29	about 0.76
95th percentile	0.01	not specified	0.006	0.44	0.93	0.88	about 2.27
maximum	0.006	about 0.007 1.02 [ng/g$^{b)}$]	0.007	0.46	1.21	1.39	about 3.08
	Exposed and control persons (Kraft et al. 2017, 2018)						
	Exposed persons: whole blood concentrations					**Control persons: plasma concentrations**	
PCB congener	**PCB 28**	**Σ 209 PCBs**				**Σ 209 PCBs**	
median	0.041 µg/l$^{a)}$	454 ng/g$^{b)}$		1.6 µg/l$^{a)}$		226 ng/g$^{b)}$	1.58 µg/l$^{a)}$
95th percentile	0.130 µg/l$^{a)}$	1404 ng/g$^{b)}$		4.9 µg/l$^{a)}$		642 ng/g$^{b)}$	4.49 µg/l$^{a)}$
maximum	0.137 µg/l$^{a)}$	2152 ng/g$^{b)}$		7.5 µg/l$^{a)}$		933 ng/g$^{b)}$	6.53 µg/l$^{a)}$

$^{a)}$ converted from the data from the studies in g blood lipids. Assumptions: a factor of 3.5 for whole blood, a factor of 7 for plasma
$^{b)}$ blood lipids

The concentrations of the 6 indicator congeners (PCB 28, PCB 52, PCB 101, PCB 138, PCB 153 and PCB 180) were determined in the plasma of 188 women and pregnant women between the ages of 16 and 45, who may have been exposed to PCBs via indoor air from 2009 to 2018. A median of 0.36 µg/l plasma and a 95th percentile of 1.39 µg/l plasma with a minimum value below the limit of quantification and a maximum value of 2.95 µg/l plasma was determined for the sum of the 6 indicator congeners (Göen and Drexler 2018).

1.4 Evaluation

Prenatal toxicity:

At the NOAEL for developmental toxicity for Aroclor 1254 of 5 µg/kg body weight and day, the concentration in monkeys was 10 µg/l whole blood, which is equivalent to a total PCB concentration of 20 µg/l plasma; at the NOAEL for Aroclor 1016 of 8 µg/kg body weight and day, this would correspond to a total PCB concentration of 12 µg/l plasma. The LOAELs (lowest observed adverse effect level) for total PCBs are 80 and 27 µg/l plasma, respectively. Both NOAELs are in the same order of magnitude, so that a similar potency can be assumed for PCBs with a low and a high degree of chlorination.

The BAT value for the plasma concentrations of the PCB indicator congeners is 15 µg/l; it applies to the non-dioxin-like PCB congeners. The derivation of the BAT value is based on the data from animal studies; the liver hypertrophy observed in rats was considered to be the critical toxic effect. The margin to the NOAEL for developmental toxicity in monkeys of 20 µg/l plasma and 12 µg/l plasma for total PCBs is not sufficiently large with exposure at the BAT value. In addition, epidemiological data in humans indicate that chlorinated biphenyls induce toxic effects on development. For this reason, Pregnancy Risk Group B applies also at levels of exposure that do not exceed the BAT value.

Prerequisite for Pregnancy Risk Group C:

Data for humans

Extensive epidemiological studies have been conducted for the most sensitive end points of PCB exposure: developmental neurotoxicity and a reduction in birth weights. These are used to determine the plasma concentration at which PCBs do not cause prenatal toxicity in humans.

On the basis of the study of Jacobson et al. (2002), a NOAEL for developmental neurotoxicity of 7 µg/l plasma was derived for total PCBs or of 3.5 µg/l plasma for the 6 PCB indicator congeners. This NOAEL was confirmed by other meta-analyses (El Majidi et al. 2013).

This value does not contradict the dose–response relationships derived for the end points reduced birth weights and postnatal weight development. However, it is questionable whether the dose–response relationships determined in the studies can be causally related to PCBs (Casas et al. 2015; Iszatt et al. 2015). Even if this were the case, it was calculated that the body weight (birth weight and postnatal weight development) would be reduced by only 1% after exposure to PCB indicator congeners at a concentration of 3.5 µg/l maternal plasma, which is 15 times lower than the range of variation for lower than average birth weights of newborn babies.

A negative effect on the thyroid status of newborn babies is also not expected at a burden from PCB indicator congeners of 3.5 µg/l maternal plasma (El Majidi et al. 2014).

Data for animals

When animal studies are available, the NOAEC (no observed adverse effect concentration) for developmental toxicity derived from rodents should generally be 10 times the MAK value in order to compensate for the lack of human data and to justify assignment to Pregnancy Risk Group C. This can also be applied by analogy to the body burden and thus also to the BAT value. A total PCB concentration in plasma of 2 µg/l plasma (1 µg PCB indicator congeners/l plasma) would be derived on the basis of the higher of the two NOAELs for developmental toxicity in monkeys of 20 µg/l plasma for total PCBs. It is to be assumed that there are fewer differences between monkeys and humans than between rodents and humans, which means that, taking the epidemiological data into account, a margin of less than 10 times the BAT value would probably still be appropriate. Therefore, the data from animal studies would not contradict the value of 3.5 µg PCB indicator congeners/l plasma derived from epidemiological studies.

Summary: On the basis of the data and calculations described above, it is concluded that prenatal toxicity is not to be expected up to a concentration of PCB indicator congeners of 3.5 µg/l plasma.

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