Chlorinated biphenyls

Supplement 2016

MAK value (2015)	**0.003 mg/m³ I**[1)] **(inhalable fraction)**
Peak limitation (2015)	**Category II, excursion factor 8**
Absorption through the skin (2012)	**H**
Sensitization	**–**
Carcinogenicity (2015)	**Category 4**
Prenatal toxicity (2015)	**Pregnancy Risk Group B**
Germ cell mutagenicity (2015)	**Category 5**
BAT value	**–**
BAR value (2011)	**PCB 28 0.02 µg/l plasma/serum**
	PCB 52 < 0.01 µg/l plasma/serum
	PCB 101 < 0.01 µg/l plasma/serum

Since the last supplement appeared in 2013 (supplement "Chlorinated biphenyls" 2013), new data have been published for the toxicokinetics of PCB 3, PCB 11, Aroclor 1242 and Aroclor 1254 after inhalation, which are described below. The possible derivation of a MAK value for monochlorinated, dichlorinated and trichlorinated biphenyls is also discussed.

Mechanism of Action

Genotoxicity

Arene oxide, which forms rapidly during metabolism at cytochrome P450 preferably in the para position, is assumed to be responsible for the genotoxicity of monochlorinated and dichlorinated biphenyls. Arene oxides are strongly electrophilic compounds that react readily with cellular components such as proteins and DNA. Hydroquinones and semiquinones are also formed and are likewise very reactive. Evidence was provided that PCB 3 (4-chlorobiphenyl) and the quinone metabolites

1) (PCB 28 + PCB 52 + PCB 101 + PCB 138 + PCB 153 + PCB 180) × 5

covalently bind to the DNA and have mutagenic effects in vitro and in vivo (supplement "Chlorinated biphenyls" 2013).

An in vivo study in Swiss mice demonstrated this dose-dependent mechanism also after exposure to Aroclor 1254. The comet assay revealed an increase in the incidence of DNA single strand breaks in sperm with a simultaneous increase in chromosomal aberrations in the spermatocytes of the first meiotic metaphase. Oxidative DNA damage was detected after sperm DNA had been additionally treated with endonuclease III and formamidopyrimidine. The decrease in the expression of the DNA repair enzymes *OGG1* and *APEX1* demonstrates the inhibition of DNA repair (Attia et al. 2014).

Carcinogenicity

The following was described as a possible mechanism of the carcinogenicity of higher chlorinated PCBs in the liver of Sprague Dawley rats: Considerable amounts of PCB accumulate in the liver tissue, inhibiting some mixed-function oxygenases and inducing others. This may lead to the formation of quinones, which are ultimately responsible for the formation of oxygen radicals. Hydrogen peroxide formed from dismutase-catalyzed oxygen radicals influences the mitotic signal chain resulting in the proliferation even of already initiated tumour cells. Furthermore, apoptosis is inhibited in pre-neoplastic cells (supplement "Chlorinated biphenyls" 2013).

Various mechanisms are assumed because the PCB mixtures always consist of fractions of lower and higher chlorinated PCBs.

To clarify the question of the degrees of chlorination that are responsible for the carcinogenic effect on the liver, the study of Mayes et al. (1998), which was described in the 2013 supplement (supplement "Chlorinated biphenyls" 2013), is reviewed with regard to the composition of the Aroclor mixtures used in this study, their TEQ level (toxic equivalents) and the incidence of liver tumours.

Table 1 shows that it is very unlikely that the monochlorinated to trichlorinated biphenyls caused the liver tumours because their fraction in Aroclor 1016 is 100 times higher than that in Aroclor 1254 and 1260; the latter, however, induce 3 to 4-fold higher incidences of carcinomas. The tumours, in particular carcinomas, seem to be caused mainly by pentachlorinated and hexachlorinated biphenyls.

Although the correlation between liver carcinomas and the TEQ level is not good, it correctly predicts that Aroclor 1016 is the weakest Aroclor mixture. Taking as an example the adenomas of the particularly sensitive females (see Table 5), Aroclor 1254 is the most potent, which approximately correlates with the TEQ level.

The human HaCat keratinocyte cell line was exposed to 5 μM PCB 28, PCB 52 and Chicago Airborne Mixture for 48 days. The telomere length, telomerase activity, cell growth and cell cycle distribution were examined. There was minimal cytotoxicity, which was not observed after exposure to 2 μM. All other tests were carried out only with concentrations of 5 μM. On day 18 and thereafter, telomerase activity was reduced by 30% to 35% after exposure to PCB 28 and PCB 52 and by 20% to 28% after exposure to Chicago Airborne Mixture. After exposure to Chicago Airborne Mixture, the telomere length was reduced significantly on day 30 and by

Table 1 Composition of the various Aroclor mixtures, TEQs and liver tumours at about 5 mg/kg body weight and day in the study of Mayes et al. (1998) with Sprague Dawley rats

	controls	Aroclor 1016	1242	1254	1260
		degree of chlorination % fraction			
monochlorinated		0.83	0.08	0.00	0.00
dichlorinated		17.64	14.48	0.12	0.15
trichlorinated		**54.98**	**42.83**	0.66	0.48
mono + di + trichlorinated		**73.45**	**57.39**	**0.78**	**0.63**
tetrachlorinated		25.84	33.49	19.67	2.41
pentachlorinated		0.69	6.64	**45.33**	11.96
hexachlorinated		0.01	1.70	31.38	**39.28**
heptachlorinated		0.00	0.10	2.76	36.38
octachlorinated		0.00	0.01	0.07	7.67
nonachlorinated		0.00	0.00	0.02	1.59
decachlorinated		0.00	0.00	0.00	0.07
TEQs (PCDD/F)		0.002	0.1	0.01	0.08
TEQs (PCB)		0.11	7.7	47.6	7.1
hepatocellular adenomas ♂ + ♀	5/100	6/100	15/100	33/100	28/100
excess incidence		1%	10%	28%	23%
hepatocellular carcinomas ♂ + ♀	3/100	2/100	3/100	6/100	8/100
excess incidence		0	0	3%	5%

5% on days 42 and 48. PCB 28 and PCB 52 caused a 10% and 20% decrease in length, respectively, on day 18 and thereafter and PCB 52 induced a 40% decrease on day 42 and thereafter. The number of cells per plate decreased in all PCB-treated cell cultures. Morphological changes to the cells were not observed. PCB 52 produced a small increase in the number of cells in S-phase, and there was a change in the number of cells in the G0/G1-phase after treatment with PCB 28 and Chicago Airborne Mixture. The authors discuss that reduced telomerase activity leads to a shortening of the telomeres resulting in telomere fusion and instability of the chromosome. This mechanism might contribute to the carcinogenicity of PCBs (Senthilkumar et al. 2011).

Immortal human HaCat keratinocytes and primary NFK keratinocytes were exposed to PCB 153 for 48 and 24 days, respectively. In HaCat cells, PCB 153 reduced telomerase activity, telomere length and cell growth and increased intracellular superoxide levels. In NFK cells, telomerase activity was not detected, the telomere

length was not shortened, cell growth was reduced and superoxide levels were increased. The authors assumed that PCB 153 may induce premature telomere shortening with potential adverse effects in all cells with significant telomerase activity, such as stem cells (Senthilkumar et al. 2012).

Toxicokinetics and Metabolism

Groups of 8 male Sprague Dawley rats were given 15 g diet containing **Aroclor 1242** doses of 0.436 mg/kg daily for 30 days. According to the authors, this corresponds to about 45 µg/kg body weight and day at a body weight of about 200 g. Similar total PCB amounts were found in the brain, liver and lung (about 30 µg/kg wet weight), the amounts in adipose tissue were about 20 times higher. The individual PCB congeners were analyzed in adipose tissue, the brain, liver and lung. Most PCB concentrations of the individual congeners in the liver and lung were similar. PCB 1 was not detected in the liver, but in the brain, adipose tissue and lung. PCB 3, PCB 4 and PCB 10 were not found in the liver. Rats were exposed also by inhalation to Aroclor 1242 vapour in whole-animal exposure chambers for 23 hours per day at a concentration of 0.9 µg/m^3. According to the authors, this corresponds to about 0.65 µg/kg body weight and day. Assuming an inhaled volume of 0.8 l/min/kg body weight and 100% absorption, this corresponds to about 1 µg/kg body weight and day. Although the exposure of the rats amounted to only one hundredth of that of the diet reference group, both types of administration led to very similar tissue concentrations even in the case of the higher chlorinated and less volatile PCBs (Casey et al. 1999). As oral absorption of PCB by rats is very good, it was already assumed in the 2013 supplement that the vapour condensed on the animals' fur and PCB was additionally ingested (supplement "Chlorinated biphenyls" 2013). Therefore, the tissue data of the animals exposed by inhalation cannot be included in the evaluation. The study shows that the levels of exposure to PCBs in the liver and lung after oral treatment are very similar. Despite the similar burden, only liver tumours were found in the oral carcinogenicity studies, but no lung tumours. This suggests a primary effect on the liver.

Another inhalation study with **Aroclor 1242** was carried out in male Sprague Dawley rats. The animals were exposed nose-only to Aroclor 1242 either once at 2.4 mg/m^3 or repeatedly at 8.2 mg/m^3 for 4 or 10 days, for 2 hours a day. According to the authors, the high concentration corresponds to 1.4 mg/animal in 10 days, which means 0.7 mg/kg body weight and day at a body weight of 200 g. The composition of the vapour differed considerably from that of liquid Aroclor: 90% was made up of monochlorinated to trichlorinated PCBs, while the liquid contained 40%. The TEQ concentration was 3.7 ng/m^3 in the air, 1464 ng/kg lipids in the liver and 11 ng/kg lipids in the lung. After 4-day exposure, the total PCB concentration was 6 mg/kg lipids in the liver, 1.2 mg/kg lipids in the lung and 19 µg/kg lipids in the blood. After 10-day exposure, the levels in the liver and blood were about the

Table 2 Half-lives in hours of various congeners in the liver, lung, blood, adipose tissue and brain of rats after inhalation exposure to Aroclor 1242 at 2.4 mg/m³ (Hu et al. 2010)

Congener number	Liver	Lung	Blood	Adipose tissue	Brain
dichlorinated					
6	1.75	5.00	3.96	64.06	1.35
8	3.61	5.56	9.47	37.08	1.61
15	3.07	6.36	5.52	–18.04[1)]	2.28
trichlorinated					
16	2.51	9.01	19.32	26.59	20.71
17	5.48	8.30	18.14	–3396.16	2.00
18[2)]/30	4.35	6.28	12.37	29.88	10.84
20/28[2)]	7.34	9.34	11.53	–20.84	9.18
21/33[2)]	3.01	3.54	8.41	16.52	3.19
22	1.03	1.71	22.96	9.23	1.37
24	2.05	9.41	3.58	–13.29	–5.90
25	2.41	1.79	2.15	14.69	–
26[2)]/29	4.07	5.18	3.79	63.09	1.97
31	4.00	4.46	8.40	23.05	3.19
32	4.18	4.24	22.47	838.19	3.68
37	4.83	2.83	2.81	–26.48	4.53
tetrachlorinated					
49[2)]/69	24.83	28.00	–33.65	–15.73	17.75
52	6.21	7.53	16.33	–31.23	46.00
59	2.92	2.07	7.36	82.93	35.23
60	8.34	9.00	9.63	–6.62	12.37
61/70[2)]/74[2)]/76	4.17	–12.70	11.48	–17.87	6.89
64	4.30	9.39	9.49	–115.71	2.96
66	6.18	12.93	13.56	–12.01	4.24
77	5.76	12.93	3.33	6.44	1.83
pentachlorinated					
83	24.53	22.95	11.41	–9.18	–5.63
99	15.01	55.99	22.50	–9.36	–11.29
105	4.82	4.06	5.17	–13.75	–179.83
112	–95.46	83.65	29.44	–6.66	7.10
118	3.93	28.98	12.15	–11.18	3.90

[1)] negative values indicate congener accumulation rather than elimination
[2)] main congener in coelution

same, while in the lung they increased to 6.7 mg/kg lipids. The biological half-lives of total PCBs were 5.6 hours in the liver, 8.2 hours in the lung, 8.5 hours in the brain and 9.7 hours in the blood. In the adipose tissue, not a decrease, but an increase in the concentration was observed (redistribution). Table 2 shows the half-lives of the individual congeners after short-term exposure and recovery for up to 12 hours.

The fraction of monochlorinated biphenyls in air was 5% (15% was reported elsewhere in the publication). There was no evidence of monochlorinated biphenyls in the tissues. PCB 28 was the congener present in the tissues in the highest concentrations (determined together with PCB 20 because it was not possible to separate the two congeners). In all tissues, the PCB ratio shifted with time (the single exposure as compared with the 10-day exposure) in favour of higher chlorinated PCBs; for example, the fraction of pentachlorinated PCBs was 3% in air and 30% in the liver after 10 days (Hu et al. 2010).

A toxicokinetics study with inhalation exposure was carried out using a 65:35 mixture of **Aroclor 1242** and **1254** to simulate the PCB profile of exposure to airborne PCBs in Chicago. Male Sprague Dawley rats were exposed to total PCB concentrations of 0.52 mg/m^3 for 1.6 hours a day, on 5 days a week, for 4 weeks. 45% consisted of the sum of PCB 1 (monochlorinated), PCB 4 (dichlorinated) and PCB 8 (dichlorinated). The total dose per animal was 134 µg; at a body weight of 200 g, this corresponds to about 35 µg/kg body weight and day. The total PCB concentration in the liver and lung was the same, while in the blood and adipose tissue it was twice as high. The TEQ concentration was highest in the liver and adipose tissue, whereas in the lung it was only 1/1000 of that in the adipose tissue. As in the study above, monochlorinated biphenyls were not found in the tissues, presumably because of rapid elimination. In the exposure air, however, the fraction of monochlorinated biphenyls was 11%, and the ratio had shifted markedly in favour of higher chlorinated PCBs (Table 3). PCB 28 (+ PCB 20) was the congener present in the highest concentration in the lung and brain. Most of the total of 115 PCB congeners examined were found in the liver (95 congeners) (Hu et al. 2012).

There are several genotoxicity tests with positive results for **PCB 3** or its metabolites (supplement "Chlorinated biphenyls" 2013). Therefore, the metabolism of this congener is of interest and toxicokinetics studies were carried out with this congener.

When rats were given a single intraperitoneal injection of 600 µmol PCB 3/kg body weight (120 mg/kg body weight), 3% of the dose was identified in the urine as 4′-PCB 3-sulfate, 4′-OH-PCB 3, 3′-PCB 3-sulfate and 2′-PCB 3-sulfate and presumably a catechol sulfate (ortho-dihydroxymonosulfate); glucuronides were also found. The serum concentration of 4′-PCB 3-sulfate was 6.18 mg/l (Dhakal et al. 2012).

After 2-hour exposure to a PCB 3 concentration of 2 mg/m^3 (35 µg/animal and 175 µg/kg body weight) via nose-only inhalation, female Sprague Dawley rats eliminated 27% in the form of sulfates (3′-PCB 3, 3-PCB 3 and 4′-PCB 3) in the first 24 hours. After the inhalation of PCB 3 for 2 hours at 1.52 mg/m^3, the serum con-

Table 3 Percentage of biphenyls with different degrees of chlorination after inhalation exposure in vapour, liquid and various tissues in rats (Hu et al. 2012)

Degree of chlorination	Vapour	Chicago air	Liquid	Blood	Lung	Liver	Brain	Adipose tissue
monochlorinated	11	2	0	0	0	0	0	0
dichlorinated	45	21	15	4	7	7	7	2
trichlorinated	28	29	23	23	45	28	56	25
tetrachlorinated	10	15	33	26	19	19	9	20
pentachlorinated	5	20	21	36	20	34	25	39
hexachlorinated	1	8	5	12	10	10	2	13
heptachlorinated	0	4	0	0	0	1	0	1
octachlorinated	0	1	0	0	0	0	0	0
nonachlorinated and decachlorinated	0	0	0	0	0	0	0	0

centrations of 4′-PCB 3-sulfate, 4′-OH-PCB 3, 3-PCB 3-sulfate and 3′-PCB 3-sulfate were 470, 7, 28 and 61 µg/ml, respectively. The serum half-life of the sulfates was one hour and that of phenol was 0.5 hours. The concentrations rapidly decreased also in the liver and lung. The concentrations in the liver were always higher than those in the lung (Table 4). This suggests that hydroxylation takes place mainly in the liver (Dhakal et al. 2013).

Another group of rats was exposed to PCB 3 concentrations of 2.06 mg/m^3 for 2 hours. After 24 hours, about 45% of the dose was eliminated with the urine and 18% with the faeces. About 2% of the dose was eliminated unmetabolized with the urine, 4% was detected in the faeces, and 13% was metabolized as catechol sulfate, which is a potentially toxic dihydroxy compound. There was no statistically significant decrease in the values for free T4 in serum, and the 8-oxo-desoxyguanosine levels in the urine were not significantly increased (Dhakal et al. 2014).

Table 4 Determination of the sulfate and phenol metabolites of PCB 3 in the liver, lung and brain in rats after inhalation exposure to PCBs (Dhakal et al. 2013)

	At the beginning		After one hour		After 2 hours		After 4 hours	
	phenol	sulfate	phenol	sulfate	phenol	sulfate	phenol	sulfate
liver	213 ± 123	842 ± 80	48 ± 25	584 ± 123	39 ± 51	572 ± 89	34 ± 17	292 ± 23
lung	31 ± 27	22 ± 7	17 ± 11	ND	7 ± 7	ND	4 ± 3	ND
brain	27 ± 6	3 ± 0.3	11 ± 6	ND	ND	ND	ND	ND

ND: not detected

Further studies were carried out with PCB 11 (3,3′-dichlorobiphenyl), which was found in Chicago air. However, it is not a component of commercial PCB mixtures but is associated with pigments, paints and resins and apparently develops inadvertently in the production of pigments, although the exact source is not known. Male Sprague Dawley rats were exposed to PCB 11 vapour for 2 hours at a concentration of 0.106 mg/m^3. This corresponds to a dose of 1.8 µg per animal. Immediately after the end of exposure, the exposure levels in the lung were 10 times higher than in the liver (related to the lipid level of the tissues). The half-lives were 1.9, 1.8 and 2.1 hours in the lung, serum and liver, respectively. 4-OH-PCB 11 was detected in the liver, but not in the lung or serum and had a half-life of 2.4 hours (Hu et al. 2013). The study demonstrated that also PCB 11 may be metabolized to a hydroxy compound and metabolism may be rapid; however, as the metabolite is not formed in the lung, the liver is probably the target organ rather than the lung.

Another study monitored the time course of the distribution of ^{14}C-labelled PCB 11 in 35 rat tissues. The animals get an intratracheal instillation of 100 µl. The radioactivity was rapidly eliminated via the urine and faeces. The initial half-times in the tissues were between 9 and 33 minutes, and in the second phase of elimination between 2.8 and 9.5 hours. Most of the dose was absorbed via the lung. Accumulation was observed in the adipose tissue and skin (Hu et al. 2014).

Conclusion: The two studies of Hu et al. (2010, 2012) using Aroclor mixtures demonstrated that the total PCB concentrations in the lung and liver are identical after inhalation and that monochlorinated PCBs are not detectable in the lung or liver because of the short half-times. However, TEQ exposure of the liver is much higher than that of the lung. This might be evidence that the liver, rather than the lung, is the target organ of a carcinogenic (tumour-promoting) effect, even after inhalation.

The studies with PCB 3 showed that it rapidly hydroxylates and is detoxified as a sulfate, 13% of it being metabolized via a potentially toxic dihydroxy compound. The lung burden with phenolic metabolites is clearly lower than that of the liver. Therefore, the liver is probably also the primary potential target organ after inhalation.

Effects in Humans

The 2013 supplement (supplement "Chlorinated biphenyls" 2013) included a detailed discussion of human data. The following studies have since been published based on a cohort with high levels of occupational exposure.

Workers involved in the disposal of transformers and capacitors containing PCB were exposed to high PCB levels. The following data were obtained for these workers under a health care programme. The concentrations of 18 PCB congeners and of thyroid hormones in plasma were determined in 300 persons exposed to PCBs (48 female and 252 male participants; exposure level and duration not reported).

Thyroid diseases were also recorded in a medical examination. The participants were divided into 4 groups based on their PCB exposure. The prevalence of thyroid diseases was 10.1% before exposure, 16.5% at the time t2, 12.8% at the time t3 and 14.7% at the time t4 (no other details in the abstract; general population: about 10%). The workers with thyroid diseases had lower average PCB levels in the serum than any of the other participants. The concentration of free thyroxine was lower and that of TSH was higher in the groups with higher PCB exposure. There were no significant differences between the groups for free triiodothyronine. When compared with the general population, the prevalence of thyroid diseases was increased as of the second examination; this finding should be interpreted with caution, in consideration of a selection and detection bias (Gube et al. 2015).

In a further cross-sectional study carried out in this collective, nerve conduction was examined in 175 male and 29 female patients by means of electroneurography. Following adjustment for possible confounders, 167 patients with pathological neuropathy of the tibial nerve were found to have significantly increased PCB 126, PCB 180 and PCB 189 levels and those with pathological neuropathy of the sural nerve had significantly increased PCB 156, PCB 167, PCB 180 and PCB 189 levels (Werthan et al. 2015). There are no data available for a control group. This study does not provide unequivocal evidence that occupational exposure to PCBs caused neuropathy of the tibial and sural nerves.

Malignant melanomas

A 10-year update study of the cohorts of workers from 3 capacitor factories (NIOSH capacitor cohorts from New York, Massachusetts and Indiana) examined mortality from various forms of cancer. The subcohort results were described in various publications and in the 2013 supplement (supplement "Chlorinated biphenyls" 2013).

The total cohort comprised 24 865 workers who were exposed to PCBs for more than 1 day between 1960 and 2008. Overall mortality did not differ from that of the general U.S. population. The risk of dying from cancer in relation to all tumour localizations was slightly, yet significantly increased (SMR: 1.05; 95% CI: 1.01–1.09). The risk of dying from a melanoma was significantly increased among workers exposed for longer than 3 months (29 cases; SMR: 1.59; 95% CI: 1.06–2.28), but not among women or in the Massachusetts cohort. Mortality was not increased for other tumours. The probability of dying from cancer or intestinal cancer was increased among long-term female workers. The risk of uterus, prostate and stomach cancer increased with cumulative exposure, although the number of cases was very small, and there were multiple myelomas. The authors stated that the increased mortality for various tumours was not consistent between the cohorts. Likewise, the risks for various tumours differed between men and women. These inconsistent results might be due to differences in the exposure determination, different production processes at different plants and different PCB mixtures. In addition, data re-

garding the family history, genetic susceptibility, smoking habits or exposure to the sun were not reported (Ruder et al. 2014).

A carcinogenic effect of PCBs on humans cannot be reliably derived from this study because the target organs were not consistent and no information was provided about possible confounders or co-exposure to other substances.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

Another inhalation study with **Aroclor 1242** was carried out in male Sprague Dawley rats. The animals were exposed nose-only to Aroclor 1242 about?concentrations of 8.2 mg/m^3 for 2 hours a day, for 4 or 10 days. Toxic effects on the respiratory tract were not detected. Bronchoalveolar lavage (macrophage count, protein level, lactaldehydrogenase and cytokines) and the histopathology of the nose and lung, liver and thymus were unchanged compared with in the control animals (Hu et al. 2010).

An toxicokinetics study with inhalation exposure was carried out using a 65:35 mixture of **Aroclor 1242** and **1254** to simulate the exposure profile to airborne PCBs in Chicago. Male Sprague Dawley rats were exposed to total PCBs at 0.52 mg/m^3 for 1.6 hours per day, on 5 days per week, for 4 weeks. BALF (cell count, protein level, LDH and cytokines), histopathology of the nose, lung, liver, kidneys, thymus, thyroid and spleen and CYP1A1, 1A2, 2B1 and 2B2 activities in the liver and lung were unchanged. In the blood, glutathione (GSH) decreased by 24% and glutathione disulphide (GSSG) increased by 100%, accompanied by an increase in the haematocrit, but there were no other haematological changes (Hu et al. 2012). The reduced GSH levels and the increased GSSG levels may be evidence of oxidative stress.

Reproductive and developmental toxicity

Developmental toxicity

All studies relevant to the evaluation of developmental toxicity were described in detail in the 2013 supplement (supplement "Chlorinated biphenyls" 2013). The results are summarized below.

Monkeys were the most sensitive species for monochlorinated, dichlorinated and trichlorinated biphenyls and lower chlorinated mixtures. The NOAEL (no observed adverse effect level) for toxic effects on prenatal development after exposure to Ar-

oclor 1016 was 4.5 µg/kg body weight and day for monochlorinated, dichlorinated and trichlorinated biphenyls and lower chlorinated mixtures. Developmental neurotoxicity was observed only at 24 µg/kg body weight and day and above. Exposure to Aroclor 1254, as a representative of tetrachlorinated and higher chlorinated biphenyls and their mixtures, yielded an almost identical NOAEL of 5 µg/kg body weight and day for developmental toxicity. Therefore, both monochlorinated, dichlorinated and trichlorinated biphenyls andlower chlorinated mixtures as well as tetrachlorinated and higher chlorinated biphenyls and their mixtures can be evaluate together as regards the end point developmental toxicity.

Genotoxicity

All studies relevant to the evaluation of developmental toxicity were described in detail in the 2013 supplement (supplement "Chlorinated biphenyls" 2013). The results are summarized below.

Arene oxide, which readily forms in metabolism at cytochrome P450 preferably in the para position, is assumed to be responsible for the mechanism of the genotoxicity of monochlorinated and dichlorinated biphenyls. Arene oxides are strongly electrophilic compounds that readily react with cellular components such as proteins and DNA. The hydroquinones and semiquinones also formed are likewise very reactive. Evidence was provided that PCB 3 (4-chlorobiphenyl) and the quinone metabolites covalently bind to the DNA and have mutagenic effects in vitro and in vivo. Binding to the sulfhydryl groups of proteins induced GSH depletion, oxidative stress and toxicity in the cells. Most of these studies were carried out with PCB 3, while others examined biphenyls that are dichlorinated or trichlorinated on the same ring (PCB 12 and PCB 38). Genotoxicity studies are available only for a few monochlorinated, dichlorinated and trichlorinated biphenyls (PCB 1, 2, 3, 12, 15 and 38) and their mixtures (Aroclor 1016, Aroclor 1242, Kanechlor 30 and Clophen 30).

Genotoxicity studies with mixtures such as Aroclor 1254 yielded mainly negative results (supplement "Chlorinated biphenyls" 2013).

As the studies of the mutagenicity of lower chlorinated biphenyls play a decisive role in the evaluation of both carcinogenicity and germ cell mutagenicity, they are again described in detail below in comparison with the studies of higher chlorinated biphenyls.

In vivo treatment of male BigBlue rats with **PCB 3** doses of 113 mg/kg body weight (intraperitoneal, once a week for 4 weeks) and 4-hydroxy-4′-chlorobiphenyl led to a significant induction of mutations in the liver. There was an increase in the mutation frequency in the lung, but it was not significant. Also in female BigBlue rats an increase in mutations in the liver and lung was found, but this increase was likewise not significant (Jacobus et al. 2010; Robertson and Ludewig 2011).

On day 10 of gestation, higher intraperitoneal doses of the **Aroclor 1221** mixture (1000 mg/kg body weight as compared with the breeding colony control animals) caused mutations in foetal melanoblasts which were manifest as black spots on grey fur in the offspring. At 300 and 500 mg/kg body weight, there was no difference to the breeding colony control group. At 500 mg/kg body weight and above, there were significant differences compared with the concurrent control group; the frequency of the spots in this group was very low (3.9%) and outside the range of 5.6%–11% established in the historical control animals. In many cases, the doses approached the maximum levels tolerated by the dams. At 1000 mg/kg body weight, the litter size was significantly reduced; at the other dose levels, the litter size decreased, but it was not significantly different to that of the concurrent control group (Schiestl et al. 1997).

On day 10 of gestation, the **Aroclor 1260** mixture, about 91% of which consisted of pentachlorinated, hexachlorinated and heptachlorinated biphenyls, induced mutations in foetal melanoblasts after asingle intraperitoneal injection of 500 mg/kg body weight compared with in both the concurrent control group and the breeding colony control group. At a dose of 75 mg/kg body weight, there was no difference to either control group. The litter size decreased compared with that in the controls, but it was not significantly different to that of the controls (Schiestl et al. 1997).

In BigBlue mice, **Aroclor 1254** induced a small increase in mutations in the liver (0.01% Aroclor in the diet, for 7 weeks, at about 50 mg/kg body weight and day) (Davies et al. 2000).

A dominant lethal test after short-term oral treatment of male rats with the **Aroclor 1242** mixtures (gavage; single dose of 625, 1250 and 2500 mg/kg body weight or 5 daily doses of 125 and 250 mg/kg body weight and day) yielded negative results. Dominant lethal tests in male rats after short-term oral treatment or long-term feeding yielded negative results with the **Aroclor 1254** mixture (5 daily doses of 75, 150 and 300 mg/kg body weight and day by gavage or 0, 25 and 100 mg/kg diet for 70 days, about 1.9 and 7.5 mg/kg body weight and day) (Green et al. 1975).

The following study was published after the 2013 supplement. Swiss mice were given intraperitoneal doses of **Aroclor 1254** of 0, 1, 2 or 4 mg/kg body weight and day for 5 weeks; afterwards, the sperm were investigated using the comet assay and the spermatocytes of the first meiotic metaphase were tested for chromosomal aberrations and changes in the gene expression of apoptotic and DNA damage repair genes (*p53, PARP1, BAX, XRCC1, APEX1* and *OGG1*). The doses were established on the basis of the Aroclor 1254 concentrations found post mortem in human tissues. In the comet assay, the incidence of DNA single strand breaks was increased only in sperm that were investigated 3 or 24 hours after the last treatment and only at 4 mg/kg body weight. Cyclophosphamide was used concurrently as a positive control. In addition, chromosomal aberrations were significantly increased in the spermatocytes of the first meiotic metaphase at 4 mg/kg body weight. After the additional treatment of the sperm DNA with endonuclease III or formamidopyrimidine, oxidative DNA damage was detected at 2 mg/kg body weight and day

and above at the investigations after 3 and 24 hours or 3 hours, respectively. The mRNA expression of *p53, PARP1* and *BAX* increased 1.5-fold in the testes at 4 mg/kg body weight and day. The decrease in the expression of DNA repair enzymes *OGG1* and *APEX1* that was found 3 hours after the last treatment indicates the inhibition of DNA repair. *OGG1* expression was also reduced 24 hours after the last treatment, whereas APEX 1 expression had recovered by then (Attia et al. 2014). The authors discussed the inhibition of DNA repair as a possible mode of action for gonadal toxicity and carcinogenicity.

Conclusion: Monochlorinated to trichlorinated PCBs and their metabolites and mixtures (Aroclor 1221) were mutagenic both in vitro and in vivo. Tetrachlorinated and higher chlorinated mixtures (Aroclor 1254 and Aroclor 1260) induced mutations in vivo sporadically and at high doses, although the in vivo doses of lower and higher chlorinated Aroclor were similar. Secondary genotoxicity by redox cycling and the inhibition of DNA repair may be a mechanism of action.

Carcinogenicity

As described in the 2013 supplement (supplement "Chlorinated biphenyls" 2013), PCB mixtures with a higher degree of chlorination caused increased incidences of hepatocellular carcinomas in the liver of rats (Mayes et al. 1998; Schaeffer et al. 1984) and mice (Ito et al. 1973), whereas such findings were not induced by lower chlorinated PCBs at the same external dose (Table 5).

In the study of Ito et al. (1973), the animals were exposed for only 32 weeks;

Table 5 Carcinogenicity of Aroclor, Kanechlor and Clophen mixtures

Author:	Mayes et al. 1998
Substance:	**Aroclor 1016**, **Aroclor 1242**, **Aroclor 1254**, **Aroclor 1260**
Species:	**rat**, Sprague Dawley, 50 ♂ and 50 ♀ per substance and dose group
Exposure :	oral, via the diet
Dose:	1 control group of 100 ♂ and 100 ♀ for all 4 mixtures
	Aroclor 1016: 2/2.7, 4/5.4, 8/11.2 mg/kg body weight and day for ♂ and ♀; PCDD: 0.6 µg/kg; PCDF: 0.035 mg/kg
	Aroclor 1242: 2/2.8, 4/5.7 mg/kg body weight and day for ♂ and ♀; PCDD: 0.0 µg/kg; PCDF: 2.9 mg/kg
	Aroclor 1254: 1/1.4, 2/2.9, 4.3/6.1 mg/kg body weight and day for ♂ and ♀; PCDD: 20 µg/kg; PCDF removed (originally: 23 mg/kg)
	Aroclor 1260: 1/1.4, 2/2.8, 4.1/5.8 mg/kg body weight and day for ♂ and ♀; PCDD: 0.0 µg/kg; PCDF: 4.9 mg/kg
Duration:	2 years, 7 days/week
Toxicity:	Aroclor 1254 and Aroclor 1260 high dose groups: body weight gains ↓

Table 5 (Continued)

Tumours	Dose				
		0	low	middle	high
liver:					
Aroclor 1016 – ♂ survival about 45% (controls) to 30% (highest exposure group; from graph); ♀: mortality higher in control animals than in exposed animals					
hepatocellular adenomas	♂	4/100 (4%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
	♀	1/100 (1%)	1/50 (2%)	**5/50 (10%)***	**5/50 (10%)***
hepatocellular **carcinomas**	♂	3/100 (3%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
	♀	0/100 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Aroclor 1242 – ♂ survival about 45% (controls) to 52% (highest exposure group; from graph); ♀: mortality higher in control animals than in exposed animals					
hepatocellular adenomas	♂	4/100 (4%)	1/50 (2%)	–	3/50 (6%)
	♀	1/100 (1%)	**10/50 (20%)****	–	**12/50 (24%)****
hepatocellular **carcinomas**	♂	3/100 (3%)	1/50 (2%)	–	1/50 (2%)
	♀	0/100 (0%)	0/50 (0%)	–	2/50 (4%)
Aroclor 1254 – ♂ survival about 45% (controls) to 20% (highest exposure group; from graph); ♀: mortality higher in control animals than in exposed animals					
hepatocellular adenomas	♂	4/100 (4%)	2/50 (4%)	2/50 (4%)	6/50 (12%)
	♀	1/100 (1%)	**18/50 (36%)****	**26/50 (52%)****	**27/50 (54%)****
hepatocellular **carcinomas**	♂	3/100 (3%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
	♀	0/100 (0%)	0/50 (0%)	**4/50 (8%)***	**6/50 (12%)****
Aroclor 1260 – ♂ survival about 40% (controls) to 30% (highest exposure group; from graph); ♀: mortality higher in control animals than in exposed animals					
hepatocellular adenomas	♂	4/100 (4%)	2/50 (4%)	5/50 (10%)	**7/50 (14%)***
	♀	1/100 (1%)	**9/50 (18%)****	**10/50 (20%)****	**21/50 (42%)****
hepatocellular **carcinomas**	♂	3/100 (3%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
	♀	0/100 (0%)	1/50 (2%)	1/50 (2%)	**5/50 (10%)****

*$p \leq 0.05$;**$p \leq 0.01$
no historical control data reported

Author:	Schaeffer et al. 1984
Substance:	Clophen A30 (1% mono, 20.7% di, **57.4% tri**, 17.3% tetra, 1.8% penta, 1.08% hexa, 0.6% hepta, 0.1% octachlorobiphenyl); Clophen A60 (0.2% mono, 1.1% di, 2.2% tri, 3.1% tetra, 19.8% penta, **43.2% hexa**, 25.3% hepta, 4.7% octa, 0.3% nonachlorobiphenyl)
Species:	**rat**, Wistar, 139–152 ♂ per substance and dose group (with interim examinations)
Exposure:	oral, via the diet

Table 5 (Continued)

Dose:	Clophen A30 and Clophen A60: 100 mg/kg diet (about 5 mg/kg body weight and day)[a)]		
Duration:	832 days, 7 days/week		
Toxicity:	incidence of bile duct hyperplasia for Clophen A30 and A60 ↑, liver cysts for Clophen A60 ↑		
	Exposure		
	controls	Clophen A30	Clophen A60
Tumours and pre-neoplasms[b)]			
liver:			
foci	17/53 (32%)	43/87 (49%)	0/85
neoplastic nodules	2/53 (4%)	35/87 (40%)	34/85 (40%)
hepatocellular carcinomas	1/53 (2%)	3/87 (3%)	52/85 (61%)

[a)] conversion factor: 0.05 long-term (EFSA 2012), [b)] only animals that were examined after > 800 days

Author:	Ito et al. 1973			
Substance:	Kanechlor 300, 400 and 500			
Species:	**mouse**, dd, 12 ♂ per dose, 6 controls			
Exposure:	oral, via the diet			
Dose:	100, 250 or 500 mg/kg diet (about 15, 37.5, 75 mg/kg body weight)[c)]			
Duration:	32 weeks, 7 days/week			
Toxicity:	at 100 mg/kg and above liver weights ↑, at 250 mg/kg and above hypertrophy of hepatocytes, bile duct hyperplasia, increase in oval cells with increase in chlorination, decrease in amyloid degeneration in the liver with increase in dose and degree of chlorination			
	Dose (mg/kg diet)			
	0	100	250	500
Tumours and pre-neoplasms				
liver:				
Kanechlor 500[d)]				
nodular hyperplasia	0/6	0/12	0/12	7/12 (58%)
hepatocellular carcinomas	0/6	0/12	0/12	5/12 (42%)

[c)] conversion factor: 0.15 long-term (EFSA 2012), [d)] no tumours with Kanechlor 300 and 400

therefore, it cannot be ruled out that Kanechlor 300 and 400 might have caused carcinomas in the liver after prolonged exposure. Nevertheless, the higher potency of Kanechlor 500 is obvious.

Manifesto (MAK value/classification)

MAK value. Derivation of a MAK value for monochlorinated to trichlorinated PCBs:

From the inhalation studies carried out to date with PCB 3 and PCB 11, it can be concluded that the liver, rather than the lung, is the primary target organ of these PCBs. Monochlorinated biphenyls were not found in the tissues although they accounted for 11% of the concentration in the air after exposure to a mixture of Aroclor 1242 and 1254.

PCB 28, a trichlorinated biphenyl, is the congener with the highest body burden of monochlorinated to trichlorinated PCBs in rats. A comparison of the half-lives would be important for extrapolation to humans.

The half-life of PCB 28 in the blood of humans occupationally exposed to Aroclor is 4.6 years (Seegal et al. 2011). In rats, it was found to be 11 hours after short-term exposure to PCB 20 and PCB 28 (Hu et al. 2010); however, the congener accumulates in adipose tissue. To be able to compare the data, the half-life after prolonged exposure should therefore be considered, like in humans with initial accumulation and then redistribution from the adipose tissue to the blood. Furthermore, the metabolism of monochlorinated to trichlorinated congeners in rats and humans should be known for a more accurate extrapolation between species. However, such data are not available.

In the study of Hu et al. (2012), exposure to total PCBs (85% of which were monochlorinated to trichlorinated PCBs) in the air (1.6 hours × 0.52 mg/m^3) was about 35 times higher than the MAK value for PCBs with more than 4 chlorine atoms (8 hours × 0.003 mg/m^3), and there were no toxic effects on the lung, nose, liver or thymus; the exposure lasted for only 4 weeks. However. effects are expected to occur, if monochlorinated to trichlorinated PCBs form reactive oxygen species or adducts with macromolecules. It must be borne in mind when evaluating the carcinogenicity that the 100-fold higher levels of monochlorinated to trichlorinated PCBs investigated in the oral carcinogenicity studies did not induce liver carcinomas and caused a far lower incidence of adenomas than higher chlorinated PCBs, if monochlorinated to trichlorinated PCBs cause liver tumours at all.

As the level of exposure in the 4-week study calculated above was 35 times higher than the MAK value of 0.003 mg/m^3 I, this should therefore offer sufficient protection from adverse effects induced by monochlorinated to trichlorinated PCBs.

Peak limitation. Because of their systemic effect with long half-lives, all chlorinated biphenyls have been listed in Peak Limitation Category II with an excursion factor of 8.

Prenatal toxicity. Monkeys were found to be the most sensitive species for monochlorinated, dichlorinated and trichlorinated biphenyls and lower chlorinated mixtures; after exposure to Aroclor 1016, birth weights were reduced at 18 µg/kg body weight and day and above and deficits in behaviour and learning were ob-

served at 24 µg/kg body weight and day and above. The NOAEL for toxic effects on prenatal development was 4.5 µg/kg body weight and day for monochlorinated, dichlorinated and trichlorinated biphenyls and lower chlorinated mixtures based on exposure to Aroclor 1016.

Exposure to Aroclor 1254 as a representative of tetrachlorinated and higher chlorinated biphenyls and their mixtures yielded an almost identical NOAEL of 5 µg/kg body weight and day for developmental toxicity. Therefore, monochlorinated, dichlorinated and trichlorinated biphenyls and lower chlorinated mixtures as well as tetrachlorinated and higher chlorinated biphenyls and their mixtures can be considered together as regards the end point developmental toxicity.

The body burden was estimated from Aroclor 1254 because blood level data in monkeys are available for this mixture. At the NOAEL of 5 µg/kg for developmental toxicity in monkeys, the level of Aroclor 1254 in blood is 10 µg/l. Human data (Schettgen et al. 2011 b in supplement "Chlorinated biphenyls" 2013) have shown that after exposure to total PCBs at a concentration of 4.28 µg/m³ the blood level is 10 µg/l plasma. Therefore, at the MAK value the difference from the NOAEL in monkeys is insufficient. Epidemiological data obtained from humans provide evidence of developmental toxicity caused by chlorinated biphenyls (supplement "Chlorinated biphenyls" 2013).

Therefore, it cannot be ruled out that toxic effects on development may be induced by exposure at the level of the MAK value, and all chlorinated biphenyls have been classified in Pregnancy Risk Group B.

Carcinogenicity. After oral and inhalation exposure with PCB, the PCB burden in rat livers and lungs is similar. The metabolism to potentially genotoxic hydroxy compounds occurs/happensmainly in the liver, sothis is assumed to be the target organ also after inhalation. Changes in the respiratory tract or lung that might indicate carcinogenicity were not observed after almost identical PCB exposure in the liver and lung. Evidently, the assumed genotoxicity of monochlorinated to trichlorinated PCBs does not play a role in possible local carcinogenicity. Genotoxicity apparently plays only a minor role in the systemic carcinogenicity in the liver. Carcinogenic effects of monochlorinated to trichlorinated PCBs on the liver were not detected in oral studies; however, as inhalation exposure to PCBs at the workplace always takes place in the form of mixtures containing both monochlorinated to trichlorinated PCBs and higher chlorinated PCBs, a common MAK value also requires common classification. All chlorinated biphenyls have been classified in Carcinogen Category 4.

Germ cell mutagenicity. No difference was found between lower chlorinated and higher chlorinated biphenyls as regards the doses that yield positive results in genotoxicity tests: some tests in mammalian cells provided evidence of DNA strand breaks, sister chromatid exchange, micronuclei and chromosomal aberrations (lower chlorinated biphenyls: PCB 2, PCB 3 and Aroclor 1221; higher chlorinated biphenyls: PCB 52 and PCB 77). Likewise, there was little difference in the mutagenic

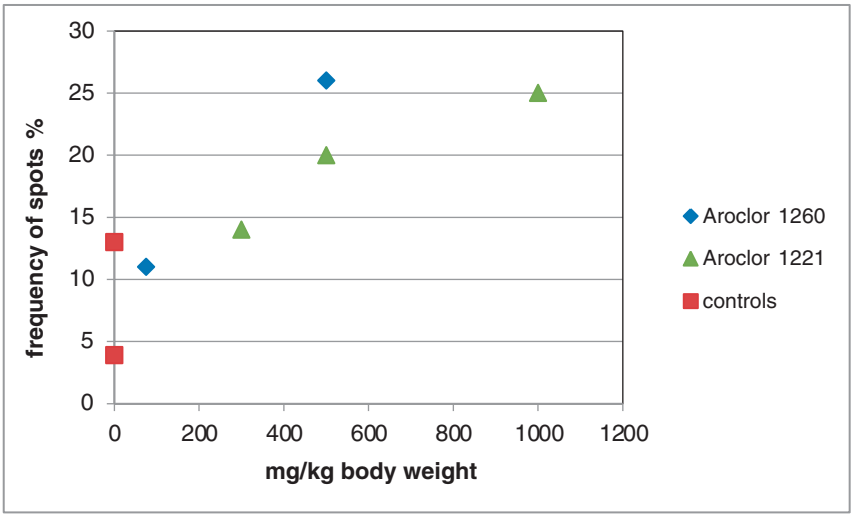

Figure 1 Percentage of the offspring of mice with spots on their fur in spot test (Schiestl et al. 1997)

effects in spot tests with Aroclor 1260 (only pentachlorinated and higher chlorinated PCBs: about 70% hexachlorinated and heptachlorinated) and Aroclor 1221 (monochlorinated to tetrachlorinated PCBs: 51% monochlorinated) (see Figure 1; Schiestl et al. 1997).

The classification of higher chlorinated biphenyls in Category 5 for Germ Cell Mutagens was based on the study of Schiestl et al. (1997). Mutations were induced only at high doses (Aroclor 1260: 500 mg/kg body weight). Therefore, provided the MAK and BAT values are observed, only a very small contribution to the genetic risk for humans is expected as the MAK value for tetrachlorinated and higher chlorinated PCBs ensures? that the body burden in humans corresponds to the NOAEL of 10 µg/kg body weight for rats.

This conclusion also applies to Aroclor 1221 (1000 mg/kg body weight) as can be seen from the data obtained by Schiestl et al. (1997). In addition, the effect on the liver, as the critical end point, of lower chlorinated PCBs is less pronounced than that induced by tetrachlorinated and higher chlorinated PCBs (see carcinogenicity studies). PCB 3, which is the most potent PCB of the lower chlorinated biphenyls, induced mutations in the liver of male BigBlue rats after the administration of 113 mg/kg body weight and day once a week for 4 weeks (total dose: 452 mg/kg body weight). The doses that induce mutations are thus in the same dose range. This means that lower and higher chlorinated biphenyls can be evaluated together as regards their germ cell mutagenicity. All chlorinated biphenyls have been classified in Category 5 for Germ Cell Mutagens.

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