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Polychlorinated Biphenyl (PCB) carcinogenicity with special emphasis on airborne PCBs

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Abstract

Polychlorinated biphenyls (PCBs) are industrial chemicals used in various applications requiring chemical stabilityand have now become widely dispersed. Their characteristics of persistence, low water/higher lipid solubility, contribute to their ability to bioconcentrate and bioaccumulate. Traditionally PCBs have been regulated as food contaminants and the general population is primarily exposed by that route. PCBs in foodstuffs are generally higher chlorinated, resistant to metabolic breakdown, and elicit toxic changes that are thought to be predominantly receptor/parent PCB-driven. But for certain occupational exposures, and for those persons residing or working in contaminated buildings, and in large cities, an inhalation route of exposure may predominate. Airborne PCBs are, in contrast to foodborne PCBs, lower chlorinated, more volatile, and subject to metabolic attack. In this review, we have explored (geno-) toxic manifestations of PCBs typical of those found in air. Here metabolic conversion of the parent PCB to hydroxylated and other metabolic progeny appear to play a dominant role, especially in genotoxicity. We should be cognizant of the impact of exposures to airborne PCBs for those individuals who are occupationally exposed, for persons living near contaminated sites, for those who work or go to school in contaminated buildings, and especially cognizant of the young, the socio-economically disadvantaged and medically-underserved or nutritionally-deficient populations.

1. Introduction - Sources of PCBs

PCBs have been commercially manufactured since the 1920's for use as dielectrics in transformers and capacitors, as cooling fluids in hydraulic systems, in the formulation of lubricating and cutting oils, in pesticides and flame retardants, and as plasticizers in paints, copying paper, adhesives, sealants and plastics [1,2]. The stability of these compounds, one of their commercial attributes, has led to their worldwide distribution in the environment, as first reported by Jensen in 1966 [3]. The production of PCBs peaked in the 1970's and has steadily declined thereafter as many countries throughout the world have banned their use or limited their production. Nevertheless these compounds remain in use today in our environment and represent a potential human health hazard [4–6].

An overlooked source of PCB exposure is airborne PCBs. Regular monitoring of environmental PCBs in water, fish, and sediment of the Great Lakes and other regions in the US started in the 1980's [7]. Such non-atmospheric sources of PCBs are carefully monitored

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and regulated. Air as a source of PCB exposure, however, was nearly completely ignored until a decade ago. Systematic measurements of atmospheric PCBs started only in the 1990's. The first urban monitoring site in the USA was installed in Chicago in 1995. The level of PCB contamination in the air is strongly influenced by temperature. In Chicago air concentrations between 100–300 pg/m^3 in winter and up to 5,000–16,000 pg/m^3 on hot summer days were reported (reviewed in [8]). The levels at the sources of these atmospheric PCBs may even be significantly higher. Inhalation exposure is considered to be a major route of occupational exposure to PCBs, and it was estimated that in capacitor workers, for example, a maximum of 80% of adipose PCBs may have been absorbed by inhalation exposure [9]. Recently high levels of PCBs were measured in indoor air in buildings constructed in the 1970's using joint sealants that contained 4–9% PCBs. Indoor air concentrations up to 13,000 ng/m^3 were measured in some classrooms of a contaminated school [10], which is more than an order of magnitude above the NIOSH guidelines of 1 pg/m^3 for occupational settings. Other possible sources for indoor PCBs are believed to be data screen terminals [11], ceiling tiles and fluorescent lights [12]. It was reported that the concentration of PCBs in indoor air can be at least an order of magnitude higher than outdoor air [13–15], however, regional outdoor levels can be very high due to activities like building renovations, dredging, or contamination from cement factory exhaust [16–18]. The serum levels of workers engaged in sealant removal was 2–10 times higher at the end of these activities than they had been one year before [19]. Thus under certain circumstances the intake from inhalation exposure exceeds PCB intake from food.

PCBs in foods, like fish or mothers' milk, and in human adipose tissue are usually the higher chlorinated ones, where congeners like PCBs 153, 180, 183 and others predominate. Airborne PCBs are very different, since they require volatilization. Major congeners in Chicago air, for example, are lower congeners, like PCBs 4, 8, 11, 18, 28, 52, 95, 112, to name some (Figure 1) [20]. As a consequence of this difference, in two populations in Italy the more urban group had significantly higher levels of lower chlorinated PCBs (PCB52 was about 100-fold higher) than the population in a more rural environment [21]. In Germany, PCB28 and PCB52 were the prevailing congeners in indoor air of contaminated schools [10,22]. Elevated levels of PCB28 and PCB52 were measured in the blood of teachers from these schools compared to non-contaminated schools, whereas the mean blood levels of higher chlorinated PCBs, i.e. PCB138, 153 and 180 were almost identical [22]. Children in schools with 690 – 20,800 ng PCB/m^3 air had median levels of 6, 9, and 5 ng/l PCB28, 52, and 101, respectively, whereas children in non-contaminated schools had levels below the detection level of 1 ng/L [23]. Both groups had no significant differences in PCB138, 153 and 180 levels, indicating that indoor air exposure contributed to the PCB body burden. In Germany the non-occupational tolerable indoor air PCB concentration was set at 300 ng/m^3 based on a tolerable daily intake (TDI) of a total of 1 ug/kg body weight [24]. Not only were these levels exceeded in several schools, but this TDI is also based on a chronic toxicity study with a commercial PCB mixture, which measured hepatic enzyme induction as endpoint [25]. Airborne PCB profiles are distinctly different from those of commercial PCB mixtures, like Aroclor 1254, and enzyme induction in the liver is an inappropriate endpoint of toxicity for inhalation exposure of airborne PCBs.

2. Carcinogenicity of PCBs

PCBs have been categorized by the International Agency for Research on Cancer (IARC) as "Probably carcinogenic to humans" (Group 2A) [26], and by the National Toxicology Program 11th Report on Carcinogens as "Reasonably anticipated to be human carcinogens". A detailed summary of the health effects of PCBs was prepared for the Agency for Toxic Substances and Disease Registry (ATSDR) and published in 1990 as a Toxicological Profile [27]. Other detailed reviews are available in the literature, emphasizing animal data, human

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studies, and mechanistic studies of the genotoxic effects of PCB individual congeners and mixtures [1,28,29]. A summary of recommendations for selected IARC-classified agents was recently published [30,31].

3. PCBs are Initiators and Promoters of Carcinogenesis

The process of carcinogenesis in many, if not all, tissues involves at least two stages, initiation and promotion, based on observations originally seen in mouse skin and later demonstrated in other tissues [32,33]. Mechanistically, an initiator has been defined as an agent which irreversibly alters the DNA sequence (i.e. a genotoxic compound), whereas a promoter has been defined as an agent that alters the expression of genetic information (epigenetic changes) in the cell [33]. Although their potency varies, the various commercial halogenated biphenyl mixtures have been uniformly reported to have promoting activity in various liver models [29,34]. It had been widely assumed that PCBs do not have initiating activity, but in several studies Oesterle and Deml consistently found a small number of enzyme altered foci in livers of rats treated only with the PCB mixture Clophen A50 (reviewed in [35]). The same was noted for the brominated biphenyl mixture fireMaster BP-6 [36]. Hayes and coworkers had used the modified Solt-Farber initiation-selection protocol to investigate the initiating activity of several PCBs and mixtures [37], with negative results. Our mechanistic studies predicted that the choice of PCBs in the Hayes study was not fortuitous, because the selected PCBs were so slowly metabolized that detection of initiating events was precluded. Our data, however, clearly show that several lower chlorinated PCB congeners and two PCB3 metabolites are positive in this initiation assay [38,39]. In addition, the brominated congener 3,3′,4,4′-tetrabromo-biphenyl (PBB77) was found to have both, initiating and promoting activity [40]. Because the long term administration of PCB mixtures and certain congeners leads to the development of hepatic tumors, PCBs by definition have both initiating and promoting activities. Besides liver tumors, several PCB mixtures and congeners were reported to also promote lung tumors in a mice model [41,42] and to cause lung tumors in long term rat studies conducted by the National Toxicology Program (NTP), something to keep in mind in connection with airborne PCBs. PCBs are classified as proven animal carcinogens and probable human carcinogens. The risk of airborne exposure for human health is just beginning to receive the attention that it deserves. It is the intent of the authors to devote the space below to issues related to lower chlorinated PCBs, as predominate in air, and their adverse effects, especially related to genotoxicity and carcinogenicity.

4. Metabolic Activation of Lower Chlorinated PCBs to Reactive Intermediates

It has long been recognized that biphenyl and halogenated biphenyls, particularly the lower chlorinated congeners, are hydroxylated in vivo and in vitro (see review by [43]). These hydroxylation reactions are primarily catalyzed by isoforms of cytochrome P-450. Our experiments with PCB3 (4-chlorobiphenyl) and rat liver microsomes showed that five mono- and three di-hydroxy metabolites were formed [44]. The metabolism of PCB3 by cytochrome P-450 probably involves an arene oxide intermediate [43,45]. Other arene oxides could be involved in the oxidation of the mono- to the di-hydroxy forms. Arene oxides are strong electrophiles which may react with critical cellular targets. The dihydroxybiphenyls may be further oxidized by various enzymes like peroxidases [46], prostaglandin synthase [47] and cytochrome P-450s to the corresponding quinones with the formation of a semiquinone intermediate. Ortho- and para-quinones are formed from diOH-PCB3 in vitro and demonstrate high reactivity toward nitrogen and especially sulfur nucleophiles [48]. Other experiments demonstrated that the microsomal metabolism of PCB3 resulted in the formation of adducts with nucleotides in vitro, preferentially with

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purines rather than pyrimidines [45]. Most likely at least 1 of the 4 adducts seen is derived from an arene oxide intermediate, the 3 other adducts after further oxidation probably from a quinone [45]. These results suggest that several metabolic pathways and chemical species could be involved in PCB-induced DNA adduction, without, however, telling us exactly which enzymes or metabolites are involved.

5. PCBs as Mutagens and Genotoxins

The formation of PCB-DNA adducts was also reported in cellular systems [49], and studies in vivo demonstrated covalent binding of radiolabeled PCB metabolites to nucleic acids [50–52]. The assumption that PCBs are not mutagenic is based on very little (and often contradictory) data. Of 209 possible congeneric PCBs, only five congeners, one bromo-, a few fluoro-biphenyls and five commercial PCB mixtures have been tested in the Ames bacterial mutagenicity test. Most tests gave negative results, however, Aroclor 1221, 4-bromobiphenyl, and some lower fluorinated biphenyls were positive [53]. The mutational spectra gave evidence for two mutagenic species. The reported positive effects with PCB3 [54] were not confirmed by Schoeny [55]. Thus lower halogenated biphenyls may or may not be mutagenic in bacteria, but it should be considered that the Ames test is insensitive towards whole groups of compounds, like DES, benzene and reactive oxygen species (ROS). One recent publication reported a small, but significant increase in lac I mutations in livers of transgenic (BigBlue) mice after exposure to Aroclor 1253 [56]. Clearly this and other mutagenicity tests, including those that measure chromosome mutations and genome changes, and an analysis of more congeners is needed.

Recently we have shown that several PCB3 metabolites induce gene mutations, chromosome breaks, chromosome loss and polyploidization in cells in culture and we provided the first evidence that a PCB congener is mutagenic in vivo. As seen, the early attempts to measure the genotoxicity of PCBs did not account for bioactivation of lower chlorinated congeners. Clearly, under the right metabolic conditions certain lower chlorinated PCBs can be bioactivated to genotoxins. The questions remain, which are the active metabolites, which kinds of genotoxic damage are important, what are the mechanisms of these genotoxicities, and are these issues really relevant for inhalation exposure situations as those in our inner cities and contaminated buildings?

A series of PCB3 metabolites were tested in various genotoxicity assays to determine their activity and genotoxicity profile. Both, the 3,4- and particularly the 2,5-quinone were very efficacious and potent inducers of gene mutations at the HPRT locus (Table 1). Neither of the corresponding dihydroxy metabolites nor the phenols had any activity in this assay. The 2,5-quinone (2,5-pQ) was also by far the most potent and efficacious inducer of chromosome breaks as determined by Crest-negative micronuclei induction. This suggests that at least some of the HPRT gene mutations may be due to breaks in the X-chromosome. The *ortho*-quinone (3,4-oQ), 3,4- (3,4-Cat) and 2,5-dihydroxy (2,5-HQ) and 4-monohydroxy metabolites (4-OH) induced some chromosome breaks at the highest concentration tested, but their by far stronger activity was the induction of chromosome loss (Crest-positive micronuclei). In this respect 4-OH and 2-OH were the most potent metabolites tested, while the dihydroxy and quinone metabolites produced significant chromosome loss at more than 10-fold lower concentrations (above results were published in [57]. Two unique effects stand out: only one metabolite, the 3,4-catechol, induced sister chromatid exchanges (SCE), and only the 2,5-hydroquinone (2,5-HQ) caused tetraploidization of cells, and this with an efficacy of nearly 100% at 7.5 μM concentration [58]. Tetraploidization followed by uneven chromosome loss is believed to be a major pathway of carcinogenesis. The mystery surrounding this polyploidization is, however, the mechanism by which it occurs. According to the staining pattern (all dark) the cells were not in the second M-phase as they should be.

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Time-lapse microscopy showed that these cells were arrested in first G2/M, but then went out of G2/M and shortly afterwards fused with surrounding cells. This intriguing observation is under further analysis.

Very interesting also is the fact that 2,5-HQ and it's oxidation product 2,5-pQ have such different profiles. To gain further insight into the mechanism and potential organ specificity of effects, two cell lines were employed that differ in their amount of myeloperoxidase (MPO), an enzyme found in bone marrow cells and others and expected to oxidize hydroquinones to quinones. The 2,5-pQ induced DNA strand breaks, measured with the COMET assay, in both cell lines and at 37 and 6°C; The 2,5-pQ also increased intracellular ROS while decreasing GSH levels. On the other hand 2,5-HQ induced COMETs and ROS only in MPO-positive HL-60 cells and at 37°C, indicating that this metabolite needs to be bioactivated by MPO [59].

These results show that metabolites of PCB3 are indeed genotoxic and that each metabolite induces its own, specific type of DNA damage. What these results do not explain is the mechanism of genotoxicity for the individual endpoints, whether this is of any importance *in vivo* or which metabolic activation pathway(s) could be leading to these effects. To address these questions, male transgenic BigBlue rats were injected ip with PCB3, 4OH-PCB3, 3-methylcholanthrene (3-MC), or corn oil and the induction of point mutations was analyzed in the lacI indicator gene. PCB3 increased the mutation frequency in the liver (significantly) and lung (non-significantly) of BigBlue rats, and changed the mutation spectrum in both organs from predominantly transitions to predominantly to GC → TA transversions. 4OH-PCB3 had a similar, but smaller and effect that was below the level of statistical significance [60,61]. Female rats were by far less susceptible to mutation induction in the liver, reminding us that gender differences have to be considered [62] This demonstrates that this PCB congener is mutagenic *in vivo* in the target organ liver and most likely also in the lung. However, this still does not explain the mechanism of genotoxicity (DNA adduction or ROS?), the metabolic activation pathway (*ortho*- or *para*-quinone, or epoxide or other metabolite?), or whether the most likely route of exposure, inhalation of contaminated indoor or outdoor air, may pose a significant risk for carcinogenicity in humans.

6. Oxidative DNA Damage

There is considerable evidence that lower chlorinated PCBs produce reactive oxygen species (ROS) and intracellular oxidative stress [46,63]. Free radicals, particularly hydroxyl radicals, may produce 8-oxodeoxyguanosine (8-oxodG), a DNA lesion that is highly mutagenic, producing G → T transversions [64]. Hydroxyl radicals can also attack fatty acids (linoleic acid, linolinic acid, oleic acid, etc) and form lipid peroxidation-derived enals, such as acrolein, crotonaldehyde, trans-4-OH-2-nonenal (4-HNE), and malondialdehyde (MDA) [65]. These products can then modify DNA bases, resulting in cyclic adducts by interaction of their difunctional groups with NH_2 group in dA, dG ordC residues in DNA [66–68]. These cyclic adducts are mutagenic, producing base substitutions and deletions, for example G → T mutations from propano-dG and C → A mutations from various etheno adducts [64,69,70]. Therefore the question of mutagenicity of PCBs, especially congeners that are prone to metabolic activation to redox cycling intermediates, like those from airborne PCBs, should be re-analyzed.

7. PCBs cause Karyotype Changes

Induction of chromosome aberrations and genome mutations may be an essential part of PCB carcinogenicity. Aroclors or Kanechlors produced chromosome aberrations in embryos of PCB-treated ring doves [71] and in bone marrow cells of mice in vivo [72], and chromosome aberrations in lymphocytes [73] and sarcoma cells in vitro [72]. Sargent and

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coworkers [73] also tested two congeners, 3,3′,4,4′-tetrachlorobiphenyl (TCB; PCB77) and 2,2′,5,5′-TCB (PCB 52) and found chromosome breakage and rearrangements with both and a more-than-additive effect in combinations of the two PCBs in human lymphocytes in vitro. Both congeners also induced preneoplastic foci and chromosome aberrations in rats in vivo, and the combination of the congeners again had a more than additive effect [74,75]. The most common types of aberrations were trisomy of chromosome 1 on its long arm and monosomy of chromosome 3 on its short arm. Specific chromosome aberrations and hepatocellular carcinoma correlated so that they hypothesized that “genes involved in the development of hepatic carcinoma may reside in chromosome 1 and/or 3 of the rat” [75]. These data indicate that we need to better understand the mechanism of these effects and structure-activity relationships for all PCB congeners, if we want to understand the cancer risks associated with daily inhalation exposure to PCB congeners that may be bioactivated to clastogens and aneugens. Our experiments with PCB3 metabolites are a first step in that direction, but more work needs to be done.

8. PCBs cause Telomere Shortening

Telomeres are small but very important segments of chromosomes that are needed for chromosome stability. PCB3 and the two metabolites tested, 2,5-quinone and 3,4-diOH catechol, cause telomere shortening [76]. The effect was strong in TERT-immortalized human primary fibroblasts and immortal keratinocytes (HaCaT) and not significant in human primary fibroblasts, possibly because senescence started to interfere at the end of the experiment. Shortening of telomeres would indicate that cells exposed to these compounds may senesce prematurely in animals/humans.

Also measured was telomerase activity in cells exposed for 6 h to PCB3-2,5pQ and PCB3-3,4diOH. A significant increase in activity in HaCaT and TERT-immortalized fibroblasts was found. PCB3 did not increase the telomerase activity in HaCaT at the very high concentration tested. These findings seem to contradict each other, since an increased telomerase activity should prevent telomere shortening, which was observed with the same compounds after 6 and 12 weeks of exposure. However, telomerase activity was measured early, after only 6 h of exposure, and may not be maintained for long and of course, why and how was telomerase activity increased: a feed-back mechanism signaling that the telomerase is not functioning correctly, a consequence of signaling pathway activation, a consequence of transient c-myc or growth factor activation?

Another puzzling aspect is the fact that not only the quinone, but also the mother compound, PCB3 itself, reduced telomere length. The quinone was expected to produce intracellular oxidative stress, a factor known to produce telomere shortening [77]. In addition, the quinone can bind to DNA (and presumably RNA) and to proteins [45,48], which could interfere with the telomerase function. The 3,4diOH metabolite is expected to be oxidized with the formation of ROS and reactive semiquinone-quinone. PCB3 on the other hand is not very reactive. Since these first observations we now have evidence that several additional PCB congeners cause a shortening of the telomeres and, during long-term exposure (1–4 weeks), to a reduction in telomerase activity in immortal human HaCaT keratinocytes (Senthilkumar et al, unpublished results). Since stem cells and the basal cells of permanently proliferating tissues like skin and GI tract express and depend on telomerase activity [78–80], a chronic exposure to these PCB congeners could have so far unrecognized consequences.

Overall these new observations are extremely interesting; they pose a number of important questions that need to be answered: what is the mechanism of telomere shortening by these different compounds?; what is the cause of telomerase activity increase or decrease and how

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persistent is it?; which PCB congeners and metabolites have this effect ? and can we deduce a structure-activity relationship?, which in tern may help us to unravel the mechanism(s). Obviously we are only at the beginning of extended series of experiments that are needed to understand the risk that PCBs may cause through this newly discovered mechanism. If we understand the effects of PCBs on the telomerase complex (hTERT and its RNA template, hTR) we will be better equipped to understand the need to include telomere/telomerase research in the analysis of the effects of many man-made compounds.

9. Exposure of Humans to Airborne PCBs

The importance of airborne PCBs is now becoming understood. A PubMed search with the 2 keywords “PCB” and “air” produced 136 hits for the three most recent years (2007–2009) alone, more than in the three previous decades (1970’s – 90’s) together. Little is known, however, about the toxicity of these airborne PCBs and the consequences of exposure by inhalation compared to ingestion. Airborne PCBs are lower chlorinated and therefore relatively easily metabolized. This results in low levels of those PCB congeners detectable in blood, but at the same time provides bioactivated intermediates. Although our daily exposure to these airborne PCBs may be low under most circumstances, children playing near Superfund sites in hot summer days, workers moving dried dredging material or demolishing buildings containing PCBs, or families living unknowingly in buildings with high indoor PCB concentrations, may be exposed to significant levels of these airborne PCBs for extended periods of time. We should strive to understand the potential risks of such exposure, and to understand the mechanisms of toxicity, so that we can devise recommendations, protective strategies, predictions about possible susceptibility factors and/or interactions with other compounds. Very often Superfund sites, contaminated buildings, and multiple chemical exposures are found in poor neighborhoods, with medically underserved and nutritionally deficient children. Understanding and, if needed, ameliorating the risks is a matter of environmental justice and social responsibility.

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References

1. Ludewig, G.; Esch, H.; Robertson, LW. Polyhalogenierte Bi- und Terphenyle. In: Dunkelberg, H.; Gebel, T.; Hartwig, A., editors. Handbuch der Lebensmitteltoxikologie. Wiley-VCH; Weinheim: 2007. p. 1031-1094.
2. WHO. Environmenal Health Criteria 2. WHO; Geneva, Switzerland: 1976. Polychlorinated Biphenyls and Terphenyls; p. 85
3. Jensen S. A new chemical hazard. New Sci. 1966; 32:612.
4. Hu D, Hornbuckle KC. Inadvertent polychlorinated biphenyls in commercial paint pigments. Environ Sci Technol. 2010; 44:2822–7. [PubMed: 19957996]
5. Hu D, Martinez A, Hornbuckle KC. Discovery of non-aroclor PCB (3,3′-dichlorobiphenyl) in Chicago air. Environ Sci Technol. 2008; 42:7873–7. [PubMed: 19031874]
6. Rodenburg LA, Guo J, Du S, Cavallo GJ. Evidence for unique and ubiquitous environmental sources of 3,3′-dichlorobiphenyl (PCB 11). Environ Sci Technol. 2010; 44:2816–21. [PubMed: 20384375]
7. Schneider AR, Stapleton HM, Cornwell J, Baker JE. Recent declines in PAH, PCB, and toxaphene levels in the northern Great Lakes as determined from high resolution sediment cores. Environmental Science & Technology. 2001; 35:3809–3815. [PubMed: 11642437]

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8. Hornbuckle, KC.; Carlson, DL.; Swackhamer, DL.; Baker, JE.; Eisenreich, SJ. Polychlorinated Biphenyls in the Great Lakes. In: Hites, RA., editor. The Handbook of Environmental Chemistry. Vol. 5. Springer-Verlag; Berlin/Heidelberg: 2006. p. 13-70.
9. Wolff MS. Occupational exposure to polychlorinated biphenyls (PCBs). Environ Health Perspect. 1985; 60:133–8. [PubMed: 3928344]
10. Kohler M, Zennegg M, Waeber R. Coplanar polychlorinated biphenyls (PCB) in indoor air. Environ Sci Technol. 2002; 36:4735–40. [PubMed: 12487293]
11. Digernes V, Astrup EG. Are datascreen terminals a source of increased PCB-concentrations in the working atmosphere? Int Arch Occup Environ Health. 1982; 49:193–7. [PubMed: 6461609]
12. Harris MG. PCB exposure from fluorescent lights. Am J Public Health. 1985; 75:892. [PubMed: 3927757]
13. Balfanz E, Fuchs J, Kieper H. Sampling and analysis of polychlorinated biphenyls (PCB) in indoor air due to permanently elastic sealants. Chemosphere. 1993; 26:871–880.
14. Vorhees DJ, Cullen AC, Altshul LM. Exposure to polychlorinated biphenyls in residential indoor air and outdoor air near a Superfund site. Environ Sci Technol. 1997; 31:3612–3618.
15. Wallace JC, Basu I, Hites RA. Sampling and analysis artifacts caused by elevated indoor air polychlorinated biphenyl concentrations. Environ Sci Technol. 1996; 30:2730–2734.
16. Cullen AC, Altshul LM, Vorhees DJ. Effect of sediment remediation on polychlorinated biphenyl concentrations in tomatoes grown near New Bedford Harbor. Integr Environ Assess Manag. 2007; 3:484–90. [PubMed: 18046797]
17. Ishikawa Y, Noma Y, Mori Y, Sakai S. Congener profiles of PCB and a proposed new set of indicator congeners. Chemosphere. 2007; 67:1838–51. [PubMed: 17267022]
18. Jartun M, Ottesen RT, Steinnes E, Volden T. Painted surfaces--important sources of polychlorinated biphenyls (PCBs) contamination to the urban and marine environment. Environ Pollut. 2009; 157:295–302. [PubMed: 18706746]
19. Kontsas H, Pekari K, Riala R, Back B, Rantio T, Priha E. Worker exposure to polychlorinated biphenyls in elastic polysulphide sealant renovation. Ann Occup Hyg. 2004; 48:51–5. [PubMed: 14718345]
20. Zhao HX, Adamcakova-Dodd A, Hu D, Hornbuckle KC, Just CL, Robertson LW, Thorne PS, Lehmler HJ. Development of a synthetic PCB mixture resembling the average polychlorinated biphenyl profile in Chicago air. Environ Int. 2010; 36:819–27. [PubMed: 19375801]
21. Turci R, Finozzi E, Catenacci G, Marinaccio A, Balducci C, Minoia C. Reference values of coplanar and non-coplanar PCBs in serum samples from two Italian population groups. Toxicol Lett. 2006; 162:250–5. [PubMed: 16242275]
22. Schwenk M, Gabrio T, Papke O, Wallenhorst T. Human biomonitoring of polychlorinated biphenyls and polychlorinated dibenzodioxins and dibenzofuranes in teachers working in a PCB-contaminated school. Chemosphere. 2002; 47:229–33. [PubMed: 11993638]
23. Liebl B, Schettgen T, Kerscher G, Broding HC, Otto A, Angerer J, Drexler H. Evidence for increased internal exposure to lower chlorinated polychlorinated biphenyls (PCB) in pupils attending a contaminated school. Int J Hyg Environ Health. 2004; 207:315–24. [PubMed: 15471095]
24. ARGEBAU. Projektgruppe Schadstoffe der Fachkommission Baunormung. Richtlinie fur die Bewertung und Sanierung PCB-belasteter Baustoffe und Bauteile in Gebauden (PCB-Richtlinie). DIBt-Mitt. 1995:41 .
25. Chen T, Dubois K. Studies on the enzyme inducing effects of PCBs. Toxicol Appl Pharmacol. 1973; 26:504–512. [PubMed: 4203826]
26. IARC. Overall evaluations of carcinogenicity: an updating of IARCmonographs volumes 1 to 42. IARC Mongr Eval Carcinog Risks Hum. 1987; 7(suppl):1–440.
27. ATSDR. Toxicological profile for polychlorinated biphenyls (PCBs). 1990.
28. Safe S. Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). Crit Rev Toxicol. 1990; 21:51–88. [PubMed: 2124811]

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29. Silberhorn EM, Glauert HP, Robertson LW. Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. Crit Rev Toxicol. 1990; 20:440–96. [PubMed: 2165409]
30. Robertson, LW.; Ruder, AM. Polychlorinated biphenyls (PCBs). IARC; 2010. p. 166-183.
31. Ward EM, Schulte PA, Straif K, Hopf NB, Caldwell JC, Carreon T, DeMarini DM, Fowler BA, Goldstein BD, Hemminki K, Hines CJ, Pursiainen KH, Kuempel E, Lewtas J, Lunn RM, Lynge E, McElvenny DM, Muhle H, Nakajima T, Robertson LW, Rothman N, Ruder AM, Schubauer-Berigan MK, Siemiatycki J, Silverman D, Smith MT, Sorahan T, Steenland K, Stevens RG, Vineis P, Zahm SH, Zeise L, Cogliano VJ. Research recommendations for selected IARC-classified agents. Environ Health Perspect. 2010; 118:1355–62. [PubMed: 20562050]
32. Diamond L, O'Brien TG, Baird WM. Tumor promoters and the mechanism of tumor promotion. Adv Cancer Res. 1980; 32:1–74. [PubMed: 7008542]
33. Pitot HC, Sirica AE. The stages of initiation and promotion in hepatocarcinogenesis. Biochim Biophys Acta. 1980; 605:191–215. [PubMed: 6249365]
34. Glauert, HP.; Robertson, LW.; Silberhorn, EM. PCBs and Tumor Promotion. In: Robertson, LW.; Hansen, LG., editors. PCBs Recent Advances in Environmental Toxicology & Health Effects. The University Press of Kentucky; Lexington, KY: 2001. p. 355-371.
35. Ludewig, G. Cancer Initiation by PCBs. In: Robertson, LW.; Hansen, LG., editors. PCBs Recent Advances in Environmental Toxicology & Health Effects. The University Press of Kentucky; Lexington, KY: 2002. p. 337-354.
36. Jensen RK, Sleight SD, Aust SD. Effect of varying the length of exposure to polybrominated biphenyls on the development of gamma-glutamyl transpeptidase enzyme-altered foci. Carcinogenesis. 1984; 5:63–6. [PubMed: 6140088]
37. Hayes MA, Safe SH, Armstrong D, Cameron RG. Influence of cell proliferation on initiating activity of pure polychlorinated biphenyls and complex mixtures in resistant hepatocyte in vivo assays for carcinogenicity. J Natl Cancer Inst. 1985; 74:1037–41. [PubMed: 2860266]
38. Espandiari P, Glauert HP, Lehmler HJ, Lee EY, Srinivasan C, Robertson LW. Polychlorinated biphenyls as initiators in liver carcinogenesis: resistant hepatocyte model. Toxicol Appl Pharmacol. 2003; 186:55–62. [PubMed: 12583993]
39. Espandiari P, Glauert HP, Lehmler HJ, Lee EY, Srinivasan C, Robertson LW. Initiating activity of 4-chlorobiphenyl metabolites in the resistant hepatocyte model. Toxicol Sci. 2004; 79:41–6. [PubMed: 14976334]
40. Dixon D, Sleight SD, Aust SD, Rezabek MS. Tumor-promoting, initiating, and hepatotoxic effects of 3,3′,4,4′-tetrabromobiphenyl (34-TBB) in rats. J Am Coll Toxicol. 1988; 7:687–697.
41. Anderson LM, Logsdon D, Ruskie S, Fox SD, Issaq HJ, Kovatch RM, Riggs CM. Promotion by polychlorinated biphenyls of lung and liver tumors in mice. Carcinogenesis. 1994; 15:2245–8. [PubMed: 7955061]
42. Anderson LM, Ward JM, Fox SD, Isaaq HJ, Riggs CW. Effects of a single dose of polychlorinated biphenyls to infant mice on N-nitrosodimethylamine-initiated lung and liver tumors. Int J Cancer. 1986; 38:109–16. [PubMed: 3087890]
43. Safe, S. Metabolism, uptake, storage and bioaccumulation. In: Kimbrough; Jensen, editors. Halogenated Biphenyls, Terphenyls, Naphthalens, Dibenzodioxins and Related Products. Elsevier; New York: 1989.
44. McLean MR, Bauer U, Amaro AR, Robertson LW. Identification of catechol and hydroquinone metabolites of 4-monochlorobiphenyl. Chem Res Toxicol. 1996; 9:158–64. [PubMed: 8924585]
45. McLean MR, Robertson LW, Gupta RC. Detection of PCB adducts by the 32P-postlabeling technique. Chem Res Toxicol. 1996; 9:165–71. [PubMed: 8924587]
46. Oakley GG, Devanaboyina U, Robertson LW, Gupta RC. Oxidative DNA damage induced by activation of polychlorinated biphenyls (PCBs): implications for PCB-induced oxidative stress in breast cancer. Chem Res Toxicol. 1996; 9:1285–92. [PubMed: 8951230]
47. Wangpradit O, Mariappan SV, Teesch LM, Duffel MW, Norstrom K, Robertson LW, Luthe G. Oxidation of 4-chlorobiphenyl metabolites to electrophilic species by prostaglandin H synthase. Chem Res Toxicol. 2009; 22:64–71. [PubMed: 19105592]

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48. Amaro AR, Oakley GG, Bauer U, Spielmann HP, Robertson LW. Metabolic activation of PCBs to quinones: reactivity toward nitrogen and sulfur nucleophiles and influence of superoxide dismutase. Chem Res Toxicol. 1996; 9:623–9. [PubMed: 8728508]
49. Dubois M, Pfohl-Leszkowicz A, Grosse Y, Kremers P. DNA adducts and P450 induction in human, rat and avian liver cells after exposure to polychlorobiphenyls. Mutat Res. 1995; 345:181–90. [PubMed: 8552139]
50. Daubeze M, Narbonne JF. Incorporation of labeled 2,4,5,2′,4′,5′-hexachlorobiphenyl into the nuclear fraction of rat hepatocytes in vivo. Toxicology. 1984; 31:315–8. [PubMed: 6204423]
51. Morales NM, Matthews HB. In vivo binding of 2,3,6,2′,3′,6′-hexachlorobiphenyl and 2,4,5,2′,4′,5′-hexachlorobiphenyl to mouse liver macromolecules. Chem Biol Interact. 1979; 27:99–110. [PubMed: 113111]
52. Pereg D, Tampal N, Espandiari P, Robertson LW. Distribution and macromolecular binding of benzo[a]pyrene and two polychlorinated biphenyl congeners in female mice. Chem Biol Interact. 2001; 137:243–58. [PubMed: 11566292]
53. Glatt H, Anklam E, Robertson LW. Biphenyl and fluorinated derivatives: liver enzyme-mediated mutagenicity detected in Salmonella typhimurium and Chinese hamster V79 cells. Mutat Res. 1992; 281:151–6. [PubMed: 1371835]
54. Wyndham C, Devenish J, Safe S. The in vitro metabolism, macromolecular binding and bacterial mutagenicity of 4-chloribiphenyl, a model PCB substrate. Res Commun Chem Pathol Pharmacol. 1976; 15:563–70. [PubMed: 825937]
55. Schoeny R. Mutagenicity testing of chlorinated biphenyls and chlorinated dibenzofurans. Mutat Res. 1982; 101:45–56. [PubMed: 7043248]
56. Davies R, Clothier B, Smith AG. Mutation frequency in the lacI gene of liver DNA from lambda/lacI transgenic mice following the interaction of PCBs with iron causing hepatic cancer and porphyria. Mutagenesis. 2000; 15:379–83. [PubMed: 10970442]
57. Zettner MA, Flor S, Ludewig G, Wagner J, Robertson LW, Lehmann L. Quinoid metabolites of 4-monochlorobiphenyl induce gene mutations in cultured Chinese hamster v79 cells. Toxicol Sci. 2007; 100:88–98. [PubMed: 17686921]
58. Flor S, Ludewig G. Polyploidy-induction by dihydroxylated monochlorobiphenyls: structure-activity-relationships. Environ Int. 2010; 36:962–9. [PubMed: 20471090]
59. Xie W, Wang K, Robertson LW, Ludewig G. Investigation of mechanism(s) of DNA damage induced by 4-monochlorobiphenyl (PCB3) metabolites. Environ Int. 2010; 36:950–61. [PubMed: 20129669]
60. Lehmann L, HLE, PAK, LWR, Ludewig G. 4-monochlorobiphenyl (PCB3) induces mutations in the livers of transgenic Fisher 344 rats. Carcinogenesis. 2007; 28:471–8. [PubMed: 16950798]
61. Maddox C, Wang B, Kirby PA, Wang K, Ludewig G. Mutagenicity of 3-Methylcholanthrene, PCB3, and 4-OH-PCB3 in the Lung of Transgenic Bigblue Rats. Environ Toxicol Pharmacol. 2008; 25:260–266. [PubMed: 18438460]
62. Jacobus JA, Wang B, Maddox C, Esch H, Lehmann L, Robertson LW, Wang K, Kirby P, Ludewig G. 3-Methylcholanthrene (3-MC) and 4-chlorobiphenyl (PCB3) genotoxicity is gender-related in Fischer 344 transgenic rats. Environ Int. 2010; 36:970–9. [PubMed: 20739065]
63. Srinivasan A, Lehmler HJ, Robertson LW, Ludewig G. Production of DNA strand breaks in vitro and reactive oxygen species in vitro and in HL-60 cells by PCB metabolites. Toxicol Sci. 2001; 60:92–102. [PubMed: 11222876]
64. Marnett LJ, Burcham PC. Endogenous DNA adducts: potential and paradox. Chem Res Toxicol. 1993; 6:771–85. [PubMed: 8117915]
65. Nair J, Barbin A, Velic I, Bartsch H. Etheno DNA-base adducts from endogenous reactive species. Mutat Res. 1999; 424:59–69. [PubMed: 10064850]
66. Chaudhary AK, Nokubo M, Marnett LJ, Blair IA. Analysis of the malondialdehyde-2′-deoxyguanosine adduct in rat liver DNA by gas chromatography/electron capture negative chemical ionization mass spectrometry. Biol Mass Spectrom. 1994; 23:457–64. [PubMed: 7918689]
67. Chung FL, Chen HJ, Nath RG. Lipid peroxidation as a potential endogenous source for the formation of exocyclic DNA adducts. Carcinogenesis. 1996; 17:2105–11. [PubMed: 8895475]

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68. Winter CK, Segall HJ, Haddon WF. Formation of cyclic adducts of deoxyguanosine with the aldehydes trans-4-hydroxy-2-hexenal and trans-4-hydroxy-2-nonenal in vitro. Cancer Res. 1986; 46:5682–6. [PubMed: 3756915]
69. Basu AK, Wood ML, Niedernhofer LJ, Ramos LA, Essigmann JM. Mutagenic and genotoxic effects of three vinyl chloride-induced DNA lesions: 1,N6-ethenoadenine, 3,N4-ethenocytosine, and 4-amino-5-(imidazol-2-yl)imidazole. Biochemistry. 1993; 32:12793–801. [PubMed: 8251500]
70. Nath RG, Randerath K, Li D, Chung FL. Endogenous production of DNA adducts. Regul Toxicol Pharmacol. 1996; 23:22–8. [PubMed: 8628916]
71. Peakall DB, Lincer JL, Bloom SE. Embryonic mortality and chromosomal alterations caused by aroclor 1254 in ring doves. Environ Health Perspect. 1972; 1:103. [PubMed: 17539068]
72. Odashima, S. The cooperative development in Japan of methods for screening chemicals for carcinogenicity. In: Montesano, R., et al., editors. Screening Tests in Chemical Carcinogenesis Publ No 12 Inter Agency Res Cancer. Lyon; France: 1976. p. 61
73. Sargent L, Roloff B, Meisner L. In vitro chromosome damage due to PCB interactions. Mutat Res. 1989; 224:79–88. [PubMed: 2505070]
74. Sargent L, Dragan YP, Erickson C, Laufer CJ, Pitot HC. Study of the separate and combined effects of the non-planar 2,5,2′,5′- and the planar 3,4,3′,4′-tetrachlorobiphenyl in liver and lymphocytes in vivo. Carcinogenesis. 1991; 12:793–800. [PubMed: 1827616]
75. Sargent LM, Sattler GL, Roloff B, Xu YH, Sattler CA, Meisner L, Pitot HC. Ploidy and specific karyotypic changes during promotion with phenobarbital, 2,5,2′,5′-tetrachlorobiphenyl, and/or 3,4,3′4′-tetrachlorobiphenyl in rat liver. Cancer Res. 1992; 52:955–62. [PubMed: 1737357]
76. Jacobus JA, Flor S, Klingelhutz A, Robertson LW, Ludewig G. 2-(4′-Chlorophenyl)-1,4-Benzoquinone Increases the Frequency of Micronuclei and Shortens Telomeres. Environ Toxicol Pharmacol. 2008; 25:267–272. [PubMed: 18438462]
77. von Zglinicki T. Oxidative stress shortens telomeres. Trends Biochem Sci. 2002; 27:339–44. [PubMed: 12114022]
78. Bachor C, Bachor OA, Boukamp P. Telomerase is active in normal gastrointestinal mucosa and not up-regulated in precancerous lesions. J Cancer Res Clin Oncol. 1999; 125:453–60. [PubMed: 10480337]
79. Harle-Bachor C, Boukamp P. Telomerase activity in the regenerative basal layer of the epidermis inhuman skin and in immortal and carcinoma-derived skin keratinocytes. Proc Natl Acad Sci U S A. 1996; 93:6476–81. [PubMed: 8692840]
80. Stern MM, Bickenbach JR. Epidermal stem cells are resistant to cellular aging. Aging Cell. 2007; 6:439–52. [PubMed: 17635170]

Figure 1.
Average PCB concentration in Chicago air for the calendar year 2007. Data are depicted as a weight percentage, and are taken from a study by Zhao et al, 2010 [20].

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Table 1

Genotoxic profile of PCB3 metabolites, 2-hydroxy-PCB3 (2-OH-), 3-hydroxy-PCB3 (3-OH-), 4-hydroxy-PCB3 (4-OH-), 3,4-dihydroxy PCB3 (3,4-Cat), 3,4-ortho quinone (3,4-oQ), 2,5-hydroquinone (2,5-HQ), and 2,5 para quionone (2,5-pQ). Numbers are LOEL (μM) for that endpoint.

Compound	Gene mutations (TG-resist.)[1]	MN chromos. Breaks[1]	MN chromos. Loss[1]	SCE or Polyploidy[2]	COMETS & Others (HL-60, Jurkat)[3]
PCB3	-	-	-	-	
2-OH-	-	-	50		
3-OH-	-	-	100		
4-OH-	-	75	75		
3,4-Cat	-	25	15	5 (SCE)	
3,4-oQ	0.6	15	5	-	
2,5-HQ	-	5	2.5	7.5 (PP)	COMET @ 37C, not 6C, in HL-60, not in Jurkat 0.1 (ROS ↑)
2,5-pQ	0.5	1	2.5	-	COMET @ 37C & 6C in HL-60 & Jurkat 0.1 (ROS ↑), 2.5 (GSH ↓)

MN: micronucleus assay; SCE: sister chromatid exchange assay; PP: polyploidy; TG: thioquanine. These data are associated with the following published studies:

[1] Zettner [57]

[2] Flor [58]

[3] Xie [59]