# GENERAL REMARKS

This one-hundred-and-seventh volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of exposure to polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). The *IARC Monographs* programme has conducted several evaluations of the carcinogenicity of these agents (IARC, 1978, 1979, 1987; Table 1). At the meeting of the Advisory Group to Recommend Priorities for the IARC Monographs in 2008, PCBs were identified as an agent with high priority for re-evaluation (IARC, 2009). In the framework of the re-evaluation of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) in October 2009 (IARC, 2012), the congener PCB-126 was upgraded to Group 1, and the Working Group recommended that there be an in-depth re-evaluation of agents with properties similar to TCDD (IARC, 2012). In February 2013, the *IARC Monographs* Working Group undertook a re-evaluation of PCBs and PBBs. A summary of the findings of this meeting appears in *The Lancet Oncology* (Lauby-Secretan *et al.*, 2013).

## 1. Considerations for definitions and nomenclature of PCBs and PBBs

Four decades after national governments began to ban their production and use, PCBs and PBBs remain a major concern to human health and the natural environment. Epidemiological studies in occupational settings generally studied workers exposed to the "fresh" product, by inhalation or dermal contact, while studies in the general population assessed individuals exposed primarily through intake of contaminated food, for which the exposure profile is difficult to assess. In contrast, experimental studies assessed individual congeners, combinations of a few congeners, or "fresh" commercial PCB products; however, none of these are identical to the PCB or PBB profiles to which people are exposed today. Indeed, most human exposure today is to complex mixtures originating from commercial products that have been altered by environmental processes (i.e. weathering, transport, and bioaccumulation).

The reason that PCB and PBB mixtures in the environment today differ from the original commercial products is that after release into the environment, the congener composition changes through partitioning, chemical transformation, and bioaccumulation. Partitioning refers to processes by which different congeners separate into air, water, sediment, and soil. Some congeners tend to volatilize or disperse as aerosols, providing an effective vehicle for long-range transport. Congeners with low chlorine or bromine content tend to be more volatile, and also somewhat soluble in water. Many congeners adsorb to organic materials in sediments and

**Table 1 Historical overview of the *IARC Monographs* evaluations of PCBs and PBBs**

| Agent | Volume | Reference | Evidence in humans | Evidence in experimental animals | Mechanistic considerations | Group |
|---|---|---|---|---|---|---|
| PCBs | 7 | IARC (1974) | No formal evaluation | No formal evaluation | – | – |
| | 18 | IARC (1978) | No formal evaluation | No formal evaluation | – | – |
| | Suppl. 1 | IARC (1979) | Inadequate | Sufficient | – | 2B[a] |
| | Suppl. 4 | IARC (1982) | Inadequate | Sufficient | – | 2B |
| | Suppl. 7 | IARC (1987) | Limited | Sufficient | – | 2A |
| PCB-126 | 100F | IARC (2012) | – | Sufficient | Mechanistic upgrade | 1 |
| PBBs | 18 | IARC (1978) | No formal evaluation | No formal evaluation | – | |
| | 41 | IARC (1986) | Inadequate | Sufficient | No evidence for genotoxicity | – |
| | Suppl. 7 | IARC (1987) | Inadequate | Sufficient | No evidence for genotoxicity | 2B |

[a] Possible target organs in humans identified as "skin (melanoma)" and "all sites"
PBB, polybrominated biphenyl; PCB, polychlorinated biphenyl

soils; adsorption tends to increase with chlorine or bromine content of the congener and with the organic content of the other material. Chemical transformation refers to the dechlorination or debromination of congeners. This can occur through photolysis, especially for some PBB congeners, or through interactions with bacteria. Chemical transformation is not synonymous with detoxication, as congeners having carcinogenic activity can be formed through dechlorination. Bioaccumulation occurs because PCBs and PBBs are absorbed by fish and other animals, and are highly soluble in lipids, while metabolism and elimination are relatively slower than absorption. Bioaccumulation through the food-chain tends to concentrate congeners of higher chlorine and bromine content.

The nomenclature of PCBs is complex. Publications often attempt to find dichotomies in these mixtures, or refer to PCBs in loose terms, such as:

- Higher and lower chlorinated
- Non-*ortho*, di-*ortho*, and similar terms
- Planar and non-planar
- Dioxin-like and non-dioxin-like
- Aryl hydrocarbon receptor-activating and non-activating
- High and low toxic equivalency (TEQ)
- Estrogenic and non-estrogenic
- Immunotoxic and non-immunotoxic.

The Working Group considered how to characterize the agents to be evaluated. The possibilities included:

- Specific congeners (e.g. PCB-126, PBB-153);
- Groupings of a small number of congeners (e.g. PCB-126 plus PCB-153);
- Commercial products (e.g. Aroclor 1242, Firemaster FF1);
- Large subsets of congeners (e.g. dioxin-like PCB congeners);
- PCBs or PBBs as a class.

Since human exposure always occurs to mixtures, the Working Group considered that it was appropriate to evaluate PCBs and PBBs each as a group.

## 2. Analysis of PCBs and PBBs

There are some difficulties in assessing and comparing PCB or PBB concentrations in any medium because of differences in analytical methods between laboratories, and differences in the numbers and types of congeners reported. Since there are 209 congeners, values reported

are rarely for true total PCB or PBB concentrations, but rather for a few selected congeners, or a "total" PCB or PBB concentration reported on the basis of analysis of a certain number of congeners only. Thus both the number and the specific congeners analysed must be considered when comparing results among studies. Another complication is that some authors present results for concentrations in total serum (usually called "wet weight"), while others report concentration in the lipid fraction of serum or other media (called "lipid adjusted"). The rationale for lipid adjustment is that these compounds are lipophilic, although there is some evidence that lipid adjustment poses risk of bias. Some investigators now report results as wet weight concentrations with serum lipids considered as a covariate. A further complication is that concentrations are reported in different units in different studies, and cannot always be directly compared.

Several biomarkers of exposure have been used as indicators of the internal dose or the body burden of PCBs or PBBs. These include measurement in blood (serum or plasma), adipose tissue, maternal or cord blood, breast milk and hair. In principle, blood lipid concentrations reflect recent exposures and the full spectrum of congeners to which a person is exposed, while the profile in adipose tissue reflects long-term intakes. However, recent exposure to less chlorinated congeners could result in higher non-equilibrium levels in the circulation. Levels in breast milk largely reflect the concentrations in adipose tissue.

A common theme with PCBs and PBBs is that major industrial accidents have resulted in unforeseeable human dietary exposure. In the 1968 Yusho incident in Japan, leaking Kanechlor 400 contaminated rice oil destined for human consumption. The 1979 Yucheng incident in Taiwan, China, also involved contamination of rice oil, this time by Kanechlor 500. And during 1973–1974, PBBs were unintentionally shipped as an animal feed supplement, contaminating milk, eggs, other dairy products, beef, pork, sheep, and chickens in Michigan, USA. Each incident involved relatively small amounts of PCBs or PBBs, but soon affected thousands of people. It should be noted that the effects of these incidents are not limited to cancer. The Yusho and Yucheng incidents also involved major effects on skin, such as severe chloracne, and recent studies have linked PBB exposure in Michigan to increased risks of spontaneous abortion, genitourinary conditions in male offspring, and suggestions of altered ovarian function.

## 3. Assessment of exposure to PCBs in epidemiological studies

Epidemiological studies investigating the potential carcinogenic effects of PCBs are basically of three types: occupational cohorts, environmental cohorts, and case–control studies. Most cohort studies were unable to quantify PCB exposures, although in some studies potential PCB exposure was estimated, or a qualitative scale was used. Within some cohort studies, more detailed analyses were achieved through nested case–control studies that collected additional information, sometimes including biomarkers, for specific subgroups of cancer cases and controls. Studies (nested case–control, and case–control) with biomarkers of exposure allow quantification of PCBs in serum or adipose tissue.

In this last group of studies, PCB exposure has been evaluated in a variety of ways: as to a group of congeners; as more or less specific commercial products; as specific PCB functional groupings; as specific combinations, such as PCB-118 + PCB-126; or as specific congeners.

There are several challenges in the interpretation and evaluation of the evidence for PCBs and cancer:

- In studies of workers and consumers of food items allegedly or known to have been "contaminated" with PCBs, it is usually not possible to determine the actual level of exposure.
- PCB exposure usually occurs to mixtures, and while these are often analysed as individual congeners in studies using biomarkers, many congeners are highly correlated and disentangling results for specific congeners is difficult.
- Several specific congeners are rarely or never included in epidemiological studies, primarily because they are excluded from "batch" gas chromatography analyses in many laboratories. Different studies focus on different PCBs; sometimes congeners are grouped and these groupings may differ across studies. Analytical results for specific congeners are best interpreted as markers for exposure to PCBs in general.
- In the occupational cohorts, the exposure route is usually dermal and inhalation, while in the environmental cohorts and case–control studies, the exposure route is usually ingestion (PCB exposure through diet).
- A few environmental studies refer to acute exposures (accidents), while most studies refer to long-term exposures (occupational exposure, and contamination of diet) and long-term consequences of accidents.
- Latency considerations are usually not possible when using biomarker samples collected long after exposure. This may be a cause for concern in interpreting findings on less persistent lower-chlorinated PCBs, but it would be less so for the persistent highly chlorinated PCBs.
- In principle, the use of biomarkers should reduce exposure-measurement error; studies evaluating biomarkers for many PCB congeners tend to generate multiple comparisons, potentially increasing the number of false-positive associations.
- Sampling may be problematic when adjusting plasma or serum measurements by lipid content, because of lipid degradation in samples. Most cohort studies could not take into account relevant confounders, while some of these were considered in the nested case–control and case–control studies.
- Very few studies have addressed interaction or effect modification with other environmental exposures such as tobacco smoke and other chemicals.

## 4. Genotoxicity of PCBs

Many early tests for genotoxicity with PCBs, performed 10 years ago or more, reported negative results. However, almost all of these studies are not suited for hazard assessment, primarily due to the low doses tested and, in case of studies in vitro, the lack of an exogenous metabolic system. If retested with metabolic activation, many PCB congeners would show genotoxicity. Most PCB mixtures and the few congeners that were tested gave negative results in the Ames test with and without metabolic activation [reviewed in (Silberhorn *et al.*, 1990; Ludewig, 2001)]. A negative result in the Ames test is not uncommon for compounds with complicated and multistep activation pathways such as that proposed for less chlorinated PCBs, i.e. metabolic activation to quinones. Thus a bacterial test for mutagenicity is probably not an appropriate assay for evaluating the genotoxicity of PCBs.

## 5. The pleiotropic carcinogenicity of PCBs

In experimental animals, commercial PCB mixtures and some individual congeners are complete carcinogens, producing neoplastic

lesions primarily in the liver (hepatocytes and biliary tract); however, benign and malignant tumours have also been observed in many other organs of the treated animals (lung, oral mucosa, thyroid gland, uterus, skin, and the mammary gland in the offspring of treated mothers).

Accidental release of PCBs into food in Taiwan, China, and in Japan, has led to acute and chronic PCB toxicity in thousands of people. Examination of the mortality rate of the Yusho victims in Japan 40 years after the event revealed an increased risk of all types of cancer combined, cancers of the liver and lung in men, and cancer of the liver in women (Onozuka *et al.*, 2009). A similar 24-year follow-up study of Yucheng victims in Taiwan, China, found increased mortality from liver disease, but no increase in risk of cancer of the liver (Tsai *et al.*, 2007). After reviewing all epidemiological studies on occupational and environmental exposure to PCBs, the Working Group concluded that there was *sufficient evidence* of carcinogenicity in humans, on the basis of an increased risk of malignant melanoma; one study found a significant association with uveal melanoma in exposed workers. In addition, increased risks were seen in some studies between exposure to PCBs and non-Hodgkin lymphoma, and for cancer of the breast in some subgroups of women. Positive findings were observed in individual studies for cancers of the brain, prostate, stomach, and pancreas.

PCBs bioaccumulate in fatty tissue, so higher marine mammals are particularly exposed. Reports of cancers in marine wildlife living in areas with high measured PCB concentrations provide another source of cancer data. For example, a large cell immunoblastic lymphoma in a bottlenose dolphin (*Tursiops truncates*) with high blood PCB concentrations (Jaber *et al.*, 2005); uterine leiomyomas in 257 female Baltic grey seals (*Halichoerus grypus*) (Bredhult *et al.*, 2008); and undefined carcinomas in 38 stranded wild California sea lions (*Zalophus californianus*), which were reported to be strongly associated with high PCB concentrations measured in the animals (Ylitalo *et al.*, 2005).

## 6. Toxicity and carcinogenicity of PBBs

The Working Group also considered the evidence on carcinogenicity of PBBs. The chemical structure of PBBs resembles that of PCBs, with substitution by bromine rather than chlorine atoms. PBBs were used primarily as flame retardants in the 1970s, but production has been discontinued in most countries for many years. Following the accidental release of PBBs in Michigan, USA, the one study that investigated cancer reported adjusted odds ratios of up to 23-fold for cancer of the digestive system and up to 33-fold for lymphoma, with an exposure–response trend across exposure groups. This study included cancer results until 1993; the study has not yet been updated to include cancers that have occurred during the subsequent 20 years. Concerning experimental and mechanistic studies, while there is an extensive body of literature on the carcinogenicity of PCBs, their brominated analogues have received much less attention and study. PBBs will likely be found to exhibit their toxicity and disease potential via many of the same pathways as their chlorinated counterparts, with equivalent or greater toxicity.

The information contained in this volume has contributed to the report "Health risks of PCB in the indoor climate in Denmark," published by the Sundhedsstyrelsen (Danish Health and Medicines Authority, 2013) and was considered during the evaluation of non-dioxin like PCBs by the Joint FAO/WHO Expert Committee on Food Additives (June 2015).

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