DERIVATION OF HEALTH BASED HUMAN BIOMONITORING VALUES FOR PCB IN HUMAN BLOOD SAMPLES

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Introduction

Polychlorinated Biphenyls (PCBs) are persistent synthetic organochlorines. Due to their lipophilicity they accumulate in the food chain and in human lipid tissue and can cause a variety of dose-dependent adverse health effects in different tissues and organs. Although their prohibition in the early 1980ies led to a significant decrease of the body burden of the population, PCBs are still widespread due to their high persistency in the environment and may still be emitted, e. g. in case of improper recycling activities.
Through Human Biomonitoring studies PCB concentrations in human blood have been measured since several decades to observe the body burden of these substances in the general population as well as in specifically exposed subgroups. Nevertheless until 2012 there was no approved health based guidance value in Germany, which would have allowed environmental health practitioners and epidemiologists to interpret PCB-Human Biomonitoring data according to its relevance for human health.
Health based guidance values for Human Biomonitoring in Germany (HBM values) are regularly derived by the German "Human Biomonitoring Commission" according to the knowledge and judgment of its members and published by the Federal Environment Agency. Per definition of the HBM-Commission the HBM II value marks the "concentration in the body matrix of a substance above which relevant adverse health effects may occur, and hence immediate action to reduce exposure must be taken and expert care in environmental medicine will be required", whereas the HBM I value represents the concentration "below which […] no adverse health effect should be expected."[1]
With this review we provide the relevant information needed to derive HBM values for PCB.

Materials and methods

A critical literature review was carried out, to evaluate the current state of research on health effects of PCB, under special consideration of publications from the recent decade. The review focused specifically on epidemiological data and on those studies that have been published later than the large monographs edited by the US Agency for Toxic Substances and Disease Registry (ATSDR) in 2000, by the World health Organization (WHO) in 2003 and by the European Food Safety Agency (EFSA) in 2005. These reviews had already evaluated the scientific knowledge on PCB effects from studies published during earlier decades. In total 320 publications have been evaluated for our review. Recently published monographs such as those issued by the Canadian Institut National de Santé Publique Québec (INSPQ) in 2007, by the ATSDR in 2011, by the Nordic Expert Group in 2012 and by the Danish Health and Medicines Authority in 2013 were taken into account as well. Based on this review the critical toxic endpoints were identified by a weight of evidence approach. Key studies on the dose response relationship based on human data were selected, and critical effect levels in human blood were derived by following the benchmark dose (BMD) approach.

Results and discussion

The main health effects of PCB discussed in literature cover neurotoxicity, immunotoxicity, reproductive toxicity, thyroid effects, liver effects, dermal effects, cardiovascular effects, diabetes and carcinogenicity. The majority of the studies focused on neurotoxic and immunological effects.

The neurotoxic effects of PCB have been largely investigated. There is a high number of epidemiological studies (mainly birth cohorts), evaluating age dependent neurodevelopmental deficits in mental and motor-neurological development of babies and infants after perinatal PCB exposure.

15 birth cohorts on neurodevelopmental effects could be identified. In 11 of these cohorts at least one adverse effect parameter was associated with exposure to PCB. 9 studies showed significant associations, whereas in two cases significance disappeared after adjustment for MeHg. In 5 of these cohorts neurotoxic effects even for elder children (6-11 years) could be detected.
In 4 cohorts the authors did not find any association. But in two of these 4 studies the exposure level to PCB was quite low, in one case the influence of the family environment has not been taken into account as a confounder and in the fourth study no follow up has been carried out after the base assessment.
The heterogeneity of the cohort studies complicates the comparison of the findings; e. g. different congeners have been used to assess perinatal PCB exposure in different matrices such as umbilical cord blood, blood from the placenta or maternal blood and breast milk respectively. Neurological or neuropsychological test methods differed and tests have not always been carried out in the same age groups. Furthermore the duration of the cohorts varied and only a few cohorts covered elder children as well.
Nevertheless the findings in the vast majority of the cohorts show a dose dependent impairment of the neurological development of children, including intellectual functions measured by different IQ tests. A large cohort study from Slovakia reported deficits in hearing functions as well. Overall there is a high epidemiological evidence for adverse PCB effects on neurodevelopment after perinatal exposure. In some cohorts the neurotoxic findings are persisting in elder children (11 and 12 years) and so far can be considered as not reversible.
Data from animal experiments supports the epidemiological data. Monkeys and rats showed delayed neurobehavioral and motor-neurological development after the application of commercial PCB mixtures.
Neurotoxic effects of PCBs have been investigated in adults too, but with fewer and less specific findings. Workers claimed subjective concentration deficits but no neurological disorders could be objectified after exposure to high doses of PCB. After the mass poisoning of cooking oil 1968 in Yusho (Japan) and 1979 in Yu-Cheng (Taiwan) adults showed a reduced velocity of nerve conduction. And in fish eaters in the Great Lakes area (Michigan) deficits of memory and learning capacity was associated with fish consumption, but aside from PCB the fish was contaminated by other neurotoxic pollutants too.
Overall there is high evidence that the developing nervous system represents a main target organ for PCB toxicity, whereas adults seem to be less vulnerable.

Also the immunological effects after perinatal PCB exposure are well investigated. In several cohorts infants showed increased infection rates for cold, respiratory infections, otitis media and chickenpox, reduced allergy rates, lower antibody titers after vaccinations and changes in lymphocyte subpopulations associated with their prenatal and postnatal PCB exposure.
Workplace studies provide less clear outcomes. Adults show only unspecific alterations, such as shifts in lymphocyte subpopulations and antibodies in epidemiological studies. Nevertheless the epidemiological findings in the birth cohorts are supported by the data from animal experiments, where monkeys as well as rodents showed reduced immune responses after exposure to high levels of PCB.
Overall there is suggestive evidence from the birth cohorts for PCB dependent adverse effects on the developing immune system, going along with increased infection rates and a suppression of immune responses after vaccinations.
Therefore immunological effects in children after perinatal exposure to PCB can be considered as a sensible endpoint. Adults seem to be less vulnerable than children.

Apart of the neurodevelopmental and immunological endpoints there are several studies reporting further PCB effects. But the epidemiological data is either less strong or effects occur only in higher concentrations. For this reason we decided not to use these effects as points of departure for quantitative risk assessment. A good overview is given by the recently published monographs.

More than 70 epidemiological studies on carcinogenic effects of PCB have been carried out since 1976. Data from these studies is sometimes contradictory and inconsistent. Occupational exposure in most of the cases has only been estimated and was not measured by Human Biomonitoring, in several studies there was a mixed exposure including other carcinogenic compounds, and the outcomes mostly were not dose dependent.
Environmental Human Biomonitoring studies showed dose dependent carcinogenic effects in the general population for certain congeners, but the target organs differed from the occupational studies and the relevant congeners differed from one study to another. However tumor cases have been reported for several organ systems after PCB exposure, with some consistency for melanoma, non-Hodkin lymphoma and breast cancer.

Animal studies on rodents exposed to different higher chlorinated PCB mixtures showed an increase of liver tumors, of tumors in the gastrointestinal tract and in the thyroid gland. Lower chlorinated mixtures showed only limited evidence. Overall the International Agency for Research on Cancer concluded that there is sufficient evidence in humans and experimental animals and classified PCB as carcinogenic to humans (Group 1).[2]
The contradictory and inconsistent epidemiological findings may be a result of a large variety of different mechanisms by which PCB enrolls its carcinogenicity. Whereas dl-PCBs activate the AhR receptor, ndl-PCBs mediate carcinogenesis by several other receptors. Some congeners act by immune suppression while others generate inflammatory responses. Furthermore endocrine disruptions are triggered by PCBs and might participate in carcinogenicity. Metabolism of PCBs can create reactive oxygen species.
Tests on genotoxicity give mainly negative results at gene or chromosome level, except of a few contradictory findings attributed mainly to the production of reactive metabolites. Especially metabolism of some mono-and dichlorinated congeners produces highly reactive electrophilic intermediates which are considered to be genotoxic and mutagenic. But although there is suggestive evidence that some lower chlorinated congeners might act as indirect primary genotoxic agents, the vast majority of PCB carcinogenicity can be attributed to secondary mechanisms and tumor promotion. There is no hint for a direct genotoxicity of PCB congeners and a threshold for carcinogenicity can be assumed.

Neurotoxic and immunotoxic effects can be considered as the critical endpoints of PCB toxicity. Infants were identified as the most vulnerable group for adverse PCB effects. For quantitative risk assessment we chose three key studies which had carried out benchmark dose (BMD) calculations for these effects: the Michigan cohort as a key study for the neurotoxic effects, the cohort from Slovakia for the endpoint hearing impairment, and the cohort from the Faroese Islands for the immunological effects. Table 1 shows the benchmark doses and the lower confidence levels (BMDL) for the different endpoints.

Table 1: Benchmark doses and lower confidence levels for critical endpoints of PCB toxicity

Cohort Study	**BMD / BMDL**	**µg PCBtotal / g lipid**
Michigan cohort[3]	BMD5[p0=0,05]*	0.94-1.05
	BMDL5 [p0=0,16]**	0.42-0.69
Slovakian cohort[4]	BMD5	1.01-3.31
	BMDL5	0.67-3.31
Faroese cohort[5]	BMDL5	0.84-2.18

* p0=0,05: bottom 5th percentile of the distribution of the test scores in a non-exposed population
** p0=0,16: one standard deviation below sample mean

According to the Benchmark calculations we considered, that below a concentration of 0.5 µg total PCB per g lipid there may not occur any relevant adverse health effects, whereas PCB levels exceeding 1.0 µg total PCB per g lipid may lead to an increase of relevant neurotoxic and immunotoxic effects in infants and children.
This consideration is supported by a different approach chosen by the Canadian INSPQ who calculated a NOAEL of 0.9 µg PCB / g lipid from different birth cohorts on neurotoxicity.[6] The findings from animal studies support our considerations too; e. g. Rice et al. (1999) who tested monkeys for adverse PCB effects on neurotoxicity and detected a LOAEL of 1.8-2.8 µg PCB / g lipid.[7]
Infants and children were identified as the most vulnerable group. But given that the data from the birth cohorts shows clearly, that perinatal exposure is considered as most important, a health based guidance value should include women at childbearing age as a target group as well.
Although there is limited evidence for adverse effects on adult men and postmenopausal women in the same range of PCB body burden, the available data does currently not allow the derivation of a health based guidance value for this target group.

Based on this risk assessment and converting our results from lipid based concentrations to serum based values by application of conversion factors the German "Human Biomonitoring Commission" derived the following HBM values for children and women at childbearing age:

HBM-I = 3.5 µg PCB/L serum
HBM-II = 7.0 µg PCB/L serum

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