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5th International PCB Workshop – Summary and Implications

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1.0 Introduction

In this overview, we present a summation of new and novel findings presented at "The Fifth PCB Workshop: New Knowledge Gained from Old Pollutants" workshop, as well as identify data gaps and research needs and issues for future discussion. An overarching state-of-the-science view is important to the goal of preventing negative health consequences. Continued research is needed to more fully characterize exposure (populations exposed, quantities, duration, frequency, etc.) in order to link exposures with disease. In order to make risk assessment more dynamic, understandable, and appreciated, better tools are needed to evaluate environmental mixtures of PCBs. Currently, there are still many roadblocks to evaluating risk associated with this large group of 209 congeners – all of which have different physiochemical properties, variable fate and transport mechanism in the environment, and a range of ability for persistence, bioaccumulation, and biological activity.

Relative to the previous workshop, the scientific presentations had a decreased emphasis on toxicology; rather, more than half the sessions dealt with environmental sources, fate and transport, or transformations. Toxicological assessments focused on developmental neurotoxicity relative to previous assessments that focused on endocrine disrupting effects. A wealth of epidemiological data was discussed, though the focus was on Anniston with very little discussion on the Slovak population (even though current PCB levels are higher in Slovakia). There were also a number of common themes and findings between the 2004 and 2008 workshops. Several investigators continue to utilize chirality as a tracer of biological processes, a field that is continually expanding as analytical techniques improve. In associated research, assessment of congener-specific information continues to advance knowledge of sources of release and mechanisms movement in the environment. Further, more data are continually available documenting lighter (i.e., lower chlorinated) congeners in the air. Microbial remediation approaches are not yet perfected for PCBs, though data indicate research is headed in a successful direction.

Approximately 100 presentations in the form of talks and posters were included in the workshop. The presentations were generally divided into: emissions and transport of PCBs in natural and urban settings; chiral aspects of PCB transport; metabolism and distribution; new aspects of environmental metabolism of PCBs – from microbes to plants to animals;

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reproduction, developmental and cardiovascular effects of PCBs; updates on Anniston – the most highly exposed PCB community in the U.S. to date; and new and novel approaches for evaluating PCB mixtures (e.g., PCB toxic equivalency factors, TEFs) – and the implications of such for risk assessment. New and novel findings are discussed by topic. The citations throughout this document refer to the presenter and the program topic (based on the section that it appears); the workshop program and conference abstracts are publicly available[1].

2.0 Characterization in the Environment

Several investigators reported on studies characterizing PCBs in the environment, aiding in the understanding of how PCBs enter the environment, and furthering knowledge of fate and transport issues. A great deal of data will be generated as part of a large-scale environmental monitoring program to evaluate the spatial distribution and sources of atmospheric PCBs in the Chicago urban industrial region (Hornbuckle et al., Characterization in the Environment). This type of effort will aid in the characterization of atmospheric sources of PCBs (*e.g.*, sediments, building materials) and the distribution of such in the cities given that currently, these components are almost completely undefined. Modeling was also used to evaluate atmospheric PCB source types, locations and magnitude in urban areas of New Hersey (Rodenburg, Characterization in the Environment). Using a holistic approach to incorporate location, type, and intensity of atmospheric PCB sources, the model suggested that several types of highly-localized PCB sources exist in urban areas (with different types of sources located in different areas).

Multiple reports documenting the direct impact of PCBs in the environment on human exposure were discussed, highlighted by findings reported by Herrick *et al*. showing that PCB-contaminated sealants result in increased soil concentrations of PCBs, and subsequently, result in elevated PCB levels in construction workers employed to remove the caulk. The authors also evaluated serum levels and congener profiles of PCBs in construction workers removing the caulk and found that serum levels were elevated, but the profiles were very different as compared to PCBs measured in age-matched referents.

Harrad et al. presented data suggesting that exposure to PCBs in dust may have a more significant role as a pathway of human exposure than initially thought (particularly for small children), thus further characterizing contributions of indoor contamination to human exposure. This finding was based on measurement of PCBs in household dust from Canada and the UK and subsequent comparison of exposure estimates relative to dietary intake. Norstrom et al. used a PBPK model to evaluate congener profiles in human serum following exposure to PCBs via inhalation relative to other routes. Under the conditions modeled, the authors reported that air concentrations of PCBs did not significantly impact the concentration of PCBs in serum – rather, dietary intake was the largest contributor. The authors also noted that the pharmacokinetic model did not accurately predict serum concentrations of lower chlorinated congeners. They also suggested that lipid-normalization may not be appropriate for rapidly metabolized congeners.

Biomonitoring data collected as part of the CDC's NHANES was presented by Patterson et al. This dataset provides the most robust characterization of PCB levels in the general U.S. population. Importantly, these data provide reference ranges for background exposures and thus can be used to determine potential excess exposures. These data are particularly useful as it allows for the assessment of internal doses of chemicals – the preferred dose metric for

[1]National Institute of Environmental Health Sciences. (2008) The 5th PCB Workshop – New Knowledge Gained from Old Pollutants. May 18–22, 2008. Iowa City, Iowa, USA. National Institute of Environmental Health Sciences. (2008) The 5th PCB Workshop – New Knowledge Gained from Old Pollutants. May 18–22, 2008. Iowa City, Iowa, USA. Program and Conference Abstracts. Available online: http://tools.niehs.nih.gov/srp/events/index.cfm?id=303

persistent, bioaccumulative compounds. Biomoniotoring data indicated that lower chlorinated PCBs are higher in those aged 12–19, but go down with age; higher chlorinated congeners increase with age, and level out by age 60+. PCB congener patterns varied with age, a function of the varied kinetic parameters among congeners. Data also indicated that people who eat fish and shellfish often have higher body burdens of PCBs than those who do not (and particularly for those that consume contaminated fish and shellfish).

Collectively, workshop presentations showed that contaminated soil and indoor air/dust contribute to human exposure, surficial sediments and urban areas clearly contribute to ambient air concentrations, higher air concentrations of PCBs are generally observed in the summer relative to the winter, bioaccumulation may not be as important as repeated exposure for lower chlorinated PCBs, hot-spots (i.e., sources) are highly localized, and that congener specific analyses will continue to contribute to the understanding of source identification and apportionment.

3.0 Chiral aspects of PCB transport, metabolism and distribution

This section of the symposium included a series of presentations on the importance of chiral analyes as related to toxicity evaluations. Huhnerfuss reported on interesting findings resulting from an analysis of chiral PCBs and their metabolites in human livers. Several highly enatioselective MeSO2-PCB compounds were measured (*e.g.,* MeSO2-PCBs 3–149 and 3–132 in liver, lung and adipose tissues of rats exposed to Clophen A50 (a technical PCB product). The results support theories of enatioselective transformation and retention of MeSO2-PCBs in vivo. Differences in toxicity among PCB atropisomers in rodents indicated that MeSO2-PCBs 84, 136 and 139 clearly showed enantioselective toxicity and deposition when administered individually (Korwel et al.). However, additional studies using complex mixtures provided a complex set of results, thus highlighting the need to further understand the role of cytochrome P450 (CYP) enzymes and other biotransformation processes in entantioselective disposition and toxicity. The session concluded with an overview of the enantiomeric fraction of chiral PCBs in humans; studies in the literature provide a growing body of evidence that the enantiomeric enrichment observed in mammals and in humans is due to enantioselective biotransormation processes (Lehmler). However, additional studies are needed to determine if the enantiomeric enrichment observed in humans was a result of exposure to enantiomerically enriched PCBs or due to biotransformation.

New research has also shown that chiral analyses, particularly when used in conjunction with molecular biology techniques, may provide new pathways for understanding microbial degradation of PCBs. Results of a series of analyses by Lee et al. demonstrated evidence of more than one microbial consortium responsible for dechlorination and also characterized the enantiomeric fractions during microbial removal of chlorine under a number of conditions. The use of chiral PCBs as markers of biochemical weathering in aquatic food webs was also discussed. Although PCBs are released into the environment as racemates, thus nonracemic residues in environmental media are indicative of degradation process (Wong). Enantioselective analyses of PCBs in aquatic invertebrates and fish demonstrated that nonracemic PCBs were due to biotransformation. The importance of chiral analyses when evaluating environmental samples was highlighted by Harrad et al.; these authors suggest that because of the unique signatures of chiral PCB congeners 95 and 149 in topsoil and out door air from the UK, a substantial proportion of atmospheric PCBs are from primary sources (i.e., racemic) rather than volitilzation from the soil. The authors further suggested that destruction of remaining PCB stocks would thus result in reductions in human exposure.

Together with other presentations on the chiral aspects of PCB transport, metabolism and distribution, the science indicates that 19 of the 209 PCB congeners display axial chirality. In

the environment, this results in changes in enantiomeric fractions with variations in seasons, and that PCB biodegradation (primarily dechlorination) is often dependent on chirality. Continued improvement in chiral techniques will clearly afford unexpected insights into environmental processes. As related to toxicity and health, enzymatic metablism can favor specific enantionmers, and that often enantiomers mark specific biological processes (e.g., enantioselective induction of CYPs; influence of chirality on ability to penetrate the blood brain barrier). These data collectively highlight the need to further assess chiral PCBs to determine if they are a human health concern, given that studies have indicated chiral PCBs are episodic and that they have the greatest effect on calcium release from microsomal stores by sensitizing channels termed ryanodine receptors (RyRs). Moreover, further research is needed to determine potential human health implications of enantiomeric enrichment of traditionally-toxic PCB congeners

4.0 New aspects of environmental metabolism of PCBs: From microbes to plants to animals

Several investigators presented findings related to rhizosphere bioremediation (i.e., enhancement of microbial activity and biodegradation in the root zone, a beneficial effect of plants). New strategies to enhance the intrinsic bioremediation of PCBs in sediments (*e.g*., incubation in the presence of low concentrations of H2 or fermentable organic acids) resulted in stimulated dechlorination, thus documenting the use of readily available and non-toxic alternative electron acceptors for bioremediation (Novak). Similar findings were reported by Paul and Ghosh demonstrating microbial degradation of di- and tri-PCBs in sediment amended with activated carbon. Correra et al. presented findings of a robust study characterizing the effect of different PCB congeners on the soil microbial community structure, the expression of genes involved in PCB metabolism as well as PCB degradation. Using a series of experiments in aerobic soil slurries prepared with poplar rhizosphere soil, microbial activity, microbial community structure, and the abundance and expression of biphenyl dioxygenase (BPH) genes were quantified following exposure to 8 individual congeners or two commercial Aroclor mixtures. Results indicated that PCBs significantly impacted the microbial community structure as well as BPH expression patterns. These data support the hypothesis that PCB congeners affect the bacterial activity in soil and thus result in different biodegradation rates. New insights into rhizosphere bioremediation were also reported by Leigh et al. Using stable isotope probing, this group of researchers demonstrated that increased populations of PCB-degrading bacteria were associated with pine trees in comparison to other species. Schnoor et al. also presented a series of exciting data characterizing degradation of airborne PCBs by plants (Schnoor et al and Liu and Schnoor). Using hybrid poplars as a model plant, data demonstrated evidence of in-vivo metabolism. This group of researchers also identified metabolites and measured the induction of genes likely responsible for the observed transformations. A similar study indicated that PCBs were not taken up by alfalfa (Yamaguchi and Lee).

PCB metabolism in aquatic animals was also discussed as it highlights the importance of understanding the uptake, biotransformation and elimination of PCBs in fish since these processes contribute to accumulation and subsequent ingestion/exposure in humans. New data on metabolism and breakdown in animals and humans was limited to a single investigation of the extent to which OH-PCBs interact with family 2 sulfotransferases as substrates and inhibitors (Duffel et al.). Results indicated clear differences in interactions between rat and human isoforms; humans were more sensitive to inhibition and were also capable of catalyzing sulfation of OH-PCBs. Intraspecies differences between isoforms were also noted. Additional studies by these authors demonstrated significant differences in the specificity of rat sulfotransferases for OH-PCBs under oxidative conditions, thus suggesting their potential contribution to producing oxidative stress.

Data characterizing new aspects of environmental metabolism collectively indicated that further understanding dechlorination is within reach, and is important to fully characterize effects in the environment, wildlife and humans. Under anaerobic conditions, dechlorination can result in mass loss, whereas under aerobic conditions, PCB degradation can be biostimulated to result in co-metabolic pathways. Exposures to different PCB congeners modifies the structure of the microbial community and under some conditions, can result in higher numbers of bacteria belonging to phyla involving "PCB degraders." These data support the potential for phytoremediation at hot spots. However, further research is still needed to identify effective plant species to enhance aerobic PCB degradation and to further characterize degradation and metabolism (e.g., glucuronidation and sulfation) in animals and humans. The later is particularly important given the potential for metabolites to pass through the food chain, and because there is potential for additional toxicity under some situations (e.g., oxidative stress).

5.0 Reproductive, Developmental and Cardiovascular Effects of PCBs

The majority of presentations at the workshop were associated with characterizing toxicity. Primary endpoints of interest included reproductive, developmental and cardiovascular effects, as highlighted by a series of presentations by Sharma, Hennig, Cassis, and Walker. Sharma opened the session and presented data characterizing mechanisms by which PCBs affect biological systems. The primary focus of this series of studies was the development and validation of experimental systems for evaluating gene-environment effects on female reproductive health. Using these experimental models, the authors reported a number of developmental outcomes (*e.g.*, preterm birth, reduced litter size, diminished righting reflex) in Aroclor 1254-exposed mice. This was followed by results of an applied study evaluating the relationship between nutrition and lifestyle, exposure to environmental toxicants and disease (i.e., nutritional paradigm in environmental toxicology) (Hennig). Findings indicated that an increase in cellular oxidative stress and an imbalance in antioxidant status are critical events in PCB-mediated induction of inflammatory genes and endothelial cell dysfunction. The authors further demonstrated that diet-derived lipids and bioactive compounds can alter key events in PCB cytotoxicity, therefore demonstrating that nutrition can modulate environmental insults in the vasculature (which supports the theory that life-long exposures to PCBs is associated with vascular inflammation and atherosclerosis). Discussions about the (lack of a) margin of exposure between levels in the environment and levels used in experimental effects were focused on developmental effects, supported by measurements of follicular fluid levels of PCBs in humans (Foster).

Based on a series of in vivo and in vitro evaluations, Cassis reported that PCB 77 may contribute to the development of obesity and obesity-associated atherosclerosis based on findings that, in mice, PCB 77 exposure was associated with altered adipocyte differentiantion, adipocyte hypertorophy, proinflammatory cytokine levels, and body weight. Additional studies using TCDD further characterized the role of aryl hydrocarbon receptor (AhR) in alterations in blood pressure regulation (Walker). PCB associations with key events in cardiovascular disease were supported by findings presented by Choie et al. and Majkova et al. These groups further characterized proinflammatory responses associated with oxidative stress in vascular endothelial cells following exposures to dioxin-like PCBs and demonstrating that PCB-induced pro-inflammatory parameters are regulated through caveolae. And thus, inhibition of this step may be an important target for preventing PCB toxicity. Lastly, Shen et al. reported that PCBs can influence paraoxonase activity in rats, an antioxidant enzyme which may contribute to the risk of cardiovascular and other diseases.

Many other studies reported on mechanisms of action, genotoxicity, metabolic breakdown following exposure (and potential toxicity of metabolites). Several of these studies evaluated

lower chlorinated congeners, particularly as they relate to toxicities associated with inhalation exposures and toxicity of metabolites. Genotoxicity was addressed in a number of presentations that collectively further characterized key events and/or dose-response relationships following exposure to PCBs in vivo and in vitro (Xie et al; Klingelhutz et al; Flor and Ludewig). There were several reports characterizing the association between PCB exposure and oxidative stress (Chaudhuri; Wagner et al; De et al; Kuppusamy et al.)

A fair number of studies reported on mechanisms or cellular interactions. Data on interactions of hydroxylated PCBs and PCB metabolites with sulfotransferases in rodents and humans were reported, aiding in further characterization of species differences (Ekuase et al; Liu et al). Interactions of PCBs with receptors other than AhR were reported by a number of authors and included pregnane X receptor (PXR) and altered thyroid hormone (TH) status, (Kopec et al; Zoeller). Active transport was also addressed, though Milanowski reported that PCBs were not substrates for the multi-drug resistance transporter under the conditions studied.

Dutta et al presented a series of assessments related to the identification of genomic biomarkers of PCB exposure in humans, highlighted by the identification of specific genes that could be used as potential diagnostic biomarkers for PCB-induced renal diseases. An interesting dataset was presented by Curran, characterizing genetic susceptibilities associated with PCB-induced developmental toxicity.

A series of findings presented by Seegal demonstrated that non-dioxin-like PCBs can alter central dopamine function in both humans and monkeys, and suggested that gender differences be further examined. Specifically, reductions in dopamine via inhibition of transport were observed (PCB 95 was more potent than 153, both of which were more potent than dioxin-like PCBs). The authors also reported that exposure to Aroclor mixtures (A1016 and A1260) decreased dopamine in primates. Pessah presented a detailed structure-activity relationship for PCBs and ryanodine receptor (RyR) and provided quantitative QSARs, thus supporting its involvement in PCB toxicity. Collectively, these data support that non-dioxin-like PCBs may also alter behavior and neurochemical function. The role of oxidative stress was also discussed as a mechanism associated with PCB 95, as data are suggestive that exposures lead to the formation of reactive oxygen species and subsequent neuronal cell death. The role of mitochondrial dysfunction was also discussed, as was the role of steady state levels versus the number of excursions over a threshold relative to PCB toxicities.

Several reports from epidemiological studies provided useful data characterizing effects in humans. As part of a longitudinal study of PCB exposures and child development in eastern Slovkia, Sovcikova et al. did not find an association between pre- and postnatal PCB concentrations and children's IQ at 45 months of age. Lack of effects were also reported by Turyk et al.; findings of a cross sectional, prospective study of adults from the Great lakes basin indicated that PCBs were not associated with diabetes. And using data from the EU 5thFP PCBRISK project, Trnovec et al. utilized benchmark dose calculations to evaluate human health outcomes after long-term and low-dose environmental exposures to PCBs. Results indicated that the proportion of the population considered at risk (i.e., serum concentrations below the BMDL) to neurobehavioral effects ranged from 2.1% for the least protective criteria to 23.7% for the most protective criteria.

Collectively, the toxicity data presented at the workshop suggested that PCB-induced inflammation is triggered through toll-like receptors. Data also indicated that PCBs inhibit angiogenic processes and appear to be associated with a number of endpoints related to cardiovascular effects. Key events may include disruption of endothelial barrier function, oxidative stress, and endothelial cell dysfunction, though further research to characterize these effects is needed. Evidence continues to build supporting an association between PCBs, obesity

and disease; data were presented demonstrating a direct correlation between DL-PCBs and obesity (and subsequent inflammation, etc.) as well as PCB 77 induced events resulting in oxidative stress. Data also suggest that sustained AhR activation may be associated with hypertension and coronary heart disease in humans based on animal models of atherosclerosis, hypertension, and CV; associated with oxidative stress (contribute to hypertension). Additional evaluations are necessary to more fully characterize these effects at environmentally relevant exposure concentrations given that several studies suggest a very low (or no) margin of exposure.

6.0 Anniston: the most severe US PCB community exposure

Silverstone et. al. presented data showing an association between PCB exposure and the development of diabetes as well as aggregate cardiovascular disease risk factors in Anniston individuals ages 35 to 54. However, associations were not found when analyses were based on the whole study group with consideration for confounders. Interesting data were also presented by Foushee and Wolf regarding self-reported conditions and perceptions of exposure in Anniston residents. This study was part of the Anniston Community Health Study (ACHS) and indicated that Anniston residents generally perceived (two-thirds of the residents) that they had been personally exposed to PCBs and that they suffered negative health effects (e.g., allergies, diabetes, cancer) as a result. Results showed overall ratings of poor soil, air and water quality.

Residents of the Anniston community continue to await the results of exposure and health effects studies, many of which are tied to litigious action. As more data become available, the exposures in Anniston appear to be more like a “dioxin” exposure as the levels of dioxin-like PCBs are much higher in Anniston adults relative to non-dioxin like PCBs, thus suggesting a potential parallel to the highly-exposed Yusho/Yucheng cohort Further, data very clearly indicate trends in elevated exposures for sub-populations within Anniston that are linked to living in contaminated areas and consumption of locally raised foodstuffs. Assessments of adverse health effects presented at the workshop are suggestive of alterations in child IQ (related to mothers' PCB levels), but also suggested that parental IQ and working memory were related to adult PCB levels. While these effects appear to be related to non-dioxin like PCBs, dioxin-like PCBs may be implicated in the suggested increase in diabetes at younger ages in association with elevated PCBs as well as potential associations with heart disease. The ACHS provides an opportunity to further evaluate exposures and health effects associated with PCBs; these data will significantly contribute to scientific assessments of health risk associated with exposures to PCBs at environmental levels as well as in highly-exposed populations.

7.0 New and Novel approaches; Implications for Risk Assessment

Given the complexity of assessing the risk of PCBs in the environment, novel and updated approaches are needed in order to address the variations in effects among the 209 congeners. This is of particular importance for many congeners (e.g., the highly-chlorinated PCB 209 or the lesser-chlorinated mono- and di- substituted congeners) that do not act via mechanisms traditionally associated with dioxin-like PCBs or nondioxin-like PCBs associated with neurotoxicity. For example, while the TEF approach accounts for dioxin-like PCB congeners acting through the AhR, it does not account for non-dioxin like PCBs which are typically >99% of the mass and act through a different mechanism(s) (Kodavanti and Birnbaum). It was noted that some of the non-dioxin-like PCBs may be similar in structure and activity to polybrominated diphenyl ethers (PBDEs); however, this class of compounds is also difficult to assess as the degree of bromination clearly impacts both the physiochemical properties as well as toxicity (i.e., current data suggest that BDE 209 is less toxic in laboratory studies than

tetra-, penta-, and hexa- substituted congeners). Thus, additional assessment tools are needed to fully assess the human health risk of halogenated chemical mixtures.

Several authors presented data further characterizing mechanisms of toxicity and key events/effects that may be useful in the development of new approaches for risk assessment. Lein provided results from a series of in vivo and in vitro studies that supported the hypothesis that non-dioxin-like PCBs disrupt normal patterns of neuronal connectivity via effects on dendritic growth and plasticity. These data demonstrated developmental neurotoxicity, including cognitive and behavioral deficits, at low doses (nano-molar concentrations for in vitro effects) from non-dioxin-like PCBs. The authors identified several potential receptors likely to be involved including those that bind thyroid hormone, estrogen, dopamine, and ryonadine (RyRs). Further speculation on the findings suggested that deficits in spatial learning at low doses were associated with neuronal connectivity and dendritic growth, which were both associated with alterations, calcium signaling and altered expression and activity of RyRs (with emphasis on the influence on chirality). The identification of these (and other) specific neurodevelopmental events targeted by PCBs lends further support for evaluation of AhR-independent endpoints when assessing human health risk.

Many of these concepts were discussed and/or incorporated in the development of a neurotoxicity equivalency scheme (NEQ) as reported by Simon. This novel approach includes PCBs other than those included in the traditional dioxin TEF approach, and also provided estimates of relative potency for thyroid hormone-related effects for both PCBs and other chemicals (Simon et al.). The authors published an initial scheme and specifically noted that it was important to incorporate the many different modes of action when predicting congener potency (as well as the many different adverse effects for which they are associated). Though other modes of action may be involved, NEQ scheme provides an approach for non-dioxin-like PCBs not included in the TEF scheme. However, when considered with the research above, additional research is needed to improve the current state of the science. Specifically further characterizing the mode of action and the relative toxicity of all environmentally relevant PCB congeners would greatly enhance the ability to generate a novel approach upon which PCB risk assessment can be based.

8.0 Discussion

Several themes of the 2008 workshop as they relate to protecting the environment and the human population from negative health consequences were identified:

1. Need to evaluate outliers as these datasets underscore the vulnerable relationship (i.e., evaluate the tails in the distribution of effects)
2. “Total” or “indicator” PCB measures have great utility, particularly for screening and prioritization
3. Measurement of specific congeners is important for characterization of sources, pathways and mechanisms
4. PCBs are associated with several nuclear receptors – it's not just the AhR (PXR/CAR, RyRs, thyroid hormone receptors, estrogen receptors, etc. are also involved)

Risk assessors need to consider the many potential effects of PCBs – data shows that PCBs are not just associated with developmental neurotoxicity. Effects such as adult neurotoxicity, endocrine disruption, reproductive effects, skin/teeth/bone/nails, and immune dysfunction should be considered – particularly as they relate to chronic liver and kidney diseases, cardiovascular disease, diabetes, obesity, and cancer. And to further complicate assessment, exposures and effects from other compounds, such as other organochlorines, PBDEs, PFCs, meals solvents and pharmaceuticals/PCPs may be important to include in evaluations.

In the future, it is recommended that scientists design targeted studies to answer key uncertainties in PCB risk assessment. Specifically, dose-response studies are needed to more fully characterize effects; these studies are needed for evaluation of multiple endpoints (data point to several types of adverse effects potentially associated with exposures). In order to improve extrapolation between species, studies characterizing the key pharmacokinetic parameters are needed to better quantify comparisons of body burden between animals and humans. Importantly, researchers should also consider studying PCB mixtures that resemble actual exposures. Studies should include environmentally relevant doses. Recent data also indicate that PCB 77 (or PCB 66) should not be used for mechanistic studies given its affinity for AhR, but metabolic breakdown to reactive intermediates (*i.e.*, it is not just dioxin-like). Lastly, additional assessments are needed to improve and/or further develop approaches for evaluating PCBs, as the dioxin-like TEF approach is not protective of all PCB effects. Further understanding these issues is important to protecting public health, as most PCBs ever made are still present in the environment.

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