Some bifocal views of risks of BFRs

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Abstract
Brominated flame retardants (BFRs) have been on the research agenda for decades but intensively so only for less than ten years. Even though BFRs include some 20-30 chemicals or mixtures of chemicals one class has been most intensively researched, the polybrominated diphenyl ethers (PBDEs). In addition focus has been directed towards tetrabromobisphenol A (TBBPA) and hexabromocyclododecanes (HBCDDs). Environmental levels are rather well documented for all these three BFR types, while human exposure is particularly well established for the PBDEs. Some major exposure differences are observed between continents and between humans with different occupations. The toxicological profile of different PBDE congeners has emerged over time, with endocrine, neurotoxic and neurobehaviorial effects of particular concern. Hydroxylated PBDE metabolites have shown endocrine related effects as well as inhibition of the oxidative phosphorylation. We conclude that risk assessment requires improvements to generate better and comparable data.

Integrated view on BFR risks
In recent decades scientific and public interest in BFRs has increased strongly, especially for the PBDEs. Clearly this is due to increasing and/or high concentrations of some of the PBDE congeners in both humans and wildlife. Although many of the presently used BFRs have been produced as early as the 1960's, it is in the last decade in particular that scientist, regulators and the public have become more interested in these groups of compounds. Still the interests focus on the BFRs known to have been or being produced at the highest volumes; TBBPA, the PBDEs (DecaBDE, PentaBDE and OctaBDE) and HBCDD. A range of BFRs with lower production volumes have been identified in the environment and in humans and these are occasionally discussed in the scientific literature. While TBBPA is a simple one compound BFR with only a very limited number of derivatives being used, PBDEs are made up of a large number of congeners in commercial products and as abiotic transformation products and/or as metabolites via debromination of higher PBDE congeners. Further, HBCDD is when technically prepared forming at least five isomers among which α-, β-, and γ-HBCDD are the three major ones, all three forming enantionmeric pairs due to their chirality. Proper risk assessments have had to await improved knowledge of commercial versus environmental mixtures of these complex compound classes (PBDEs and HBCDDs). This is relevant for assessing PBDE and HBCDD exposure, toxicity, abiotic transformations, metabolism and more.

The aim of this plenary is to highlight in an interactive manner some of the risks presently being, or not being discussed for BFRs. The key areas for assessing risks, exposure and toxicity, are discussed in particular. Comparisons are made, present methodologies are questioned, and suggestions are put forward.

Originally, the approach in toxicology for example for PBDEs was to consider these compounds as analogues of PCBs, or even dioxin-like compounds. However, ultimately conflicting information became available with respect to the mechanism of action, which at first had not excluded a dioxin like mechanism of action. Based on the non-planar configuration of PBDEs it is now accepted that PBDEs might at best show some toxicological similarity to non-dioxin, *ortho* substituted PCBs like PCB 153. Consequently, PBDEs are no longer considered to be dioxin-like compounds. These results are based on highly purified individual PBDE congeners and after in depth analysis of technical PBDE products reviling the presence of polybrominated dibenzofurans (PBDFs) in these products.

Nevertheless, there are clearly a number of non Ah receptor mediated endpoints that require the attention of the toxicologist and risk assessor and it has become clear that the more sensitive endpoints of PBDEs are of endocrine, neurotoxic and neurobehaviorial nature. However, a distinct structure activity relationship for these effects and PBDEs is at present not directly obvious and it can even be questioned whether the observed effects

are really specific for PBDEs and/or *ortho* substituted PCBs. None the less, a mechanistic similarity between non- dioxin and *ortho* substituted PCBs and PBDEs appears evident from a number of recent studies.

Focusing on DecaBDE exposure, i.e. mainly exposure to BDE-209, is evidently episodic for the general population but not for people employed in electronic dismantling, rubber industry or DecaBDE production. Still there may be individuals continuously exposed to elevated BDE-209 concentrations. BDE-209 being a large and heavy perbrominated molecule is behaving differently to PBDEs with an intermediate number of bromine substituents. The compound is truly a semi-persistent compound; stable enough to undergo long range transport but easily metabolised. The highest exposures are related to workers exposed to DecaBDE and in small children. The compound is poorly transferred over the placenta, poorly via mother's milk and only occasionally observed in food. There are clear indications that BDE-209 exposure is occurring via particle/dust intake. BDE-209 has some similarities to hexachlorobenzene (HCB), while very little is known how it relates to decabromobiphenyl (BB-209). Tri- to heptaBDEs are indeed persistent compounds with great similarities to PCBs, DDTs and other legacy POPs but also exposure to these compounds are more complex than previously observed for the POPs. Some very high concentrations of PBDEs have been observed in young children drawing our attention to risks of developmental effects. BDE-209 is forming lower brominated diphenyl ether metabolites (nonaBDEs and octaBDEs) and a set of hitherto non-structurally identified compounds. PBDEs with an intermediate degree of bromine substituents form hydroxylated PBDE metabolites (OH-PBDEs) among which some are accumulated in blood.

It is clear, that several PBDEs and their metabolites are *in vivo* endocrine disruptors and neurotoxic agents. From a toxicological and mechanistic point of view, it is interesting and intriguing to explore to which extent the observed effects are actually caused by their parent compounds or their metabolites. OH-PBDEs are, as several other substituted phenolic compounds potential disruptors of the oxidative phosphorylation. Although the significant role of metabolites of PBDEs has been known for years, it is remarkable how little attention this has been given to support a more adequate risk assessment. Human data on OH-PDBEs are relatively scarce and clearly inadequate to establish, e.g., the internal variation of these metabolites in humans at background and occupational levels. This argument is probably most true for decaBDE, which is at present commonly used as a flame retardant all over the world. DecaBDE is a BFR with a remarkably short half live in experimental animals and humans in view of its high hydrophobicity.

HBCDDs, and then in particular one of its isomers, the α-HBCDD, is most strongly bioaccumulated in wildlife. The levels are similar of HBCDDs and some of the PBDE congeners as determined in humans living in Europe. The HBCDD is not a major BFR in North America according to our present knowledge. TBBPA has a very short half life and not bioaccumulative. Continuous exposure to TBBPA may still keep up a certain exposure level in humans. However, there are still major data gaps on BFR exposure except for PBDEs and possibly for HBCDD to enable better risk assessments.

It can also be discussed whether regulatory authorities are using the recent *in vivo* and *in vitro* data adequately. When looking at the EU risk assessments for PBDEs, including decaBDE, the focus seems to be on classical long term rodent studies. Without doubt these standard studies provide an adequate method to do a risk assessment for long term background exposure if adequately safety factors are applied. However, regulatory authorities should be more progressive when using various more modern *in vivo* studies that focus on sensitive life stages. In addition, results of a wide array of mechanistic *in vitro* studies with human cells could also be better applied to risk assessment, when concentration–effect relationships would be linked to actual human blood or tissue concentrations. By doing this, risk assessors would on the one hand use the wealth of recent scientific information for these compounds in a better way and on the other hand obviate the need for large safety factors due to the translation of data from one species to another (rodents to humans). In addition, such alternative risk assessment approaches would allow a better discrimination between different life stages and exposure situations and provide more certainty in risk assessment applications.

Improving risk assessment requires better and comparable data. This goes for exposure analysis as well as in toxicology. We propose the use of molar based exposure levels, food analysis making it possible do comparisons

between countries and individuals with specific diets within countries and not the least congener based reports on concentrations, omitting sum of concentrations for PBDEs, PCBs etcetera. Since polybrominated phenolic compounds are formed as PBDE metabolites and are present as technical BFR products we need much more exposure and toxicity data on those compounds. It is motivated by their rather high concentrations relative the parent compounds in humans.