Brominated flame retardants – toxicity in experimental *in vivo*-models

Per Ola Darnerud

Toxicology Div., National Food Administration, P.O. Box 622, SE-751 26 Uppsala, Sweden (poda@slv.se)

Brominated flame retardants (BFRs) are a group of chemicals that has had, and still have, a large and ubiquitous use for fire protection purposes. Because of their appearance in environmental and human samples, in later years often at increasing levels over time, the interest in these compounds has grown considerably. One BFR subgroup, the polybrominated diphenyl ethers (PBDEs), have been studied with special interest because of their structural resemblance with other persistent organic pollutants such as polychlorinated biphenyls (PCBs) and dioxins, the large global production of PBDEs, and the fact that PBDEs are found in biota even at remote sampling locations. This presentation will discuss the toxicity of BFRs with special focus on the PBDEs based on in vivo models, and the use these findings in human risk assessment.

The three major technical PBDE preparations used are the penta-, octa- and deca-BDEs, and the presentation will therefore follow this nomenclature when discussing the PBDE toxicity. Also, a few studies have used specific PBDE congeners for distribution and effect studies in experimental animals, which could circumvent comments regarding purity problems and effects of contaminants on the observed result. Regarding the production of commercial PBDE, there has been a trend to move from the low-brominated preparations to more high-brominated, and today the full-brominated decaBDE make up more than 75 % of the global consumption. However, there are differences between commercial markets, and the American PBDE consumption involves lower brominated preparations.

The pentaBDE preparations are comparatively most toxic, resulting in effects in experimental models at lowest concentrations. The acute toxicity is low (LD_{50} 0.5 – 5 g/kgbw) and repeated exposure results in changes of liver and thyroid size and histology (at 10 mg/kgbw). Also immunotoxicity caused by exposure to the pentaBDE congener BDE-47 is suggested in mice. In several studies, thyrotoxic effects of pentaBDE are shown: Weanling or adult rats and mice exposed to commercial preparations or to pure congeners (10-18 mg/kgbw) respond with decreased serum thyroxine (T4) levels, whereas TSH and triiodothyronine (T3) seem to be affected only at higher doses. Thyroid hormone disturbances have been observed also neonatally, which may be of special importance regarding developmental toxicity. In rat pups of pentaBDE-exposed dams, decreased T4 levels were observed after maternal exposure to 10 mg/kgbw during gestation day 6 to postnatal day 21.

Perhaps the most sensitive effect observed after neonatal exposure to tetra and pentaBDE congeners (BDE-47 and -99) is behavioural effects, specifically impairment of habituation and of learning and memory functions (from doses of 0.6-0.8 mg/kgbw).

The effect have been seen in mice and rat pups, but also adult mice showed symptoms of altered behaviour after neonatal exposure (to BDE-99). The effects on behaviour and thyroid hormone levels may be correlated, as a proposed mechanism for the CNS effects includes PBDE-derived thyroid hormone disturbances resulting in impairment of brain development.

Compared to the pentaBDEs, the higher brominated PBDE preparations, the octa- and deca-BDEs, show toxic effects at higher doses, and in other end-points. Thus, the octaBDE give, apart from morphological liver changes in the rat, certain effects on fetal development, such as reduced ossification, bent ribs and sternebrae changes in rats and rabbits (from 2-15 mg/kgbw). Regarding the deca-BDE, effect could be detected on the liver, thyroid and kidney morphology in the rat after exposure to 80 mg/kgbw, and at even higher exposure levels foetal resorptions were registered. The carcinogenicity study on decaBDE is important, being the only study of tumour induction performed on PBDEs. In this study, adenomas and carcinomas are observed, but at very high doses.

In spite of many gaps in the knowledge of PBDE toxicity, even much less is known of many of the other BFR, including tetrabrombisphenol A (TBBPA) and hexabromocyclododecane (HBCD). The toxic response to TBBPA exposure was low in experimental models. In acute, but also in subacute and chronic studies, effects (reduced body weight and erythrocyte, serum protein and triglyceride concentrations) was observed first after doses in grams per kg body wt. However, at somewhat lower doses (250 mg/kgbw) a slight renal impairment was suggested. In case of HBCD, Some of the observed effects were also seen only at very high doses including (at 750 mg/kgbw) some decreases in food intake and increases in liver weight. A performed cancer study showed some effects but data were inconsistent. However, a recent publication has shown that HBCD could affect behaviour in mice three months after a dosage to the pups at postnatal day 10 with a dose of 0.9 mg/kgbw. This finding has to be confirmed but is anyhow an indication of that effects will be seen at considerably lower exposure levels than earlier has been used for “classical” toxic end-points. It will also be a challenge for toxicologists to explain in what way and to what extent the observed mouse behaviour alterations will relate to human risk assessment of PBDEs.

In a comparison, the lower brominated PBDE preparations are those with the highest biological activity of the BFR compounds mentioned above. At the same time, this PBDE group contain the type of PBDE congeners normally found in the highest concentration in man and in the environment. Why these low-brominated congeners dominate in spite of a comparably low present production could not be easily explained, but may be a consequence of several factors, e.g. presence of old environmental stores and degradative formation from higher brominated PBDE congeners. The margin of safety in exposure has earlier been discussed and was found to be quite large (ca 10^6), if the (Nordic) estimated food intake (ca 0.7 ng/kgbw) was compared to the LOAEL found for pentaBDE effects in experimental models (ca 0.7 mg/kgbw). However, several factors may decrease this safety margin: First, rodents and men have very different retention half-lifes of many persistent pollutants, including PBDE. This must be considered when using dietary data in human risk assessment. Second, the PBDE intake via food may not be the main intake, especially

for persons where very high body burdens have been observed (measured e.g. in fat or breast milk). In this case, direct exposure from fire-protected equipment such as furniture, electronic devices, electrical cables, carpets etc. may be more important. Third, the surprisingly high levels found in human samples from North America suggest a completely other type of human exposure than was earlier estimated e.g. for Europe and Japan. Four, there are still important data gaps regarding PBDE toxicity. Five, combined exposure, a reality for man and other organism in the environment, may lead to synergistic effects or other kinds of combined effects that are not foreseen.

Taken together, the margins may not be all that safe and especially young individuals may have a too small safety margin. Therefore, we must try to limit our exposure to the BFR compounds, and this has to be coupled to a better knowledge of human BFR intake, for example to find out why certain persons have considerably higher PBDE body burdens than the rest of the population. Regarding gaps in our knowledge on effects of BFR exposure, it is easy to mention many and the bottom line would likely say that "more research is needed". However, if some special gaps are to be mentioned I would stress the lack of carcinogenicity data of other PBDE preparations than the decaBDE, the lack of good exposure data also including non-dietary exposure and of toxicokinetic data, and the too few studies that have been interested in combinatory effects. At the same time, there has been a tremendous increase in BFR research in the latest years, and several of the gaps occurring today will be certainly be filled in a few years from now.