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Interim Public Health Risk Assessment of Certain PBDE congeners

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National Industrial Chemicals Notification and Assessment Scheme
GPO Box 58, Sydney NSW 2001, Australia www.nicnas.gov.au

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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia.

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GPO Box 58
Sydney NSW 2001
AUSTRALIA
Attention: Office Manager
Tel: +61 (02) 8577 8800
Freecall: 1800 638 528
Fax: +61 (02) 8577 8888
Email: info@nicnas.gov.au

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Overview

Background

Polybrominated diphenylethers (PBDEs) are a subgroup of polybrominated flame retardants (PBFRs) consisting of 209 structurally related chemicals, or congeners. Some members of the group have been widely used as flame retardants to increase the fire safety of plastics and other materials in homes, cars and offices. The PBDEs can be subdivided based on the number of bromine atoms in the molecule, which varies between one and ten. Preliminary toxicity assessment and results of several international studies have indicated that the most toxic and bioaccumulative congeners are in the tetrabrominated to hexabrominated range, and these are found in commercial pentaBDE and octaBDE. This report therefore focuses on the tetrabrominated to hexabrominated congeners as the major contributors to risk.

Commercial pentabromodiphenyl ether (pentaBDE) and octabromodiphenyl ether (octaBDE) are not solely comprised of pentabrominated and octabrominated congeners, respectively, as suggested by the names. These names refer to an average number of bromines. PentaBDE contains mostly congeners in the tetrabrominated (BDE-47), pentabrominated (BDE-99, BDE-100) and hexabrominated (BDE-153, BDE-154) range. OctaBDE commonly contains hexabrominated (BDE-153, BDE-154), heptabrominated (BDE-183), octabrominated (BDE-196, BDE-197, BDE-203), nonabrominated (BDE-206, BDE-207) and decabrominated (BDE-209) congeners. The major congeners listed above are numbered according to an internationally accepted numbering system.

OctaBDE and pentaBDE were declared Priority Existing Chemicals (PECs) for full risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989*, (the Act) by notice in the *Chemical Gazette* of 3 January 2006. The reasons for declaration were that in animal studies, pentaBDE and octaBDE caused liver and thyroid effects, and changes in neurobehavioral development when individual congeners were administered to neonatal mice at a critical phase of brain development. OctaBDE showed toxicity to embryos in rats and rabbits. Commercial penta and octaBDE contain components which are known to bioaccumulate and these have been detected in breast milk in Australia.

No applications for assessment were received for octabromodiphenyl ether. The chemical was therefore removed from the Australian Inventory of Chemical Substances (AICS) on 6 February 2007 under section 63 of the Act. Manufacture and importation of octaBDE is not permitted under the NICNAS exemption categories except as laboratory standards for analytical determination consistent with section 21 (6) (a) of the Act. Persons importing octaBDE for analytical purposes must comply with annual reporting obligations as required under the Act.

This report addresses potential risk to the public following exposure to PBDE congeners. Results of studies commissioned by the Australian Government Department of the Environment and Water Resources (DEW) for the first time provide levels of these congeners in the Australian environment.

Use

PentaBDE and octaBDE are not manufactured in Australia. These chemicals were imported into Australia and comprised approximately 19% and 11% of all PBFRs imported into Australia in 1998/1999. Information collected for the present assessment indicates that importation of pentaBDE and octaBDE ceased mid 2005. PentaBDE is mainly used in polyurethane foams, for example in furnishings, while octaBDE is used in acrylonitrile/butadiene/styrene (ABS) hard plastics used in applications such as electrical equipment casings.

Articles such as electronic equipment, furniture and cars containing commercial pentaBDE or octaBDE have also been imported into Australia. However, with a voluntary phase out of the manufacture of these chemicals by the major international manufacturers and international regulatory activity such as bans on production and restriction of use in articles, it is expected that there will be a decline in the quantities of these chemicals imported in articles.

Monitoring data

An Environment Protection and Heritage Council study published in 2005 indicated low levels of PBFRs in breast milk of Australian mothers. The study reported the presence of 11 ng/g lipid weight (lw) (range 6-18 ng/g lw) of total polybrominated diphenyl ethers in breast milk. For the study, 157 samples were collected and analysed as 17 pooled samples. The PBDEs found in breast milk included a >90% contribution from the five major bioaccumulative congeners found in pentaBDE and to some extent in octaBDE, BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154.

Recent studies commissioned by DEW measure levels of PBDE congeners in human serum, sediments and indoor dust.

The monitoring results for human serum indicated that the mean level of the five major PBDE congeners, BDE-47, 99, 100, 153 and 154, in adult Australians, was 11.0 ng/g lipid weight (lw) for men, 8.2 ng/g lw for women, and 9.5 ng/g lw in women of childbearing age. Little temporal or regional variation was seen. However, higher concentrations were seen in younger age groups compared with adults. For toddlers in the 0-4 age group, the mean results were 48.3 ng/g lw for females and 44.6 ng/g lw for males. The higher levels in younger age groups were consistent with limited international data showing similar trends.

Due to differences in study design, particularly the number and identity of congeners measured, comparison with international results can only be made with confidence for the five major bioaccumulative congeners, BDE-47, 99, 100, 153 and 154, which are derived from pentaBDE, and, in part, from octaBDE. For overall human serum and breast milk levels, the Australian results are at the high end of results seen in Europe, although they are much lower than the results from similar studies conducted in North America.

In the aquatic environment, Australian levels were found to be low compared with samples from industrialised countries such as Europe and North America. Indoor dust measurements show that the level of the congeners related to pentaBDE are slightly higher than those seen in Europe, but very much lower than the results seen in the USA and Canada. The dust results are particularly important, in that recent work has demonstrated that indoor dust exposure is one of the major sources of human uptake of PBDEs, and is likely to be the major factor responsible for the very wide distribution in human serum and breast milk levels of PBDEs.

Health effects

Based on toxicity studies of commercial pentaBDE, the PBDEs in the tetra- to hexabrominated range have low acute toxicity by oral, dermal or inhalation routes. They are not skin or eye irritants, or sensitisers. Clinical signs of toxicity were not seen following 28 day repeat dosing at 1% in food. Available information indicates that they are neither genotoxic, nor result in foetal death or malformation when administered during pregnancy. No information is available on the carcinogenic potential; however they are not considered likely human carcinogens.

Following repeated dosing of laboratory animals, liver enlargement and induction of metabolic enzymes was seen at comparatively low doses. More subtle effects of pentaBDE or individual congeners on specific mechanisms of toxicity, particularly during development, were further examined in a large number of studies. These studies indicated that certain developmental effects, particularly on the brain and the reproductive organs, were seen at low doses following treatment of rat or mouse pregnant dams or neonates.

Effects on the brain resulting in changes in neurobehavioural development have been reported in a number of studies. In one group of studies, the habituation to new environments of mice pups treated with as little as 0.8 mg/kg bw BDE-99 was found to be disrupted several months after treatment.

In a second group of studies, the offspring of pregnant rat dams treated with BDE-99 or BDE-47 showed higher activity levels, along with ultrastructural changes in the ovaries of female offspring and decreased sperm production, without any other changes in sexual function, in the male offspring. Reduced thyroid hormone (thyroxine) levels were seen in the dams following treatment, and the effects in pups could be correlated to the change in maternal thyroxine levels. The maternal thyroxine reduction and effects in pups were seen at 0.06 mg/kg bw in the dams, the lowest dose tested. However several other studies on the effect of PBDE treatment indicated that effects on thyroxine levels only occurred at much higher treatment doses.

Changes in thyroxine levels in dams or pups have been implicated in the developmental effects in the brain and reproductive organs. There are physiological differences between rodents and humans that make rodents more susceptible to thyroid mediated effects of this type, and therefore the rodent results must be considered as conservative compared with humans. Several human studies on the relationship of thyroxine and PBDE levels have been inconclusive.

Risk Characterisation

The risk posed by the PBDE levels in the Australian biomonitoring data is characterised by a Margin of Exposure (MOE) approach. The MOE approach involves comparison of a No Observed Adverse Effect Level (NOAEL) in an animal model with the estimated or measured human dose or exposure to provide a MOE. NOAELs were not identified in the studies described above on the subtle effects of pentaBDE or individual congeners. The Lowest Observed Adverse Effect Levels (LOAELs) from these studies have therefore been carried forward for risk characterisation. In the case of biomonitoring data, the MOE calculation requires estimation of the blood levels in the animal following treatment at the LOAEL for comparison with the human biomonitoring results. Some measured data are available in animals to allow the treatment doses in rats or mice to be related to expected serum levels. While the use of LOAEL values results in calculation of higher MOE values than would be the case if the NOAELs were used, the remaining assumptions used in the derivation are conservative, resulting in the MOE representing a “worst case” scenario.

Application of the animal LOAEL values from the identified critical studies to humans and derivation of the appropriate serum levels corresponding to the LOAELs is subject to a number of uncertainties, and it is accepted that these uncertainties result in highly conservative risk estimations. However, in the absence of information to quantify the uncertainties, these assumptions are appropriate.

In particular, the LOAELs are derived from rodent testing, and rodents are expected for physiological reasons to be much more susceptible to reductions in thyroxine levels than humans. This is borne out by several unsuccessful attempts to correlate human thyroxine levels with PBDE levels. In addition, the conservative calculation does not account for the likelihood that the effect on thyroxine levels is related to the peak PBDE level at a critical time following dosing, which is unlikely to be reached in the Australian population.

The effects on pups dosed following birth are most applicable to human infants. The LOAEL in neonatal mice of 0.8 mg/kg bw BDE-99 corresponds to a blood level in the mice of 6600 ng/g lipid of BDE-99. Comparison with the human infant level of 48.3 ng/g lw for the five major tetra- to hexabrominated congeners provides a worst case MOE of 136. The tetra- to hexabrominated congener levels have been selected for estimation of MOE for this effect, as studies indicate that these congeners are much more potent than the higher brominated congeners.

The effects on pups following dosing of pregnant rat dams can be used to determine the risk to infants from tetra- to hexabrominated PBDE congener levels in women of child-bearing age. The MOE calculation involves derivation of the rodent blood level corresponding to the LOAEL for pregnant rats of 0.06 mg/kg bw BDE-99. Adult rodent blood levels of PBDEs change more rapidly than those of neonates because of rapid elimination in adults. Two blood levels can be calculated, the peak level immediately following dosing, and a "plateau" level several days following dosing. The calculated levels are 2000 ng/g lw 24 h after dosing corresponding to a peak level and 120 ng/g lw, 5 days after dosing, corresponding to a plateau level. A highly conservative worst case MOE of 12 is obtained on comparison of the plateau level in rodents with the human biomonitoring level in women of child bearing age of 9.5 ng/g lw for the five major tetra- to hexabrominated congeners The plateau level is used to calculate the worst case MOE on the conservative assumption that the effect is related to steady state concentrations rather than peak concentrations; use of the peak level would give a higher MOE of 210.

Regulatory action

There is no evidence of any adverse health effects in adults, newborns or in children from exposure to PBDEs. However, given that these chemicals have the potential to cause developmental effects in the offspring of treated laboratory rats, the potential for these effects to occur in humans cannot be completely ruled out.

Importation of pentaBDE and octaBDE is not currently occurring in Australia; however, the commercial unavailability of these products results from voluntary cessation of production by the major manufacturers as well as regulatory bans in place in the European Union. Information available to NICNAS indicates that pentaBDE and octaBDE production is occurring in some countries.

Given the outcome of the conservative risk calculations a precautionary approach is adopted to ensure that human exposure to the tetra- to hexabrominated PBDEs is minimised. Under Section 61 of the *Industrial Chemicals (Notification and Assessment) Act, 1989*, the importation and/or manufacture of pentaBDE is prohibited while it remains a Priority Existing Chemical.

Regulatory action has already been taken for octaBDE under Section 63 of the Act. OctaBDE has been removed from AICS as no applications for assessment were received since its declaration as a Priority Existing Chemical.

The regulatory action on pentaBDE will be reviewed on completion of the full risk assessment of pentaBDE, and further regulatory action may be recommended as appropriate.

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Acronyms and Abbreviations

Ah	aromatic hydrocarbon BDE-
XXX	an individual PBDE congener
Ci	Curie
decaBDE	decabromodiphenyl ether
DEW	Australian Government Department of the Environment and Water Resources
dw	dry weight
EU	European Union
FSH	follicle stimulating hormone
g	gram
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
L	litre
LH	luteinising hormone
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
lw	lipid weight
MOE	margin of exposure
µ	micro
ng	nanogram (10^{-9} g)
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
octaBDE	octabromodiphenyl ether
Pa	Pascal
pentaBDE	pentabromodiphenyl ether
PBDE	polybrominated diphenyl ethers
PEC	Priority Existing Chemical
pg	picogram (10^{-12} g)
PTU	6-*n*-propyl-2-thiouracil

RoHS	Restriction of Hazardous Substances (i.e. European Union Directive on the Restriction of the use of certain hazardous substances in electrical and electronic equipment)
STP	sewage treatment plant
T3	Tri iodothyronine
T4	thyroxine
TSH	Thyroid Stimulating Hormone
TTR	transthyretrin
UDPGT	Uridinediphosphate-glucuronosyltransferase
UNEP	United Nations Environment Programme

1. Introduction

Three commercial polybrominated diphenyl ethers (PBDEs), pentabromodiphenyl ether (pentaBDE, CAS # 32534-81-9), octabromodiphenyl ether (octaBDE, CAS # 32536-52-0), and decabromodiphenyl ether (decaBDE, CAS # 1163-19-5), were declared as Priority Existing Chemicals (PECs) for full risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act). DecaBDE was declared as a PEC in the *Chemical Gazette* of 5 June 2005, while octaBDE and pentaBDE were declared as PECs in the *Chemical Gazette* of 2 January 2006. OctaBDE and pentaBDE were declared as PECs due to their adverse health and environmental effects.

OctaBDE is no longer a PEC following its removal from the Australian Inventory of Chemical Substances (AICS) on 6 February 2007 under Section 63 of the Act. The PEC assessments will identify the health and environmental hazards of pentaBDE and decaBDE and the potential for environmental, occupational and public exposure in Australia so that the risk of adverse effects to the environment, workers and the public can be determined

The different isomeric constituents are referred to as congeners, and the congeners of brominated diphenyl ethers with one to ten bromine atoms per molecule are named according to a IUPAC scheme as BDE-1 to BDE-209. In this review, the terms pentaBDE, octaBDE and decaBDE refer to specific commercial products, while individual congeners are named according to the IUPAC scheme. Where necessary, the congener is specified as tetrabrominated, pentabrominated, etc.

In biomonitoring and environmental studies, individual congener concentrations are measured. These may clearly indicate the original commercial product, in cases where the individual congeners are present at similar proportions to those in the commercial product. As the different congeners have differences in properties such as bioaccumulation and volatility, it is common for distribution to be shifted from that in the original product. It is known that, in particular, certain hexabrominated congeners are contained in both commercial pentaBDE and octaBDE. Also transformations between congeners, such as metabolic debromination, have been seen under specific circumstances (Stapleton, 2006), and accordingly it is rare that biomonitoring studies show a congener distribution similar to that of a single commercial product or a simple sum of commercial products.

Reviews of the toxicology of the PBDEs have consistently found that the highest toxicity, as well as the highest bioavailability and bioaccumulation potential, relates to PBDEs in the group with four to six bromine atoms per molecule (EU, 2001, 2002, 2003; Darnerud et al., 2001; Hardy, 2002; McDonald, 2002; Health Canada, 2004). These are the specific PBDE congeners contained in commercial pentaBDE and to some extent in octaBDE. It is found that these congeners dominate in Australian blood and breast milk samples, particularly on a molar basis (Harden et al., 2005; Toms et al., 2006a), as has been found in many other international sampling programs. The combination of high levels of these congeners compared with the other PBDE congeners in human biomonitoring

studies, and the high toxicity compared with those of higher bromine content indicate that the risk to Australians from exposure to PBDEs is dominated by the specific risk associated with this group of congeners, and particularly with the use of commercial pentaBDE.

This report therefore focuses on the tetrabrominated to hexabrominated congeners as the major contributors to risk. The interim public health risk assessment reviews risk arising from exposure to the levels of PBDEs found in Australian human biomonitoring and environmental monitoring studies. The PBDEs found in the biomonitoring and environmental monitoring studies are largely derived from the three commercial products, pentaBDE, octaBDE and decaBDE. PentaBDE and octaBDE are not pure single chemicals, although current commercial decaBDE product contains >97% of a single chemical species. PentaBDE consists of a number of geometrical isomers of tetrabrominated, pentabrominated and hexabrominated diphenyl ethers, while octaBDE contains hexabrominated to decabrominated isomers.

The breakdown of decaBDE and octaBDE either by UV light or by biological debromination has been postulated to add to the levels of the lower brominated PBDE congeners in the environment, but the European Union assessments of these commercial PBDE mixtures have indicated that this is likely to be minimal under realistic environmental conditions (EU, 2002, 2003). It is evident from the studies which have indicated the formation of congeners with four to six bromine atoms by either of these routes (Stapleton et al., 2004a; Stapleton et al., 2004b; Bezares-Cruz et al., 2004; Ahn et al., 2006) that the congener mixture formed is very different from that arising directly from use of commercial pentaBDE. Congeners formed by breakdown which are minor contributors or not found in the commercial products may be used as markers to indicate the presence of breakdown products. The relative contribution of these marker congeners to the total PBDE mix in environmental monitoring and biomonitoring results may potentially be used to apportion the contribution of such breakdown to the observed PBDE mix.

This report has been subject to internal peer review within NICNAS. External peer review was undertaken by Professor Brian Priestly, Director, Australian Centre for Human Health Risk Assessment, Monash University. In addition, conclusions relating to critical hazard endpoints for the risk assessment and their applicability to humans have also been reviewed by the Advisory Group on Chemical Safety, which is an independent body established to provide advice on toxicological, occupational health and safety and public health issues that may arise during the assessment of chemicals by NICNAS and the Office of Chemical Safety within the Department of Health and Ageing.

2. Identification

The polybrominated diphenyl ether structure consists of a diphenyl ether unit, with one to ten of the hydrogen atoms substituted by bromine atoms. The formula is therefore $C_{10}H_{10-x}Br_xO$, where x ranges from 1 to 10. Taking into account the different possible geometric isomers, this results in 209 possible individual chemicals, referred to as congeners. All of the three commercial mixtures consist of mixtures of congeners with different degrees of bromination.

The three mixtures which have been dominant in commerce are named according to their average degree of bromination as decabromodiphenyl ether, octabromodiphenyl ether, and pentabromodiphenyl ether. There are reports of a fourth mixture, tetrabromodiphenyl ether (tetraBDE), having been used in the past. Reports indicate that tetraBDE did not differ greatly in composition from commercial pentaBDE (WHO, 1994).

The composition of commercial pentaBDE covers the bromination range of tetrabrominated to hexabrominated, with small amounts of tribrominated congeners. The dominant congeners are tetrabrominated and pentabrominated (La Guardia et al., 2006). OctaBDE commonly contains congeners from the hexabrominated to nonabrominated range, with the major contributions from one heptabrominated congener, followed by a range of octabrominated congeners, and a maximum of 12% hexabrominated congeners (EU, 2003); however a formulation of different composition with low content of hexabrominated congeners has also been reported (La Guardia et al., 2006). DecaBDE in its current formulation is almost totally comprised of a single decabrominated congener, but past formulations also contained approximately 20% nonabrominated congeners (La Guardia et al., 2006).

The commercial mixtures are produced by direct bromination of diphenyl ether, and the directing properties of the ether group limit the range of individual congeners formed in this reaction. Accordingly, certain specific congeners dominate commercial pentaBDE, and it is also these congeners which dominate biological samples. The individual congeners are named according to a scheme devised for the polychlorinated biphenyls (PCBs) as similar geometrical considerations apply to the isomers of each group, although it should be noted that the presence of the ether group constrains the PBDE structure to be non-planar (Sanders et al., 2005).

The following identity information for the pentaBDE mixture applies to the commercial product, rather than specifically only to pentabrominated congeners.

IUPAC name	benzene, 1,1'-oxybis-, pentabromo derivative
CAS preferred name	pentabromodiphenyl ether
CAS number	32534-81-9

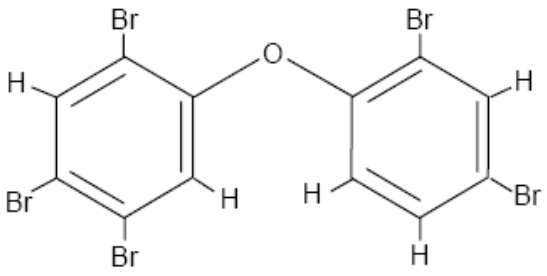
Synonyms	**Trade names**
PeBDE	DE 71
PentaBDE	Bromkal 70-5 DE
PeBDPE	Bromkal 70
PeBBE	Bromkal G 1
PeBBO	Saytex 125
PeBDPO	FR 1205
pentabromo biphenyl oxide	FR 1215
pentabromodiphenyl oxide	DE 60FTM
pentabromo phenoxybenzene	Planelon PB 501
pentabromobiphenyl ether	Tardex 50
pentabromophenyl ether	

The individual congeners contained in commercial pentaBDE which are of most importance in biomonitoring and environmental sampling are:

BDE-28	2,4,4'-tribromodiphenyl ether
BDE-47	2,2',4,4'-tetrabromodiphenyl ether
BDE-99	2,2',4,4',5-pentabromodiphenyl ether
BDE-100	2,2',4,4',6-pentabromodiphenyl ether
BDE-153	2,2',4,4',5,5'-hexabromodiphenyl ether
BDE-154	2,2',4,4',5,6'-hexabromodiphenyl ether

Of the two hexabrominated congeners found in commercial octaBDE, BDE-153 is more prevalent than BDE-154.

The structure of the individual pentabrominated congener, BDE-99, is shown below.



3. Physical and Chemical Properties

PBDEs are highly water insoluble, hydrophobic substances. Commercial pentaBDE is a viscous liquid, but pure congeners and the other commercial products are solids at room temperature. Commercial penta and octaBDEs are not flammable and do not present a physico-chemical hazard (EU, 2001, 2002, 2003).

The extreme hydrophobic nature of the PBDEs is reflected in their octanol-water partition coefficients. Log Kow values are difficult to obtain for such hydrophobic chemicals, but have been measured to be above 6 (EU, 2001, 2002, 2003).

The PBDEs are large molecules, with molecular weights ranging between 407 (tribrominated) and 959 (decabrominated). The vapour pressures are accordingly low, with the vapour pressures decreasing from $1.6\text{-}2.7 \times 10^{-3}$ Pa at 25°C for tribrominated BDEs to $1.2\text{-}2.3 \times 10^{-7}$ Pa at 25°C for octabrominated BDEs, measured from gas chromatography retention times (Watanabe & Tatsukawa, 1990). This information is consistent with the conclusion that the vapour pressure decreases by a factor of 6 to 9 with each added bromine atom (Wong et al., 2001). The vapour pressures indicate that vapour phase transport is a significant issue for the lowest brominated congeners, and becomes less important as molecular weight increases. PBDE mixtures which have been subjected to vapour phase transport are therefore expected to be enriched in tri- and tetrabrominated congeners.

4. Importation and Use in Australia

4.1 Importation

PentaBDE and octaBDE are not currently being imported into Australia in the form of pure chemicals or plastic precursors such as masterbatch. Information collected for the present assessment indicates that importation of pentaBDE and octaBDE ceased mid 2005. In 1998/99, the annual import volumes in these forms were 72 tonnes for pentaBDE and 47 tonnes for octaBDE (NICNAS, 2001). In 2003/04, the importation had reduced to <30 tonnes per annum pentaBDE and <10 tonnes per annum octaBDE. (NICNAS, 2005).

No information is available as to the past importation of pentaBDE or octaBDE incorporated into imported articles such as furnishings, car parts, or electrical and electronic equipment. While it may be possible to obtain information as to the overall imports of articles of types which may contain pentaBDE or octaBDE, the quantity of pentaBDE or octaBDE per article is not known, nor the proportions of articles of a given type which may contain pentaBDE or octaBDE.

No importers of articles indicated to NICNAS that they were currently importing articles containing pentaBDE or octaBDE, although there remains the possibility that importation of articles containing these products may occur through companies which did not respond to the NICNAS Declaration Notices. Similar constraints to those described above exist for estimation of current imports of pentaBDE or octaBDE incorporated in articles, but it is highly improbable that significant quantities of pentaBDE or octaBDE are being currently imported in article form, given that the world-wide availability of these chemicals is extremely limited.

It is reported that pentaBDE of different composition to the originally produced commercial products is currently available from China (UNEP, 2006), although China has enacted a set of controls over hazardous substances similar to that in use in the EU Directive on the Restriction of the use of certain Hazardous Substances in electrical and electronic equipment (RoHS Directive). This may have the effect of removing this commercial source in future.. The commercial availability indicates that there is a potential for future importation of commercial pentaBDE into Australia.

4.2 Uses

All commercial PBDE products have found their main use as flame retardants, normally in conjunction with antimony trioxide or a phosphorus compound as a synergist. There are reports that pentaBDE may have been used as a completion fluid in oil wells in the North Sea (EU, 2001), but these reports have not been confirmed and do not reflect any known use in Australia.

The different PBDE products have different properties, particularly as these concern compatibility with different plastic materials, and therefore have specific and generally non-interchangeable uses. PentaBDE has predominantly been used in polyurethane materials, such as furniture foams, and can comprise up to 30% of polyurethane foams (NICNAS, 1999; EU, 2001). OctaBDE was mostly used in acrylonitrile/butadiene/ styrene (ABS) hard plastics in appliances and computer casings (NICNAS, 1999; EU, 2003).

The articles in which the PBDEs have been used typically have long useful lives, and accordingly many of the older articles which may contain pentaBDE or octaBDE are expected to be still in use.

5. Exposure

Release of PBDEs to the environment can occur during formulation of flame retardant mixtures and manufacture of articles, during the service life of articles containing the flame retardants, and on disposal, through landfill, incineration or recycling. In Australia, widespread release is likely to result from emission from articles during service life or on disposal to landfill, although past direct release in industrial wastewater may account for high localised concentrations.

PBDEs are always used as additive flame retardants; that is, they do not bond into the polymer matrix but are physically encapsulated by the matrix. It is possible for additives in plastics to migrate through the plastic to the surface, a process known as blooming. However the rate of blooming can be very variable, depending on the physical properties, particularly molecular size of the flame retardant, internal structure of the plastic material, and the compatibility of the flame retardant-polymer system. Without measurements on a specific system, it is not possible to say whether this process will happen at an appreciable rate.

Availability of a PBDE from a surface, whether concentrated at the surface by blooming or in the same concentration as in bulk material, requires escape from the surface or direct contact with the surface. Escape by volatilisation is likely to be restricted effectively to the lower brominated PBDEs, due to the very low vapour pressure of the higher brominated congeners. Other possible release mechanisms include breakdown of the parent material, as with old, friable, polyurethane foams, or loss of unstable bloomed layers as dust or during washing. The relative contribution of various sources to levels of PBDEs in the environment has not been determined. A study will be commissioned to determine the major sources of PBDEs in the indoor environment.

Due to lack of available information about the rates of release of pentaBDE or octaBDE from articles, the uncertainties associated with changing release rates as the articles age, and the difficulties associated with estimating the likelihood of particular articles being flame retarded with pentaBDE or octaBDE, monitoring data serves as the best information for estimating human exposure to tetra- to hexabrominated PBDE congeners from articles. Monitoring data is also necessary for understanding the relationship of exposure via food and exposure from dust in the indoor environment.

5.1 Monitoring data

An Environment Protection and Heritage Council (EPHC) study published in 2005 analysed the concentrations of various PBDE congeners in human breast milk (Organochlorine pesticides (OCPs) and polybrominated diphenyl ethers (PBDEs) in the Australian population: Levels in human milk; Harden et al., 2005). Several further studies on PBDEs in human samples and the environment were later commissioned by the Australian Government Department of the Environment and Water Resources (DEW). These cover sediments (Toms et al., 2006b), indoor air and indoor dust (Toms et al., 2006c), and human serum (Toms et al., 2006a). The studies commissioned by DEW are available at http://www.environment.gov.au/settlements/chemicals/bfrs/index.html. A study on PBDE levels in Australian food is being conducted by Food Standards Australia New Zealand (FSANZ).

Together these studies help to produce a picture of the exposure pathways for PBDEs in Australia. The information is limited in the case of the dust and indoor air studies by the comparatively small number of premises sampled in Queensland only, and in the case of the human biomonitoring studies by the use of pooled samples, which does not allow for measurement of inter-individual variability. However international information is available to allow comparisons and use of models which have been derived based on overseas results.

Reporting of monitoring data is complicated by the observation that the distribution of individual results covers orders of magnitude in concentrations; this has been observed for dust monitoring (Wilford et al., 2005) and human breast milk (Schecter et al., 2003). The distribution of results is log normal (Wilford et al., 2005). In these circumstances, the mean value is strongly affected by variations in the few values at the high concentration end, particularly where a comparatively small number of samples are tested. The median value is much less affected by changes in the small number of higher concentration results. However many of the studies which have been reported involved use of pooled samples, for which a median value cannot be derived. Accordingly, arithmetic mean values are generally given in the following discussion, but, information about the distribution of results is also included where available.

It should further be noted that, for a log normal distribution of individual concentrations, results reported as medians are expected to be much lower than those reported as means; for example Schecter et al. (2003) reported a mean value of 40.8 ng/g lipid weight (lw) and a median value of 18.4 ng/g lw for BDE-47 in US breast milk (47 individual samples). Comparisons are also complicated by the use of different analysis sets of PBDEs between studies, and reported measurements of ∑PBDE are commonly not directly comparable for this reason.

5.1.1 Environmental monitoring

Australia

Sediment results do not directly relate to human exposure, as exposure to PBDEs in sediment is likely to only be via uptake into aquatic organisms, followed by ingestion by aquatic food species. This exposure is more closely represented by food monitoring results. However the sediment results are important in

understanding human exposure in that they are representative of the amounts of PBDEs released into waterways in Australia, and therefore represent the concentrations and congener patterns seen in Australian cities compared with those seen overseas. It is noted in the report on PBDE concentrations in Australian sediments (Toms et al., 2006b) that Australian sediment PBDE concentrations are generally low compared with North America, Europe and Asia, and the majority of the samples were greatly dominated by BDE-209 (derived from decaBDE), unlike samples particularly from North America where the major constituents of pentaBDE, BDE-47 and BDE-99, comprised major parts of the sample. The highest level of tetrabrominated BDE-47 determined in the study was 560 pg/g dry weight (dw) near a sewage treatment plant (STP) (Bremer River, downstream), compared with up to 100 000 pg/g dw in San Francisco Bay sediments (Oros et al., 2005).

Limited results are available for the concentration of PBDE congeners in air and dust within Australian homes and offices (Toms et al., 2006c). While these do not comprise a comprehensive survey, the results allow the levels in Australian interior environments to be compared with those found in other countries. The results for three major PBDE congeners, BDE-47 and BDE-99 which are derived from pentaBDE, and BDE-209 from decaBDE, are given in Table 1 along with international comparison results.

The results for indoor air are compromised by the presence of contaminants of BDE-47 and BDE-99, the two major congeners in pentaBDE, in the sampling device, leading to a high limit of quantification (LOQ) for these congeners. Accordingly, in most cases, the results can only be used to give an upper limit for the levels of pentaBDE related congeners in indoor air. Where these two congeners were found above the limit of quantification in indoor air (one home and one office), BDE-47 was present at higher levels that BDE-99, consistent with vapour phase transport (Wilford et al., 2005).

International comparison

Limited international data is available for comparison of indoor air PBDE levels; however Wilford et al. (2005) indicates that there is strong correlation between indoor air PBDE levels and the levels of PBDEs in dust in the same house, particularly for the congeners which comprise pentaBDE. Accordingly, the larger comparison dataset for domestic dust may be used to give the best estimate of the relationship of Australian indoor PBDE levels to those seen internationally.

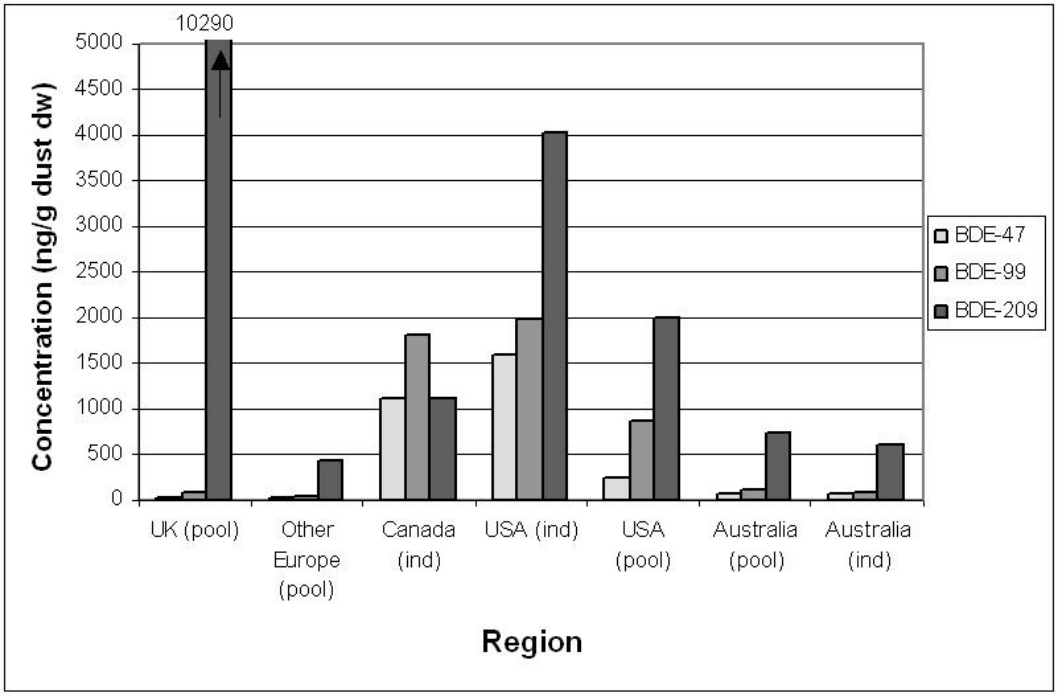
Large directly comparable indoor dust datasets are available for the USA (43 homes) (Sharp & Lunder, 2004; Costner et al., 2005; Stapleton et al., 2005; Schecter et al., 2005; Sjodin et al., 2004) and Canada (68 homes) (Wilford et al., 2005), with individual home data being available from several studies in the USA. Two studies with individual home data are also available from Kuwait (Geveo et al., 2006), and Singapore (Tan et al., 2006). A number of European studies have been restricted to pooled dust samples (Santillo et al., 2003; Sjodin et al., 2004, Sjodin et al., 2006; Al Bitar, 2004; Knoth et al., 2002), allowing comparison only of mean values between these studies and the Australian data. Table 1 shows the comparison between the Australian data for BDE-47 and 99, as markers of pentaBDE, and BDE-209, the major constituent of decaBDE, with a number of international studies. These were the only congeners which were both analysed for and detected in all the studies included in this table. Results are given in ng/g dust dry weight (ng/g dw).

The pool for Scotland reported by Santillo et al. (2003) was considered an outlier, as the results for BDE-47 and BDE-99 were reported by the author as indicating inclusion of one or more highly contaminated households, and inclusion of this would give an average result which is not representative of the remaining 9 pools in this study. In this pool of 10 houses, BDE-47 was present at 1980 ng/g dw, and BDE-99 at 2100 ng/g dw.

Table 1. International comparison of indoor dust concentrations of BDE-47, 99 and 209 in ng/g dw

	BDE-47			BDE-99			BDE-209		
Country	*Mean*	*Median*	*Max*	*Mean*	*Median*	*Max*	*Mean*	*Median*	*Max*
UK[a] (100 pooled)	27.2			79.8			10290		
Other Europe[b] (259 pooled)	21.6			32.8			425		
Kuwait[c] (17 individual)	6.6	2.7	65	6.0	3.4	36	129	83	338
Singapore[d] (31 individual)	110	20	1500	340	24	6300	2200	1000	13000
Canada[e] (64 individual)	1100	300	33000	1800	430	60000	1100	630	10000
USA[f] (43 individual)	1595	674	10538	1977	626	13841	4028	1680	65777
USA[g] (10 pooled)	230			880			2000		
Australia[h] (10 pooled)	60			106			732		
Australia[i] (8 individual)	55.0	34.3	210	79.8	48.8	294	619	401	2230

a. data from Santillo et al. (2003) and Sjodin et al. (2006). Data from the Scottish pool reported by Santillo et al. were omitted as these were identified as an outlier (see text).
b. data from Santillo et al. (2003), Sjodin et al. (2004), Al Bitar (2004), and Knoth et al. (2002)
c. data from Gevao et al. (2006)
d. data from Tan et al. (2006)
e. data from Wilford et al. (2005)
f. data from Stapleton et al. (2005), Schecter et al. (2005), Sharp & Lunder (2004), and Costner et al. (2005)
g. data from Sjodin et al. (2004)
h. data from Sjodin et al. (2006)
i. data from Toms et al. (2006c)



The Australian results for BDE-47 and BDE-99 are somewhat higher than the levels found across a number of studies in Europe, by a factor of around 2 to 3, but are low compared with those seen in the North American studies. In particular, it is noted that the median level seen in the Australian study of individual homes and offices is below the minimum level seen in any of the 43 individual homes tested in the USA for both BDE-47 and BDE-99, and within the 5th percentile for 64 individual homes in the Canadian study for BDE-47; the maximum Australian values for these congeners, from an office source, are in the 20th percentile of homes in the USA.

The mean values indicate that there is approximately 20-30 times the concentration of pentaBDE in house dust in the USA and Canada, compared with Australia. For BDE-209, the international comparison is very different, with the highest mean levels seen in the UK, followed by North America. Australian samples showed similar levels to continental Europe for this congener.

5.1.2 Human biomonitoring

Australia

Two major recent studies on concentrations of PBDEs in pooled human serum and breast milk samples from across Australia (Harden et al., 2005; Toms et al., 2006a) provide information on the actual absorbed dose of these chemicals in the Australian population and the relative levels compared with overseas countries. The reports provide analysis of the concentrations, including international comparisons. The serum report shows that there are significantly higher levels of total PBDEs in younger members of the population, particularly toddlers, compared with adults.

For purposes of this interim report, the results for the higher congeners have not been included in the comparisons, and all international comparisons are made on the basis of the small set of congeners which have been part of the measurement set for almost all studies, BDE-47, 99, 100, 153 and 154. The choice of this set for the current report is on the basis of their toxicological significance, as discussed later. This approach avoids distortion of the comparison by use of measurement sets comprising different congeners. A similar approach for international comparisons was used by Hites (2004). Due to experimental difficulties in determining the heptabrominated to decabrominated congeners (de Boer & Wells, 2006) and the high limits of detection for these congeners, the results for the higher congeners have greater uncertainty than the results for the major tetra- to hexabrominated congeners.

The study of PBDE levels in Australian pooled breast milk in 2002/03 (Harden et al., 2005) showed some regional variability, although the small sizes of the pools (17 separate pools containing 157 samples) may mean that inter-individual variability in results accounted for most of the observed variations. The five major congeners accounted for approximately 91% of the total for the 16 congeners analysed. A mean value across the pools of 10.1 ng/g lw was found, with the dominant congener in all pools being BDE-47 (~50% of total PBDEs). The study also examined three pools consisting of 24 individual breast milk samples which had been collected in 1993. The results from 1993 and 2002/03 were very similar, indicating that overall no increases in Australian population levels of these PBDE congeners occurred during the 10 year period.

In the study of PBDE levels in Australian pooled serum (Toms et al., 2006a), high correlation is seen between the pool total PBDE levels and the levels of the five major pentaBDE congeners. The data for the pentaBDE congeners show no indication of an increase between the first sample collection, 2002/03, and the later collection, 2004/05, and, overall, a slight decrease in the concentration of these congeners in adults is seen on comparing the Northeast results for the two collection times. Due to different group definitions, comparisons for age groups below 16 are not possible.

The serum results by region, gender and age group are shown in Table 2. Results are in ng/g lw. All Australian regions were sampled in 2002/03, while only the Northeast region was sampled in 2004/05. The <16 age group in the 2002/03 sample collection is compared with the 5-15 age group in the 2004/05 sample collection. While the average ages of these groups were similar, comparison of the age range shows that there was an unknown contribution from under 5 year olds in the <16 age data. This may explain the higher results for the <16 age group in the 2002/03 data compared with the 5-15 age group in the 2004/05 data.

Table 3 presents the average concentration across all Australian regions for individual congeners in ng/g lw, by gender and age group. The 2004/05 data is pooled with the 2002/03 data, as the differences seen between these two sampling times for the Northeast region are minor. The summary group “adults” includes all pools from 16-30 to >60, and, for women, the summary group “child-bearing age” includes ages 16 to 45.

The results showing higher concentrations in the very young age group are supported by information from Norway (Thomsen et al., 2002) and a single study of two members of one family in the USA (Fischer et al., 2006).

Table 2. Sum of 5 tetra- to hexabrominated congeners (BDE-47, 99, 100, 153, 154) by region, age group and gender. Concentrations in ng/g lw.

		Region					
	Age Group	Northeast	Northeast (2005)	Southeast	Rural	West	South
Female	0-4		44.6				
	5-15 (<16)	26.3	16.4	17.5	31.0	9.7	
	16-30	10.8	8.6	15.3	9.3	12.5	6.9
	31-45	14.7	7.3	7.2	8.8	8.3	6.2
	46-60	5.2	7.7	6.1	6.2	6.5	8.0
	>60	8.2	4.7	4.8	10.9	5.7	6.5
Male	0-4		48.3				
	5-15	23.5	19.8	23.2	20.3	20.7	21.5
	16-30	16.7	11.3	17.9	13.1	12.1	12.2
	31-45	13.3	9.7	11.3	12.7	14.4	10.0
	46-60	10.8	8.8	12.1	8.7	9.7	8.0
	>60	6.6	7.6	6.5	20.4	5.9	4.7

Table 3. Individual concentrations of 5 tetra- to hexabrominated congeners, averaged across Australian regions, by age group and gender. Concentrations in ng/g lw.

		Congener					
	Age Group	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	Sum
Female	0-4	25.0	9.0	7.2	6.3	0.9	48.3
	5-15	9.6	4.0	2.5	3.6	0.4	20.2
	16-30	5.1	2.2	1.3	1.7	0.2	10.6
	31-45	4.2	1.7	1.0	1.6	0.2	8.7
	46-60	3.1	1.0	0.8	1.5	0.2	6.6
	>60	3.2	1.2	0.8	1.3	0.2	6.8
	Adult	3.9	1.5	1.0	1.5	0.2	8.2
	Childbearing age	4.6	1.9	1.1	1.6	0.2	9.5
Male	0-4	23.0	7.9	6.5	6.4	0.9	44.6
	5-15	9.1	4.3	2.5	5.0	0.5	21.5
	16-30	6.3	2.5	1.6	3.2	0.3	13.9
	31-45	5.3	2.3	1.5	2.6	0.3	11.9
	46-60	4.5	1.6	1.1	2.2	0.3	9.7
	>60	4.1	1.4	1.0	1.9	0.3	8.6
	Adult	5.0	1.9	1.3	2.5	0.3	11.0

The Australian breast milk study (Harden et al., 2005) showed results which are consistent with those of the serum study, with results for the same five congeners on a lipid weight basis being similar to those for the serum of women of child-bearing age, as shown in Table 4. The results appear to show a preferential partitioning of the less brominated congeners into breast milk.

Table 4. Concentrations of 5 tetra- to hexabrominated congeners in serum of women of child-bearing age and in breast milk. Concentrations in ng/g lw.

	Congener					
	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	Sum
Serum	4.7	2.0	1.1	1.6	0.2	9.7
Milk	5.6	1.9	1.3	1.1	0.1	10.1

International comparison

A large body of international biomonitoring work, particularly in breast milk, is available for international comparison. The studies include both pooled and individual studies. Of these studies, the most valuable information comes from several studies which have either looked at the time course of PBDE levels within a population, or at the inter-individual variation within a population.

In a series of papers, the levels of a group of PBDE congeners similar to those listed in Tables 3 and 4 were determined in Swedish pooled breast milk over the period 1972 to 2004 (Meironyté et al., 1999; Meironyté Guvenius & Norén, 2001: Sjodin et al., 2003; Fangstrom et al., 2005). Sampling was conducted at least every second year from 1988 onwards. This time period included the time when use of pentaBDE and octaBDE was phased out in this market, reported by Meironyté Guvenius & Norén (2001). A rapid increase in PBDE concentrations in breast milk was seen up to 1996. Following the discontinuation of use of these products in Sweden, the total PBDE level decreased. Individual congener results were compiled in 2005, and it was found that a decrease was seen for BDE-47, 99 and 100. Each of these decreased by a factor of at least two from the peak concentration by 2004. However, for BDE-153, no clear decrease was seen over this time frame (Fangstrom et al., 2005).

Several large studies of individual breast milk PBDE concentrations have been reported; two in the USA (one in 2001 of 47 participants reported by Schecter et al., 2003, and one in 2002/03 of 20 reported by Lunder & Sharp, 2003) and one in the Netherlands (one 1998 study with 103 participants reported by de Winter-Sorkina et al., 2003). These have all shown similar patterns of inter-individual variation across the population. While the overall results were different, with the Netherlands median for the dominant congener, BDE-47, being 1.23 ng/g lw, and the two US studies having medians of 18.4 ng/g lw and 24 ng/g lw, all of the studies have shown an approximately lognormal distribution with a small number of samples showing a much higher concentration than the median, and a distribution of concentrations covering one or more orders of magnitude.

Based on the information in the studies of individuals in the USA, it may be estimated that the maximum concentration in serum is around ten times the median value, or five times the mean value.

A study of 15 individuals in Sweden looked at the relationship between PBDE concentrations in maternal serum, breast milk and cord blood (Meironyté Guvenius et al., 2003). It was found that there was an approximately 1:1 relationship of the concentrations of tetra- to hexabrominated congeners between maternal serum and breast milk, on a lipid weight basis. Partitioning to breast milk was higher for tetrabrominated BDE-47 compared with hexabrominated BDE-153. In cord blood, there was evidence that placental transfer of penta- and hexabrominated congeners was reduced, although similar levels of BDE-47 were seen on a lipid weight basis. Based on these results, it seems possible to use both serum and breast milk results together to measure PBDE concentrations within a population, at least for the tetrabrominated to hexabrominated congeners.

In the USA, McDonald (2005) compared results of a number of studies of PBDE levels in breast milk, adipose tissue and serum of individual samples from women. The set of congeners examined in each study and included in the total PBDE level is not reported. Results for each medium are similar when expressed in lipid weight terms. For all media together, a median concentration of 47.9 ng/g lw and a mean concentration of 90.3 ng/g lw were obtained. The 95th percentile concentration was 302 ng/g lw.

Hites (2004) compiled a large number of studies on PBDE concentrations in environmental and human samples. All human samples were analysed in terms of the single set of PBDE congeners, BDE-47, 99, 100, 153 and 154. The samples covered the time period from 1970 to 2002. The highest reported levels in blood and milk, respectively, reported from Europe were 6.03 ng/g lw for Sweden in 2001; and 4.43 ng/g lw for Sweden in 1999. European and Japanese blood and breast milk levels for these five congeners were generally in the range 1-4 ng/g lw over the period from 1990 to 2001. In the USA, the maximum levels reported by Hites were 193 ng/g lw in milk in 2000, and 41.3 ng/g lw in foetal blood in 2001. It should be noted that the results tabulated by Hites are geometric mean values for a population, and therefore will generally be lower than equivalent arithmetic mean values, as represented by the pooled blood and milk studies performed in Australia.

Serum data are also available from New Zealand. Samples were taken from 23 individuals in 2001. The combined mean for BDE-47, 99, 100, 153 and 154 was 6.83 ng/g lw. In this study, the median was 6.12 ng/g lw, indicating a smaller spread of individual results than has been observed in a number of other biomonitoring studies (Harrad & Porter, 2006).

5.1.3 Discussion of monitoring results

The results for individual congener concentrations in biomonitoring studies do not reflect the composition of commercial pentaBDE in that the concentration of BDE-99 relative to BDE-47 is generally low. In the commercial product, BDE-99 is the dominant congener, but this is reversed in many biological samples. In fish, there is evidence of specific reductive debromination of BDE-99 to BDE-47, which may contribute to the different bioaccumulation behaviour of these major congeners, particularly in seafood samples (Stapleton et al., 2004b). The biomonitoring results also show a large contribution from BDE-153, which is present in the samples at a level disproportionate to its level in commercial pentaBDE, and it is possible that commercial octaBDE use also contributed to the

level of BDE-153 in these samples. Due to the low bioaccumulation potential of the higher congeners in commercial octaBDE (EU, 2003), and the relatively low content of BDE-154 in this product, BDE-153 is expected to be the only major congener in octaBDE to accumulate in the body to any extent. However the longer halflife of BDE-153 compared with any of the other congeners (Geyer et al., 2004) may lead to a relative increase in this congener over long exposure times, even without exposure to additional sources of BDE-153 such as octaBDE.

An aspect of international biomonitoring studies which has been the subject of specific interest is the variability of concentrations of the PBDEs among members of a single population, with up to two orders of magnitude difference between individuals in some cases e.g. Schecter, 2003. Recent work has indicated that the large differences in concentrations in blood serum and breast milk are likely to relate to differences in exposure, particularly to pentaBDE related congeners in household dust (Sjodin et al., 2004; Jones-Otazo et al., 2005). Similar variability in house dust concentrations, with results spanning several orders of magnitude, has been seen (Wilford et al., 2005). Exposure calculations for Canadian dust and food levels of PBDEs (Jones-Otazo et al., 2005) indicated that the indoor dust route is the dominant contributor to PBDE intake; in the case of the higher indoor PBDE levels used in the calculations, by a very large factor. However, in these calculations, food was found to be the main source of human intake when the lowest indoor PBDE levels were used. It is noticeable that North America, with much higher levels of the lower brominated PBDE congeners in household dust compared with elsewhere in the world, also shows much higher levels of these congeners in human serum and breast milk. In this context it is worth noting that the high BDE-209 levels in indoor dust in the UK are not reflected by greatly elevated levels of lower PBDE congeners in human serum and breast milk compared with the remainder of Europe.

The sample size for determination of indoor dust levels in Australia is small (8 homes and offices (Toms, 2006c), plus one pool of 10 homes (Sjodin et al., 2006)). This does not allow for characterisation of the variability in PBDE levels between homes in Australia. In addition, the use of pooled samples for Australian blood serum and breast milk obscures the variability of these levels. It is clear that the mean levels of lower brominated PBDEs in both types of samples are low compared with North America. However it is not certain whether this indicates that the whole distribution is moved to lower concentrations, i.e. even the outliers have much lower concentrations than the outliers in North America, or whether there are individual homes and people in Australia with levels similar to those seen at the higher concentration end of the North American studies, but these outliers are rare compared with in North America.

Another question which arises from the observations of variability of PBDE levels in indoor dust concerns the sources of the dust. Many articles currently in use inside homes could potentially contain levels of PBDEs of 10% or greater, and it is likely that the majority of homes would contain at least some articles containing PBDEs as flame retardants. The occurrence of pentaBDE in homes is much more likely in North America than elsewhere in the world, due to the high proportion of pentaBDE production and use in this area (Bromine Science and Environmental Forum, 2000). However the precise conditions which lead to elevated levels of PBDEs in indoor dust have not been studied, although several of the indoor dust studies have attempted to examine linkages to some specific

equipment, such as foam furniture and computers. Hale et al. (2002) showed that old and crumbling polyurethane foam could be a specific pathway for release of pentaBDE to the environment.

Other sources of dust exposure to PBDEs, such as from office work or in the interiors of cars or aircraft, have not been studied sufficiently to determine their contribution to overall intake.

5.2 Bioaccumulation studies

Data generated from laboratory and field studies, along with a large volume of data for monitoring levels of PBDEs in biota show that the components of commercial pentaBDE are readily bioavailable, and can accumulate through the food chain. The available data indicate these compounds are bioavailable through different exposure routes such as water, sediment, soil and food. In particular, tetrabrominated BDE-47 (present at around 37% in commercial pentaBDE formulations), and the two pentabrominated congeners, BDE-99 and BDE-100, have very high bioconcentration and bioaccumulation factors and are generally the most dominant congeners measured in biota. The two major but unidentified hexabrominated congeners, which can be tentatively assigned to be BDE-153 and BDE-154, also have high bioconcentration factors of >2500 L/kg and >5600 L/kg in carp (*Cyprinus carpio*) (EU, 2001; CITI, 1982a). Levels of these substances have been measured in marine predators including dolphins, seals and birds (EU, 2001).

An overall bioconcentration factor in carp was also measured for commercial octaBDE (EU, 2003; CITI, 1982b). The reported value for the overall bioconcentration factor was 4 L/kg, indicating that the overall test substance was not bioaccumulative. However the hexabrominated congeners in octaBDE are known to be bioaccumulative based on the measurements using pentaBDE.

6. Health Effects

The following information summarises the overall toxicity of pentaBDE (representative of the toxicity of tetra- to hexabrominated congeners) or individual congeners in the tetra- to hexabrominated range. Commercial octaBDE is also likely to contribute to the hexabrominated congeners found in the Australian population biomonitoring results, as this substance contains approximately 10% hexabrominated congeners (NICNAS, 1999; EU, 2003). However, the majority of commercial octaBDE is hepta- or octabrominated, and congeners in these ranges are not as bioaccumulative as the tetra- to hexabrominated congeners (EU, 2003) and are not major contributors to the overall PBDE levels in Australian serum (Toms et al., 2006a). Accordingly, results of toxicity testing conducted using commercial octaBDE are considered to largely reflect the toxicity of the higher brominated congeners which are not generally found at high levels in the Australian serum studies, rather than the hexabrominated congeners. Results of testing on commercial octaBDE are included only where these are considered to add to the understanding of the overall toxicity of PBDEs.

To avoid duplications, and noting the high quality of the previously published international report, the summary information is mostly taken from the EU Risk Assessment Report for pentaBDE (EU, 2001). This document gives a comprehensive review of data available to the time of its compilation, and includes all critical studies, apart from toxicokinetics studies and studies on endocrine related effects, where recent research has been conducted. Studies which relate to critical effects for purposes of assessment of risk in the environmental concentration range, particularly those relating doses and serum concentrations, and those relating to thyroid related endocrine effects, are discussed in full.

6.1 Absorption, distribution, metabolism and excretion.

The individual PBDE congeners in the tetrabrominated to hexabrominated range are readily absorbed orally and by inhalation; dermal absorption has been observed to a lesser extent. In the body, there is a large degree of localisation to adipose tissue, particularly for the lower brominated congeners. These also readily partition to breast milk. Metabolism of pentabrominated and tetrabrominated congeners has been demonstrated to result in small amounts of conversion to hydroxylated metabolites (EU, 2001). The excretion in rats is mainly faecal, although adult mice have been shown to readily excrete tetrabrominated BDE-47 in urine. The difference in excretion routes results in different half lives for this congener in rats and mice (Staskal et al., 2005).

Based on mass balance considerations and by extrapolation of the results in rats, the human half life has been estimated to be in the range of several years for individual tetrabrominated to hexabrominated congeners (Geyer et al., 2004).

Several specific quantitative studies of the toxicokinetics of the individual congeners BDE-47 and BDE-99 in mice yield information which is important for

relating oral dose levels in toxicological studies with the corresponding levels in blood.

In a comprehensive study of toxicokinetics of tetrabrominated BDE-47 via oral, dermal, intravenous, intraperitoneal and intratracheal routes in mice, the distribution to adipose tissue, liver, brain, skin, kidney, muscle, blood and lung was studied (Staskal et al., 2005). The overall distribution was independent of route of exposure, apart from localised concentrations which could be related to the exposure route – higher lung levels in the intratracheally dosed animals and higher levels in abdominal fat and muscle in intraperitoneally dosed animals. In animals, five days after oral gavage of 1.0 mg/kg bw, >70% of the retained radioactivity was found in the liver, with approximately 8% in each of liver and skin, >3% in lung, >2% in muscle, >1% in kidney, and <1% in blood and brain. The blood level five days after dosing was 13 ng/g wet weight, corresponding to approximately 2600 ng/g lipid weight.

The time course of distribution was also examined in animals treated by oral gavage at 1.0 mg/kg bw. At up to 3 h after dosing, the highest concentration of approximately 50% of the retained dose was found in the liver. Twenty-four hours after dosing, the majority (>60% of the retained dose) was contained in the adipose tissue, and the proportion in the adipose tissue reached a maximum of around 80% of the retained dose at 10 days. Liver, brain, kidney, muscle, lung and blood all showed maximum levels both in absolute terms and as a proportion of retained dose within the first 24 h after dosing. The maximum blood level of BDE-47 reached 69.2 ng/g wet weight 3 h after dosing. Detectable concentrations were found in all examined tissues 21 days after dosing, with a blood level of 4.6 ng/g wet weight. In neonatal 10 day old mice, BDE-47 was found in blood, brain, skin, fat, kidney and liver (Staskal et al., 2006). Most tissue concentrations were higher in neonatal animals than in those dosed at an equivalent level in adulthood.

Distribution of tetrabrominated BDE-47 and pentabrominated BDE-85 and 99 in adult female C57BL mice were studied by whole body autoradiography (Darnerud & Risberg, 2006). Animals were treated with 20 µmoles/kg bw, equivalent to 11.3 mg/kg bw for BDE-85 and 99, and 9.7 mg/kg bw for BDE-47. The dose in each case contained 250 µCi/kg bw of radiolabel. Dose was administered by intravenous injection; for BDE-85 and 99, results following oral gavage treatment were also obtained. For BDE-85 and 99, autoradiography was performed at 1, 6, 24 h, 4 days and 16 days after dosing; for BDE-47, the time course of distribution was only followed to day 4. Whole body radiography was also performed on pregnant dams, and, for BDE-47 only, male C57BL mice.

No major differences between the behaviour of the three congeners in autoradiographic distribution were observed. The distribution was characterised by high, but time decreasing, uptake into fatty tissues. Initial uptake was into brown fat, but after 24 h white fat levels became more pronounced. Other tissues which accumulated radioactivity included liver, adrenal cortex, lung, ovaries and nasal epithelium. The 16 day autoradiographs were reported to show significantly weaker radioactivity overall compared with the 4 day results.

For specific tissues, the brain showed intermediate initial levels of radioactivity. Remnants of the label could be observed after 16 days. The thyroid was not specifically labelled by the administered radioactivity. The lung at all times showed higher levels than blood, and slow reduction in levels. Testes showed no

localisation of radioactivity, but, accumulation was seen in ovaries, with localisation to follicular structures. Oral administration led to no difference in distribution pattern apart from increased levels of radioactivity in the gastrointestinal tract.

In the pregnant mice, foetal levels of radioactivity were low, with major localisations in the foetal liver and intestinal contents. Very low levels of radioactivity were seen in the foetal brain.

The study was complemented by quantitative radioactivity measurements in lactating dams and their offspring, for BDE-85 and 99 only. Dams were treated intravenously with 1.1 mg/kg bw BDE-85 or 99, containing 25 µCi/kg bw of radiolabel, on day 11 post partum. One and four days later, the dams were milked, and, after 4 days, dams and offspring were sacrificed for tissue and whole body measurements of radioactivity. Radioactivity in the milk was similar for the two congeners, and decreased over the four days (380 ng/g wet weight to 110 ng/g wet weight). The whole litter was calculated to contain 20% and 24% of the administered dose of BDE-85 and 99, respectively. In conjunction with the autoradiography measurements, this indicated that maternal – foetal transfer was low during gestation but maternal – infant transfer was higher during lactation.

In the dams, concentrations in adipose tissue on a whole tissue basis were much higher than in the liver. Offspring liver and kidney levels were similar to those in the dams, but higher plasma levels were seen in the offspring, compared with the dams (27 ng/g wet weight v 7 ng/g wet weight at 4 d after dosing, equivalent to 5400 ng/g lipid weight and 1400 ng/g lipid weight).

For adult female rats, blood concentrations at 1 and 5 days after intraperitoneal injection of a mixture containing a number of PBDE congeners, each at 3 µmol/kg bw, is available (Malmberg et al., 2004). For BDE-47 and BDE-99, similar results were seen, with BDE-47 being present at 500 pmol/g wet weight in blood at 24 h, and 41 pmol/g wet weight at 5 days, and BDE-99 being present at 560 pmol/g wet weight at 24 h, and 32 pmol/g wet weight at 5 days. Hexabrominated congeners showed higher blood levels at 24 h, but the levels were in a similar range to the penta- and tetrabrominated congeners at 5 days.

The human maternal-infant transfer of the sum of the total body content of tri- to hexabrominated PBDEs, represented by 25 congeners, was determined by measurement of individual and sum PBDE levels in maternal blood, cord blood, placenta and breast milk, from 4 subjects (Hirai et al., 2004). The total PBDE level was similar in placenta and maternal blood at 1042 and 968 pg/g lipid, but lower in cord blood, at 333 pg/g lipid. Breast milk levels were higher, at 1509 pg/g lipid. BDE-47, 153, 100, 99 and 28 and/or 33 together comprised more than 65% of the sum of the congeners.

6.2 Acute toxicity

PentaBDE has very low acute toxicity by the oral route, with reported oral LD50 values ranging from 2640 – 6200 mg/kg bw. For dermal toxicity, no mortalities were seen at up to 11000 mg/kg bw/day. In an acute inhalation toxicity study, mortalities were not seen up to 200 mg/L, although the fraction of the aerosol in the respirable size range was not clear (EU, 2001).

6.3 Irritation and sensitisation

PentaBDE was slightly irritating to rabbit skin, producing slight erythema and oedema which resolved within 72 h in some animals. In eye irritation testing, mild conjunctival irritation was seen. Slight respiratory tract irritation was observed at high exposure concentrations in inhalation toxicity testing. In a Magnussen and Kligman Maximisation test in guinea pigs, no evidence of sensitisation to skin was seen (EU, 2001).

6.4 Repeat dose studies

A number of repeat dose studies (28 to 90 days) have been undertaken using pentaBDE by dietary administration. In addition, a number of studies using repeated dose administration of pentaBDE, or individual congeners in the bromination range covered by pentaBDE, for study of more specific endpoints have also been reported. A similar pattern of effects has been seen across these studies.

No treatment related mortalities were seen. The major effects were in the liver, with increases in absolute and relative liver weights. Histopathological changes included enlarged centrilobular and midzonal liver parenchymal cells in which the cytoplasm had large areas of finely granular "ground glass" structures containing eosinophilic "round bodies" and/or vacuolisation. The other major effects were observed in the histopathology of the thyroid. In a 28-day study using low doses, with a maximum of 1 mg/kg bw/day, a NOAEL was set at the highest dose used. In the other studies, higher doses, ranging between 2 and 100 mg/kg bw/day, were used and no NOAEL could be set. The LOAEL in a 90-day study was set at 2 mg/kg bw/day based on histopathological changes in the liver (EU, 2001).

Commercial octaBDE showed a similar pattern of repeat dose toxicity, with major target organs being liver and thyroid, although effects were generally seen at higher doses than for pentaBDE. Kidney effects were also reported for octaBDE, but only at a very high dose of 781 mg/kg bw/day (EU, 2003).

Other more specific effects have been observed at lower doses, in additional studies, particularly on thyroid hormone levels and neurobehavioural development, and these are discussed below.

6.5 Reproductive and developmental effects

PentaBDE has been tested for developmental toxicity in rats (2 studies). Effects on reproductive and developmental parameters were seen only at doses producing significant maternal toxicity. The results indicate that pentaBDE is not a specific developmental toxin (EU, 2001). Commercial octaBDE was reported to show slight specific foetotoxic effects, although only at higher doses than are likely to be relevant for humans exposed via the environment (EU, 2003). It is also unlikely that these effects relate to the major bioaccumulative congeners observed in the environment, as they have not been observed for pentaBDE, which also contains the two bioaccumulative congeners, BDE-153 and 154, found in octaBDE.

A number of additional developmental studies focussing on more specific endpoints have been conducted using pentaBDE or individual congeners in the

bromination range covered by pentaBDE. A number of more specific effects have been observed, at lower doses, in additional studies, particularly on neurobehavioural development, and these are discussed below.

6.6 Genotoxicity

A number of in vitro genotoxicity studies have been undertaken using commercial pentaBDE. The majority of the studies showed negative results, and the overall conclusion based on the total group of studies is that pentaBDE is not genotoxic (EU, 2001).

6.7 Carcinogenicity

There is insufficient information on the carcinogenic potential of commercial pentaBDE and octaBDE.

6.8 Endocrine related effects

A large number of studies have been published concerning the effects of PBDEs, particularly those in the tetra- to hexabrominated range, on metabolic enzyme induction, particularly in the liver, direct endocrine effects, particularly on the thyroid, or on developmental effects related to effects on the endocrine system.

Metabolic enzyme induction is discussed in this section, primarily as the induction of metabolic enzymes in the liver and elsewhere is accompanied by changes in the endocrine system in experimental animals, due to the direct effects of these enzymes on hormone systems. Uridinediphosphate-glucuronosyltransferase (UDPGT) induction increases the metabolism of thyroxine (T4), and induction of certain P450 isoforms such as aromatase has direct effects on steroidogenesis in the reproductive systems. Metabolic enzyme induction via the aromatic hydrocarbon (Ah) receptor is also a major factor in dioxin toxicity.

Thyroid hormones are shown to be affected by treatment with PBDEs. This is in part attributed to the chemical resemblance between hydroxylated metabolites of PBDEs to thyroxine, although UDPGT induction may also play a part in the effects on the thyroid hormone system. Repeat dose studies have shown histopathological effects on the thyroid in addition to liver effects, and alteration of thyroid homeostasis may be responsible for these observations.

Some studies have also shown effects on development of the reproductive system.This may be due either to effects of PBDEs on reproductive hormones, hormone receptors, or an indirect effect due to thyroid hormone disruption during development.

Finally, a number of studies have shown effects of PBDEs on neurobehavioural development. A number of factors may be involved in these effects; however there are indications that a major factor may be the thyroid status of the dam or neonate during critical periods of neurological development.

Of the large number of studies relating to these effects, the focus in the following discussion is on several critical studies, particularly those which elucidate mechanisms of action and where the most critical effects are seen in the

experimental animals. Preference is also given to in vivo studies and in vitro results are only discussed where necessary to elucidate mechanisms.

6.8.1 Metabolic enzyme induction

Examination of the dioxin like activity as measured by Ah receptor activation by commercial pentaBDE or congeners in the range covered by commercial pentaBDE has given variable results (Peters et al., 2004; Chen & Bunce, 2003). It is not clear whether there is specific Ah receptor activation or whether the results are due to impurities. However the commercial product does show dioxin-like activity, though this is not likely to be directly due to the PBDE structure itself (Sanders et al., 2005).

Testing for pentoxy-resorufin-O-deethylase (PROD) and uridinediphosphate-glucuronosyltransferase (UDPGT) activities has shown that commercial pentaBDE or congeners in the range covered by commercial pentaBDE produce metabolic activation of the phenobarbital type (Sanders et al., 2005).

A study was conducted with commercial pentaBDE to examine the effects of chemicals known to affect the thyroid hormone status in vivo, on the results of testing using the US EPA Endocrine Disruptor Screening Program male and female pubertal protocols (Stoker et al., 2004). Liver enzyme induction and thyroid hormone levels were measured in groups of male or female Wistar rats treated daily by gavage with commercial pentaBDE (DE-71) for 5 days (both sexes), 20 days (females) or 31 days (males). Doses of 0, 3, 30 or 60 mg/kg bw/day were used. Dosing commenced between post natal day 21 and post natal day 23 in all cases.

UDPGT activity was increased in both sexes and both exposure times at 60 mg/kg bw/day, to between 200% and 350% of controls. EROD activity (a measure of dioxin like enzyme induction) was increased in both sexes and both exposure times at 30 and 60 mg/kg bw/day, up to approximately 16 fold, with no apparent difference between sexes. PROD activity was increased in both sexes and both exposure times at 30 and 60 mg/kg bw/day, up to approximately 200 fold in males and 220 fold in females. PROD activity induction was much higher after the longer exposure times, and higher induction was seen in males (up to 28 fold) than in females (up to 10 fold) after the five day treatment. The relation of these results to the thyroid hormone status are discussed below

6.8.2 Thyroid hormone effects

In a number of vivo test systems, dose-dependent depletion of T4 was seen after treatment with commercial pentaBDE or congeners in the range covered by commercial pentaBDE. This was observed with a single dose of 60 µg/kg bw of pentabrominated BDE-99 in a study of developmental effects following oral dosing of the dam. However, in other studies with a focus on thyroid hormone levels, no effect was seen at higher repeated doses. As thyroid hormone depletion is the most sensitive effect seen in experimental animals, and has been implicated in the further effects seen at very low doses, a review of the results of rodent studies on thyroid hormone levels is discussed.

In a study conducted to examine the immunological and endocrine effects of commercial pentaBDE (DE 71), single and repeat doses were administered

(Fowles et al., 1994). Groups of 6 female C57BL/6J mice received a single gavage dose of 0, 0.8, 4, 20, 100 or 500 mg/kg bw DE 71 in peanut oil, while groups of 6 to 8 female C57BL/6J mice received daily gavage doses of 0, 18, 36 or 72 mg/kg bw/day DE 71 in peanut oil for 14 days. Total T4 levels were reduced in most groups, including the lowest single dosed group, with a maximum reduction to approximately 60% of controls. Free T4 was reduced in the repeat dosed animals.

In a study by Zhou et al. (2001), 28 days old weanling Long-Evans rats were administered the commercial PBDEs, DE-71 (pentaBDE), DE-79 (octaBDE) and DE-83R (decaBDE) orally at doses of 0.3 to 100 mg/kg bw/day (and to 300 mg/kg bw/day for DE-71) for four days. Serum analyses were conducted for total T_4, triiodothyronine (T_3) and thyroid-stimulating hormone (TSH).

While no effects were seen for DE-83R, dose-dependent depletion of T4 was statistically significant from 10 mg/kg bw/day for DE-79 and from 30 mg/kg bw/day after DE-71 treatment. Serum total T4 was decreased by 80% by DE-71 at 300 mg/kg bw/day. Lesser dose related effects on serum T_3 levels were seen. The decrease was statistically significant only at 100 mg/kg bw/day after DE-71 treatment, with a maximum reduction of 30%. The two mixtures showed no effect on serum TSH levels.

In the follow up developmental study using DE-71, groups of Long Evans female rats were dosed daily by gavage from days 6 through 22 of gestation excepting day of parturition with 0, 1, 10 and 30 mg/kg bw/day (Zhou et al, 2002). Dams and offspring were studied for effects on thyroid hormones (T3 and T4) levels.

The effects were only seen for T4, with T3 levels being unaffected by treatment. T4 levels in offspring were decreased in a dose dependent manner during lactation (post natal days 4 and 14), with a maximal reduction of 66%; any reduction at post natal day 1 could not be measured due to the control levels being close to the limit of detection. Following weaning and consequent cessation of treatment via milk, T4 levels in offspring returned to normal by post natal day 36. For dams, reduced T4 levels were seen at the highest dose on post natal day 22, when studies of dams ceased. In offspring, the NOEL for reduction in serum T4 was 1 mg/kg bw/day, while in dams, the NOEL for T4 reduction was higher at 10 mg/kg bw/day. Increased UDPGT activity was only seen in dams and offspring at the highest level tested. TSH levels were not reported.

A 28-day gavage study was conducted with commercial pentaBDE (DE-71, reported to be 0.21% tribrominated, 46% tetrabrominated, 49% pentabrominated and 4% hexabrominated) in juvenile Sprague-Dawley rats (CD IGS, Charles River), commencing at around 36 days age. Groups of 10 animals per sex were used. Doses were 0.5, 5 or 25 mg/kg bw/day. No clinical signs of toxicity were seen, and the major effects seen were on liver weight, thyroid hormones and microsomal enzyme activities. Serum T4 levels were reported to be significantly reduced in both sexes at 25 mg/kg bw/day. Total T3 but not free T3 was reduced in 25 mg/kg bw/day in males only. Results were only presented graphically and UDPGT induction was not determined (Rowsell et al., 2004).

The effects of commercial pentaBDE (Bromkal 70-5 DE) and the individual tetrabrominated congener BDE-47 on thyroid hormone levels were investigated in female Sprague-Dawley rats and C57BL/6 N mice following repeated dosing by

gastric intubation for 14 days. Doses used were 18 or 36 mg/kg bw/day Bromkal or 1, 6 or 18 mg/kg bw/day BDE-47. Reductions in total and free T4 were seen in both species for both test substances, although to a lesser extent than for the positive control, Aroclor 1254. Bromkal 70-5 DE produced a greater effect than BDE-47. TSH levels were unaffected (Hallgren et al., 2001; Hallgren & Darnerud, 2002). Serum levels of the PBDEs were measured in rats, and the serum BDE-47 level corresponding to significantly reduced T4 was found to be 400 µg BDE-47/g lipid, while a NOEL for total PBDE in plasma was suggested to be 200 µg PBDE/g lipid (Darnerud et al., 2004).

A study examined the effects of commercial pentaBDE (DE-71) on liver enzyme induction and thyroid hormone levels in rats for 5 days (both sexes), 20 days (females) or 31 days (males), at 0, 3, 30 or 60 mg/kg bw/day (Stoker et al., 2004). The results seen for liver enzyme induction were described previously.

Serum T4 levels were decreased in both sexes at both exposure times at 30 and 60 mg/kg bw/day. For males, a significant decrease in serum T4 was also seen following 31 days of treatment at 3 mg/kg bw/day and above. T3 levels were not significantly different in any group except the males treated for 31 days at 30 and 60 mg/kg bw/day, where a small significant decrease was seen. TSH levels were increased in males treated for 31 days at 30 and 60 mg/kg bw/day, while females treated for 20 days showed a non-significant increase at the higher dose only. In thyroid gland sections from both sexes treated for 20 or 31 days at 60 mg/kg bw/day, increased follicular epithelial height and decreased colloid areas were seen. No histological changes were seen in reproductive tissues. Liver enzyme induction results showed up to 350% increase in UDPGT activity.

A series of studies was conducted in rats to examine the effects in the liver, thyroid, reproductive system and neurobehavioural development following treatment of dams with either pentabrominated BDE-99 or tetrabrominated BDE-47 at low single doses during gestation (day 6), with subsequent transfer to offspring both during gestation and lactation (Kuriyama et al., 2004; Kuriyama et al., 2005a; Kuriyama et al., 2005b; Andrade et al., 2004). The doses used were 60 or 300 µg/kg maternal bw for BDE-99 and 140 or 700 µg/kg maternal bw for BDE-47. A positive control treatment using the goitrogen, 6-*n*-propyl-2-thiouracil (PTU), was included in these studies. PTU has been shown in humans to mostly affect the mother, with limited placental and lactational transfer to infants (Mandel & Cooper, 2001).

For BDE-47, dams treated with 700 µg/kg maternal bw showed a reduction in serum T4 and TSH on post natal day 1, but no difference in thyroid hormone levels from controls at the end of lactation on post natal day 22 (Kuriyama et al., 2004). Among male offspring, T4 levels were unaffected except on post natal day 22, when the 700 µg/kg maternal bw offspring showed an increased T4 level. T3 levels were not affected at post natal day 22, but were reduced at post natal days 1 and 14 for 700 µg/kg maternal bw, and at post natal day 14 for 140 µg/kg maternal bw. TSH was also significantly reduced for this group alone (Andrade et al., 2004).

For BDE-99, dams treated with 60 or 300 µg/kg maternal bw showed a reduction in serum T4 on post natal day 1, and dams treated with 60 µg/kg maternal bw additionally showed reduction in serum T3 and TSH. No difference in thyroid hormone levels compared with controls was seen at the end of lactation on post

natal day 22. Among the offspring, T4 levels were unaffected except on post natal day 22, when the 300 µg/kg maternal bw offspring of both sexes showed a significant decrease; females also showed reduced free T4. Total T3 levels were not affected at post natal day 22, but were reduced at post natal day 1 for 300 µg/kg maternal bw (males only). For this group, however, free T3 levels were increased. TSH was also significantly reduced for the 60 µg/kg maternal bw group (both sexes) on post natal day 14 (Kuriyama et al., 2005b).

The studies showing a LOAEL of 60 µg/kg maternal bw BDE-99 or 140 µg/kg maternal bw BDE-47 are closely related to the developmental study by Zhou et al. (2002), where no effect on maternal T4 was seen at 10 mg/kg bw/day commercial pentaBDE, and the offspring T4 levels were unaffected at 1 mg/kg bw/day. The latter results are consistent with the repeat dose results in a number of the other studies discussed above. Serum T3 levels were not affected to the same extent as T4 levels.

In a detailed study of competitive interactions of PBDE congeners with thyroxine for binding to human transthyretrin (TTR), a group of di- to heptabrominated congeners were tested both in the presence and absence of metabolic activation from several sources (Meerts et al., 2000). A group of hydroxylated PBDEs were also synthesised and tested in the T4-TTR competition assay. These were not selected on the basis of their likely occurrence as metabolites of common PBDE congeners, but rather for their close structural resemblance to T2, T3 and T4, respectively.

None of the parent PBDEs were active in the competition assay. Following metabolic activation, the degree of activity was increased in many cases, particularly with phenobarbital induced microsomes, with greater than 60% competition observed for BDE-15, 28, 30, 47, 51, 75, 77, 100 and 119. This group includes two major congeners found in the environment, BDE-47 and 100. BDE-99 was more weakly competitive following phenobarbital induced activation. The other activation systems used resulted in less positive or strongly positive results, and, in particular, the major environmental congeners, BDE-47, 99 and 100, were inactive following use of these activation systems. The synthetic thyroid hormone analogues were strong competitors for T4 binding, particularly the T3 and T4 like hydroxylated PBDEs.

It is clear from these studies that one of the major effects of treatment of laboratory animals with PBDEs in the tetra- to hexabrominated range is a decrease in T4 levels. There are two major mechanisms which may be responsible for this decrease; induction of UDPGT which conjugates T4 and increases its removal, and competitive interaction of hydroxylated metabolites with TTR, the major T4 binding protein in rodents, resulting in release of T4 and removal by normal metabolic processes. The latter process may be of limited importance, as the levels of hydroxylated metabolites following dosing with PBDEs are low (Malmberg et al., 2004). The effects on T4 levels are consistent with the observation of thyroid histopathological changes in repeat dose studies, as such changes are known to follow disturbance of thyroid homeostasis. However some studies on thyroid hormone status did not detect major effects on TSH levels, possibly due to their limited duration.

The relevance of thyroid hormone depletion to humans, particularly as it relates to the TTR competition mechanism, is not clear, as there are major differences in T4 transport between rodents and humans, with humans having a different major T4 carrier. In humans, the major carrier is thyroxine binding globulin, (TBG) which gives tighter binding than TTR (McDonald, 2002). This is important, as thyroid hormone depletion has a major role in a number of the toxicological effects seen in animal models.

6.8.3 Effects on reproductive development

In the series of studies described above, treatment of dams at low single doses of 60 or 300 µg/kg maternal bw for BDE-99 and 140 or 700 µg/kg maternal bw for BDE-47 during gestation (day 6), a number of effects on the reproductive system were seen (Kuriyama et al., 2004; Kuriyama et al., 2005a; Kuriyama et al., 2005b, Andrade et al., 2004; Talsness et al., 2003).

Scanning electron microscopy showed a number of ultrastructural changes in the ovaries of female offspring of dams treated with BDE-99 at adulthood. For the lower dose of 60 µg/kg maternal bw and the positive control, PTU, overabundance of vesicles appearing to be liposomes was seen, while degenerative changes were seen at 300 µg/kg maternal bw (Talsness et al., 2003).

In male offspring of dams treated with BDE-99, organ weights, sperm parameters, hormone levels and reproductive behaviour were examined at adulthood. No effects were seen on absolute weights of testes, epididymis, prostate or seminal vesicle, although reduced relative weight was seen for testes and epididymis. Testicular morphology was not affected by treatment. Sperm production was significantly reduced in the treated groups, while the percentage abnormal sperm was unchanged, and the treated groups showed no difference from normal males in ability to father litters, or in developmental parameters for the litters. Testosterone and lutienising hormone (LH) levels were unchanged. Similar changes were seen in the offspring of dams treated with PTU. Male sexual behaviour was generally unaltered by treatment (Kuriyama et al., 2005a; Kuriyama et al., 2005b).

For male offspring of dams treated with BDE-47, decreased levels of follicle stimulating hormone (FSH) were seen on post natal day 22 at 700 µg/kg maternal bw. Absolute testes weight was decreased at 700 µg/kg maternal bw, but no difference was seen when the results were expressed in relative terms (Andrade et al., 2004).

Pubertal delay in both sexes and effects on androgen dependent tissues have been seen following repeated treatment with levels of 30 mg/kg bw/day and above of commercial pentaBDE (Stoker et al., 2004; Stoker et al., 2005). In vitro testing of a number of congeners in the range covered by commercial pentaBDE showed estrogen receptor agonism. Strong androgen receptor antagonism was also seen for several of the congeners contained in commercial pentaBDE (Hamers et al., 2006).

In vitro testing indicates that PBDE effects in animals may be related to direct interactions of PBDEs or their metabolites; however the levels at which pubertal delay and effects on androgen dependent tissues were seen are comparatively high. At lower doses, the only effects seen in developmental studies were similar

to those which followed treatment of the dams with PTU, and are likely to be attributable to maternal hypothyroxemia at a critical stage of gestation.

6.8.4 Neurodevelopmental effects

A number of studies have examined neurobehavioural effects following gestational or neonatal exposure of mice to tetrabrominated and pentabrominated individual PBDE congeners. Treated animals showed differences in habituation behaviour which persisted in some cases for at least 6 months following dosing.

In a series of studies, NMRI mouse neonates were treated with a single oral dose of 0.8 or 12 mg/kg bw BDE-99, in a fat emulsion vehicle on post natal day 10 (Eriksson et al., 2001), or on post natal day 3, 10 or 19 with 8 mg/kg bw (Eriksson et al, 2002; Viberg et al., 2002). Neurobehavioural development was assessed by a variety of methods. Each of the papers report on the results of habituation studies, where a group of males randomly selected from a smaller number of litters was placed in a new environment and the activity scores were measured over three twenty minute intervals in the first hour in this environment. These studies were conducted at 2 or 4 months of age. Habituation was assessed by means of comparison of the 0 to 20 minute scores with the 40 to 60 minute scores. For control animals, the high initial activity levels for locomotion, rearing and total activity seen in the first 20 minute period reduced dramatically over this test period, and this pattern was considered "normal" habituation. In addition, the performance in a Morris swim maze and the uptake of BDE-99 into the brain were measured in individual studies.

No overt signs of toxicity were seen in the animals in any of the reported studies. However, for animals dosed at post natal day 3 or 10, the normal habituation pattern was disrupted. During the period 0 to 20 minutes after placement in a new environment, the animals were hypoactive compared with controls, but activity levels did not decrease normally over the observation period, and during the period 40 to 60 minutes, activity levels were higher than controls. It was found that this disruption of habituation worsened between 2 and 4 months, particularly at 0.8 mg/kg bw (Eriksson et al., 2001). The highest effect was seen for dosing on post natal day 10, while no effect was seen for dosing on post natal day 19 (Eriksson et al., 2002).

At five months of age, swim maze tests (Morris Water maze type) were conducted for animals treated at 12 mg/kg bw/day on post natal day 10. These showed the ability of adult mice to learn and memorize spatial navigation tasks. A four day acquisition period was followed by reversal learning on the fifth day. All mice improved their ability to locate the platform during the acquisition period, and no difference in performance was seen between treated and untreated animals. A difference in latency was observed in the reversal learning phase, with apparent reduced learning capacity in the treated animals (Eriksson et al., 2001).

The uptake of radiolabelled BDE-99 into the brain following postnatal dosing was also examined. There was significant uptake of radioactivity into the brain when 1.5 MBq/kg bw radiolabelled BDE-99 (specific activity 447.7 MBq/mmol) was administered at post natal day 3, 10 or 19. This corresponded to 1.9 mg/kg bw BDE-99. The proportion found in the brain for any of the dosing times was in the range 0.37% to 0.51% of the administered dose at 24 h after dosing, and this

decreased over 7 days to 0.13% to 0.28% of the administered dose (Eriksson et al., 2002).

The effects of neonatal exposure on the nicotinic receptors in the brain was studied by examining the response to the cholinergic agent, nicotine, at 2 months after dosing on post natal day 10 with 8 mg/kg bw BDE-99. Control animals showed increased activity compared with a preceding period in response to injection of 80 µg/kg bw nicotine, while BDE-99 treated animals showed decreased activity, similar to animals neonatally treated with PCB-52 or nicotine, indicating an effect on the cholinergic nicotine receptors in the brain (Viberg et al., 2002). In a study where mice were neonatally exposed to nicotine followed by adult exposure to BDE-99, effects on habituation behaviour were also seen (Ankarberg et al., 2001).

Habituation and swim maze studies were also conducted with the tetrabrominated congener BDE-47. These were conducted in parallel with studies on BDE-99 (Eriksson et al., 2001). Animals were treated on post natal day 10 with 0.7 or 10.5 mg/kg bw BDE-47. These were the same doses in molar terms to those used for pentabrominated BDE-99 in the same study. A similar habituation effect was seen for treatment with the higher dose of BDE-47 as that seen for the higher dose of BDE-99, although the effects were not as pronounced. At the lower dose of BDE-47, statistically significant habituation effects were not seen. BDE-47 also did not affect swim maze performance significantly. These results indicate that the tetrabrominated congener is not as potent in disruption of neurobehavioural development as the pentabrominated BDE-99 (Eriksson et al., 2001).

The effect of strain and sex on the neurobehavioural effects was examined in a further study. Habituation was studied at 2, 5 and 8 months of age in C57/B1 mice of both sexes, which had been dosed with 0.4, 0.8, 4, 8 or 16 mg/kg bw BDE-99 on post natal day 10. No signs of toxicity or changes in body weights were seen. Effects on habituation from 0.8 mg/kg bw and at all test intervals were seen in both sexes. Some deterioration in terms of reduced habituation capacity at 8 months compared with that at 2 months was seen at higher doses. The results in females were similar to those in males, and to those seen earlier for NMRI mice (Viberg et al., 2004).

The results of this study were used to examine models to calculate a benchmark dose for neurobehavioural endpoints. For the study in male and female C57/B1 mice, a single model could be used for the two sexes. The benchmark dose corresponding to a 10% increased risk was calculated to be 0.92 mg/kg bw (Sand et al., 2004).

Viberg et al. (2003a) reported neurodevelopmental effects in NMRI mouse neonates following a single oral dose of 0.45, 0.9 or 9.0 mg/kg bw of hexabrominated BDE-153 (in a fat emulsion vehicle), on post natal day 10.l

Effects were observed on the habituation behaviour of mice, with longer times taken by treated mice to habituate to a change in circumstances, as measured by time taken for reduction of initial high activity levels after the change in circumstances. Measurements were conducted at 2, 4 and 6 months of age. For the lowest dose, slight but statistically significant deviations from control animals were only seen at six months. The effects were dose-related. In addition, swim maze tests (Morris Water maze type) were conducted at six months. These

showed the ability of adult mice to learn and memorize spatial navigation tasks. A four day acquisition period was followed by reversal learning on the fifth day. All mice improved their ability to locate the platform during the acquisition period, but animals exposed neonatally to the higher doses of BDE-153 displayed significantly longer latencies to locate the platform on days 2 to 4. No NOAEL was identified in this study, based on the statistical significance of the results at 6 months of age. The LOAEL was 0.45 mg/kg bw.

Studies (Viberg et al., 2003b Viberg et al., 2006) conducted with four individual PBDE congeners in each of the higher bromination ranges reported similar types of effects except in the case of BDE-183, the heptabrominated congener tested. Where effects were seen, these occurred in each case at higher doses of PBDE than in the studies on tetra- to hexabrominated congeners.

For the neurodevelopmental studies described above, the study methods used were not a standard protocol, nor did the tests use a standard test strain, leading to difficulty in interpretation of results.

Several specific issues concerning these studies make the interpretation less clear. One involved use of a small number of litters for testing, resulting in potential large influence of genetic differences. However, the reproducibility of the habituation results over a range of doses, studies and treatment times indicate that genetic differences between litters would not contribute greatly to the observed effects. This has been further examined, where animals from nine separate litters were compared with nine animals randomly chosen from three litters. Treatment with BDE-99 on post natal day 10 gave the same results in each of the groups (Eriksson et al., 2005). In addition, the habituation measurements were reported to be carried out over specific time windows, but it is not clear if measurements were randomised by groups to remove the effects of diurnal variation of activity.

In the series of studies examining effects in the liver, thyroid, reproductive system and neurobehavioural development of treatment of dams at low single doses of 60 or 300 µg/kg maternal bw for BDE-99 and 140 or 700 µg/kg maternal bw for BDE-47 during gestation (day 6), the offspring were examined for developmental milestones and tested for activity levels in an open field test on post natal days 35 36 and 71 (Kuriyama et al., 2004; Kuriyama et al., 2005a; Kuriyama et al., 2005b, Andrade et al., 2004; Talsness et al., 2003).

On post natal day 36, higher activity levels were seen for offspring of animals treated at 300 µg/kg maternal bw BDE-99 compared with controls, while at puberty on post natal day 71, both BDE-99 treated groups showed higher activity than controls. The effects seen in the BDE-99 treated groups were similar to those seen in the positive control group. A difference in effects between the test and positive control animals in the later open field test is postulated by the study authors (Kuriyama et al., 2005a), however, this appears to be due to separate pairwise comparisons of each result set with the negative control. While statistical significance was not found for the difference of positive control results from the negative controls, the deviation from negative control appeared similar in type to that in the PBDE treated groups, and it is unlikely that a pairwise comparison of the PBDE treated groups with the positive controls would show any significant differences. Development of the cliff drop aversion reflex was also found to be significantly delayed in the 300 µg/kg maternal bw BDE-99 male offspring and the positive control offspring of both sexes (Kuriyama et al., 2005a Kuriyama et

al., 2005b). Offspring of animals treated at 700 µg/kg maternal bw BDE-47 were also reported to be more active than controls on post natal days 35 and 36, with the females showing a more pronounced effect (Kuriyama et al., 2004).

As a similar spectrum of effects was seen in the pups following PBDE treatment of the dams compared with PTU treatment of the dams, these studies do not clearly establish a specific effect of the PBDE treatment on the developing foetus or pup, but rather a developmental effect resulting from maternal toxicity. This is important as it indicates that the observed effects are related to the maternal PBDE levels rather than the foetal PBDE levels, and the study therefore establishes a maternal LOAEL, but cannot be used to derive an effect level in the pups.

Major individual congeners contained in commercial pentaBDE affected phospholipase A2 activity and resultant release of the second messenger, arachidonic acid, from phospholipid membranes in neuronal cultures. Effects were also seen on protein kinase C relocation and Ca^{2+} uptake, indicating that mechanisms apart from thyroid hormone disruption may affect the development of the nervous system (Kodavanti et al., 2002; Kodavanti & Ward, 2005).

The discussion above indicates that there is evidence linking effects on neurobehavioural development in laboratory animals to changes in thyroid status in the dams during gestation, or in the neonate; however evidence also points at direct effects on second messengers and the developing cholinergic system (McDonald, 2002).

The wide variety of studies conducted using commercial pentaBDE or individual congeners has largely examined mechanistic relationships between the lower brominated PBDEs and the very well studied PCBs and PCDDs. While some of the issues arising for the latter groups of compounds have been reflected in the studies on the PBDEs, particularly thyroid hormone and effects on neurobehavioural development, the overall results indicate that the PBDEs do not show the same spectrum of effects at low doses as the coplanar PCBs or the PCDDs. PBDE induced toxicity is similar to that of the non-coplanar PCBs, which do not act via an Ah receptor mediated mechanism.

7. Studies In Humans

No epidemiological studies of PBDEs effects in humans have been reported. Little information is available on the overall effects of PBDEs in humans. Several studies that reported possible effects have significant limitations and cannot be used for risk assessment. Several studies have examined the relationship of thyroid hormone status in humans relative to the serum PBDE levels, but no trends were established (Mazdai et al., 2003; Julander et al., 2005).

8. Summary of Toxicity Data

8.1 NOAEL Identification

Based on toxicity studies of commercial pentaBDEs the PBDEs in the tetra to hexabrominated range have very low acute toxicity, with no irritant or sensitising effects.

The critical effects seen on single or repeat dosing with pentaBDE or congeners in the bromination ranges covered by pentaBDE have been observed in the liver, the thyroid hormone, neurobehavioural development, and development of the sex organs. Of these, the liver effects of enlargement and enzyme induction were the best characterised until comparatively recently and were used in the derivation of the reference dose (RfD) by the US EPA (1990). However these effects may be considered to be an adaptive change, and, accordingly, are not appropriate for selection of a NOAEL.

The effects seen on neurobehavioural development, sperm counts and ovarian microstructure in rat offspring following intravenous dosing of dams during gestation with a single dose of 60 µg/kg maternal bw BDE-99 are not clearly distinguished from the effects seen in dams where maternal hypothyroxemia is specifically induced by the goitrogen PTU. As there is no evidence of specific effects of the PBDEs on pups after gestational or lactational transfer, these effects should be considered to derive from a maternal effect of the timed dose, with the resultant maternal hypothyroxemia causing the observed effects. Thus this study is considered to indicate the lowest dose in adults at which effects can be seen. No NOAEL was identified, and the LOAEL is 60 µg/kg bw for BDE-99. Equivalent studies have only been conducted for pentabrominated BDE-99 and tetrabrominated BDE-47, and it is not possible to infer the potency of further congeners directly from these results. The results of this study are not consistent with those of several other studies where thyroid hormone effects were only seen at much higher doses, and doses higher than those used in this study did not result in any perturbation of thyroid hormone levels, including during pregnancy in rats.

For mouse pups, clear effects on neurobehavioural development were seen following gavage on post natal days 3 and/or 10. These effects have been the subject of some discussion, both for PBDEs and for PCBs where similar effects are seen, with hypothyroxemia induced in the pups being a likely contributor to the effects, but there is debate as to whether additional mechanisms contribute.

A number of different congeners covering a range of bromination levels have been tested using the same basic protocol; however some differences between the studies such as the choice of times after dosing for testing mean that the effect levels were reported on different bases across the group of studies. For example, for BDE-153, the lowest dose only resulted in significant effects on neurobehavioural development when the animals were tested at 6 months of age, while no effects were seen at the time intervals used more commonly in the group of studies, 2 and 4 months.

NOAELs for BDE-47 of 0.7 mg/kg bw and for BDE-153 of 0.45 mg/kg bw were identified based on effects at 2 and 4 months following dosing. For BDE-99, the lowest tested dose of 0.8 mg/kg bw was identified as the LOAEL. This is the same level in molar terms as the LOAEL identified for BDE-153 of 0.9 mg/kg bw, and the NOAEL for BDE-47. In further studies of higher brominated PBDEs, none showed effects at as low a molar level as BDE-99 and BDE-153.

Accordingly, it can be concluded that BDE-99 and BDE-153 have similar potency for this endpoint, BDE-47 has lower potency; while the heptabrominated and above congeners that were tested have a much lower potency. A benchmark dose corresponding to a 10% increased risk was calculated to be 0.92 mg/kg bw for BDE-99, and this may be used to approximate benchmark doses for other tested congeners. Further to this, an approximation that the tested congeners are representative of all congeners of a particular bromination level may be used to rank the approximate benchmark doses for congeners with four or more bromines, particularly the environmentally relevant BDE-100 and 154. Assuming that the neurodevelopmental toxicity peaks at five to six bromine atoms, the tribrominated congeners may be expected to be no more toxic for this endpoint than the tetrabrominated BDE-47. However the possibility remains that the potencies are not predominantly due to the bromination level, but rather relate to the substitution pattern. In the absence of information to establish the effect of substitution pattern, the potency will be assumed to relate only to bromination level.

Risk assessment involves calculation of a Margin of Exposure (MOE). The MOE approach involves comparison of a NOAEL in an animal model with the estimated or measured human dose or exposure to provide a MOE. While NOAELs were identified in some of the studies described above, the highest toxicity to both pups and dams was seen for BDE-99, and NOAELs were not identified in the critical studies on this congener. The LOAELs from these studies of 0.8 mg/kg bw in pups and 0.06 mg/kg bw in dams have therefore been carried forward for risk characterisation.

8.2 Relationship of administered dose to blood concentrations

Toxicokinetic information to establish the relationship of blood concentrations to administered dose in rodents is available for BDE-99 and BDE-47, particularly for the latter in mice. Mouse toxicokinetic data are highly relevant to the studies on neurobehavioural development following dosing of pups, as the experimental procedures and dosing regime are similar. For dosing of adults, mouse data are less useful, as the LOAEL was determined in rats, and mice differ from both rats and humans by being able to eliminate BDE-47 comparatively rapidly via urine.

In adult mice, the distribution of BDE-47 through the body after a single dose was found to be reasonably independent of the initial dose level, allowing determination of blood levels over a range of doses. However the blood level varies significantly over time after dosing, and it is not clear to what extent observed toxicological effects relate to the peak concentration and to the integrated concentration over time. Accordingly selection of the time after dosing that provides a representative concentration is difficult. This is less of an issue in neonatal mice, where the elimination is slower and a plateau concentration is maintained for a longer time after dosing.

In neonatal mice at 10 days of age, gavage dosing of 1 mg/kg bw BDE-47 in corn oil resulted in a blood level of 45 to 50 ng/g blood on a wet weight basis from 1 to 5 days after dosing (Staskal et al., 2006). The LOAEL observed in neonatal mice was 0.8 mg/kg bw BDE-99 or 0.9 mg/kg bw BDE-153, based on effects on neurobehavioural development. These are equimolar doses after correcting for the molecular weight difference. The data from Staskal et al. (2006) may be used to relate the blood concentrations to the administered dose, by assuming that the toxicokinetics behaviour is similar between BDE-47, 99 and 153, by the relationship:

$$BC = \frac{TBC \times D \times 1000}{TD \times MW}$$

where

BC = blood concentration (wet weight basis) corresponding to the LOAEL
TBC = blood concentration (wet weight basis) corresponding to the dose in the toxicokinetic study
D = LOAEL dose
TD = dose used in the toxicokinetic study
MW = molecular weight of the test substance, BDE-99 or BDE-153

This relationship is based on the assumption that BC/D = TBC/TD, i.e. that a constant proportion of an administered dose will partition to serum.

Using TD = 1 mg/kg bw and TBC = 45 ng/g wet weight (Staskal et al., 2006), and D = 0.8 mg/kg bw for BDE-99 (Eriksson et al., 2001) or 0.9 mg/kg bw for BDE-153 (Viberg et al., 2003a), and MW = 564.75 for BDE-99 or 643.62 for BDE-153, the blood concentration relating to the LOAEL in neonatal mice was calculated as approximately 64 pmol/g wet weight, for either congener. Assuming 0.5% lipid in serum, this may be calculated to be equivalent to approximately 6600 ng/g lipid of BDE-99 for 1 to 5 days after dosing

For adult rats, data are available on blood concentrations at 1 and 5 days after intraperitoneal treatment with a mixture containing a number of PBDE congeners, each at 3 µmol/kg bw (Malmberg et al., 2004). For BDE-47 and BDE-99, similar results were seen, with BDE-47 being present at 500 pmol/g wet weight in blood at 24 h, and 41 pmol/g wet weight at 5 days, and BDE-99 being present at 560 pmol/g wet weight at 24 h, and 32 pmol/g wet weight at 5 days. It is noted that the proportion of the administered dose in rat plasma after 5 days is very similar to that observed after oral treatment of mice with a similar dose of BDE-47, 1 mg/kg bw, and that little difference in oral and ip availability is seen (Staskal et al., 2005). This study also indicated that a higher proportion was retained in plasma 5 days after oral dosing with 0.1 mg/kg bw compared with 1 mg/kg bw, by a factor of approximately 1.7, suggesting that removal from the blood is slower at lower doses.

The LOAEL observed for adult rats was 60 µg/kg bw BDE-99, based on effects on neurobehavioural and reproductive development in the offspring. This is equivalent to approximately 0.1 µmol/kg bw BDE-99. The data from Malmberg et al. (2004) may be used to relate the blood concentrations to the administered dose by the relationship:

$$BC = \frac{TBC \times D}{TD}$$

where

BC = blood concentration (wet weight basis) corresponding to the LOAEL
TBC = blood concentration (wet weight basis) corresponding to the dose in the toxicokinetics study
D = LOAEL dose
TD = dose used in the toxicokinetics study

This relationship is again based on the assumption that BC/D = TBC/TD.

Using D = 0.1 µmol/kg bw BDE-99 (Talsness et al., 2003; Kuriyama et al., 2005a), TD = 3 µmol/kg bw and TBC = 560 pmol/g wet weight (24 h) or 32 pmol/g wet weight (5 days) (Malmberg et al., 2004), an effect concentration in blood is derived to be approximately 17 pmol/g wet weight at 24 h after exposure and 1 pmol/g wet weight at 5 days after exposure. Assuming 0.5% lipid in serum, and the molecular weight of BDE-99 of 564.75, this is calculated to be equivalent to approximately 2000 ng/g lipid at 24 h after dosing or 120 ng/g lipid, at 5 days after dosing.

Staskal et al. (2005) have shown that equilibration of PBDE between the blood compartment and adipose tissue is likely to be incomplete 24 h after dosing. Therefore, the 24 h figure is likely to correspond to the peak level, while the 5 day figure will be more indicative of the plateau concentration in blood. However it has been observed that retention of BDE-47 in mice is higher by a factor of approximately 1.7 at a dose of 0.1 mg/kg bw compared with 1 mg/kg bw. This indicates that in rats treated at 60 µg/kg bw BDE-99 the corresponding blood level is approximately 200 ng/g lipid at 5 days.

While this blood level is indicated as a LOAEL for thyroid mediated effects in the studies by Kuriyama et al (2005a, 2005b), a number of related studies, particularly the study by Zhou et al. (2002) on treatment of rat dams though pregnancy and lactation, have shown no thyroid effects at such low concentrations, and NOAELs for thyroid effects were identified (including during development) as being ≥1 mg/kg bw/day of combined congeners in pentaBDE. Darnerud et al. (2004) calculated a NOEL for total PBDE in plasma of 200 µg PBDE/g lipid. It is also noted that correlations between human thyroid hormone status and the individual blood PBDE levels were not found, as discussed in Section 7.

9. Risk Characterisation

Exposure information from North America suggests that dust exposure is the main pathway for human exposure to PBDEs. At the lower dust concentrations of pentaBDE related congeners in Australia, compared with those in North America, it is possible that the food intake pathway is proportionately more important. Dust levels are expected to be more responsive to rapid change than levels in food. Results from Sweden indicate that, at least for the most prevalent of these congeners, comparatively rapid response to control measures can be seen.

Importantly the relative contribution of various sources to levels of PBDEs in the environment has not been determined. A study will be commissioned to determine the major sources of PBDEs in the indoor environment.

9.1 Risk Assessment Approach

Risk is estimated only for the tetrabrominated to hexabrominated congeners, as direct information from developmental neurobehavioural studies indicates that congeners in the bromination range from four to six bromine atoms per molecule have higher activity than those with higher levels of bromination. In addition, experimental difficulties in determination of higher brominated congeners (de Boer & Wells, 2006) result in a higher degree of uncertainty as to the actual serum levels of these congeners.

The risk assessment method used involves calculation of a Margin of Exposure (MOE). The MOE approach involves comparison of a NOAEL in an animal model with the estimated or measured human dose or exposure to provide a MOE. For the critical studies identified in Section 8, NOAELs were not determined and the LOAELs have therefore been carried forward for risk characterisation.

Application of the animal LOAEL values from the identified critical studies to humans is subject to several uncertainties, and it is accepted that these uncertainties result in highly conservative risk estimations. However, these assumptions are appropriate in the absence of information to quantify the uncertainties. The uncertainties related to the toxicological data are:

- The applicability of rodent thyroid hormone effects to humans, particularly where these relate to a TTR binding mechanism (McDonald, 2002). This is because TTR is the main thyroid hormone binding protein in rodents, while humans have thyroid binding globulin (TBG) as a main carrier. This also affects the effects mediated by metabolism of thyroid hormones, due to the higher binding affinity of TBG compared with TTR. Accordingly, rodents are considered more sensitive than humans to thyroid mediated effects. This uncertainty is not sufficient to conclude that equivalent effects will not occur in humans at some dose level. It is also noted that a variety of additional mechanisms have been proposed to play some part in the observed effects, and it is not possible to determine the applicability of these additional mechanisms to humans.

- The results reported by Kuriyama et al. (2005a, 2005b) from a comprehensive study of developmental effects of BDE-99 administered to rats during pregnancy include measurement of reductions in thyroxine levels. The effects on maternal thyroxine levels have been implicated in the developmental effects reported in these studies. However effects on the thyroid hormone system have been measured in rats in a number of other studies and effects on thyroxine levels observed in these studies were at much higher concentrations (Hallgren et al., 2001; Hallgren & Darnerud, 2002; Zhou et al., 2001; Zhou et al., 2002; Stoker et al., 2004).

In the case of human biomonitoring data, the MOE calculation requires knowledge of the blood levels in the animal at the LOAEL for comparison with the human biomonitoring results. As serum levels of PBDEs were not measured in the studies where the LOAELs were determined, the appropriate serum levels must be estimated from toxicokinetic data in the same species. While this approach leads to uncertainties in estimating the corresponding serum levels, available information does not allow quantification of these uncertainties, discussed below:

- Long term repeated dosing of humans will not result in high peak levels of serum PBDEs, whereas this may occur at critical development phases in the single dose animal studies used for derivation of the LOAELs. The dose in these studies was administered during a potentially critical time window. Peak levels immediately following dosing are much higher than the conservative LOAEL equivalent serum levels derived from plateau levels. There was a seventeen fold reduction in serum level in rats from the peak level at 24 hour post dosing to the plateau level at day 5 after dosing, and the plateau level is used in the MOE calculation.

- For the calculation of the MOE in pregnant women, data from a toxicokinetic study involving treatment of rats at 3 µmol/kg bw was compared with toxicological data for dosing at approximately 0.1 µmol/kg bw. From comprehensive toxicokinetic data in mice it is determined that the proportion of the administered dose found in serum varied with the dose. A higher proportion of the administered dose was retained in serum at lower doses.

In addition to the uncertainties discussed above, the calculations are performed using the toxicity results for the most active congener tested, BDE-99, while the dominant congener in the biomonitoring studies is BDE-47, which was shown to be less active in both pups and dams. This again serves as a " worst case" risk estimation for total PBDE concentrations.

Considering the uncertainties discussed above and the conservative assumptions used to derive the MOEs, it is highly probable that these MOE overstate the risk to humans.

9.2 Calculation of Margins of Exposure (MOEs)

Comparison of the measured level in male toddlers of 48.3 ng/g lw with the LOAEL for effects on neurobehavioural development in neonatal mice of 6600 ng/g lw (BDE-99) provides a worst case MOE of 136.

The effects on pups following dosing of pregnant rat dams can be used to determine the risk to infants from tetra to hexabrominated PBDE congener levels in women of child-bearing age. The MOE calculation involves derivation of the rodent blood level corresponding to the LOAEL for pregnant rats of 0.06 mg/kg bw BDE-99. Adult rodent blood levels of PBDEs change more rapidly than those of neonates because of rapid elimination in adults.

For adult female pregnant rats, it is unclear from toxicokinetic studies whether to use the peak serum concentration or an indicative "plateau" value for comparison purposes. Taking the serum level 5 days after dosing as the conservative plateau value (as it is more indicative of average serum values over the treatment period), the LOAEL for neurobehavioural and reproductive developmental effects is 120 ng/g lw. McDonald (2005) derived a LOAEL of 230 ng/g lw from the same toxicological data set by using a less refined assumption that PBDEs were uniformly distributed throughout the body. The serum level calculated using the peak value at 24 h after dosing is 2000 ng/g lw.

A highly conservative worst case MOE of 12 is obtained on comparison of the plateau level in rodents with the human biomonitoring level in women of child-bearing age of 9.5 ng/g lw for the five major tetra- to hexabrominated congeners The plateau level is used to calculate the MOE on the conservative assumption that the effect is related to steady state concentrations rather than peak concentrations. Use of the peak level would give a higher MOE of 210. In addition, a wide variation in human PBDE blood concentrations in Australia is expected, as observed in international studies.

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10. Conclusion

Considering the uncertainties and conservative assumptions used to derive the MOEs, it is highly probable that they overstate the risk to humans. To date, no advserve effects from exposure to PBDEs have been reported either in adults or in children. However, the uncertainty is not sufficient to conclude that equivalent effects will not occur in humans at some dose level.

However, the risk characterisation, using the most conservative worst-case assumptions, indicates that current Australian levels of PBDE congeners with four to six bromine atoms per molecule give a a low MOE for infants based on serum levels identified for women during pregnancy. These assumptions are used because it is not possible to quantify the uncertainties in the calculation.

The PBDE congeners in the bromination range of four to six bromine atoms per molecule are mostly derived from the commercial product pentaBDE, but the commercial octaBDE also contributes to the level of hexabrominated congeners, particularly BDE-153, in the human environment. With removal of octaBDE from the AICS, regulatory action to address the public health risk will apply to pentaBDE.

Due to lack of available information about the rates of release of pentaBDE from articles, the uncertainties associated with changing release rates as the articles age, and the difficulties associated with estimating the likelihood of particular articles being flame retarded with pentaBDE, further research is required to refine the risk assessment.

11. Regulatory Action

There is no evidence of any adverse health effects in adults, newborns or in children from exposure to PBDEs. However, given that the tetra to hexabrominated congeners have the potential to cause developmental effects in the offspring of treated laboratory rats, the potential for these effects to occur in humans cannot be completely ruled out.

Importation of pentaBDE and octaBDE is not currently occurring in Australia; however, the commercial unavailability of these products results from voluntary cessation of production by the major manufacturers as well as regulatory bans in place in the European Union. Information available to NICNAS indicates that pentaBDE and octaBDE production is occurring in some countries.

Given the outcome of the conservative risk calculations a precautionary approach is adopted to ensure that human exposure to the tetra- to hexabrominated PBDEs is minimised. Under Section 61 of the Industrial Chemicals (Notification and Assessment) Act, 1989, the Minister for Health and Ageing will prohibit the importation and/or manufacture of pentaBDE while it remains a Priority Existing Chemical.

Regulatory action has already been taken for octaBDE under Section 63 of the Act. OctaBDE has been removed from AICS as no applications for assessment were received since its declaration as a Priority Existing Chemical.

The regulatory action for pentaBDE will be reviewed on completion of the full risk assessment and further regulatory action may be recommended as appropriate.

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