European Commission

Recommendation from the Scientific Committee on Occupational Exposure Limits for Diphenyl ether, Octabromoderivative (commercial mixture)

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Employment, Social Affairs and Inclusion

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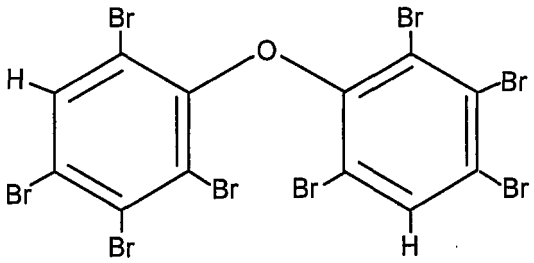
8 hour TWA:	0.2 mg of the commercial mixture/m^3
STEL(15min):	-
Notation:	-
BLV:	-

Substance identification

Synonyms:	octabromodiphenyl ether, OBDPE, OBBE, octabromobiphenyl oxide, OBBO, OCTABDE, octabromo phenoxybenzene and benzene, 1,1' oxybis-, octabromoderivative
EU Classification: Repr. 1B H360Df	May damage the unborn child. Suspected of damaging fertility.
CAS No.:	32536-52-0
MWt:	801.38 g/mol

Twelve congeners of octabromodiphenyl ether (octaBDE) can be identified (194 BDE to 205 BDE). The structural formula of a representative octabromodiphenyl ether congener is given below:



Conversion factor (20 °C, 101 kPa): 1 ppm = 33.3 mg/m^3

This evaluation is based on the EU RAR (2003), the references based therein and a small number of more recent studies identified using the on-line database PubMed.

Physico-chemical properties

Commercial octaBDE is supplied as a mixture of polybrominated diphenyl ethers (PBDEs). OctaBDE constitutes less than 40% of the overall mixture, heptaBDE

accounts for between 43 and 58% of the mixture and penta-, nona, and deca-BDEs account for between 10 and 30% of the mixture.

The physical properties of pure octaBDE are not well established. The commercial product is an off-white powder or flaked substance and has a range of melting points depending on composition. The water solubility is reported as 0.5 ug/L in water and the log octanol-water partition coefficient (log Kow) is 6.29 at 25 °C. The EU RAR cites, for commercial products, several ranges of melting points, of 167-257 °C, 130-155 °C and 70-150 °C. At high temperatures, octaBDE decomposes rather than boils. The commercial product has a vapour pressure of 6.59 x 10^{-6} Pa at 21 °C and a calculated saturated vapour concentration (SVC) of 30 µg/m^3 at 21 °C.

Under certain conditions of combustion or pyrolysis, ocaBDE and other PBDEs can form brominated dibenzofurans and brominated dibenzo-*p*-dioxins.

1. Occurrence/use and occupational exposure

No octaBDE is produced in the EU and its use in Europe is declining. It is estimated that about 450 tonnes were imported to the EU as the commercial product in 1999 and that a further 1 350 tonnes were imported in finished articles or masterbatch (i.e. polymer pellets containing additives).

OctaBDE has been used in combination with antimony trioxide as a flame retardant in polymers. In Europe, >95% of its use was in acrylonitrile-butadiene-styrene (ABS) polymers at weight loadings of 12 to 18%. Other minor uses were in high impact polystyrene (HIPS), polybutylene terephthalate (PBT) and polyamide polymers at typical loadings of 12 to 15%. The main use of the flame-retarded polymers is in the casings of office equipment and business machines.

All applications of octaBDE have been prohibited in the EU since 2004 (EC, 2003). The Waste Electrical and Electronic Equipment (WEEE) Directive, however, imposes new requirements for reuse/recycling that may expose workers to octaBDE in discarded older equipment.

It can be concluded from the above that very limited exposure of workers may continue into the future due to recycling of equipment containing octaBDE, but no exposure is anticipated in manufacturing industry.

1.1. Methods of exposure monitoring and analysis

As reported by the EU RAR, octaBDE is a solid with a very low vapour pressure (6.6 x 10^{-6} Pa at 21 °C) and a calculated saturated vapour concentration (SVC) of 30 µg/m^3 at 21°C. Exposure to the vapour will thus not exceed 30 µg/m^3 at ambient temperature, and inhalation of dust and skin contact are the predominant routes of exposure. The EU RAR predicts very low levels of octaBDE in air, based on the EUSES risk assessment tool (ECB, 2005).

Since commercial octaBDE is a mixture of polybrominated diphenyl ethers (PBDEs) containing less than 40% octaBDE, there are few reports of analysis of the substance alone in workplace or environmental samples. OctaBDE in commercial mixtures and in environmental (e.g. air) samples may be analysed by gas chromatography (GC) or high performance liquid chromatography (HPLC), with limits of detection in the order of 0.01 ng/m^3 in air being achievable. Concentrations of PBDEs in air have been measured using high resolution gas chromatography-mass spectrometry (GC-MS) (Sjödin *et al,* 1999). There is no established standard method.

Levels of octaBDE in workplace air have not been specifically investigated. Pettersson-Julander *et al* (2004) have evaluated exposure to brominated flame retardants within an electronic recycling facility, personal air monitoring being carried out over a 2-year period (Pettersson-Julander *et al*, 2004). A total of 22 PBDEs and 2 other bromine containing organic compounds were analysed and evaluated in 17 personal air samples. The most abundant congeners of PBDE were #209 (decaBDE, <0.7-61 ng/m^3) and #183 (heptaBDE <0.1-32 ng/m^3) indicating the use of the commercial octaBDE mixture, followed by PBDE #99 and #47 (<1.3-25 and <0.9-16 ng/m^3, respectively). Levels of detection for the different congeners ranged from < 0.9 to 0.01 ng/m^3, with the majority lying below 0.1 ng/m^3 (Pettersson-Julander *et al*, 2004). Another study has also showed the presence of PBDE and other brominated flame retardants in air samples from an electronic recycling facility (Sjödin *et al*, 1999). The level present in office air was reported to be at most 0.08 ng/m^3 (Sjödin *et al*, 1999).

To control the OEL of 0.2 mg/m^3 of the octBDE commercial mixture and considering that the mixture contains around 50% octaBDE the concentration of the latter should not exceed 0.1 mg/m^3.

2. Health significance

2.1. Toxicokinetics

Only limited data are available on absorption, distribution and metabolism of octaBDE, although the substances, together with the other PBDEs, have a recognised bioaccumulation potential. There are no data on the efficiency of uptake following different routes of exposure, rates of elimination or bioaccumulation. Four octa-BDE isomers (octa-1, octa-2, BDE-203, and octa-3) are reported to have calculated half-lives of 72, 85, 37 and 91 days, respectively, with the shortest half-life for BDE-203 (Thuresson *et al*, 2006).

2.1.1. Human data

Measurements of octaBDE in human adipose tissue, blood and milk confirm that at least some octaBDE is absorbed and that it accumulates in lipids (EU RAR, 2003). OctaBDE has been reported in samples of adipose tissue taken from the general population (Stanley *et al*, 1991), and the presence of other PBDEs in human tissues has also been reported (EU RAR, 2003). Based on the high lipophilicity of octaBDE, its potential to bioaccumulate in adipose tissues and the detection of hexaBDE, one component of commercial octaBDE, in breast milk (Meironyté *et al*, 2001), excretion of octaBDE in human breast milk may also be anticipated (EU RAR, 2003). Several congeners of octaBDE have been found in the serum of French women (21 to 93% of 72 samples), in adipose tissue (14 to 78% of 86 samples) and in breast milk (34 to 100% of 63 samples) (Antignac *et al* (2009). The maximum serum levels measured in this study were 67 ng/g lipid weight for octaBDE-202, 2.995 for octaBDE-201, 5.040 for octaBDE-197, 0.826 for octaBDE-203 and 0.982 for octaBDE-196, respectively.

Sjödin and co-workers demonstrated significantly higher levels of all PBDE congeners in the serum of subjects (n=19) working in a plant dismantling electronic goods such as personal computers, television sets and radio, compared with controls, heptaBDE being the major compound detected (Sjödin *et al*, 1999). Elevations were also seen in cleaners and computer clerks in the same plant. Increased levels of PBDEs in the plasma of workers have also been reported by other researchers (Hagmar and Bergman, 2001; Hovander *et al*, 2001; Thomsen *et al*, 2001a; Thomsen *et al*, 2001b). Jakobsson *et al* showed that octaBDE-203 and 3 others congeners could be quantified in the serum of exposed computer technicians and that the levels found were positively correlated with the duration of computer work among technicians (dose-response relationship) (Jakobsson *et al*, 2002). Qu *et al* (2007) found detectable serum levels of BDE-196, BDE-197, BDE-203 in exposed workers versus a non-occupationally-exposed referent group, and similar observations were made by Thuresson and co-workers (Thuresson *et al*, 2005, 2006).

2.1.2. Animal data

The extent of absorption and elimination of octaBDE in animals cannot be assessed from the data available (EU RAR, 2003). The physico-chemical properties of octaBDE dictate that dermal absorption will be limited, and the EU RAR estimated that only 4 to 5% of octaBDE applied to the skin will be absorbed. The estimation made in the EU RAR for dermal absorption was done for a commercial mixture of octaBDE and the

calculation was based on the variation of the dermal absorption in relation to the chlorination degree for the BDEs (Garner and Matthew, 1998). These data are not considered to provide a valid estimate of dermal absorption of pure octaBDE.

Absorption of octaBDE following oral administration or inhalation has been demonstrated in rats (Great Lakes, 1976, 1978). OctaBDE was found to accumulate in the liver, adipose tissue and the lung of rats exposed by the inhalation route (Great Lakes, 1978). Studies with other PBDEs suggest that the extent to which these compounds are absorbed and accumulate in the liver increases with decreasing bromination. More than 90% of an oral dose of decaBDE was eliminated in the faeces within a few days, whereas only 14% of an oral dose of tetraBDE was eliminated in the faeces (Gill *et al,* 2004).

Commercial octaBDE has been demonstrated to induce xenobiotic-metabolising enzymes in a dose- and time dependent manner (Carlson, 1980a; Carlson, 1980b; Zhou *et al*, 2001), although there is no specific information available about octaBDE metabolism (EU RAR, 2003). As indicated, little is known about the relative rates of accumulation versus metabolism and excretion of any of the PBDEs.

2.1.3. Biological monitoring

Concentrations of PBDEs in blood or serum, breast milk and adipose tissue have been measured in a number of human studies (EU RAR, 2003; Gill *et al,* 2004), using high resolution GC-MS.

2.2. Acute toxicity

2.2.1. Human data

There are no published case reports of adverse effects in humans following acute exposure.

2.2.2. Animal data

Data from animal studies show that octaBDE has a low acute toxicity via the oral, dermal or inhalation routes (EU RAR, 2003). Data from animal studies undertaken by industry indicate that exposure of rats to 60 000 mg/m^3 commercial octaBDE for one hour caused tachypnoea but no deaths. Exposure to 2 000 or 60 000 mg/m^3 was associated with reduced motor activity, reddening of the skin, and eye squint (Great Lakes, 1975a). Industry studies have also established that no deaths occurred following oral administration to rats of 10 000 mg/kg body weight (bw) (Ethyl Corp., 1984a) and the LD_{50} following oral administration was estimated to be >5 000 mg/kg bw (Great Lakes, 1987). No deaths followed administration of 2 000 mg/kg bw to the skin of rabbits (Great Lakes, 1975b).

Neonatal male mice were exposed on postnatal day 3 or 10 to BDE 203, given as a single oral dose of 21 µmol/kg body weight (Viberg *et al*, 2006). At the adult age of 2-3 months, the mice were observed for performance in a spontaneous behaviour test and the Morris water maze test. BDE-203 and BDE-206, when administered on neonatal day 10, caused disturbances in spontaneous behaviour, leading to disrupted habituation and a hyperactive condition in adults at the age of 2 months. These behavioural changes were also seen in 2-month-old mice exposed to BDE-203 on neonatal day 3. Furthermore, exposure to BDE-203 on neonatal day 10 affected learning and memory functions in adult mice. These authors have also shown that BDE-203 affects a number of proteins involved in normal maturation of the brain,

including significant increases in CaMKII and synaptophysin in the hippocampus (Viberg, 2009).

2.3. Irritation and corrosivity

2.3.1. Human data

No information is available on the irritancy of octaBDE to humans.

2.3.2. Animal data

The available animal data on octaBDE indicate that it is not an eye or skin irritant (EU RAR, 2003). However there was some evidence of respiratory irritation in a 2-week inhalation study in rats, with hyperplasia/hypertrophy of the goblet cells from a level of 1 mg/m^3 (Great Lakes, 2000). A 90-day study in rats at levels of 1.1 and 202 mg/m^3 commercial octaBDE showed evidence of lung inflammation and alveolar histiocytosis (Great Lakes, 2001).

2.4. Sensitisation

2.4.1. Human data

No data are available concerning the potential for octaBDE to cause skin or respiratory tract sensitisation in humans.

2.4.2. Animal data

OctaBDE showed no evidence of a skin sensitising potential in a guinea pig maximisation test (Chemical Manufacturers Association, 1996a). There is no evidence that other PBDEs cause skin sensitisation (Gill *et al,* 2004).

2.5. Repeated dose toxicity

2.5.1. Human data

There are no case reports describing adverse effects following repeated workplace exposure to octaBDE. Limited information about workplace exposure to decaBDE suggests that no adverse effects have arisen following long term exposure to concentrations of 1 to 4 mg/m^3 (IPCS, 1994a). Effects on thyroid activity were found in workers exposed to a combination of PBDEs, e.g. decaBDE and polybrominated biphenyls (PBBs) (IPCS, 1994a). PBDEs share some structural similarities to thyroid hormones and high levels of exposure to PBDEs in animal experiments have given rise to effects on thyroid function (see below). There is however a well-established association between PBBs and thyroid effects (IPCS, 1994b) and no evidence of thyroid disruption was reported in other studies of workplace exposure to PBDEs (IPCS, 1994a).

2.5.2. Animal data

Available animal data for octaBDE are derived from unpublished industry studies rather than from the peer-reviewed literature (EU RAR, 2003). These studies employed commercial octaBDE and exposures were therefore to a mix of PBDEs. The relative importance of ocaBDE as a cause of adverse health effects compared with that of other PBDEs is unclear.

Studies in rats indicate that the liver is the key target organ for octaBDE, causing increases in liver weight and liver enlargement, cellular microscopic changes and induction of a range of cytochrome-P450 (CYP) enzymes (EU RAR, 2003). Following oral administration, effects on the liver were observed following 4 weeks of exposure to approximately 8 mg/kg bw, the lowest dose tested (Great Lakes, 1976). A NOAEL was not established in this study. Similar changes were seen in a further 4-week study (Great Lakes, 1977) and in a 13-week study (Great Lakes, 1976). In all 3 studies, the LOAEL was 100 ppm in the diet (7-8 mg/kg body weight per day). Table 1 provides a summary of these oral repeat dose studies with commercial octaBDE. It is to be noted that the dose-response of these effects is low and effects observed at the lowest doses of 8.1 and 9.8 mg/kg are slight.

Table 1. Summary of repeated dose experiments with octaBDE undertaken by Great Lakes in rats with commercial octaBDE (from the EU RAR, 2003).

Duration	Conc. in diet, ppm	Dose as mg/kg bw/day	Outcome	Year
28 days	0, 100, 1 000	Males: 0, 8.1, 82.2 Females:0, 8.4, 88.3	Increased liver weight from 100 ppm, thyroid hyperplasia at 1 000 ppm, liver lesions from 100 ppm, increased Br content in liver from 100 ppm.	Great Lakes (1976)
28 days	0, 100, 1 000, 10 000	Males: 0, 9.8, 97, 1003 Females: 0, 9.9, 106, 1007	Slight reduction in body weight, increase in liver weight from 1 000 ppm, liver enlargement, liver changes ("round bodies" from 100 ppm, hepatocyte vacuolisation and necrosis mainly at 10 000 ppm), partially reversible, increase in liver Br content from 100 ppm, slight increase in urea from 10 000 ppm.	Great Lakes (1977)
13 weeks	0, 100, 1 000, 10 000	Males: 0, 7.2, 73.7, 781 Females: 0, 8.3, 85.6, 834	Reduction in body weight from 1 000 ppm, increase in liver weights from 100 ppm, increase in thyroid weights from 1 000 ppm and in kidney weights from 10 000 ppm. Partially reversible liver changes (granular cytoplasmic changes from 100 ppm, cytoplasmic vacuolisation from 1 000 ppm and scattered necrosis and fibrosis at 10 000 ppm). Partially reversible increase in liver Br content from 100 ppm, slight reduction in blood glucose, evidence of effects on liver function (small increase of the enzymes ASAT and ALAT) at 10 000 ppm, orange discoloration of urine.	Great Lakes (1977)

In a study designed to investigate hepatic enzyme activity and thyroid hormone levels, groups of weanling rats were exposed to a commercial PBDE mixture containing 30.7% octaBDE and 45.1% heptaBDE, at oral doses ranging from 0.3 to 100 mg/kg bw/day for 4 days (Zhou *et al,* 2001). A significant increase in liver weights was observed at levels of 10 mg/kg bw/day and above. Thyroxine (T4) and, to a lesser extent, triiodothyronine (T_3) levels were significantly decreased (from 10 mg/kg bw/day for T4 and from 100 mg/kg bw/day for T3), but no effects on thyroid stimulating hormone (TSH) levels were seen. CYP enzymes were markedly increased, with a 10- to 20-fold induction in ethoxy-resorufin-*O*-deethylase (EROD), 30- to 40-

fold induction in pentoxy-resorufin-*O*-deethylase (PROD) and up to 3- to 4-fold induction in uridinediphosphate-glucuronosyltransferase (UDPGT) activities. Other mixtures of PBDEs tested by the authors showed similar effects, and the authors concluded that these substances interfere with the thyroid hormone system, possibly by up-regulation of UDPGT. This study revealed a NOAEL of 3 mg/kg. This agrees with the results of other subacute and subchronic studies on commercial PBDEs (penta- and tetraBDE: DE-71, Bromkal 70, commercial octaBDE and pentaBDE) which resulted in NOAELs in the range of 2-18 mg/kg based on liver enlargement and T4 reduction as summarised in the report of the Nordic Council of Ministers (1998).

No information is available on subchronic toxicity following dermal exposure.

As reported in the EU RAR, a 14-day inhalation study in the rat using an 8-hour exposure period per day was carried out at nominal commercial octaBDE concentrations of 0,1.2,12,120 and 1 200 mg/m^3 (micronised dust) (Great Lakes, 1978). Analytical concentrations of the airborne particles were 0.6, 3.7, 23.9 and 165.2 mg/m^3, respectively. Animals at the two highest exposure concentrations showed rapid respiration by the end of the 8-hour exposure period, returning to normal by the morning following exposure. Food consumption, body weight gain, haematology, blood and urine chemistry in all dose groups were normal. The total bromine concentrations in lung, liver and fat of all of the exposed rats (except at 0.6 mg/m^3 in the liver) were higher than in the controls on a dose related basis. Liver weights were increased in exposed animals from 3.7 mg/m^3 upwards in a dose-related manner, accompanied by histological evidence of hepatocellular hypertrophy and focal necrosis in the two highest dose groups only. No changes were reported in the respiratory tract, lung or thyroid. Histopathological examination of the nasal turbinate area, lung and trachea did not reveal treatment-related lesions. According to the EU RAR, the No Observed Adverse Effect Concentration (NOAEC) in this study was 0.6 mg/m^3 (analytical concentration).

As also reported in the EU RAR, the liver changes seen in this study were confirmed in a more recent 2-week inhalation toxicity study in which rats were exposed (nose-only) to commercial octaBDE dust aerosol for 6 hours/day, 5 days/week for two consecutive weeks (Great Lakes, 2000). The targeted exposure concentrations were 1.0, 10, 100 and 250 mg/m^3 and the analytical concentrations were 1.0, 10, 110 and 250 mg/m^3, respectively. Absolute and/or relative liver weights were increased from 10 mg/m^3 in males and from 110 mg/m^3 in females, while centrilobular hypertrophy of hepatocytes (minimal to mild) was observed microscopically for all males from 10 mg/m^3 and for 4/5 females in both the 110- and 250-mg/m^3 groups. The only other dose-related change consisted of minimal to mild goblet cell hyperplasia and/or hypertrophy in the nasal tissues from 10 mg/m^3 in females and from 1 mg/m^3 in all treated males. The dose level of 1 mg/m^3 was therefore a LOAEC for local effects in this study (EU RAR, 2003), while it was a NOAEC for the systemic (liver) effects.

The above study was a dose-ranging study for a 90-day inhalation study in the rat, carried out at measured concentrations of 1.1, 16 and 202 mg/m^3 commercial octaBDE (Great Lakes, 2001). The study confirmed a treatment-related increase in liver weight, accompanied by centrilobular hepatocellular hypertrophy in the 16 mg/m^3 and 202 mg/m^3 groups. Increased kidney weights were noted at 202 mg/m^3 in females only. Absence of corpora lutea was reported in females at 202 mg/m^3 octaBDE, which was considered treatment-related. Circulating T4 and TSH values were increased in the 16- and 202-mg/m^3 groups although no effects on organ weight or microscopic appearance of the thyroid gland were reported. The NOAEC for reproductive effects in this study was reported to be 16 mg/m^3 (EU RAR, 2003). Alveolar histiocytosis and chronic active inflammatory changes were seen in the lung of all animals exposed to 202 mg/m^3, accompanied macroscopically by firmness, white

discoloration and/or enlargement in the bronchial and/or mediastinal lymph nodes, accompanied by granulomatous inflammation. These changes were attributed to dust overload at this dose level. Changes in the lung consisted of minimal chronic active inflammation in 1/10 males at 1.1 mg/m^3 and 3 animals (combined sexes) at 16 mg/m^3. At 202 mg/m^3, alveolar histiocytosis and chronic inflammation were noted in all animals. A slight increase in incidence of goblet cell hypertrophy in the nasal tissues was seen in both sexes in nasal level 2 in all exposed groups but without a dose-related trend.

Based on the decreased thyroxin levels, increased TSH levels and the slight centrilobular hepatocellular hypertrophy observed from 16 mg/m^3, a NOAEC in this study for systemic toxicity was considered to be 1.1 mg/m^3. Regarding local toxicity, a LOAEC of 1.1 mg/m^3 can be determined based on the increased incidence of chronic active inflammation even if a trend is only identified at the lowest tested doses (1.1 and 16 mg/m^3 with a minimal chronic active inflammation at both exposures.

Table 2 provides a summary of these inhalation repeat dose with commercial octaBDE.

Table 2. Summary of repeated dose inhalation experiments undertaken by Great Lakes in rats with commercial octaBDE (from the EU RAR).

Duration, days	Conc. mg/m^3	Exposure regime	Outcome	Year
14	0, 0.6, 3.7, 23.9, 165.2	8 hours/day	Increase in liver weights from 3.7 mg/m^3, liver lesions, increase in Br content of liver, lung and fat, no effects on biochemical, haematological or urine parameters.	Great Lakes (1978)
14	0, 1, 10, 110, 250	6 hours/day, 5 days/week	Increase in liver weight from 10 mg/m^3, centrilobular hypertrophy of hepatocytes from 10 mg/m^3, goblet cell hyperplasia/hypertrophy in nasal tissues from 1 mg/m^3.	Great Lakes (2000)
90	0, 1.1, 16, 202	6 hours/day, 5 days/week	Increase in lung and liver weights at 202 mg/m^3, centrilobular hypertrophy of hepatocytes from 16 mg/m^3, chronic active lung inflammation from 1.1 mg/m^3 associated with alveolar histiocytosis at 202 mg/m^3, absence of corpora lutea at 202 mg/m^3, Increased TSH and decreased T_4 levels from 16 mg/m^3.	Great Lakes (2001)

Experiments in neonatal mice have found evidence of developmental neurotoxicity but no evidence of neurotoxicity has been observed in long-term studies with PBDEs in adult animals (EU RAR, 2003). The EU RAR also notes that other PBBs are reported to affect lymphoid tissues and may affect immune function. However, no immunotoxic effects have been reported in the available studies on octaBDE.

2.6. Genotoxicity

2.6.1. In vitro

OctaBDE has given negative results in a range of in *vitro* assays. Results from different bacterial mutagenicity tests can be considered as negative, and octaBDE did not induce UDS, SCE or cytogenetic effects *in vitro* (EU RAR, 2003).

2.6.2. In vivo - Human data

No data on genotoxic effects in humans are available.

2.6.3. In vivo - Animal data

No *in vivo* animal data are available. Overall, the EU RAR concluded that it could be assumed that there was no concern for genotoxicity of octaBDE.

2.7. Carcinogenicity

2.7.1. Human data

There is no epidemiological evidence of a carcinogenic potential for octaBDE.

2.7.2. Animal data

There are no data from long-term animal experiments. While there was a scattered incidence of hyperplastic nodules in the liver in the recovery period (8 weeks and 6 months) following oral administration of octaBDE to rats, the EU RAR was unable to reach a firm conclusion on carcinogenicity.

2.8. Reproductive toxicity

2.8.1. Human data

No human data are available on the reproductive or developmental toxicity of octaBDE (EU RAR, 2003).

2.8.2. Animal data

Fertility

No specific investigations of effects on fertility in animals have been undertaken. In a 13-week dietary study in rats at levels of up to 10 000 ppm (781 mg/kg bw/day for males and 834 mg/kg bw/day for females) there was a reversible increase of the absolute and relative testes weight unaccompanied by histopathological change (Great Lakes, 1977). However, in the more recent 14-day and 90-day inhalation studies described above, no treatment-related effects on testes and epididymis weights or microscopic evidence of cellular damage in the seminiferous tubules were seen at the highest nominal exposure levels of 202 mg/m^3 or 250 mg/m^3. An absence of corpora lutea was reported in 3/10 female rats exposed by inhalation to 202 mg/m^3 for 13 weeks, but no effects were found on the mean ovary or uterus weights. A NOAEC for female fertility of 16 mg/m^3 is assumed for this end-point (EU RAR, 2003).

Developmental toxicity

No inhalation data are available on developmental toxicity of octaBDE following inhalation or dermal exposure.

In an initial oral range finding developmental toxicity study, rats were administered 0, 2.5, 10, 15, 25 or 50 mg/kg bw/day commercial octaBDE by gavage from days 6 through 15 of gestation (Great Lakes, 1986). A slight decrease in maternal body weight was evident at 50 mg/kg bw/day, unaccompanied by other signs of toxicity, and at this dose level foetal body weights were reduced. There was also increased embryo/foetal death (resorption) and retarded ossification. The foetal NOAEL was taken as 25 mg/kg bw/day and the NOAEL for the dams was 50 mg/kg bw/day (Great Lakes, 1986).

A further developmental toxicity study was carried out in the rat at dose levels of 0, 2.5, 10, or 25 mg/kg bw/day commercial octaBDE, given by gavage from days 6 through 15 of gestation (Ethyl Corp., 1985). Changes indicative of developmental toxicity were similar to those observed in the range-finding study but also included a low incidence of foetal malformation/variations). In this study, the embryo/foetal NOAEL was 10 mg/kg bw/day and the maternal NOAEL > 25 mg/kg bw/day.

A third developmental toxicity study in the rat using the same dose levels as the 2nd study described above again showed statistically significant foetal death (post-implantation loss) at 10 mg/kg bw/day in the absence of maternal toxicity (Dead Sea Bromine Co Ltd, 1987). There was no evidence of any treatment-related skeletal malformations or variations and no indication of delayed or retarded ossification in any treated group. The authors of the study concluded that the biological significance of the foetal death seen in the study was not clear, as all values fell within the range of historical control values of the laboratory (4.4-7.0%).

In an oral gavage study in rabbits, slight foetal toxicity was reported at 5 mg/kg bw/day in the presence of maternal toxicity, with a NOAEL of 2 mg/kg bw/day (Breslin *et al*, 1989). Studies in neonatal mice with other PBDEs have demonstrated possible developmental toxicity but no information is specifically available for octaBDE. Administration of a single dose of tetraBDE (10.5 mg/kg bw), pentaBDE (12 mg/kg bw) or decaBDE (2.2 mg/kg bw) to neonatal animals has been reported to give rise to evidence of neurotoxicity in adult animals (Eriksson *et al,* 2001, Viberg *et al,* 2003). The NOAEL was reported as 0.7 mg/kg bw for tetraBDE. In similar experiments, Branchi *et al* (2002) reported that repeated neonatal exposure to 0.6 mg/kg bw/day of pentaBDE caused effects on spontaneous motor activity in mice. It has been suggested that the developing mouse brain is particularly sensitive to PBDEs during the brain growth spurt. In humans, this occurs during the final three months of pregnancy and continues during the first two years of life. These experiments in mice were not performed following an internationally recognised protocol and there is some controversy about their relevance for human risk assessment. No evidence of neurotoxic effects has been found in animals exposed to PBDEs in subchronic or chronic studies.

Table 3 summarises the available developmental toxicity studies on octaBDE, and shows that developmental effects were observed in rats in two studies that were apparently unrelated to significant maternal toxicity (a decrease in maternal body weight gain during days 16-20 was the only change reported in the dams) These effects were not confirmed in a third assay in rats which was conducted with a test article containing a lesser percentage of octaBDE. Overall, the EU RAR concludes that octaBDE is a developmental toxicant. The NOAEL for developmental toxicity is considered to be 2 mg/kg bw/day, based on the study in rabbits.

Table 3. Investigations of reproductive toxicity undertaken with commercial octaBDE preparations or similar mixtures.

Species	Timing	Dose	Outcome	Study
Rats	Days 6-15 of gestation	0, 2.5, 10, 15, 25, 50 mg/kg bw/day	Decrease in maternal weight gain at 50 mg/kg bw/day, increased serum bromine levels at 25 and 50 mg/kg bw/day; reduction in foetal body weight, increased embryo/foetal death and retarded ossification at 50 mg/kg bw/day.	Great Lakes (1986)
Rats	Days 6-15 of gestation	0, 2.5, 10, 25 mg/kg bw/day	Decrease in maternal weight gain at 25 mg/kg bw/day combined with increased resorption rates and reduced foetal weights.	Ethyl Corp. (1985)
Rats	Days 6-15 of gestation	0, 2.5, 10, 25 mg/kg bw/day	No adverse maternal effects observed; increased foetal deaths at 10 and 25 mg/kg bw/day but biological significance of these deaths unclear as incidence within historical control values of the laboratory. No treatment related malformations or evidence of delayed or retarded ossification.	Dead Sea Bromine Co Ld (1987)
Rabbits	Days 7-19 of gestation	0, 2, 5, 15 mg/kg bw/day	An increase in maternal liver weight and a reduction in maternal body weight gain (not statistically significant) was observed at 15 mg/kg bw/day, some early deliveries (5 mg/kg bw/day, 15 mg/kg bw/day), slight foetal toxicity at 5 and 15 mg/kg bw/day.	Breslin *et al* (1989)

3. Recommendations

Commercial octaBDE comprises a mixture of PBDE congeners with smaller quantities of other species. Typically the octaBDE content of these preparations is less than 40%. OctaBDE is a solid with a very low vapour pressure, and inhalation of dust and skin contact is considered to represent the predominant routes of exposure. Very low levels of octaBDE are predicted in air, based on the EUSES risk assessment tool.

The available human data for octaBDE show that at least some of the substance is absorbed following oral or inhalation exposure and that it accumulates in adipose tissue, blood and milk. Very limited absorption of octaBDE via the dermal route is predicted. There are no data on the acute effects of octaBDE in humans, nor is any information available on repeat dose toxicity in humans.

Data from animal studies indicate that octaBDE has low acute toxicity, is not irritating to the skin or eyes and does not have sensitising potential. Repeated exposure of rats to octaBDE by the oral or inhalation routes produces adaptive changes in the liver, consisting of liver weight changes, induction of CYP enzymes and hepatocellular hypertrophy. These effects are seen at dose levels of approximately 7 mg/kg body weight/day in a 13-week study, the lowest dose tested. Effects on thyroid function have also been observed. Other PBDE compounds have been reported to cause developmental neurotoxicity in neonatal mice and there are also reports of immunotoxic effects. The significance of these findings in relation to octaBDE is uncertain.

In inhalation studies in rats, evidence of nasal epithelial and respiratory irritation was seen following two weeks of exposure to micronised particulates of octaBDE, and lung inflammation was additionally seen after 13 weeks of exposure. These changes were present at the lowest concentration of 1 mg/m^3 and this exposure level is therefore considered to be a LOAEC. No effect was seen on the liver at this exposure level, after either 2 or 13 weeks exposure, and 1.1 mg/m^3 was therefore a NOAEC for liver effects.

OctaBDE has not shown genotoxic potential *in vitro* but no long-term studies have been undertaken to investigate its carcinogenicity. Evidence of developmental toxicity has been seen in three studies in the rat at oral doses of 25 to 50 mg/kg bw/day, consisting of foetal deaths, resorptions and malformations, in the absence of marked maternal toxicity. In the first of these studies, the NOAEL for developmental toxicity (embryofoetal death) was 25 mg/kg bw/day, in the second it was 10 mg/kg bw/day, while in the third study statistically significant post-implantation loss was seen at 10 mg/kg bw/day, which was however within the historical control range for the laboratory. In a 90-day inhalation study in rats, the NOAEC for effects on the reproductive organs in both males and females was reported to be 16 mg/m^3 (EU RAR, 2003). In an oral gavage study in rabbits, slight foetal toxicity was reported at 5 mg/kg bw/day, in the presence of maternal toxicity, with a NOAEL of 2 mg/kg bw/day.

There are no robust data on octaBDE in exposed workers to permit establishment of a NOAEL/LOAEL on which to base an Occupational Exposure Limit, although limited information available on decaBDE suggests that no adverse effects have arisen in workers following long-term exposure to concentrations of 1 to 4 mg/m^3.

The LOAEC established in the 90-day inhalation study in the rat of 1.1 mg/m^3 for local toxicity (a minimal chronic active inflammation in the lung at 1.1 and 16 mg/m^3) is therefore used as the point of departure for setting an OEL. Since the effects seen at this and the next higher concentration of 16 mg/m^3 are minimal the OEL (8 h TWA) of 0.2 mg/m^3 for commercial octaBDE is derived. This value is considered sufficiently protective because long-term exposure of workers to the closely related decaBDE to concentrations of 1 to 4 mg/m^3 did not show effects.

The acute and short-term exposure data show that a short-term exposure limit is not indicated. The available data are inadequate to assign a skin notation, no objective data are available enabling a quantitative assessment of dermal penetration of octaBDE.

Measurement difficulties are not foreseen at the proposed limit. However, it should be noted that to control the OEL of 0.2 mg/m^3 of the octBDE commercial mixture and considering that the mixture contains around 50% octaBDE the concentration of the latter should not exceed 0.1 mg/m^3.

4. References

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