



Polybromodiphenyl ethers (Decabromodiphenyl ether)

Toxicological Overview

Key Points

Kinetics and metabolism

- Higher-brominated PBDEs (such as deca-BDE) are unlikely to undergo significant absorption. They may be metabolised to lower brominated products, and are excreted mainly in the faeces
- Lower-brominated PBDEs are likely to be absorbed orally and accumulate in body tissues such as fat and be retained for many years

Health effects of acute exposure

- The acute toxicity of PBDEs is low, following inhalation, ingestion and dermal contact

Health effects of chronic exposure

- Animal studies suggest that the main target organs following repeated exposure are the liver and thyroid. Deca-BDE has much lower toxicity than penta- or octa-BDE
- Evidence of carcinogenicity of deca-BDE in animal studies is equivocal. PBDEs do not have mutagenic properties
- Animal studies suggest that deca-BDE does not have any significant toxicity to the reproductive system

Toxicological Overview

Summary of Health Effects

Polybromodiphenyl ethers (PBDEs) are a large group of 209 compounds with similar chemical structures. Deca-, octa- and penta- brominated diphenyl ethers (BDEs) have been used in the past as flame retardants in a variety of consumer products. However, only deca-BDE is currently commercially available since the marketing and use of penta- and octa-BDE was banned throughout the EU in 2004 on the basis of the potential for the lower-brominated derivatives to bioaccumulate in the environment. Therefore most of the data in this report predominantly refers to deca-BDE and to a lesser extent to penta- and octa-BDE.

There are very few data regarding the kinetics and metabolism of PBDEs in humans. Higher brominated PBDEs (such as deca-BDE) are unlikely to undergo oral absorption. Any absorbed deca-BDE is likely to be relatively rapidly eliminated, mainly in the faeces [1]. Lower-brominated PBDEs are likely to accumulate in body tissues such as fat and be retained for many years [2]. PBDEs are not likely to be absorbed through the skin following dermal contact [2, 3].

There are very few data relating to adverse health effects in humans from acute exposure to PBDEs. Data from animal studies suggest that PBDEs have low acute toxicity and that deca-BDE is much less likely than the lower-brominated PBDEs to cause adverse health effects [2]. Data from rodent studies indicate that the key target organ for toxicity following repeated exposure to PBDEs is the liver. Penta- and octa-BDE are considerably more hepatotoxic than deca-BDE. Penta- and octa-BDE have been shown to induce liver cytochrome P-450 enzymes and to produce effects on the thyroid [1].

Deca-BDE and penta-BDE did not produce any overt fetotoxicity or teratogenicity in developmental toxicity studies in animals, whereas with octa-BDE there was some evidence of low fetotoxicity at doses producing no maternal toxicity. Single doses of penta-BDE given shortly after birth have been reported to produce neurobehavioural effects (delayed habituation behaviour) at 60 and 120 days of age [1].

The International Agency for Research on Cancer (IARC) has concluded that, based on the lack of human data and the limited evidence of carcinogenicity in animals, deca-BDE is not classifiable as to its carcinogenicity to humans (group 3) [4]. Deca-BDE is not classified as a carcinogen in the EU. No carcinogenicity data are available on the lower-brominated PBDEs [1]. PBDEs do not possess any mutagenic potential [1].

Kinetics and Metabolism

There are very few data regarding the kinetics and metabolism of PBDEs in humans.

Data from animal studies indicate that higher-brominated PBDEs (such as deca-BDE) are unlikely to undergo significant absorption following oral administration with less than 10% being absorbed [1], whilst lower brominated PBDEs such as penta- and octa-BDE are readily absorbed and are likely to accumulate in body tissues such as fat and be retained for many years. No studies were found regarding absorption in humans following inhalation exposure [2]. PBDEs are not likely to be absorbed through the skin.

Studies in various countries (Sweden, Canada, USA, UK) have indicated that PBDEs can be detected in human breast milk. Detailed studies in Sweden reported that levels increased over the period of 1972-1997, with the main compounds measured being tetra- and penta-BDE, together with small amounts of hexa-BDE. Deca-BDE was not detected [1].

Studies in experimental animals have demonstrated that many lower-brominated PBDEs such as penta-BDE are not readily metabolised. Limited information indicates that deca-BDE is metabolised to lesser brominated phenolic products [1].

The primary route of excretion for all PBDEs in animals is thought to be in the faeces, although it is unclear what proportion of this is unabsorbed material. Distribution studies with deca-BDE in rats have demonstrated that it is poorly absorbed and rapidly excreted in the faeces. There are few data regarding the bioaccumulation or route of elimination in humans. [1, 2].

Sources and Route of Human Exposure

Exposure of the general public to low levels of deca-BDE may occur via ingestion or inhalation, although uptake is likely to be insignificant. In contrast, uptake of penta-BDE may occur via the consumption of fish or cow's milk containing trace amounts of these compounds. Skin contact with treated textiles is unlikely to give rise to significant uptake since PBDEs are poorly absorbed through the skin. Small amounts of lower PBDEs may be present in the air hence exposure may also occur through inhalation [2, 3].

Exposure to deca-BDE may occur in occupational settings, although the potential for inhalation is expected to be very minimal, since the vapour pressure is extremely low. However, small inhalable particles and dust containing PBDEs may be produced when grinding solids and appropriate protective equipment is recommended in areas of potential exposure [3].

Individuals may be environmentally exposed to different forms of PBDEs than those initially released from the source due to transformation and differential partitioning in the environment and food animals [2]. For example, deca-BDE released from polymers or plastics may degrade to lower-brominated PBDEs, such as tetra-BDE or penta-BDE [2].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

There are very few data relating to adverse health effects in humans from acute exposure to deca-BDE [2, 3].

Inhalation

No data were available regarding acute exposure of humans to deca-BDE by inhalation.

Ingestion

No data were available regarding acute exposure of humans to deca-BDE by ingestion.

Dermal / ocular exposure

No evidence for skin sensitisation was found in a study of 200 human subjects to determine the skin sensitisation potential of deca-BDE [3].

Animal and In-Vitro Data

Inhalation

The toxicity of deca-BDE following acute inhalation in experimental animals is low [3]. In a study in which male and female Spartan rats were administered a single dose of either 2 mg L⁻¹ or 48.2 mg L⁻¹ commercial deca-BDE by inhalation for 1 hour, all of the animals survived. In the 2 mg L⁻¹ group the only effects seen during the observation period were respiratory difficulties in one animal and a slight ocular discharge in another. All other rats appeared normal. In the higher dose group, increased motor activity and eye squint were observed up to day 4. Respiratory difficulties were noted in 4 of the rats on different days post exposure and eye squint and ocular discharge were seen in a few of the rats between days 7 and 11 post exposure. However, all of the animals appeared normal on day 14 [3].

Rats exposed to extremely high concentrations of aerosolised dust of penta-BDE (200,000 mg m⁻³), octa-BDE (60,000 mg m⁻³) or deca-BDE (48,200 mg m⁻³) for 1 hour, showed transient signs of respiratory distress, including tachypnoea and dyspnoea [2].

Ingestion

Intragastric intubation of a single dose of a commercial preparation of deca-BDE to female Sprague-Dawley rats in the range of 126 to 2000 mg kg⁻¹ body weight (bw) in 10 % corn oil caused no adverse toxicity and no gross pathological changes up to 14 days post-exposure [3]. In another study, no adverse health effects were reported in male rats up to 14 days after exposure to a single dose of up to 5 g kg⁻¹ bw deca-BDE in corn oil by gavage [3].

Studies in rodents indicate that the penta-, octa- and deca- derivatives all have low acute toxicity with LD₅₀ values of greater than 2 to 5 g kg⁻¹ bw. No overt signs of toxicity were seen at these very high doses [1].

Mild impairments in spontaneous motor behaviour, learning and memory were observed in mice that were exposed to single low doses (concentration unknown) of penta-BDE, hexa-BDE and deca-BDE during prenatal or early postnatal periods and tested later in life [2, 5].

In acute oral studies, rats administered 10-100 mg kg⁻¹ bw penta-BDE or octa-BDE had an increase in cytochrome P450 activity which was associated with perturbations of thyroid hormones, liver enlargement and histopathological changes in the thyroid. Deca-BDE did not induce such changes at doses up to 100 mg kg⁻¹ bw [1].

Dermal / ocular exposure

Deca-BDE is not an irritant to the skin or eyes of rabbits and it is not thought to cause chloracne [3].

Health Effects of Chronic / Repeated Exposure

Human Data

General toxicity

There are very few data relating to adverse health effects in humans following repeated exposure to deca-BDE.

Inhalation

No adverse health effects were detected in workers occupationally exposed to a mixture of polybutyl terephthalate and deca-BDE for 13 years [3].

A health assessment of workers occupationally exposed to deca-BDE and polybrominated biphenyls (PBBs) showed a greater incidence of hyperthyroidism than expected and significant reductions in sensory and fibula motor velocities. No other neurological or dermatological effects were observed. However, it was not clear whether these effects were due to exposure to deca-BDE or were due to the PBBs to which the individuals were concurrently exposed, as deca-DBE was not detected in the serum of workers [3].

Ingestion

No data were available regarding repeated oral exposure of humans to deca-BDE [2].

Genotoxicity

No data were available regarding the genotoxicity of deca-BDE in humans [4].

Carcinogenicity

No data were available regarding the carcinogenicity of deca-BDE in humans.

Based on the lack of human data and the limited evidence of carcinogenicity in animals, the IARC considered deca-BDE to be not classifiable as to its carcinogenicity to humans (group 3) [4]. The U.S. EPA has classified lower-brominated PBDEs are not being classifiable as to human carcinogenicity [2].

Reproductive and developmental toxicity

No data were located regarding adverse reproductive or developmental effects in humans following exposure to deca-BDE. [2].

Animal and In-Vitro Data

Inhalation

No data were available regarding adverse health effects following chronic inhalation exposure to deca-BDE.

Ingestion

No histopathological changes in the gastrointestinal tract were reported in mice or rats given deca-BDE (<8000 and 9500 mg kg⁻¹ bw day⁻¹ respectively) for 13 weeks. Rats given dietary doses of deca-BDE (2240 mg kg⁻¹ bw day⁻¹) for 103 weeks had forestomach lesions and 7780 mg kg⁻¹ bw day⁻¹ caused stomach ulcers in mice [2].

Intermediate and chronic exposure studies in rats indicate that the liver is the key target organ for PBDE toxicity.

Repeated dietary studies have shown that adverse liver effects were more severe in rats and mice when administered lower doses of lower-brominated PBDEs (octa-BDE and penta-BDE) compared with deca-BDE [2].

Exposure to deca-BDE at 94-97% purity for 103 weeks caused hepatic lesions including neoplastic nodules in rats at above 1,120 mg kg⁻¹ bw day⁻¹, and thrombosis and degeneration at above 2,240 mg kg⁻¹ bw day⁻¹. Centrilobular hypertrophy and granulomas were observed in mice at above 3,200 mg kg⁻¹ bw day⁻¹ [2].

Based on the available data from repeated dose studies, penta-BDE was considered the most toxic of the PBDEs with a lowest observable adverse effect level (LOAEL) of 0.6 mg kg⁻¹ bw day⁻¹ based on liver toxicity, compared to 7.2 mg kg⁻¹ bw day⁻¹ and 1,120 mg kg⁻¹ bw day⁻¹ for octa-BDE and deca-BDE, respectively [1].

Genotoxicity

Deca-BDE did not induce reverse mutations in the Ames test using *Salmonella typhimurium* (strains TA 98, TA100, TA1535 and TA 1537) either with or without activation. It did not induce gene mutations in mouse lymphoma cells or induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary CHO cells [2, 4]. Cytogenic examination of bone marrow cells showed no increase in chromosomal aberrations in maternal or neonatal rats following oral exposure to deca-BDE at up to 100 mg kg⁻¹ bw day⁻¹ for 90 days [2]. Deca-BDE does not have any mutagenic potential [1].

Penta-BDE has given negative results in 4 studies to investigate its ability to induce gene mutation in *S. typhimurium* and in one study in *Saccharomyces cerevisiae*. A cytogenic study in human peripheral blood lymphocytes also gave negative results. Penta-BDE has not been tested for genotoxicity *in vivo*. However, the *in-vitro* data indicate that it does not have any mutagenic potential [1].

Octa-BDE has also given negative results in 4 studies for gene mutation in *S. typhimurium* and in one study in *S. cerevisiae*. Negative results were also obtained in studies to investigate unscheduled DNA synthesis in human fibroblasts, sister chromatid exchange in

CHO cells or chromosome aberrations in human peripheral blood lymphocytes. These data indicate that octa-BDE does not have any significant mutagenic potential [1].

Carcinogenicity

Carcinogenicity bioassay data are available for deca-BDE from dietary studies in mice and rats. In a 103 week study in mice, an increase in hepatocellular adenomas or carcinomas was seen at the lowest dose level ($3200 \text{ mg kg}^{-1} \text{ bw day}^{-1}$) but not at the higher dose ($6650 \text{ mg kg}^{-1} \text{ bw day}^{-1}$). Thyroid gland follicular cell adenomas were reported in male mice at both levels. There was no evidence of carcinogenicity in female mice.

In a 103 week study in the rat there was a dose dependent increase in neoplastic liver nodules, which was significantly greater than the controls, in males administered $1120 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ and in both sexes given $2240 \text{ mg kg}^{-1} \text{ bw day}^{-1}$. The recent EU comprehensive risk assessment of deca-BDE (under the Existing Substance Regulation) noted that the evidence for carcinogenicity of deca-BDE from those bioassays was equivocal [1, 6].

IARC has concluded that there was limited evidence for the carcinogenicity of deca-BDE in experimental animals [4].

No data are available on the carcinogenicity of lower-brominated PBDEs such as penta-BDE or octa-BDE [2].

Reproductive and developmental toxicity

In a one generation reproductive study in which male and female Sprague-Dawley rats were administered up to $100 \text{ mg kg}^{-1} \text{ bw}$ deca-BDE in the diet for 60 days prior to mating, and throughout gestation and lactation, no signs of toxicity were observed in either the adult rats or neonates during the study or at necropsy [3].

A study in which rats were exposed to low-doses of penta-BDE during development has suggested a permanent impairment of spermatogenesis, however, no effect on fertility was observed [5].

Deca-BDE and penta-BDE did not produce adverse effects in routine developmental toxicity studies. In a dietary study in rats using deca-BDE or penta-BDE, no developmental effects were seen following administration of doses up to $100 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ $200 \text{ mg kg}^{-1} \text{ bw day}^{-1}$, respectively, from 60 days prior to mating until weaning [1].

In contrast, octa-BDE has been shown to produce fetal toxicity in rats and rabbits. In the recent EU risk assessment, $2 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ was identified as the lowest no observable adverse effect level (NOAEL) in rabbits, with slight fetotoxicity being observed at $5 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ [1, 6].

Non-routine studies on specific congeners of penta-BDE have been reported to cause neurobehavioural changes in mice following a single oral administration on post natal day 3, 10 or 19. Neurobehavioural effects were detected at 60 and 120 days of age. The main effect noted was delayed habituation behaviour which was found to occur at the lowest dose tested, $0.6 - 0.8 \text{ mg kg}^{-1} \text{ bw}$ [1].

References

- [1] Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (COT) (2004). COT Statement on Brominated Flame Retardants in Fish from the Skerne-Tees Rivers System.
- [2] Agency for Toxic Substances and Disease Registry (ATSDR) (2004). Toxicological Profile for Polybrominated Biphenyls and Polybrominated Diphenyl Ethers. US Department of Health and Human Services. Atlanta, US.
- [3] International Programme on Chemical Safety (IPCS) (1994). Brominated Diphenylethers. Environmental Health Criteria 162. WHO. Geneva.
- [4] International Agency for Research on Cancer (IARC) (1999). Decabromodiphenyl oxide. Vol 71. IARC. Lyon.
- [5] Kuriyama, S. N., Talsness, C. E., Grote, K. and Chahoud, I. (2005). Developmental exposure to low dose PBDE 99: effects on male fertility and neurobehavior in rat offspring. *Environ Health Perspect* **113**, 149-54.
- [6] European Chemicals Bureau (ECB) (2002). Bis(pentabromophenyl) Ether: Risk Assessment: 1st Priority List: Volume 17.

This document from the PHE Centre for Radiation, Chemical and Environmental Hazards reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.