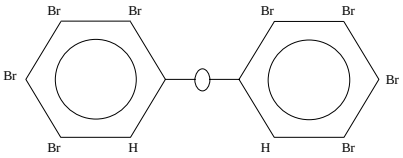
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	32536-52-0
Chemical Name	Diphenyl ether, octabromo derivative
Structural Formula	e.g. 

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Animal data show an absorption of Octabromodiphenyl ether (OBDPE) by oral or inhalation route with an accumulation of the parent compound or its metabolites in the liver and also in the adipose tissue and the lung following inhalation administration. The extent of absorption and elimination cannot be assessed from the data available. No information on the metabolism of OBDPE is available. Following oral administration, OBDPE is an inducer of xenobiotic metabolism. There are no measured data on OBDPE dermal absorption. However based on OBDPE physicochemical properties and analogy with PCBs, a dermal absorption of 4.5% may be estimated.

Evidence from humans indicates that OBDPE, HxBDPE, HpBDPE and NonaBDPE which are components of commercial OBDPE can be absorbed into the body and distributed into the blood. Distribution to the adipose tissue was evidenced at least for OBDPE and HxBDPE. There are no data available on the rate of elimination or on bioaccumulation of OBDPE from human adipose tissue neither for PeBDPO but given the high lipophilicity of these compounds and the adipose tissue accumulation observed in rats following oral or inhalation routes, it can be assumed that in humans OBDPE might bioaccumulate in these tissues as well. Following pregnancy HxBDPE and others PBDPEs such as TeBDPE and PeBDPEs are excreted in the breast milk. Unfortunately, such measurements were not carried out on OBDPE. However, based on the high lipophilicity of OBDPE, its potential to bioaccumulate in adipose tissues and the breast milk measured data with HxBDPE (one component of commercial OBDPE), excretion of OBDPE in the breast milk may be anticipated

OBDPE has a low acute toxicity in animals. Acute oral toxicity data indicate a rat LD50 greater than 28,000 mg/kg. No deaths, no weight changes or necropsy lesions were reported up to 5,000 mg/kg. At 10,000 mg/kg and 28,000 mg/kg, no deaths were observed but no more information on these studies are available. A dermal LD50 greater than 2,000 mg/kg has been demonstrated in rabbits using DBDPE applied neat under occlusive wraps for 24 hours. No deaths were observed up to 2,000 mg/kg. Local and general signs of toxicity were not reported and necropsies were not performed in this dermal toxicity study. An inhalation LC50 greater than 60 mg/l has been demonstrated in rats exposed with OBDPE during one hour. No deaths and no clinical signs of toxicity were observed up to 60 mg/l.

OBDPE is not a dermal or an ocular irritant. There is no indication of skin sensitisation in animals.

The only information concerning the effects of repeated oral and inhalation exposure to OBDPE comes from studies in rats involving administration of commercial OBDPE. These studies consistently indicate that the liver is the key target organ within 4 and 13 weeks of repeated oral dosing and within 14 days and 90 days of inhalation exposure. The changes in thyroid status are apparent within 4 and 13 weeks of repeated oral dosing from 1,000 ppm and within 13 weeks of repeated inhalation dosing from 16 mg/m3 (analytical concentration). The LOAEL is considered to be

100 ppm ≈ 7.2 mg/kg/day in the 90 day dietary study based on the liver changes (increase of liver weight and granular cytoplasmic changes) observed from 100 ppm ≈ 7.2 mg/kg/day. The NOAEC for systemic toxicity is considered to be 1.1 mg/m^3 in the 90 day rat study by inhalation route based on the liver and thyroid status changes observed at the concentration just above: 16 mg/m^3 .

Alterations in thyroid homeostasis were reported with organochlorine compounds for many species, including humans and a thyroid hormone like affinity for the serum transport protein transthyretin was shown for hydroxylated PCBs as well as for PBDPE congeners such as DiBDPE and TeBDPE. To our knowledge, no studies on transthyretin-T_4 competition have been carried out on OBDPE neither on DBDPE.

Following inhalation exposure, local toxicity was demonstrated with hyperplasia/hypertrophy of the goblet cells within 2 weeks of exposure and with chronic active lung inflammation and alveolar histiocytosis within 13 weeks of exposure. It is obvious that the observed effect at 1.1 mg/m^3 is minimal and reveals only a trend to a chronic inflammation however this value has been taken to set up the LOAEC for local toxicity.

Regarding mutagenicity no *in vivo* data are available. However based on the available *in vitro* data, OBDPE is considered as non-genotoxic *in vitro* and no concern for mutagenicity is assumed.

No chronic or carcinogenicity studies in animals are available.

No specific fertility study is available. A recent rat inhalation sub-chronic study, well conducted and specifically designed to investigate reproductive organs, did not demonstrate adverse effects on male reproductive organs. Therefore no concern is assumed for male fertility. Regarding female reproductive organs, absence of corpora lutea was shown in this study in 3/10 females at 202 mg/m^3 versus 0/10 in the control group. Since the absence of corpora lutea is considered to be an unusual finding in rats at 20 weeks of age, the 30% incidence in this group was considered treatment-related and therefore a NOAEC for female fertility of 16 mg/m^3 was considered.

Developmental effects are observed in rats in two studies (decrease of fetal body weight from 10 mg/kg/day, increase of post-implantation loss with late resorptions, increase in dead or resorbed conceptuses per litter at 25 mg/kg/day (33.2% versus 4.3%); decrease in the average number of live fetuses per litter (8.9 versus 14.6) and fetal malformation/variation and delayed skeletal ossification at 25 mg/kg/day. Those developmental effects do not seem to be related to maternal toxicity. However, these developmental effects are not confirmed in a third assay in rats conducted with a test article containing a lower percentage of the OBDPE component. In rabbits, the substance produces only slight foetotoxicity from 5 mg/kg/day (slight decrease of the fetal body weight and increase in delayed ossification). The lowest identified NOAEL is considered i.e. 2 mg/kg/day from the rabbit study. Since some of these results are indicative of developmental effects which are most likely unrelated to maternal toxicity, OBDPE is considered as a developmental toxicant.

With regard to neurotoxicity, recently behavioural disturbances have been reported when mice (10 day old) were exposed to a single oral dose of hexabromo-diphenyl ether (0.45, 0.9 and 9 mg/kg bw). Those effects are observed at 2, 4 but also 6 months of age. Nicotinic receptors were also affected in adult mouse in the previous conditions of exposure. The study has certain limitations compared with regulatory guidelines and thus uncertainty as regards interpretation of the results remains. Moreover only an abstract of this study is available with very few details. Therefore, no firm conclusion can be drawn from these data.

Environment

In order to take into account more fully the presence of the more accumulative hexabromodiphenyl ether congeners in the commercial product, the hazards to the environment of both the octabromodiphenyl ether product and hexabromodiphenyl ether congeners specifically have been addressed where appropriate. The environmental effects database for octabromodiphenyl ether does not formally meet the requirements of the SIDS data package as there is no information on the toxicity to algae. Based on the available data, the substance appears to have a very low toxicity to fish in short-term tests, with no effects being seen up to the water solubility of the substance. QSAR estimations for non-polar narcosis predict that all NOECs and L(E)C50s are above the water solubility limit of octabromodiphenyl ether. Similarly, no effects were seen in a longer-term reproduction study with *Daphnia*, for

which a 21 day NOEC of ≥ 2 μg/l was determined. Based on the results of the long-term *Daphnia* study a PNEC for surface water of ≥ 0.2 μg/l was derived for octabromodiphenyl ether using an assessment factor of 10. For the hexabromodiphenyl ether component a PNEC for surface water of 0.53 μg/l has been derived based on that derived for the commercial pentabromodiphenyl ether product.

For microorganisms, no effects were seen in a 3 hour activated sludge respiration inhibition test at a concentration of 15 mg/l. A $PNEC_{microorganisms}$ of ≥ 1.5 mg/l was derived for this endpoint using an assessment factor of 10.

Toxicity data are available for octabromodiphenyl ether for the sediment and terrestrial compartment. For sediment, no effects were seen with the worm *Lumbriculus variegatus* in a prolonged toxicity (28 day) test using two different sediment types. The lowest NOEC from these studies was ≥ 1,272 mg/kg dry weight and a PNEC for sediment of ≥ 127 mg/kg dry weight (or ≥ 49 mg/kg on a wet weight basis) was derived for octabromodiphenyl ether from the data using an assessment factor of 10 (a factor of 10 is used as this species was the most sensitive species found for another related substance, pentabromodiphenyl ether). Based on the same data, a PNEC for sediment of ≥ 7.0 mg/kg dry weight (or ≥ 2.7 mg/kg wet weight) was derived for hexabromodiphenyl ether component alone.

For the terrestrial compartment, studies on the toxicity to plants and earthworms (*Eisenia fetida*) have been carried out with octabromodiphenyl ether. No effects were seen on germination and growth in six species of plant (*Zea mays*, *Allium cepa*, *Lolium perenne*, *Cucumis sativa*, *Glycine max* and *Lycopersicon esculentum*) at concentrations up to 1,190 mg/kg dry weight. For *Eisenia fetida* no effects were seen at concentrations up to 1,470 mg/kg dry weight in a 56 day reproduction test. Based on a NOEC of ≥ 1,190 mg/kg dry weight from the plant tests, a PNEC for this end point of ≥ 23.8 mg/kg dry weight (or ≥20.9 mg/kg on a wet weight basis) can be derived for octabromodiphenyl ether using an assessment factor of 50. Based on the same data, a PNEC for soil of ≥ 1.3 mg/kg dry weight (or ≥ 1.2 mg/kg wet weight) has been derived for the hexabromodiphenyl ether component alone.

No data are available to allow a PNEC to be derived for the atmospheric compartment. However, the atmospheric concentrations of octabromodiphenyl ether are very low and so adverse effects are unlikely.

For secondary poisoning, based on the available standard mammalian toxicity tests, a PNEC of 6.7 mg/kg food can be derived for octabromodiphenyl ether. Based on the same data, a PNEC for secondary poisoning of 0.58 mg/kg food can be derived for the hexabromodiphenyl ether component alone. However, these PNECs are based on the results of standard tests, and there is some evidence from non-standard behavioural tests on mice that these standard tests may not detect more subtle effects that might be occurring with sensitive life stages or over prolonged exposure.

Based on the available laboratory data, octabromodiphenyl ether itself appears to have a low bioaccumulation potential. However, the main components of the commercial substance (hepta- to decabromodiphenyl ethers) have recently been found at low but measurable concentrations in fish, marine mammals and predatory birds' eggs (Peregrine Falcons and Common Terns), which indicates that these highly brominated substances are able to cross biological membranes and possibly that they are being accumulated in the food chain. The mere presence of a chemical in biota is not necessarily a cause for concern, and there is no evidence at this point in time of biomagnification taking place or actual environmental harm arising from this substance. However, these findings, when coupled with the uncertainties over the effects of this substance, means that further work should be considered. In addition, the possibility that the substance may photodegrade in the environment to give more toxic and accumulative products should be investigated further.

Exposure

Since 1998, production of octabromodiphenyl ether in the EU has ceased and all of this substance used within the EU is now imported. The reported world-wide demand for octabromodiphenyl ether was 3,825 tonnes/year in 1999.

The substance is used in the plastics industry, mainly as an additive flame retardant for acrylonitrile-butadiene-styrene (ABS) polymers. The commercially supplied product is a mixture of polybrominated diphenyl ethers typically consisting of ≤33% octabromodiphenyl ether. The other main components are hexabromodiphenyl ether (≤ 12%), heptabromodiphenyl ether (≤ 45%), nonabromodiphenyl ether (≤10%) and decabromodiphenyl ether (≤

0.7%).

The substance is an off-white powder or flaked material with a melting point in the range 70-257°C and a vapour pressure of 6.59×10^{-6} Pa at 21°C. The substance does not have a distinct boiling point as it decomposes at elevated temperatures. It has a very low solubility in water (~0.5 µg/l) and a high n-octanol-water partition coefficient (log Kow = 6.29).

Emissions to the environment can occur both to the atmosphere (as vapour and as dust) and waste water. Sources of release include production sites and polymer processing sites. In addition, emissions to the environment could also occur from finished articles (e.g. plastic components) during their use and at disposal.

The substance is not readily biodegradable, but there is evidence that at least some components of the commercial product have the potential to biodegrade slowly under anaerobic conditions. The substance can probably be degraded photolytically by analogy with other brominated diphenyl ethers. The products formed from this direct photolysis reaction, and also the rate and extent of the reaction, in the environment are uncertain but may include small amounts of more toxic and accumulative brominated diphenyl ethers that contain lower numbers of bromine. It is also expected to degrade in the atmosphere by reaction with hydroxyl radicals and a rate constant for this reaction of around 2.1×10^{-13} cm^3 $molecule^{-1}$ s^{-1} has been estimated.

The low vapour pressure, water solubility and high log Kow value indicate that the substance has a high potential for adsorption onto soil, sediment or suspended sediment. Laboratory studies indicate that the substance has a low potential for bioaccumulation in aquatic species, although some components of the commercial product (e.g. hexabromodiphenyl ether) have been shown to have a much higher potential for bioaccumulation.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The SIDS requirements are met. This substance has been discussed in the European Union Risk Assessment programme under EC Regulation 793/93, and is subject to marketing and use restrictions due to the risks identified. Other member states are therefore recommended, as a post-SIDS activity, to review the exposure situation in their countries to determine the need for similar measures. Some additional studies could be performed but in view of the marketing and use restrictions in several OECD countries, the sponsor country is unlikely to pursue these data gaps.

For the environment, the following work could be considered:

Further work is needed to address the concerns over the possible accumulation in, and effects on, top predators and also the possible formation of more accumulative and toxic congeners from photolytic processes in the environment. These areas are difficult to address with standard tests. Possibilities include:

a) Consideration of a more widespread monitoring project to determine whether the finding in top predators (including birds' eggs) is a widespread or localised phenomenon and to identify any possible trends.

b) Consideration of further toxicity testing on birds.

c) Consideration of an investigation on the rate of formation of degradation products under environmentally relevant conditions over a suitably prolonged time period (e.g. years).

d) Consideration of further toxicological work on the non-diphenyl ether degradation products to determine if they pose a hazard.

For health, the following work could be considered:

- Information is needed on transthyretin-T4 competition with OBDPE.
- Information on the effects of prolonged exposure: This may involve the conduct of a lifetime study in rodents depending upon the way in which the methodology for assessing lifetime exposure is developed and any data requirements that may be indicated for such a methodology.
- Further information is needed on food chain modelling.
- Information on the extent of excretion of commercial OBDPE into the breast milk.
- Information on the extent of excretion of commercial OBDPE into cows' milk. Depending upon the results submitted by Industry on milk excretion further information might be requested.
- There is a need for exposure information from local and regional sources on the concentration of OBDPE in cows' milk.

Consideration of national or regional exposure information gathering and, if indicated, a risk assessment may need to be considered for secondary poisoning from the hexabromodiphenyl ether component of the commercial product via the earthworm food chain. This is based on an existing regional risk assessment for Europe.