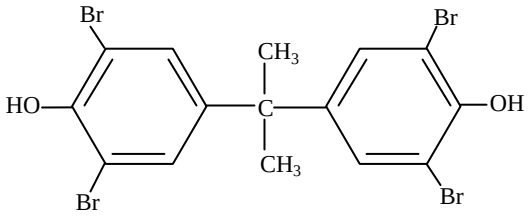
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-94-7
Chemical Name	2,2',6,6'-Tetrabromo-4,4'-isopropylidene diphenol (Tetrabromobisphenol-A; TBBPA)
Structural Formula	

SUMMARY OF THE CONCLUSIONS OF THE SIAR

Human Health

The available data indicate that TBBPA is absorbed in humans (as shown by levels of 0.3-12 µg/kg in whole blood of exposed persons). There is also evidence that once absorbed, TBBPA and/or its metabolites can be excreted in humans via breast milk (0.01-11 µg/kg lipid from 3 studies).

In experimental animals, toxicokinetic data are available in the rat only. Following oral exposure, 100 % of the administered dose of TBBPA is absorbed from the gastro-intestinal tract. The toxicokinetics following inhalation and dermal exposure have not been investigated. TBBPA is largely non-respirable (4% particles <15 µm) and therefore a relatively small proportion of particles may be expected to enter deeply into the lung following inhalation. The majority of the particles will deposit in the nasopharyngeal region of the respiratory tract and then be swallowed, while the remainder are likely to be exhaled. Regarding dermal exposure, the low water solubility, the high *n*-octanol/water partition coefficient (5.9), and the high molecular weight (>500) of TBBPA suggest that dermal absorption is likely to be low.

Information is available on distribution, metabolism and excretion following exposure via the oral route only. TBBPA is metabolised by glucuronide conjugation and to a lesser extent sulphate conjugation (accounting for around 30% of the administered dose). Excretion of TBBPA and its metabolites is predominantly in the faeces (around 95% of the administered dose) with minimal excretion in urine (<1%) at 72 hours after dosing. There is little information on the distribution/fate of TBBPA (and/or its metabolites) between being absorbed and appearing in the faeces 72 hours post-dosing, as from 4 hours after administration onwards the general systemic distribution of TBBPA and /or its metabolites appears to be very low.

No information is available on the effects of single exposure to TBBPA in humans. Available animal data indicate LC50 (1 hour), oral LD50 and dermal LD50 values in excess of 1.3 mg/l, 50 g/kg and 10 g/kg, respectively. No toxicologically significant signs of systemic toxicity were evident following exposure via any route. Thus, it can be concluded that TBBPA is of low acute toxicity by all routes of exposure.

The weight of evidence from animal studies indicates that TBBPA is not a skin, eye or respiratory tract irritant. It is not a skin or respiratory sensitiser.

Only one repeat dose inhalation study is available. Exposure of rats to concentrations of up to 18 mg/l for 4 h/d for 14 days produced no compound related, toxicologically significant systemic effects. In a 90-day rat study conducted in accordance with GLP and OECD guidelines no toxicologically significant effects were seen following oral exposure to 100, 300 or 1000 mg/kg TBBPA; therefore the NOAEL is = 1000 mg/kg/d. A decrease in serum T4

levels was observed in all treated males on days 33 and 90 and on day 33 only in all treated females. However, there was no dose response relationship associated with the finding and it did not persist in females; there were no statistically significant changes in serum levels of TSH or T3 in animals of either sex; and macroscopic and microscopic examination revealed no treatment-related changes in the liver, thyroid, parathyroid or pituitary gland. In the absence of changes in other parameters of thyroid homeostasis in a species (the rat) that is very sensitive to perturbations in thyroid hormone levels, these decreases are not considered to be adverse. The same decreases in T4 levels were seen in the 100 and 1000 mg/kg groups of the F0 and F1 generations in the 2-generation rat study (see below). However, again, given that there was little impact on other parameters associated with a disruption of thyroid homeostasis in the rat, it is deemed that the decreases observed are not toxicologically significant. In the only conventional repeated dermal exposure study, in which rabbits were dosed with up to 2500 mg/kg, no toxicologically significant compound related effects were observed.

TBBPA has demonstrated consistently negative results in a range of *in vitro* tests using bacterial strains (Ames test) and yeast both in the presence and absence of metabolic activation. In a well-conducted chromosomal aberration study using human peripheral lymphocytes and in an unconventional *in vitro* recombination assay, TBBPA tested negative. No *in vivo* data are available but in view of the negative profile *in vitro* and given that there are no structural indications that TBBPA would be genotoxic, there are no concerns for this endpoint.

There are no human or animal data available to inform on the carcinogenic potential of TBBPA. However, there is no evidence from the available *in vitro* mutagenicity data and no indications from repeated exposure studies (for example, no target organ toxicity or proliferative changes) to raise any concerns for carcinogenicity.

Information available from a 2-generation reproductive toxicity study in rats indicates that TBBPA has no toxicologically significant effects on fertility or reproductive performance at doses of 10, 100 or 1000 mg/kg, therefore the NOAEL is =1000 mg/kg/d.

The effects of TBBPA on development have been investigated in a pilot range finding study and two standard developmental toxicity studies. No evidence of developmental toxicity was seen at doses up to 2500 mg/kg/d in these studies, therefore the NOAEL is = 2500 mg/kg/d.

In addition, 2 well-conducted developmental neurotoxicity studies have been conducted in the rat and a post-natal developmental neurotoxicity study in the mouse. The rat studies involved exposure of dams during pregnancy and lactation periods. The first study was part of the 2-generation oral gavage study and included behaviour and learning/memory tests, specialised neurohistopathology and morphometric examination of the brain. This study provided no convincing evidence of an adverse effect on neurodevelopment at dose levels up to 1000 mg/kg/d. A statistically significant decrease in the thickness of the parietal cortex was observed in F2 pups of the 1000 mg/kg group on PND 11, however, the same effect was not present in these pups on PND 60. Also, no microscopic changes were reported in these animals on either PND 11 or PND 60. Therefore, the decreased thickness of the parietal cortex is regarded as a transient or chance finding that is unlikely to be toxicologically significant.

The second study included behaviour and learning/memory tests, neurohistochemistry, but no specialised neurohistology. Pregnant rats were administered 0, 50 or 250 mg/kg/d TBBPA by gavage in peanut oil from gestation day 7 to postnatal day 17 and a neurobehavioural assessment was carried out on weanling rats. The study showed limited evidence of changes in the habituation behaviour of female offspring and learning and memory in male offspring in the 250 mg/kg/d group. However, it is not possible to draw definitive conclusions from this study because the size of the reported changes was very small and there was not a convincingly consistent pattern of changes in investigations conducted at different time points. Also, the evidence of developmental neurotoxicity is weakened by the absence of consistent changes in the two genders, the lack of histopathological investigations that could provide corroborative findings, and the lack of any similar findings in the first study at dose levels of 100 and 1000 mg/kg/d.

In the mouse study, a single exposure to 10-day old neonates, to a relatively low oral gavage dose, had no effect on behaviour, learning or memory.

In a non-standard study, an effect on the kidneys (polycystic lesions associated with the dilatation of the tubules) of newborn rats dosed from day 4 up to day 21 after birth by gavage with 200 and 600 but not 40 mg/kg TBBPA was

reported. However, no similar effect was observed in 5-week old rats administered by gavage 2000 and 6000 mg/kg TBBPA for 18 days and in a comprehensive GLP- and OECD-compliant rat 2-generation study with gavage doses of up to 1000 mg/kg/d. These findings indicate that newborn rats are more susceptible to the nephrotoxic effects of TBBPA than young and adult rats. However, it is considered that this effect is likely to be the consequence of the direct gavage administration of very high doses of TBBPA to such young animals.

Overall, the data do not provide strong evidence of the potential for TBBPA to act as a developmental toxicant or neurotoxicant.

Environment

The substance is a white crystalline powder with a melting point of 181-182^{o}C and a very low vapour pressure of $<1.19\times10^{-5}$ Pa at 20^{o}C. The substance does not have a distinct boiling point as it decomposes at 200-300^{o}C. The substance is a weak acid (pKa_1 = 7.5 and pKa_2 = 8.5) and the water solubility varies with pH (0.148 mg/l at pH 5, 1.26 mg/l at pH 7 and 2.34 mg/l at pH 9; all at 25^{o}C), reflecting the increased solubility of the dissociated forms over the undissociated acid. The n-octanol water partition coefficient (log Kow) has been measured as 5.9. Similar to water solubility, the log Kow would be expected to vary with pH of the solution.

The substance is not readily biodegradable but has been shown to undergo primary biodegradation, but only limited mineralisation, under aerobic conditions in soils (18-64% primary degradation in 64 days) and sediments (36-55% primary degradation in 56 days). In addition, the substance has been shown to undergo primary degradation under anaerobic conditions in soils (10-56% degradation in 64 days) and contaminated sediments (85% degradation in 10 days). More recent studies have shown 18-22% mineralization of TBBPA over six months' incubation in soil, suggesting a mineralization half-life of > 6 months. Bisphenol-A has been identified as a degradation product of TBBPA under anaerobic conditions. The substance is also expected to degrade in the atmosphere by reaction with hydroxyl radicals and a rate constant for this reaction of around 2.96×10^{-12} cm^3 $molecule^{-1}$ s^{-1} has been estimated (atmospheric half-life of 130 hours).

The low vapour pressure, water solubility and high log Kow value indicates that the substance has a high potential for adsorption onto soil, sediment or suspended sediment. Laboratory studies indicate that the substance has a moderate potential for bioaccumulation in aquatic species (the fish BCF is around 1,234 l/kg based on ^{14}C-residues or around 485 l/kg based on parent compound measurements).

The environmental effects database meets the requirements of the SIDS data package. In addition, results from several post SIDS tests are also available. Based on the available data for fish, invertebrates and algae, the substance appears to have a high toxicity in short-term tests, with the lowest acute values being a 96h-LC_{50} of 0.54 mg/l for fathead minnow (*Pimephales promelas*), a 48h-EC_{50} of 0.96 mg/l for *Daphnia magna*, a 72h-EC_{50} of >5.6 mg/l for the freshwater algae *Pseudokirchneriella subcapitata* and a 72h-EC_{50} of 0.09-0.89 mg/l for the marine alga *Skeletonema costatum*.

In longer-term toxicity tests, NOEC/EC_{10} values of 0.16 mg/l for fish over 35 days, 0.3 mg/l for *Daphnia magna* over 21 days, ≥5.6 mg/l for the freshwater algae *Pseudokirchneriella subcapitata* over 72 hours, <0.066 mg/l for *Chironomus tentans* over 14 days, 0.017 mg/l for *Mytilus edulis* over 70 days and 0.0127 mg/l for *Acartia tonsa* over 5 days have been determined. Based on the *Acartia tonsa* data a PNEC for surface water of 1.3 µg/l was derived using an assessment factor of 10.

A number of studies have investigated the effects of tetrabromobisphenol-A on the endocrine system in aquatic organisms. The results obtained in these studies show considerable variability, and appear to be dependent on the test system used. Overall, in terms of population effects, the available studies with fish have generally shown that tetrabromobisphenol-A has little or no adverse effect on parameters such as survival, growth and reproduction that can be assigned specifically to effects on the endocrine system. For amphibians, although possible thyroid-mediated effects of tetrabromobisphenol-A are evident in some *in vitro* assays, the results of a recent, well conducted, *in vivo* assay suggest that the effects seen *in vivo* may be a result of a toxic side effect rather than direct effects on thyroid function.

Longer-term toxicity data for sediment and soil organisms are also available. The lowest NOECs found in studies using sediment are a 28-day NOEC of 125 mg/kg dry weight with *Chironomus riparius*, a 28-day NOEC of 250 mg/kg dry weight with *Hyalella azteca* and a 28-day NOEC of 90 mg/kg dry weight with *Lumbriculus variegatus.* Based on these data, a PNEC of 2.7 mg/kg wet weight is derived for sediment using an assessment factor of 10, after normalising the data to a standard organic carbon content (5%) and converting from dry weight to wet weight values.

The lowest NOECs found in studies using soil are a 56-day NOEC of 0.29 mg/kg dry weight with *Eisenia fetida*, a 21 day NOEC of 16 mg/kg dry weight with *Cucumis sativa* and a 28 day NOEC of 300 mg/kg dry weight for soil microorganisms. Based on these data, a PNEC of 0.012 mg/kg wet weight is derived for soil using an assessment factor of 10, after normalising the data to a standard organic carbon content (2%) and converting from dry weight to wet weight values.

For microorganisms, no effects were seen in a 3-hour activated sludge respiration inhibition test at a concentration of 15 mg/l. A $PNEC_{microorganisms}$ for waste water treatment plants of $\geq$1.5 mg/l can be derived from this value using an assessment factor of 10.

Exposure

The substance is imported into the EU and is used as both a reactive flame retardant (where it is chemically bonded into the polymeric material), and additive flame retardant in plastics. The main uses as a reactive flame retardant are in epoxy and polycarbonate resins. The main use as an additive flame retardant is in acrylonitrile-butadiene-styrene (ABS) resins. In addition, tetrabromobisphenol-A is used as an intermediate in the production of other reactive and additive flame retardants.

The current total amount of TBBPA produced worldwide is estimated at 150,000 tonnes/year. TBBPA is produced by the bromination of bisphenol-A in the presence of a solvent. The production process is largely conducted in closed systems. TBBPA is produced in the USA, Israel and Japan. There is currently thought to be no production of TBBPA or its derivatives in the EU. In relation to TBBPA uses, occupational exposure to TBBPA can occur in a number of ways, for example, during the addition of TBBPA powder to mixes of polymer compounds, during the production of laminates for printed circuit boards, during recycling of computers and electrical equipment, during the assembly of printed circuit boards, during the recycling of plastic housings and to employees in offices containing electronic equipment.

Consumption of TBBPA in the EU was around 13,800 tonnes/year in the late 1990s, but there has been a decline in demand since then as product manufacture has shifted away from the use of this compound, and more recent figures are around 6,500-7,500 tonnes/year. TBBPA is used in a range of consumer goods as a flame retardant. However, since the free residual monomer is likely to be less than 1,000 ppm, consumer exposure to TBBPA is likely to be insignificant.

Emissions to the environment can occur both to the atmosphere (as vapour and as dust) and waste water. Sources of release include flame retardant production sites, epoxy and polycarbonate resin 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.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently of low priority for further work due to its low hazard profile.

Note: No human health hazard of concern has been identified in an assessment performed in the European Union in the context of the EU Existing Substances Regulation (793/93/EEC).

Environment: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for the environment (high toxicity to fish, aquatic invertebrates and soil and sediment organisms). Member countries are invited to perform an exposure assessment, and if necessary

a risk assessment for the environment.

NOTE: An EU risk assessment in the context of the Existing Substances Regulation has been conducted and is available. This indicates that a possible risk to surface water, sediment and soil may exist from the use of this substance.