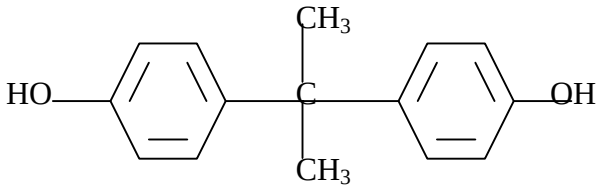
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	80-05-7
Chemical Name	Bisphenol-A (2,2-bis(4-hydroxylphenyl)propane)
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Occupational exposure to bisphenol A will be in the form of inhalation/ingestion of dust and by skin contact with the flakes, prills or powder. In consumers, the main route of exposure is orally, via polycarbonate and epoxy resin food contact applications. Very low exposures by ingestion and inhalation may arise from releases to the environment from production of bisphenol A, and its use in the manufacture and processing of epoxy resins, PVC, and thermal paper containing bisphenol A.

Data in the rat demonstrates that following oral administration absorption is rapid and extensive, although it is not possible to reliably quantify the extent of absorption. An *in vitro* dermal absorption study using human skin suggests that there is limited absorption, in the region of about 10% of the applied dose. On the basis of organ weight changes in a repeat inhalation study, it would be prudent to assume that absorption via the inhalation route can occur, but the data do not allow a quantitative estimation of absorption to be made. Extensive first pass metabolism occurs following absorption from the gastrointestinal tract with glucuronide conjugation being the major metabolic pathway. Hence distribution of unconjugated bisphenol A in likely to be limited. There is also evidence of enterohepatic circulation occurring. Elimination is mainly in the faeces with the urinary route being of secondary importance.

The key toxicological endpoints are eye and respiratory irritation, skin sensitisation, local effects of repeated inhalation exposure on the respiratory tract and effects on the liver of repeated systemic exposure and reproductive toxicity. Since bisphenol A has the potential to cause eye and respiratory tract irritation, peak exposures need to be controlled. As bisphenol A is at least capable of inducing skin responses in hypersensitive individuals, skin exposure also need to be controlled. For the observed liver effect (multinucleated giant hepatocytes), of uncertain relevance to humans, only a LOAEL of 120 mg/kg has been identified for males and a NOAEL of 650 mg/kg for females in a 2-year dietary study in mice. For reproductive toxicity, data was available from a two generation and multi-generation in the rat and a continuous breeding study in the mouse. Effects on fertility (reduction in litter size) were observed in both species at doses of >=500 mg/kg/day. For the rat it is not clear whether or not the finding could be a secondary

consequence of parental toxicity or a direct effect of bisphenol-A. Comparing the rat and mouse data similar toxicological profiles were observed for effects on fertility at approximately the same dose level. Consequently, it is considered that the NOAEL of 50 mg/kg/day identified in a rat multi-generation study is also likely to produce no adverse effects in mice for which there is only a LOAEL available.

Regarding other toxicological endpoints bisphenol A is of low acute toxicity (rodent oral LD_{50} values from 4000 to 5200 mg/kg, a rabbit dermal LD_{50} value *2230* mg/kg and a rat 6 hour LC_{50} value >170 mg/m3). Few details exist of the toxic signs observed or of target organs. Bisphenol-A is not a skin irritant, however, it is severely irritating to the eyes. There are no data from which to evaluate the potential to be a respiratory sensitiser. The aneugenic potential of bisphenol A seems to be limited to *in vitro* test systems. The relevance of the finding that it can produce rat hepatic DNA adduct spots in a postlabelling assay is not entirely clear. However, given the absence of positive results for gene mutation and clastogenicity in cultured mammalian cells, as well as in a guideline micronucleus test for clastogenicity *in vivo*, it seems unlikely at present that these will be of concern for human health. Considering all of the available genotoxicity data, and the absence of toxicologically significant tumour findings in animal carcinogenicity studies, it does not appear that bisphenol A has mutagenic potential *in vivo*. In a dietary study in rats and mice, tumour findings are not considered to be toxicologically significant and taking into account all of the available animal data the evidence suggests that bisphenol A does not have carcinogenic potential. No evidence that it is a developmental toxicant was observed in standard development studies in rats and mice. However, conflicting results have been reported between studies using low doses (in the microgram/kg range). Some studies report an adverse effect on male reproductive tract development in rats and mice. Further studies from other laboratories have not been able to replicate these data. Furthermore, in a rat multi-generation study, a decrease in pup body weight gain and delays in development were seen in all generations (F_1-F_3) at 500 mg/kg/day, albeit in the presence of maternal toxicity. Further information gathering is being undertaken to resolve the uncertainties surrounding potential effects at 'low doses' seen in controversial studies (delete this issue), however, in the interim, a provisional NOAEL of 50 mg/kg has been identified.

Environment

The environmental effects database meets the requirements of the SIDS data package. Aquatic toxicity data are reported for freshwater and marine fish, daphnia and algae. The available data cover 'conventional' adverse endpoints with significance at a population level (such as reproduction and mortality) and non-conventional responses potentially mediated by an endocrine mechanism, such as mechanistic endocrine responses. The available data suggest that endocrine responses may occur at lower concentrations.

The lowest values from acute studies with freshwater species are: 96-hour LC_{50} of 4.6 mg/l for fish (fathead minnow *Pimephales promelas*) (results for saltwater species are similar); 48-hour EC_{50} of10.2 mg/l for *Daphnia magna* (based on measured concentrations – a lower value of 3.9 mg/l is reported based on nominal concentrations, and a 96-hour LC_{50} of 1.1 mg/l is reported for the saltwater mysid shrimp *Mysidopsis bahia*); 96-hour EC_{50} (based on cell count) of 2.73 mg/l for algae (*Pseudokirchneriella subcapitata*) (a 96-hour EC_{50} (based on cell count) of 1.1 mg/l is reported for marine algae (*Skeletonema costatum*)).

Chronic studies are also reported for fish, daphnia and algae. The lowest NOEC value for a 'conventional' endpoint from chronic studies is that for egg hatchability in *P. promelas* from a full life cycle test, at 16 µg/l. The lowest values from chronic studies for invertebrates and algae are a 21-day NOEC >3.146 mg/l for *D. magna* and a 96-hour $EC_{10}$of 0.40 mg/l for *S. costatum*. Based upon the lowest NOEC value for fish a PNEC of 1.6 µg/l is derived using an assessment factor of 10. Although other effects have been reported at lower concentrations in *P. promelas* (LOEC of 1 µg/l for effects on spermatogenesis) and in aquatic snails (effects on egg production), weaknesses in the data indicates a need for further investigation, which is underway. No effects on larval growth, development or sexual differentiation were reported for the African clawed frog (*Xenopus laevis*) at nominal concentrations up to 0.5 mg/l in a 90-day flow-through study.

Toxicity data for soil-dwelling organisms are not available, but a $PNEC_{soil}$ of 23 g/kg wet weight can be derived from the aquatic PNEC using the equilibrium partitioning method for screening risk assessment purposes.

Exposure

About 700,000 tonnes of bisphenol-A are manufactured in Europe each year (based on data for 1999). It is primarily used in the production of polycarbonate and epoxy resins, and there are a number of minor uses including in the thermal paper and PVC industries. Polycarbonates are used in a range of applications including optical media, glazing, food containers and as polycarbonate blends in the electronics industry. Epoxy resins are used as protective coatings, structural composites, electrical laminates, electrical applications and adhesives. The main route of environmental exposure is from its use in the thermal paper and PVC industries.

Bisphenol A is a solid of low vapour pressure (5.3×10^{-9} kPa at 25°C), with a water solubility of ~300 mg/l at 20°C and a log octanol-water partition coefficient (log K_{OW}) of 3.4. Hydrolysis and photolysis in water are negligible but it is considered readily biodegradable, possibly with a short period of adaptation. The log K_{OW} value implies a low to moderate bioaccumulation potential in aquatic species and moderate adsorption to soils and sediment. The substance chiefly partitions to water and it may be relatively mobile in the environment.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and for non-SIDS endpoints. However, the chemical is a candidate for further work as follows:

1. Further work needs to be done on the effects on aquatic snails and spermatogenesis in fish to clarify the levels at which effects may occur, and to consider the significance of these effects. This is a post-SIDS requirement.

2. No toxicity data are available for soil organisms. These data could be generated as a post-SIDS activity (a concern has been identified for the terrestrial compartment in the European risk assessment for a number of uses). At present, it is unclear which test(s) should be performed, although chronic tests based on reproduction parameters appear to be the more sensitive for aquatic organisms.

3. If indicated by national or regional Bisphenol A usage, information gathering on exposure may need to be considered for the water compartment and, if appropriate a risk assessment undertaken. Based on an existing regional risk assessment for Europe, using a PNEC of 1.6 microgram/l and worst-case estimated emissions, a need to limit environmental risks has been identified only for Bisphenol A use in PVC and for thermal paper recycling. If there is confirmation of effects at lower concentrations, this would lead to conclusions of risks for other uses.

4. The uncertainties surrounding potential effects at low doses (delete effects) of bisphenol A on mammalian reproductive development seen in some studies needs further consideration. A steering committee is set up to further develop details of the requirement of further research. This is a post-SIDS requirement.