SIDS INITIAL ASSESSMENT PROFILE

CAS No.	101-72-4
Chemical Name	N-Isopropyl-N'-phenyl-*p*-phenylenediamine (IPPD)
Structural Formula	$CH_3CH(CH_3)NH\text{-}C_6H_4\text{-}NH\text{-}C_6H_5$

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

The health and environmental effects database meets the requirements for the SIDS data package.

Human Health

In a poorly reported human study, there is some evidence for uptake via the skin and bioaccumulation of IPPD. However, due to the poor quality of the study, no conclusions could be drawn on the extent of absorption. A single briefly reported animal toxicokinetic study indicated that IPPD does not readily penetrate unbroken skin, although no further information is available. IPPD is absorbed from the gastrointestinal tract, although no quantitative information is available on the extent of absorption.

There is no information on the effects of IPPD following acute inhalation, oral or dermal exposure in humans. However, IPPD is of moderate toxicity by the oral route in rats (typical LD_{50} = 800 mg/kg), and of very low toxicity by the dermal route in rabbits. No information is available regarding acute inhalation toxicity in animals. Evidence from human and animal studies suggests that IPPD is not a skin irritant. Animal studies also suggest that IPPD is not an eye irritant. Animal evidence demonstrates that IPPD is a skin sensitiser, and human evidence from volunteer studies and case-reports is consistent with this. There are no data available on respiratory sensitisation. No information was available concerning repeat exposure of humans to IPPD. No useful animal inhalation or dermal data are available. There were no findings of any toxicological significance in a 90-day oral rat study at thee highest dose, 57 mg/kg/day, and this may be regarded as a NOAEL. In a 28-day study a NOAEL of 223 mg/kg/day, the highest dose administered, was identified.

In vitro mammalian cell mutagenicity assays demonstrate IPPD has a potential to induce chromosome aberrations in the absence or presence of exogenous metabolic activation. The potential for direct acting genotoxicity was also demonstrated in a study of sister chromatid exchange. Negative results have been obtained in a number of *in vitro* genotoxicity studies (Ames, mammalian cell gene mutation, and unscheduled DNA synthesis). No carcinogenicity data are currently available. There were no fertility studies available, but in a 90-day repeat dose study there was no histological evidence of adverse effects in the reproductive organs of male and female rats exposed at the top dose of 57 mg/kg/day. In the only developmental toxicity study available, skeletal changes consistent with ossification retardation were observed at doses that did not produce maternal toxicity. NOAELs of 125 mg/kg/day and 62.5 mg/kg/day were identified for mothers and offspring, respectively. The relevance of this finding for human health hazard identification is uncertain.

Environment

Acute toxicity data are available for four fish species, three showing similar sensitivity. The lowest 96-hour LC_{50} is 0.34 mg/l for Rainbow trout (*Oncorhynchus mykiss*). A 14-day LC_{50} of 0.09 mg/l was obtained for fathead minnow (*Pimephales promelas*), which may indicate that IPPD (or its breakdown products) has cumulative toxicity. Aquatic invertebrates appear to be less sensitive, the 48-hour EC_{50} for *Daphnia magna* being 1.1 mg/l (NOEC of 0.56 mg/l). A 96-hour EC_{50} of 0.4 mg/l is reported for green algae. A PNEC of 0.34 µg/L can be derived for the aquatic environment using an assessment factor of 1000 with the acute toxicity result for rainbow trout.

IPPD hydrolyses rapidly (over timescales similar to those of the static tests), so some of the toxic effects may be due to hydrolysis products. One of the fish studies used flow-through conditions, with similar toxicity at 96 hours to that shown in the static tests. It therefore appears that IPPD is of similar toxicity to the hydrolysis products.

Exposure

Around 10,000-15,000 tonnes of IPPD are produced worldwide each year. It is used as an anti-degradant in rubber, mainly for car tyres. Potential release to the environment can occur from manufacture, the production of rubber for tyres, tyres in use and on disposal. Exposure to humans is expected to occur only via the workplace.

IPPD is a solid of low water solubility (~15 mg/l) and an octanol-water partition coefficient (log K_{ow}) of 3.9. Its atmospheric half-life is estimated to be between 23 and 54 minutes. It hydrolyses in water with half-lives between 2 and 11 hours depending on the water source. Biodegradation studies show rapid primary degradation but low ultimate degradation, indicating that the breakdown products may be persistent. IPPD has a potential to bioaccumulate in aquatic organisms (based on its log K_{ow}). It can be predicted that the substance will remain in water or soil once it reaches there, although degradation is expected to be rapid. Most of the release to air is also rapidly degraded but that which is not is quickly removed to water and soil.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is a candidate for further work post-SIDS as follows:

1. There is some uncertainty about which chemical species produce the toxic effects on aquatic organisms. Whilst the SIDS endpoints are fulfilled, toxic effects are apparent at low concentrations and so further investigation of the nature and properties of breakdown products could be performed.

2. The hazards to the aquatic environment and to human health due to skin sensitisation are such that member states are invited to investigate the relevance of exposure conditions in their country. In this context, further information on the persistence of IPPD in tyres and the quantities leached during the lifetime of the tyre would be useful for an environmental assessment.

3. An *in vivo* bone marrow study (micronucleus) using parenteral administration would be useful to investigate the potential observed *in vitro* for direct acting clastogenicity.