SIDS INITIAL ASSESSMENT PROFILE

CAS No.	84852-15-3 and 25154-52-3
Chemical Name	Phenol, 4-nonyl-, branched and Nonylphenol
Structural Formula	$HO\text{-}C_6H_4\text{-}C_9H_{19}$ where C_6H_4 is a 1,4-substituted benzene ring

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Nonylphenol is rapidly and probably extensively absorbed from the gastrointestinal tract and undergoes extensive first pass metabolism. The major metabolic pathways are likely to involve glucuronide and sulphate conjugation. Because of first pass metabolism, the bioavailability of unconjugated nonylphenol is probably limited following oral exposure, at no more than 10-20% of the administered dose. Nonylphenol is distributed widely throughout the body, with the highest concentration in fat. The major routes of excretion are via the faeces and urine. Regarding bioaccumulation, there are insufficient data to allow a conclusion to be drawn on whether or not nonylphenol has this potential. On the basis of the oral absorption data and high partition coefficient, it would be prudent to assume that significant absorption via inhalation can occur. Furthermore, because first pass metabolism will not take place following exposure by the inhalation route, the systemic bioavailability is likely to be substantially greater than is associated with the oral route. *In vitro* data indicate that nonylphenol is poorly absorbed across skin, although some limited skin penetration, especially to the stratum corneum, can occur.

At sufficient doses, toxicity may occur following a single ingestion or contact to the skin. In studies in animals, erosion of the stomach mucosa is sometimes seen following the administration of a lethal dose. For acute toxicity, rat oral LD_{50} values are in the range 1200 to 2400 mg/kg and via the dermal route a rabbit LD_{50} of about 2000 mg/kg is available. No data are available on the acute inhalation toxicity, although the corrosive nature of nonylphenol suggests that acute toxicity could be elicited following exposure by this route. Liquid nonylphenol can be corrosive to the skin (full thickness necrosis and ulceration within 24 hours of a 1 or 4 hour exposure) although its potency might vary according to source and exact composition. The liquid is also a severe eye irritant (irreversible effects within 7 or 21 days observation periods). Exposure to the saturated vapour (calculated to be 400 ppm) elicited mild sensory irritation of the respiratory tract in mice, but no reaction was elicited at a nominal concentration of 30 ppm. The results of several guinea pig maximisation tests indicate that nonylphenol is not skin sensitiser. It can be predicted from its low chemical reactivity that nonylphenol is unlikely to be a respiratory allergen.

In addition to 28-day and 90-day studies, information on repeated dose toxicity was available from a multigeneration study in the rat involving oral exposure for up to 20 weeks. A lowest adverse effect level (LOAEL) for repeated dose of 15 mg/kg/day was identified, based on histopathological changes in the kidneys (tubular degeneration or dilatation), although such changes were not apparent at this dose level in a 90-day rat study. At higher dose levels the liver may also be a target organ; minor histopathological changes in the liver (vacuolation in the periportal hepatocytes or occasional individual cell necrosis) were seen at doses of 140 mg/kg/day and above in some studies. No repeated-dose studies involving dermal or inhalation exposure have been conducted. The oral toxicity of

nonylphenol appears to be enhanced when dosed by gavage, with mortalities being reported at dose levels of 100 mg/kg/day.

Concerning mutagenicity, nonylphenol tested negative in two bacterial assays and an *in vitro* mammalian cell gene mutation assay. An *in vivo* micronucleus test, conducted using the intraperitoneal route, was negative. A second *in vivo* micronucleus test, which used the oral route, was also negative, although there were methodological weaknesses in this study. These results show that nonylphenol is not mutagenic.

Carcinogenicity has not been directly studied. On the basis of the information currently available concerns for cancer caused by a genotoxic or non-genotoxic mechanisms are low. As to reproductive and developmental toxicity, no human data are available. The observations of oestrogenic activity in the *in vitro* and *in vivo* screening tests, minor perturbations in the reproductive system of offspring in the multigeneration study, and testicular changes in gavage studies collectively raise concerns for reproductive toxicity, possibly mediated through action on the oestrogen receptor. The effects on reproduction related parameters in the multi generation study were marginal and there was no evidence of functional changes in reproduction; furthermore any changes that were seen occurred at exposure levels in excess of the LOAEL for repeated dose toxicity (LOAEL for renal toxicity is 15 mg/kg/day, no observed adverse effect level for reproductive changes is 15 mg/kg/day). Evidence of testicular toxicity was reported in two repeated exposure studies designed to specifically investigate the effects on this organ, but only at doses which also caused mortality. No evidence of testicular toxicity was seen in standard repeated dose studies involving dietary administration. Development was not affected in a standard rat oral gavage development toxicity study.

Environment

The environmental effects database meets the requirements for the SIDS data package. Both short- and long-term aquatic toxicity data are available for freshwater fish, invertebrates and algae. In acute studies, the lowest valid values are as follows: for fish a 96-hour LC_{50} of 0.128 mg/l (*Pimephales promelas*); for invertebrates a 96-hour EC_{50} of 0.0207 mg/l (*Hyalella azteca*); and for algae a 72-hour EC_{50} (biomass) of 0.0563 mg/l (*Scenedesmus subspicatus*). Comparable toxicity is observed with saltwater species (the alga *Skeletonema costatum* is slightly more sensitive than the freshwater species with a 96-hour EC_{50} (cell growth) of 0.027 mg/l, compared to a 72-hour EC_{50} (growth rate) of 0.323 mg/l for *Scenedesmus subspicatus*).

In long-term/chronic studies, the lowest valid values are as follows: for fish a 33-day $NOEC_{survival}$ of 0.0074 mg/l (*Pimephales promelas*); for invertebrates a 21-day $NOEC_{surviving\ offspring}$ of 0.024 mg/l (*Daphnia magna*); and for algae a 72-hour EC_{10} (biomass) of 0.0033 mg/l (*Scenedesmus subspicatus*). A 28-day $NOEC_{length}$ of 0.0039 mg/l was also obtained for the saltwater invertebrate *Mysidopsis bahia*.

As long-term NOECs from at least three species representing three trophic levels are available, an assessment factor of 10 may be applied to the chronic NOEC for algae to give an aquatic PNEC of 0.33 µg/l (as in the EU risk assessment; different levels have been derived by other authorities). A mesocosm study has been performed, giving a 20-day NOEC of 0.005 mg/l. Due to possible issues with the test design, this study is taken as supportive of the PNEC, but cannot be used as the sole basis for deriving a PNEC to protect the aquatic compartment. Concentrations of nonylphenol at which oestrogenic effects are observed appear to be higher than those producing other effects. The calculated PNEC should therefore be protective for oestrogenic effects in fish as well. A PNEC for the sediment compartment of 0.039 mg/kg can be derived from the aquatic PNEC assuming equilibrium partitioning.

For the terrestrial compartment long-term data are available for micro-organisms, plants and invertebrates. The most sensitive species group appears to be the terrestrial invertebrates with a 21-day EC_{50} (Reproduction) of 13.7 mg/kg and a 21-day EC_{10} (Reproduction) of 3.44 mg/kg reported for earthworms (*Apporec-todea calignosa*). As long-term tests are available for species from three trophic levels an assessment factor of 10 can be used on the NOEC for the species showing the most sensitive end point (in accordance with EU technical guidance), giving a $PNEC_{soil}$ of 0.3 mg/kg. A $PNEC_{oral}$ of 10 mg/kg food for secondary poisoning can also be derived from the mammalian NOAEL of 15 mg/kg body weight for reproductive effects (more details below).

Exposure

Total European Union (EU) production was 73,500 tonnes in 1997 (consumption was estimated at 78,500 tonnes). Nonylphenolis used as a chemical intermediate in the production of nonylphenol ethoxylates, plastics/resins and phenolic oximes, and as a processing aid for polymers.

It is a viscous yellow liquid with a vapour pressure of ~0.3 Pa at 25°C, a water solubility of ~6 mg/l at 20°C and pH 7, and a log octanol-water partition coefficient (log K_{OW}) of 4.48. In general, hydrolysis and photolysis in water are negligible but nonylphenol is considered inherently biodegradable. –In aquatic species, bioconcentration factors (BCFs) (on a fresh weight basis) are reported up to 1,300 in fish. Releases to the aquatic compartment arise mainly from the manufacture and use of the ethoxylates (due to degradation). Nonylphenol adsorbs strongly to soils, sludges and sediments.

Exposure may occur in workers during breaches of closed systems and during spraying of formulations produced with nonylphenol. Consumers may be exposed directly via ingestion and/or contact with very low levels of residual unreacted nonyl phenol in substances used to make pesticide products, cosmetics, pharmaceuticals (being phased out in EU), hair dyes and food (via migration from packaging polymers and papers). Indirect exposure via the environment may occur via oral intake of food and, to a lesser extent, drinking water.

NATURE OF FURTHER WORK RECOMMENDED

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

- National or regional exposure information gathering and risk assessment may need to be considered, especially for nonylphenol ethoxylate use as an indirect source of nonylphenol in the environment (based on an existing regional risk assessment for Europe, where a need to limit risks has been identified for a number of uses for both human health and the environment). Note: nonylphenol ethoxylates are being assessed separately by the US under the OECD HPV programme.

- No toxicity data are available for sediment organisms. These data could be generated as a post-SIDS activity if a concern for the sediment compartment is identified (as in the European risk assessment). In addition, various workers continue to generate data for this substance (especially in the field of endocrine disruption), and new data may need to be reviewed on a periodic basis.