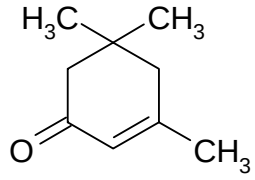
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-59-1
Chemical Name	3,5,5-trimethylcyclohex-2-enone (Isophorone)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Upon oral and inhalative administration, isophorone is well absorbed and rapidly distributed through the body of rats and rabbits. While part of the absorbed isophorone is excreted unchanged via urine and exhaled air, metabolites are mainly excreted as glucuronides. The tendency of isophorone to bioaccumulate is very low, since within 24 hours after administration more than 93% of orally administred isophorone was excreted by rats.

The acute toxicity in laboratory animals is low to moderate (oral LD50 $\geq$ 1500 mg/kg bw; dermal LD50 $\geq$ 1200 mg/kg bw; inhalative LC50 = 7000 mg/m^3). Isophorone is an eye irritant and a respiratory irritant but does not irritate the skin. It is not sensitizing in animal studies.

In subchronic studies, oral administration of high doses of isophorone (NOAEL (male rat, 90 days) = 102.5 mg/kg bw/day, NOAEL (female rat, 13 weeks) = 500 mg/kg bw/day; NOAEL (male mouse, 16 days) = 500 mg/kg bw/day, NOAEL (female mouse, 16 days) = 125 mg/kg bw/day; NOAEL (dog, 90 days) $\geq$ 150 mg/kg bw/day) caused no significant toxic effects (all NOAELs are based on slight (< 14%) reductions in body weight gain). After inhalational administration nose and eye irritation and blood and liver changes were observed (NOAEL (rat, 28 days) < 208 mg/m^3).

Although in one mouse lymphoma assay a positive result was observed, the majority of *in vitro* genotoxicity studies revealed clearly negative results. Together with the negative *in vivo* results and the negative DNA binding assay, the overall conclusion is that isophorone is not mutagenic.

There was some evidence of carcinogenicity of isophorone in male rats (kidney tumors, preputial gland carcinomas). The kidney tumors can be attributed to an α2u-globulin associated mechanism. The observed nephropathy in male rats is therefore irrelevant to other species. As the preputium is only investigated histopathologically when gross lesions are found, neither true tumor incidences from this study nor from historical controls are available. Therefore, the higher incidence of preputial gland tumors in high dose male rats cannot be put into perspective. There was equivocal evidence of carcinogenicity for male mice (liver tumors, mesenchymal tumors of the integumentary system). There was no evidence of carcinogenicity of isophorone in female rats and mice.

There is no evidence indicating that isophorone interferes adversely with the reproduction. No changes were observed in pregnancy rates, litter sizes, pups abnormalities or in histopathological examinations of the reproduction organs after long-term studies. In an inhalation teratogenicity study, the NOAEL for maternal toxicity was 289 mg/m³ (based on a reduction in body weight gain of less than 7%).

Isophorone was neither embryotoxic nor teratogenic up to the highest test concentration of 664 mg/m³ isophorone.

Environment

Isophorone has a melting point of –8.1 °C, a solubility in water of 14.5 g/l at 20 °C, and a vapour pressure of 40 Pa at 20 °C. The measured log Kow is 1.67.

According to a Mackay Level I model calculation the main target compartments for isophorone will be the hydrosphere (87.6 %) and atmosphere (11.7 %). The calculated Henrys' law constant of 0.38 $Pa.m^3/mol$ indicates evaporation from surface waters within several days. With a calculated Koc of 77 l/kg the sorption potential to soil or sediment organic matter is expected to be low.

In the atmosphere, isophorone is rapidly removed by reaction with ozone with an estimated half-life of 23 minutes. The calculated half-life for photodegradation by reaction with OH radicals is 16 h. Isophorone can be considered to be readily biodegradable. In surface waters, the main removal mechanisms are expected to be biodegradation and volatilization. Photolytical degradation in surface waters is expected to be of minor importance. Furthermore, hydrolytic degradation is not to be expected. Experimentally determined BCF values below 10 l/kg indicate a low bioaccumulation potential.

The lowest valid acute test results of aquatic testing determined for fish, daphnia, algae and bacteria were as following:

Cyprinodon variegatus:	96h-LC50 = 140 mg/l
Daphnia magna:	48h-EC50 = 120 mg/l
Scenedesmus subspicatus:	72h-EbC50 = 475 mg/l; 72h-EbC10 = 64 mg/l
Activated sludge:	3h-EC50 = 100 mg/l

In 3 fish early-life-stage tests with *Pimephales promelas* NOEC-values of 4.2 mg/l (32 d), 15.6 mg/l (32 d) and 11 mg/l (35 d) were obtained for the endpoint growth (measured as weight). The geometric mean of these 3 NOEC is 8.9 mg/l. Based on this value, a PNEC of 0.178 mg/l is calculated using an assessment factor of 50.

For the terrestrial compartment, a PNEC could not be calculated. Isophorone spiked into soils is expected to be rapidly removed by biodegradation, thus the test substance concentration will be unstable during the test period.

Exposure

The production volume of Isophorone is approx. 100,000 t/y world wide. Isophorone is widely used as a solvent for a number of synthetic resins and polymers, as well as in special application paints and printing inks. It is a chemical intermediate and an important solvent in certain herbicide formulations.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical is currently of low priority for further work based on its low hazard potential. The substance is an eye irritant. Although this does not warrant further work, this property should nevertheless be noted by chemical safety professionals and users.