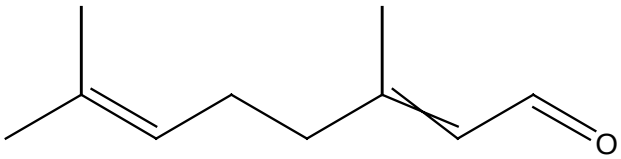
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	5392-40-5
Chemical Name	Citral
Structural Formula	 $C_{10}H_{16}O$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Citral was rapidly absorbed from the gastro-intestinal tract. Much of an applied dermal dose was lost due to its extreme volatility, but the citral remaining on the skin was fairly well absorbed. Citral was rapidly metabolized and excreted as metabolites. Urine was the major route of elimination.

Acute toxicity of this chemical is low in rodents because the oral or dermal LD_{50} values were more than 1000 mg/kg. This chemical is irritating to skin and not irritating to eyes in rabbits. There is some evidence that this chemical is a human skin sensitizer.

Several repeated dose oral studies show no adverse effect of citral at less than 1,000 mg/kg/day exposure and some histological changes in the nasal cavity or forestomach, the first exposure sites, probably due to irritation, at more than 1,000 mg/kg/day. Male and female F344/N rats received microencapsulated citral in feed at concentrations of 0, 0.63, 1.25, 2.5, 5 and 10% (resultant doses: 0, 142, 285, 570, 1,140 and 2,280 mg/kg/day) for 14 days. Minimal to mild hyperplasia and/or squamous metaplasia of the respiratory epithelium was observed in nasal cavity without inflammatory response at 1,140 and 2,280 mg/kg/day of both sexes. The NOAEL was established at 570 mg/kg/day. In an OECD preliminary reproduction toxicity screening test [TG 421], citral was administered to Crj:CD (SD) rats by gavage at doses of 0, 40, 200 and 1,000 mg/kg/day in males for 46 days and in females for 39-50 days including before and through mating and gestation periods and until day 3 of lactation. Squamous hyperplasia, ulcer and granulation in lamina propria were observed in the forestomach at 1,000 mg/kg/day of both sexes. Therefore, the NOAEL for repeated dose toxicity was 200 mg/kg/day for both sexes.

As for reproductive toxicity in the above preliminary reproductive study, no effects were detected in reproductive ability, organ weights or histopathology of the reproductive organs of both sexes, and delivery or maternal behavior. However, body weights of male and female pups were reduced in the 1000 mg/kg group. Therefore, an oral NOAEL for developmental toxicity was 200 mg/kg/day. In a teratogenicity study, SD pregnant rats were exposed to citral by inhalation for 6 hr/day on gestation days 6-15 at mean concentration of 0, 10 or 34 ppm as vapour, or 68 ppm as an aerosol/vapour mixture. Even in the presence of the maternal effects, no significant teratogenicity was noted at 68 ppm. An inhalation NOAEL of teratogenicity was established at 68 ppm (423 mg/m^3).

Seven bacterial reverse mutation studies indicate negative results with and without metabolic activation. As for non-

bacterial *in vitro* study, two chromosomal aberration results in Chinese hamster cells are negative however one positive result in sister chromatid exchange is given in the same cells. Additionally, two *in vivo* micronucleus tests in rodents indicate negative results. Based on the above information, the genotoxic potential of citral can be considered to be negative.

A NTP study shows that there was no evidence of carcinogenic activity in male/female rats and male mice but some evidence of malignant lymphoma in female mice (up to 4,000 ppm in feed in rats and up to 2,000 ppm in feed in mice).

Dermal application of citral induces prostate hyperplasia with low severity only in some strains of rats. However, the NTP oral carcinogenicity studies in rats and mice found no evidence of lesions (neoplastic or non-neoplastic) in any male reproductive organ, including the prostate. The health significance of the effects seen in the dermal studies in rats is uncertain due to dramatic strain differences and it is noted that the work has primarily been performed in a single laboratory.

Environment

Citral is readily biodegradable (92%, BOD) and its bioaccumulation potential seems to be low based on Log P_{ow} (2.8-3.0). This chemical has been tested in a limited number of aquatic species. For alga (*Selenastrum capricornutum*), 72 h EC_{50} (biomass) is 5 mg/L and 72 h NOEC (biomass) is 3.1 mg/L. For *Daphnia*, acute toxicity of 10 mg/l (24hEC50, immobilization) and 7 mg (48h-EC50, immobilization), and chronic values of 1.0 mg/L (21 d NOEC, reproduction) have been reported. Only the acute toxicity value has been reported for fish, which is 4.1 mg/L (96 h LC_{50}) for *Oryzias latipes.* A PNEC of 0.01 mg/L for the aquatic organisms was calculated from the chronic toxicity value of *Daphnia* using an assessment factor of 100.

Exposure

Production volume of citral in Japan was 1,200 tonnes in 1990-1999. This chemical is used as a food flavoring and as an intermediate for perfume and vitamin A production. This chemical is a mixture of two geometric isomers, geranial (trans confirmation, approx. 55-70%) and neral (cis confirmation, 35-45%). It is rapidly hydrolyzed at pH 4 (half-life time: Neral: 9.54 days, Geranial: 9.81days) and at pH 9 (half-life time: Neral: 30.1 days, Geranial: 22.8 days), but slowly hydrolyzed at pH 7 (half-life time: Neral: 230 days, Geranial: 106 days). This chemical is classified as "readily biodegradable". A generic fugacity model (Mackey level III) shows that if citral is released to one of the compartments of air, water and soil, it is unlikely to distribute into other compartments. According to a Japanese manufacturer, 1,200 kg/year (estimated) of citral are treated in waste water treatment plants and then released with 5,000 t/year of effluent into a river (flow rate 1.6 $x10^{11}$ t/year). The local predicted environmental concentration (PEC_{local}) is $7.5x10^{-7}$ mg/l, employing a calculation model. The highest exposure to the general population via the environment would be expected through drinking water processed from surface water. The concentration of citral in drinking water is assumed to be less than 7.5 $x10^{-7}$ mg/l. Occupational exposures at production sites may occur by the inhalation and dermal route. The estimated human exposure of a worker who operates the drum filler and does sampling assuming without protective equipment is 0.34 mg/kg/day. However, protective measures i.e. safety glasses and gloves are used during these processes. Therefore, the actual exposure to workers is lower than the estimated value.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.