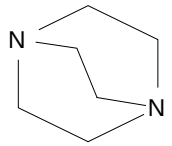
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	280-57-9
Chemical Name	1,4-Diazabicyclo[2.2.2]octane
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Specific information on the metabolism of 1,4-diazabicyclo[2.2.2]octane is not available. Since tertiary amines are poor substrates for monoamine oxidase, 1,4-diazabicyclo[2.2.2]octane might presumably be metabolized via N-oxidation by a P450 monoxygenase, or via N-oxygenation by a flavin-containing monoxygenase.

1,4-Diazabicyclo[2.2.2]octane has an acute oral LD_{50} range of 700 - 2260 mg/kg bw in rats, while the dermal LD_{50} in rabbits is >2000 mg/kg bw. The acute inhalation LC_{50} in rats is >20.2 mg/L nominal concentration (20% solution) (1 hour) or greater than the saturated vapor concentration (8 hour). In oral studies, at non-lethal doses transient depression and poor grooming were observed. At lethal doses, severe depression and ataxia rapidly progressed to coma and death within a few hours. In the dermal studies, severe erythema which disappeared within a few days was the only finding of note. In the inhalation studies, mild transient irritation of the eyes and mucous membranes and slight depression were the only notable findings. Pharmacologic effects particularly on blood pressure have been observed in cats and dogs when 1,4-diazabicyclo[2.2.2]octane is administered intravenously.

Skin and eye irritation studies in rabbits indicate that 1,4-diazabicyclo[2.2.2]octane is moderately irritating to the skin and is severely irritating to the eye. 1,4-diazabicyclo[2.2.2]octane is not a guinea pig skin sensitizer. In humans, glaucopsia (blue haze or halovision) has been reported at some foam manufacturing facilities and has been attributed to the presence of high concentrations of tertiary amines in the air. When sampling has been performed at properly ventilated foam manufacturing facilities, 1,4-diazabicyclo[2.2.2]octane concentrations are typically 1 ppm or less and no glaucopsia has been reported.

Rats were exposed via inhalation to aerosolized 1,4-diazabicyclo[2.2.2]octane 6 hours/day, 5 days/week for four weeks (20 exposures) at nominal concentrations of 0, 0.0058, 0.063 and 0.62 mg/L (analytical concentrations were 0, <0.011, 0.06 and 0.41 mg/L/6h/day). The low dose was below the analytical limit of detection (0.011 mg/L). The control animals were exposed to the vehicle (distilled water) only. One female in the high dose group died on day 5. The high-dose animals exhibited necrotic dermatitis of the ears, nose and eyes. Food consumption and body weight gain were decreased in the high-dose group. Histopathology revealed moderate chronic laryngitis in the mid- and high-dose groups. The female that died had severe acute necrotizing laryngitis. No compound-related effects were seen at the lowest dose level. Absolute and relative testes weights and relative adrenal weights (males) were statistically significantly increased at study termination; however, microscopic examination of these organs did not reveal any treatment-related effects. Since the lowest dose level could not be measured analytically, a NOAEC cannot

be ascertained. However, the LOAEC for this study was 0.06 mg/L/6h/day and is based on local toxicity at the site of contact, namely, the upper respiratory tract.

1,4-Diazabicyclo[2.2.2]octane is not mutagenic in bacteria and was not clastogenic in an *in vivo* mouse micronucleus study.

In a combined repeated-dose/reproductive/developmental toxicity screening test, rats were exposed orally to 1,4-diazabicyclo[2.2.2]octane at dose levels of 0, 100, 300 and 1000 mg/kg bw/day for 28 days. Dosing solutions were administered by gavage at a dose volume of 5 ml/kg. The control group received the vehicle (deionized water) only. Oral administration of 1,4-diazabicyclo[2.2.2]octane resulted in parental (F_0) systemic toxicity in both males and females at a dose level of 1000 mg/kg bw/day. This was evidenced by changes in clinical condition of the animals, reduced body weight and food consumption, reduced motor activity (females only), increased serum alkaline phosphatase concentrations (females only), increased liver weights (females only) and microscopic changes (inflammatory and/or proliferative lesions) in the kidneys and/or urinary bladder. With the exception of lesions in the kidneys and urinary bladder of a single 1000 mg/kg bw/day group female, none of the above findings persisted to the end of the 14-day recovery period. F_0 systemic toxicity in the 300-mg/kg bw/day group was limited to chronic inflammation of the kidneys in the males. There were no indications of F_0 systemic toxicity in the 100 mg/kg bw/day group males and females.
Mating and fertility indices were not affected by 1,4-diazabicyclo[2.2.2]octane administration. Reproductive and F_1 neonatal toxicity were exhibited at 1000 mg/kg bw/day by increased resorptions, decreased live litter size, decreased postnatal pup survival and decreased pup body weights. No indications of neonatal toxicity were observed at 100 and 300 mg/kg bw/day. Based on the data obtained, the NOAELs (no-observed-adverse-effect-level) for F_0 reproductive toxicity and F_1 neonatal toxicity were 300 mg/kg bw/day. The NOAEL for F_0 male and female systemic toxicity were 100 and 300 mg/kg bw/day, respectively.

Environment

1,4-Diazabicyclo[2.2.2]octane is a hygroscopic white crystalline solid with a melting point of 158°C, boiling point of 174°C, and vapor pressure 0.6 to 0.68 hPa at 20°C. 1,4-Diazabicyclo[2.2.2]octane has a water solubility of 610 g/L, a calculated soil K_{oc} of 95, and its log K_{ow} ranges from –1.13 to –0.49.

Using a hydroxyl rate constant of $76*10^{-12}$ cm^3/molecule.sec, the calculated half-life for indirect photolysis (reaction with hydroxyl radicals) of 1,4-diazabicyclo-[2.2.2]octane in air is 1.7 hours. Following equal releases to air, water and soil, the EPIWIN EQC Level III model predicts 1,4-diazabicyclo[2.2.2]octane to distribute in the environment to the aqueous (55.6%) and soil (43.6%) compartments. In water, hydrolysis and photodegradation are not expected to occur. 1,4-Diazabicyclo[2.2.2]octane is not readily biodegradable. Based on a log K_{ow} of -0.49, 1,4-diaza-bicyclo[2.2.2]octane has a calculated BCF of 3.2. A bioconcentration study conducted in carp determined the BCF of 1,4-diazabicyclo[2.2.2]octane to be < 13. Therefore, this chemical is not likely to bioaccumulate.

1,4-Diazabicyclo[2.2.2]octane produced EC/LC_{50} values of >100 mg/L in short-term tests with fish, daphnids, and algae. The following aquatic effect /no effect concentrations are available:
Fish [Cyprinus carpio] $LC_{\mathbf{0}}$ (96 hr) = 100 mg/L (96-h LC_{50} >100 mg/L)
Invertebrates [Daphnia magna] $EC_{\mathbf{0}}$ (48 hr) = 92 mg/L (48-h EC_{50} >92 mg/L)
Algae [Selenastrum capricornutum (new name: *Pseudokirchneriella subcapitata*)] EC_{50} (72 hr) = 110 mg/L (biomass); EC_{50} (0-72 hr) = 180 mg/L (growth rate)

Exposure

1,4-Diazabicyclo[2.2.2]octane is used primarily as a catalyst in the production of polyurethane foam. Approximately 90% of the 1,4-diazabicyclo[2.2.2]octane produced is used for this purpose. 1,4-Diazabicyclo[2.2.2]octane is also used as a chemical intermediate and as an anti-fade reagent. The global market for 1,4-diazabicyclo[2.2.2]octane in 2004 was in the range of 1000 to 5000 tonnes.

Under normal conditions and following standard manufacturing practices, there are no air emissions or aqueous waste streams associated with the manufacture of 1,4-diazabicyclo[2.2.2]octane. Low levels of air emissions may occur as a result of spills and cleaning operations. Small amounts of 1,4-diazabicyclo[2.2.2]octane from spills and cleaning operations may be present in the discharge to the wastewater treatment plant.

Occupational exposure may occur via inhalation and skin contact during polyurethane foam production. 1,4-Diazabicyclo[2.2.2]octane is not consumed in this reaction. Much of the catalyst is trapped inside the cells of the foam. 1,4-Diazabicyclo[2.2.2]octane vapors are then released during certain foam production operations, such as, the foam crushing operation; foam removal from the mold; and during the finishing, trim and repair operations. Vapors are removed from the work area through process ventilation or through general exhaust ventilation. In humans, glaucopsia (blue haze or halovision) has been reported at some foam manufacturing facilities and has been attributed to the presence of high concentrations of tertiary amines in the air. When sampling has been performed at properly ventilated foam manufacturing facilities, 1,4-diazabicyclo[2.2.2]octane concentrations are typically 1 ppm or less and no glaucopsia has been reported. Currently no occupational exposure limit exists for 1,4-diaza-bicyclo[2.2.2]octane.

Even though polyurethane foam is used in a wide variety of consumer products, the 1,4-Diazabicyclo[2.2.2]octane that is remaining in the foam after the crushing process appears to be strongly bound into the foam. Attempts to remove 1,4-Diazabicyclo[2.2.2]octane from foam by heating or solvent extraction have not been successful. Only very polar solvents, such as methanol, are effective. Data are not available for exposure to consumers. However, based on the noted difficulty in removing it from foam, consumer exposure to 1,4-Diazabicyclo[2.2.2]octane is expected to be minimal.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: This chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (skin, eye, and upper respiratory tract irritation, and developmental effects in rats at high doses). Based on data presented by the Sponsor country (relating to production by two producers in two countries which account for an unknown fraction of the global production and relating to the use pattern in two OECD countries), exposure to humans is anticipated to be low. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: This chemical is currently of low priority for further work because of its low hazard profile.