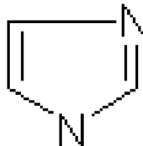


SIDS INITIAL ASSESSMENT PROFILE

CAS No.	288-32-4
Chemical Name	Imidazole
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Imidazole is readily absorbed and excreted in humans and in test animals after oral and rectal administration. Peak plasma levels are reached within 15 to 30 minutes in rats and within approx. 3 hours in humans. Elimination half-life in humans is approx. 2 to 3 hours. Therefore a potential for bioaccumulation is unlikely. Induction of microsomal P450 enzyme in the liver cells of rats and rabbits is restricted to certain isoenzymes such as 7-ethoxycoumarin-O-deethylase and isoenzyme 3a. However, no such induction was seen in the Syrian golden hamster.

Imidazole is of moderate oral toxicity in a scientifically valid study. LD₅₀ in rats was determined to be 960-970 mg/kg body weight. 80% Imidazole is corrosive to skin under occlusive conditions. Imidazole is irritating to rabbit eye when tested according to OECD TG 405. Persistent large size cornea opacity indicates the potential of severe eye injury after eye contact. No sensitization study is available.

Liver and kidney are target organs in subacute and subchronic (OECD TG 408) rat studies at dose levels of 180 mg/kg body weight per day and above. Slight centrilobular liver cell hypertrophy and relative liver weight increase was noted. Diffuse α 2u-microglobulin accumulation was noted in the proximal tubules of the renal cortex only in male rats but was considered to a species-specific effect. The NOAEL was approximately 60 mg/kg body weight per day. Red blood cells were additionally affected in 28-d experiments. Female rats receiving 125 mg/kg body weight per day or more and male rats receiving 500 mg/kg body weight per day were affected. The NOAEL was approximately 62.5 mg/kg body weight per day. This finding was, however, not confirmed in the 90-day guideline study when rats received up to 180 mg/kg body weight per day.

Imidazole was not mutagenic in bacterial test systems generally meeting OECD TG 471 with the Salmonella typhimurium strains TA 98, TA 100, TA 1535, or TA 1537, with or without the presence of metabolic activation by S-9 mix containing rat liver microsomes, with or without preincubation. Imidazole did not induce Unscheduled DNA Synthesis in rat primary hepatocytes in a study equivalent to the OECD TG 482. It was not clastogenic in the mouse micronucleus test according to the OECD TG 474 when imidazole hydrochloride was tested in vivo. The salt dissociates into protonated imidazole and chloride in the stomach following oral gavage.

No reproductive toxicity studies are available. However, no changes of the male and female reproductive organs including sperm quality were noted in a rat subchronic 3-months study according to OECD TG 408 imidazole was given by gavage at 20, 60, and 180 mg/kg bodyweight per day.. The NOAEL for these endpoints was 180 mg/kg body weight per day. In a study conducted in accordance to OECD TG 414 imidazole was developmental toxic and teratogenic at a dose of 180 mg/kg body weight per day showing some maternal toxic effects which is not likely to be the sole cause of the teratogenic effect. The incidence of external and skeletal malformations were significantly increased up to 10%. Furthermore there were soft tissue variations observed. The NOAEL was 60 mg/kg body weight per day for maternal toxicity, developmental toxicity, and teratogenicity.

No studies concerning the long-term toxicity and/or carcinogenic potential of Imidazole are available. It is, however, mentioned that imidazole was negative in the mouse fibroblast cell transformation test.

Environment

Imidazole is a colourless – yellow solid with an amine-like odour. It has a water solubility of 663 g/l at 20 °C (pH 10.5 for 68 g/l at 20 °C). Imidazole is a heterocyclic compound containing two nitrogens with $pK_a = 7.0$ and $pK_a = 14.9$. The melting point ranges from 88.3 to 89.9 °C, the boiling point is at 267.8 °C at 1013.3 hPa and the vapour pressure is 0.00327 hPa at 25°C.

The distribution of the substance between the compartments of air, biota, sediment, soil and water was calculated according to Mackay Level I fugacity model. The non-charged molecule distributes mainly to the water (99.98 %).

A soil adsorption coefficient (K_{oc}) of 9.72 was estimated for imidazole. This K_{oc} value suggests that this compound would be mobile in soil and adsorption to suspended solids would not be important. From the pK_a -value of 14.9 it can be assumed that under environmental conditions the substance is available as a cation. Therefore, binding of the substance to the matrix of soils with high capacities for cation exchange (e.g. clay) cannot be excluded. However, no data was available for ionic-ionic interactions in soil. The calculation of a Henry's law constant with the model HENRYWIN 3.1 yields a value of 0.38 Pa·m³/mol at 25 °C. Using the above described values for water solubility and vapor pressure, a Henry's law constant of 0.000034 Pa·m³/mol can be calculated. This low value and the water solubility of imidazole suggest that volatilization from water would not be an important fate process. Hydrolytic degradation is not to be expected under environmental conditions.

The half-life for photodegradation in air was calculated to be 10.7 hours. Half-lives for photolysis in water between 4.4 hours and 307 days have been reported dependant on OH concentrations and light intensity. The substance has no considerable potential for bioaccumulation ($\log K_{ow} = -0.02$, measured). The compound is readily biodegradable (OECD 301 A, 98% after 18 days 10d-window fulfilled). The EC_{50} (30 min) for activated sludge was determined to be >1000 mg/L.

The following aquatic effect concentrations are available:

Leuciscus idus LC_{50} (48 h) = 284 mg/l (nominal concentration).

Daphnia magna: EC_{50} (48 h) = 341 mg/l (nominal concentration).

Scenedesmus subspicatus: E_rC_{50} (72h) = 133 mg/l, with a NOEC of 25 mg/l (corresponding values for biomass are 127 and 10 mg/l respectively; nominal concentration)

Pseudomonas putida EC_{50} (17 h) = 1175 mg/L (nominal concentration)

Tetrahymena pyriformis : IGC_{50} (48 h) = 680 mg/L (nominal concentration)

Although no analytical monitoring of the test substance concentration was performed, and the substance is subject to photolysis in water, it is assumed that the effect values will not be below 100 mg/l.

Using the aquatic toxic effect on the most sensitive species, *Scenedesmus subspicatus*, of 133 mg/l for endpoint growth rate (127 mg/l endpoint biomass) a PNEC_{aqua} of 133 µg/l is derived by applying an assessment factor of 1000 according to the EU Technical Guidance Document. This factor is justified, because only short-term toxicity values were available.

Exposure

In 2002, the estimates for imidazole for the world market amounted to approx. 1000– 5000 tonnes/year. The substance was not imported into the European Union in 2002.

The organic compound is used in the chemical industry as an intermediate in the production of pharmaceuticals, pesticides, dye intermediates, auxiliaries for textile dyeing and finishing, photographic chemicals and corrosion inhibitors.

The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Therefore, the bulk of imidazole produced is used in the preparation of biologically active compounds.

According to Swiss, Danish, Finnish, Swedish and French Product Registers imidazole is contained in a large number of products. Due to Swiss information consumer products contain imidazole in concentrations up to 10 %. Danish, Finnish, and Swedish Product Register did not confirm that information regarding consumer products.

There is a potential of releases into the environment during the production and processing of imidazole as an

intermediate, and – according to the cited applications in the European Product Registers – from the formulation, processing and use of products containing the substance. During production and internal processing, less than 5 kg/a were emitted into the air by the German producer. Monitoring data of the substance in the sewage and effluent of waste water treatment plants are not available. The exposure of workers at the German production and internal processing plants is controlled. Imidazol is produced under closed system conditions. Exposure measurements at workplace were in a range between 0.21 mg/m³ and 0.32 mg/m³. From the reported use in consumer products, it can be concluded that most of the imidazole is released into wastewater, but part of it may also be released into the atmosphere.

RECOMMENDATION

Human Health: The chemical is a candidate for further work.

Environment: The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemical possesses properties (corrosivity to skin, irreversible damage to eyes, teratogenic effects) indicating a hazard for human health. Humans are exposed by consumer products (chemical concentrations up to 10%) and at the workplace. Therefore, the chemical is a candidate for further work. An exposure assessment and if indicated a risk assessment is recommended.

Environment:

The chemical is currently of low priority for further work because of its low hazard potential.