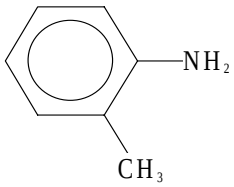
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-53-4
Chemical Name	o-Toluidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

o-Toluidine is rapidly absorbed via gastrointestinal tract and is rapidly distributed, metabolized and excreted mainly via urine. Although there are no special toxicokinetic data on absorption via skin and respiratory tract, absorption via these administration routes is shown by data from acute toxicity studies.

The LC_{50} (rat) is 852 ppm/4 hrs (approx. 3827 mg/m^3/4 hrs), and oral LD_{50} (rat) is 750 mg/kg bw. The dermal LD_{50} (rabbit) is 3250 mg/kg bw in a limited study. The predominant symptoms after inhalation or oral application were cyanosis, labored breathing, lethargy or loss of consciousness. o-Toluidine is a methemoglobin forming chemical; this was shown in rat and cat as well as in humans.

o-Toluidine is not irritating to the skin of rabbits when tested for 24 hours under semi-occlusive conditions (rabbit, ear) and is moderately irritating when tested 24 hours under occlusive conditions (rabbit, skin). However, skin necrosis developed 72 hours post treatment in 1/6 animals under occlusive conditions. o-Toluidine causes serious damage to the eyes of rabbits.

There are no valid data available to evaluate the sensitization potential of o-toluidine.

Repeated dose studies show that o-toluidine is toxic to erythrocytes and a methemoglobin forming chemical. This was demonstrated in elevated methemoglobin levels up to 19.0 % in the subacute feeding study as well as in the marked splenic toxicity in the subacute gavage and subchronic feeding studies leading to hypercellularity in the bone marrow. Further target organs were liver and kidney (hemosiderin deposition) and urinary bladder (hyperplasia). Based on the hematological findings no NOAEL could be derived, the LOAEL (rat, 14-day feeding study) is 500 ppm (approx. 23.7 and 25.5 mg/kg bw/day for males and females, respectively).

Genotoxicity test results are as typical for the class of aromatic amines. o-Toluidine showed positive as well as negative results in point mutation assays in bacteria and yeast. Results from tests with mammalian cell systems (HPRT, TK, UDS) were inconsistent, too, and appear to be protocol dependent. However, positive and negative results were independent of the presence or absence of a metabolic activation system. In in-vitro tests for chromosomal aberrations o-toluidine yielded positive results in several cell systems and did induce micronuclei in human lymphocytes in-vitro. In in-vivo tests for chromosomal aberrations o-toluidine yielded negative results in bone marrow of mice. o-Toluidine did not induce micronuclei in the in-vivo mouse micronucleus tests following intraperitoneal or oral application. However, SCE assay in mice and UDS-test in rats gave positive results in vivo. o-

Toluidine did not induce point mutations in the in-vivo SLRL-test with *Drosophila melanogaster*. Besides this, there are several, however, less reliable positive test results in *Drosophila*. Overall, o-toluidine showed potential for mutagenic activity in vitro and clastogenic activity in vitro and in vivo.

After oral administration to mice o-toluidine induced and increased incidence of hemangiomas and hemangiosarcomas and hepatocellular carcinomas or adenomas. In rats, oral administration increased the incidence of tumors in multiple organs, including fibromas, sarcomas, mesotheliomas, mammary fibroadenomas and transitional cell carcinomas of the urinary bladder. IARC classified o-toluidine in group 2A (probably carcinogenic to humans).

In the open literature, o-toluidine is suspected to cause urinary bladder tumors in workers. However, this finding cannot definitely be attributed to o-toluidine because of the co-exposure to other arylamines. There is no valid study on reproductive or developmental toxicity available, however, o-toluidine is genotoxic and carcinogenic and therefore it should be regarded as potentially toxic to reproductionaccording to EU Technical Guidance Document. In a subchronic feeding study in male rats o-toluidine hydrochloride led to degeneration of seminiferous tubules and a significant increase in relative weight of testis in systemic toxic doses. In very limited developmental toxicity studies effects on kidneys, ovaries, heart and lungs in progeny were reported that were difficult to interpret. However, due to its methemoglobin forming activity like other structurally related aromatic amino or nitro compunds o-toluidine is anticipated to exert developmental toxicity at least as a secondary consequence of maternal toxicity. As results from further testing would not affect the most stringent exposure control measures being already in place due to genotoxicity and carcinogenicity of o-toluidine, no further tests are warranted.

Environment

o-Toluidine is a light yellow liquid becoming reddish brown on exposure to air and light with a melting point of -24.4 °C for the α-form and -16.3 °C for the β-form, and a boiling point of 200.2 °C. The density of the liquid is 0.9984 g/cm^3 at 20 °C. The vapour pressure is 34.5 Pa at 25 °C. The measured log K_{ow} is 1.40. The solubility in water is 15.0 g/l at 25°C. The dissociation constant is 4.44 - 4.45. The flash point is 85 °C, the auto-ignition temperature 482 °C.

In the atmosphere o-toluidine is degraded by photochemically produced OH radicals. The half-life is calculated to be ca. 2.9 hours.

With regard to its chemical structure o-toluidine is not expected to hydrolyze under environmental conditions. o-Toluidine is readily biodegradable (MITI, comparable to OECD TG 301 C: biodegradation 65 % after 28 days, OECD TG 301 A: 88 - 90 % after 28 days, OECD TG 301 E: ca. 90 % after 28 days).

According to the Mackay fugacity model level I, the favourite target compartment of o-toluidine is water with 91.8 %, followed by air with 7.8 %. The measured and calculated Henry's law constants (0.20-0.25 Pa m^3/mol at 25 °C) prove a low to moderate potential for volatilisation from surface waters.

The available experimental bioconcentration factors (BCF) for o-toluidine indicate no significant potential for bioaccumulation in Pacific oysters (*Crassostrea gigas*) (BCF = 3.8 - 5.4) or Common bay mussels (*Mytilus edulis*) (BCF = 3.5 - 4.9). The bioconcentration factor BCF = 2.4 for o-toluidine, calculated from the octanol-water partition coefficient, confirms the low bioaccumulation potential also for fish..
K_{oc} values were calculated with PCKOCWIN v. 1.66 (K_{oc} = 74) and with the TGD equation for the anilines (K_{oc} = 52). From the measured coefficient of distribution between the sediment and water (K_d = 0.013) the K_{oc} was calculated to 0.87. These results indicate a low sorption potential of o-toluidine onto the organic phase of soil or sediments. However, adsorption of o-toluidine in soil can be enhanced by ion-ion interactions as the results with clay minerals show.

Concerning the toxicity of o-toluidine to aquatic species reliable experimental results from tests with fish, *Daphnia*, and algae are available. The tests were performed according to standard procedures or similar methods. The lowest effect values (nominal concentration) from short-term tests and from a prolonged fish toxicity test are:

Leuciscus idus: 96 h-LC_{50} = 82.5 mg/l
Poecilia reticulata: 14 d-LC_{50} = 81.3 mg/l
Daphnia magna: 48 h-EC_{50} = 0.52 mg/l
Daphnia magna: 96 h-EC_{50} = 0.249 mg/l
Chlorella pyrenoidosa: 96 h-E_bC_{50} = 55 mg/l
Selenastrum capricornutum: 72 h-E_rC_{50} = 94.5 mg/l (72h-EbC50 = 30.9 mg/l)

Reliable tests on chronic toxicity towards *Daphnia* and algae are available as well:

Daphnia magna 21 d-NOEC = 0.0126 mg/l [Endpoint Reproduction]
Daphnia magna: 21 d-LRCT = 0.1 mg/l [endpoint population growth]; derived NOEC = 0.032 mg/l
Selenastrum capricornutum: 72 h-NOEC = 31.0 mg/l [endpoint growth rate]; (2.9 mg/l [Endpoint biomass])
Microcystis aeruginosa: 8 d-EC_3 = 0.31 mg/l [endpoint cell multiplication], similar to NOEC

Based on the lowest NOEC of 0.0126 mg/l derived for *Daphnia magna* a Predicted No Effect Concentration in water ($PNEC_{aqua}$) of 0.252 µg/l can be calculated with an assessment factor of 50.

Exposure

o-Toluidine is commercially manufactured by reduction of o-nitrotoluene. In 2001, the world wide production volume of o-toluidine is estimated to be 59,000 tonnes by 11 producers. o-Toluidine is an intermediate in chemical synthesis of herbicides, rubber chemicals, dye and pigment intermediates, resin hardeners, fungicide intermediates, pharmaceutical intermediates, and others. By far the largest use is as an intermediate in the manufacture of herbicides.

No direct consumer use is known for o-toluidine. o-Toluidine is listed in the Danish, Finnish, Norwegian, and Swedish product registers as an industrial product. No consumer application is registered. The Swiss product register lists 2 analytical kits, both with a o-toluidine concentration of about 0.1 %, presumably for occupational use. An analytical substance is registered for industrial use with an o-toluidine content of less than 1 %. There are about 10 metallic mordants for industrial use with o-toluidine levels of < 0.1 %.

In the EU, the use of azo dyes releasing o-toluidine on degradation, is not permitted for textiles and other consumer articles. Thus, an exposure of consumers and of the environment due to releases from consumer products appears to be negligible.

At all 5 sites of one company in the Sponsor country o-toluidine is manufactured and processed in closed systems. The effluent concentration from the wastewater treatment plants was below the detection limit of 20 µg/l (one production site), below 25 µg/l (one processing site) and 10 µg/l (two processing sites). For one production site in the Sponsor country only data for the sum of the toluidine isomers are available.

o-Toluidine occurs in certain vegetables, in tobacco leaves and in the aroma of black tea. It is an intermediate in the biodegradation of o-nitrotoluene, e.g. at former munitions sites. Toluidine (isomers not specified, but o-toluidine likely to be present) was detected as a component of coal oil. o-Toluidine is formed during pyrolysis. Most recent detection of o-toluidine in environmental waters in the Sponsor country was in the rivers Rhine and Elbe in 1997and 1998, with the highest o-toluidine concentrations of 0.1 µg/l in the Elbe river at Schmilka.

o-Toluidine releases were up to 4 µg/cigarette. o-Toluidine was detected in contaminated outdoor air. In indoor air there was a correlation between o-toluidine concentration and exposure to environmental tobacco smoke.

In Germany for occupational settings, a Technical Exposure Limit (TRK) of 0.5 mg/m³ is set for o-toluidine. At production and processing sites of the Sponsor company, the exposure of workers is well below this limit.

There are several published reports on biomonitoring of o-toluidine. o-Toluidine concentration in urine and the level of hemoglobin adducts in blood of workers were higher than in the general population in historic studies, but not in recent studies. In general, smokers have higher levels of o-toluidine in urine and of hemoglobin adducts in blood than non-smokers. o-Toluidine was also detected in human milk.

Consumers are exposed to o-toluidine in environmental tobacco smoke, some foodstuffs, and (other) products in contact with smoke. Tobacco smoke is the predominant source of o-toluidine in humans.

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

Human Health: The substance is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (acute and subacute toxicity, methemoglobin formation, skin and eye irritation, genotoxicity, carcinogenicity, potential for reproductive toxicity). Based on data presented by the Sponsor country (relating to production by one producer which accounts for 17 – 60 % of global production and relating to the use pattern in several OECD countries as well as occupational monitoring data from several countries), exposure is controlled in occupational settings, and exposure of consumers is negligible. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor.

Environment: The substance is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for 17 – 60 % of global production and relating to the use pattern in several OECD countries as well as surface water monitoring data from one country), exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.