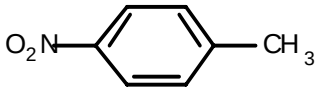
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	99-99-0
Chemical Name	4-Nitrotoluene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

4-Nitrotoluene is rapidly absorbed via skin, gastrointestinal or respiratory tract, and distributed throughout the body. The primary metabolic pathway is side-chain or ring oxidation and conjugation with glucuronic acid and inorganic sulfates with subsequent renal excretion. In rats, the involvement of enterohepatic circulation was also observed.
4-Nitrotoluene is a methemoglobin forming chemical. Tachypnea, wheezing, somnolence and cyanosis were the predominent clinical signs following oral doses near to or exceeding the LD50 values. Methemoglobinemia was reported in rats after dermal exposure to high dose levels (LD50, oral, rat: 2144 - 4700 mg/kg bw; LD50, dermal, rats: > 750 mg/kg bw, LD50, dermal, rabbits: > 20,000 mg/kg bw; LC50, inhalation, rat: > 851 mg/m³/4h; no information on particle size available).
4-Nitrotoluene is not irritating to the skin and eyes of rabbits (OECD TG 404, 405). It was not sensitizing to the skin of guinea pigs in the Single Injection Adjuvant Test (SIAT) and in the Buehler test (OECD TG 406).

In 13 week and 2 year feeding studies with rats, 4-nitrotoluene caused hematopoiesis and hemosiderin pigment accumulation in the spleen of both sexes at all dose levels tested. Methemoglobinemia was noted at study end in the 13 week study at 10,000 ppm (male: approximately 723 mg/kg bw/day, female: approximately 680 mg/kg bw/day). At high and systemically toxic exposure levels, testicular degeneration was found in the males, and lengthened estrous cycles in the females. In male rats, α2u-globulin nephropathy was observed in all dosed groups. This effect is species specific and therefore of no relevance for humans (LOAEL: 625 ppm, corresponding to approximately 42 mg/kg bw/day, based on splenic toxicity). No relevant chemical related lesions were seen in mice in 13 week feeding studies. The NOAEL based on body weight reduction was 2500 ppm (approximately 439 mg/kg bw/day). In 2-year feeding studies, male and female mice showed an increase in alveolar bronchiolar epithelialization, and syncytial alterations in hepatocytes were found in males (LOAEL 1250 ppm = approximately 155 - 170 mg/kg bw/day). Immunological dysfunction has been reported in mice. The toxicological significance of the effects is not certain.

In vitro, 4-nitrotoluene showed no mutagenic effect in good quality Ames tests with *Salmonella typhimurium* and *Escherichia coli*, with and without metabolic activation. In cultured mammalian cells, 4-nitrotoluene has demonstrated the potential to cause mutagenicity in the presence of metabolic activation. The chemical did not induce unscheduled DNA synthesis in hepatocytes. *In vivo*, 4-nitrotoluene had no genotoxic activity. The substance did not induce micronuclei in rat and mice bone marrow cells in studies performed according to the current standard (OECD TG 474), and it did not induce unscheduled DNA synthesis in rat *ex vivo* hepatocytes.

Under the conditions of the two year feed studies, there was equivocal evidence of carcinogenic activity of 4-nitrotoluene in male rats based on the increased incidences of subcutaneous skin neoplasms. There was some evidence of carcinogenic activity in female rats based on increased incidences of clitoral gland neoplasms. There was equivocal

evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms. There was no evidence of carcinogenic activity in female mice exposed to 1250, 2500, or 5000 ppm (approximately 155, 315, or 660 mg/kg bw/day).

4-Nitrotoluene had no adverse effects on most reproductive endpoints (insemination index, fertility index, time to insemination, gestation length, number of corpora lutea and number of implantation sites, live birth index) in a rat oral Reproductive/Developmental Toxicity Screening Test (OECD TG 421), even under conditions where overt systemic toxicity was observed. A reduction in the gestation index, increased prenatal loss and reduced litter size and pup weights were reported at parentally toxic doses. Testicular degeneration was found in subchronic studies at systemically toxic dose levels characterized by reduced body weights and toxicity to the spleen subsequent to the erythrocyte damaging effect of 4-nitrotoluene ($NOAEL_{reproductive\ toxicity}$: 25 mg/kg bw/day; $NOAEL_{developmental\ toxicity}$: 25 mg/kg bw/day, $NOAEL(male)_{general\ toxicity}$: 25 mg/kg bw/day; $LOAEL(female)_{general\ toxicity}$: 25 mg/kg bw/day).

Based on the available data, there was no evidence of a relevant hormonal activity of 4-nitrotoluene from various *in vitro* and *in vivo* screening tests.
Cases of poisoning from nitrotoluene are uncommon. They are reported only from early production units and relate to mixed exposures. The signs of intoxication included cyanosis, difficulties in breathing and tachycardia. In the recent open literature reports of human poisoning could not be identified.

Environment

4-Nitrotoluene has a melting point of 51.3 °C, a boiling point of 238 °C and a density of 1.29 g/ml at 20 °C. It has a vapour pressure of 13 Pa at 20°C. The log Kow is 2.37 . The solubility in water is 345 mg/l at 20 °C. The flash point is ca. 103 °C, the auto flammability (ignition temperatur) 450 °C.
With regard to its chemical structure 4-nitrotoluene is not expected to hydrolyse under environmental conditions. During 8 days of a stability experiment at pH 8 and 25 °C about 6 % of 4-nitrotoluene (purity of 99.5 %) were lost in water.
According to Mackay level I fugacity model the main target compartments for 4-nitrotoluene are air (63.6 %) and water (35 %). A measured Henry's law constant of 0.57 $Pa \cdot m^3 \cdot mol^{-1}$ indicates a moderate potential for volatilization of 4-nitrotoluene from aqueous solution. In the atmosphere 4-nitrotoluene is degraded due to indirect photolysis ($t_{1/2air}$: 20.8 days) and direct photolysis. In surface waters the half life is estimated to be 6 hours due to photodegradation.
Since in the MITI-test, only 0.8 % of 4-nitrotoluene were mineralised within 14 days, 4-nitrotoluene is not readily biodegradable. Nevertheless studies on inherent biodegradation show 4-nitrotoluene to be biodegradable under aerobic conditions with adapted bacteria (degradation 100 % after 21 d including 10 d adaptation).
Bioconcentration factors determined for fish were in the range of 3.7 – 27 and thus indicate no significant bioaccumulation potential of 4-nitrotoluene. Binding to soil organic matter has been calculated with Koc = 309. 4-Nitrotoluene can be regarded as a substance with medium geoaccumulation properties. The adsorption constants of 4-nitrotoluene were 5 - 45 l/kg on three clay minerals indicating a low adsorption by clays.

Concerning the acute toxicity of 4-nitrotoluene towards aquatic species reliable experimental results of tests with fish, daphnids, and algae are available.
The acute fish toxicity was 10.5 mg/l for Carassius auratus (48 h-LC_{50}), ca. 40 mg/l for Cyprinus carpio (96 h-LC_{50}), 50 mg/l for *Pimephales promelas* (96 h-LC_{50}), and 74 mg/l (48 h-LC_{50}) for *Oryzias latipes.* For *Daphnia magna* 48 h-EC_{50}-values of 4.2, 7.5, and 11.8 mg/l were found. In the algae growth inhibition tests with *Chlorella pyrenoidosa* the 96 h-EC_{50} was 22.2 mg/l, and with *Scenedesmus obliquus* the 48 h-ErC_{50} was 25 mg/l.
The long-term toxicity to fish (*Oryzias latipes*, *Poecilia reticulata*) for the endpoints mortality and swimming behaviour, was evaluated by two 28 days tests. The NOEC values were 0.8 mg/l and 10 mg/l. A chronic toxicity test for the endpoint hatching rate of *Oryzias latipes* yielded a 40 d-NOEC of 32 mg/l. For the endpoints mortality, growth, and swimming behaviour of *Oryzias latipes,* a 40 d-NOEC of 1 mg/l were determined. Two chronic tests with *Daphnia magna* are available. The 21 d-NOECs were 0.7 mg/l and 1 mg/l, respectively, both for the endpoint reproduction rate. In a non-guideline study with the non-standard test species, the mollusc *Lymnaea stagnalis*, a 40 d-NOEC of 0.32 mg/l was determined for the endpoint reproduction. In the growth inhibition test with algae (*Scenedesmus pannonicus*) no effect on biomass was observed at 10 mg/l 4-nitrotoluene after 4 days.

Based on the chronic aquatic toxicity data on three trophic levels (fish, invertebrate, algae), a Predicted No Effect Concentration (PNEC) can be calculated with an assessment factor of 10. Using a 40 d-NOEC of 0.32 mg/l of *Lymnaea stagnalis*, a PNEC of 32 µg/l was determined.

Exposure

About 77,000 tonnes of 4-nitrotoluene were produced worldwide in 2000; Western Europe 30,000 t/a, China 26,000 t/a, US 9,000 t/a, Eastern Europe 5,000 t/a, India 4,000 t/a, and South Korea 3,200 t/a. The total manufacturing capacity of the lead company amounts to 28,000 t/a in 2000.
4-Nitrotoluene is a basic chemical for the synthesis of intermediates which are further processed to optical brighteners, coloring agents, pharmaceuticals, and agrochemicals, and others within the chemical industry. A direct use is not known.
From the production and processing site of the lead company virtually no 4-nitrotoluene was emitted into the environment in 2001. Taking into account the detection limit (2 µg/l), the 10 percentile of the river flow (1050 m^3/s), and the dilution factor (700), for the receiving water a Predicted Environmental Concentration (PEC) of < 2.8 ng/l is calculated.
In Gemany in 1999, the 90-percentile of the 4-nitrotoluene concentrations in the River Rhine was < 0.5 µg/l and in the River Danube < 0.02 µg/l. For the River Elbe the maximum was 0.05 µg/l.
During manufacturing and processing of 4-nitrotoluene workers may be exposed through the inhalational, dermal and oral routes. At the lead company the exposure of workers is well below the German Occupational Exposure Limit of 5 ppm (28 mg/m^3). The levels of metabolic products of 4-nitrotoluene in workers are not higher than in the unexposed population.
4-Nitrotoluene is formed during tobacco smoking. At former munition manufacturing sites or at historic landfills 4-nitrotoluene might occur in groundwater and leachate. A significant indirect exposure of the general public via the environment is however not expected.

RECOMMENDATION

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 indicating a hazard for human health. Based on data presented by the sponsor country, exposure is controlled in occupational settings, and is negligible for consumers. Any exposure scenario not presented by the Sponsor country will have to be investigated, however.

Environment:
The chemical possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor 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, e.g. exposure from munitions dumps or former munitions sites.