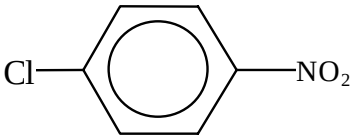
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	100-00-5
Chemical Name	1-Chloro-4-nitrobenzene
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1-Chloro-4-nitrobenzene is rapidly absorbed via skin, gastrointestinal tract or respiratory tract and distributed in the tissue predominantly in fat, blood cells, skeletal muscles, liver and kidney. Most of the substance was excreted with the urine followed by excretion with feces. 1-Chloro-4-nitrobenzene undergoes three major types of transformation *in vivo* in mammals: nitro-group reduction, displacement of the chloride in glutathione conjugation, and ring-hydroxylation. From accidental exposure of workers to 1-chloro-4-nitrophenol, large amounts of 2-chloro-5-nitrophenol, N-acetyl-S-(4-nitrophenyl)-L-cysteine, 4-chloroaniline and 4-chloroformanilide were identified.

The oral LD50 for 1-chloro-4-nitrobenzene in male rats is 294 or 694 mg/kg bw and in female rats 565 or 664 mg/kg bw. Cyanotic appearance was the predominant symptom. The 7-hour-inhalation of a highly saturated vapor-air mixture (concentration up to 77 mg/m^3) represented no acute hazard to male and female rats. In addition, the LC50 level could not be reached up to 16100 mg/m³ during a 4-hrs exposure against vapor and microcrystalline particles. The LD50 (dermal) for male rats is 750 mg/kg bw and for female rats 1722 mg/kg bw; the LD50 for male rabbits is 3550 mg/kg bw and for female rabbits 2510 mg/kg bw after acute dermal application. Cyanotic appearance was the predominant symptom. For the evaluation of acute toxicity it has to be taken into account that 1-chloro-4-nitrobenzene is a methaemoglobin forming chemical.

Experience with human exposure: all available reports relate to mixed exposure, frequently in combination with 1-chloro-2-nitrobenzene and/or nitrobenzene. A critical aspect in this context is that 1-chloro-4-nitrobenzene is rapidly absorbed via skin and the respiratory tract. The signs of acute intoxication include methaemoglobinaemia, vomiting, headache and in severe cases collapse.

The available study-reports on skin irritation have deficiencies with regard to the description of the results, nevertheless, 1-chloro-4-nitrobenzene is judged to be slightly irritating to the skin (intact or scarificed) of rabbits using a paste of the test substance and occlusive dressing and not irritating to the skin using undissolved, solid test substance and occlusive dressing.

In two available studies 1-chloro-4-nitrobenzene caused slight irritational effects to the eyes of rabbits which were reversible within 4 hours (first study: slight conjunctival injections, observed only in washed eye) resp. 8 days (second study: transient slight corneal cloudiness).

Due to the limited and poor quality information available regarding skin sensitization it cannot be concluded whether or not the chemical has a sensitizing activity.

The repeated dose toxicity via inhalation has been examined in rats for a period of 4 weeks and 13 weeks. In both studies, NOAECs were not achieved, the LOAECs were 5 mg/m³ (4 week-study) and 1.5 ppm (9.81 mg/m^3, 13 week-study), respectively, based on methemoglobinemia (3 % and 4 %, respectively) as the most sensitive effect. The maximum methemoglobin value was 42 % in females of the 24 ppm group in the 13-weeks study. The repeated dose toxicity via inhalation for a period of 13 weeks in mice revealed a NOAEC for histopathologic injury of 6 ppm (39.24 mg/m³). As target organs liver, kidney (rat only), spleen and blood were identified in both species.

Similarly, repeated dose toxicity by oral administration in rats [OECD TG 408 and 453] revealed changes predominantly consistent with methaemoglobinaemia. In the long term test a clear NOAEL could not be identified because histopathological examinations of most of the organs of the low- and mid-dose groups was performed only when macroscopic lesions were observed. The adverse effect level was 0.7 mg/kg bw/day. In the subchronic study the LOAEL was 3 mg/kg bw/day due to methaemoglobin formation and a NOAEL could not be derived. In both studies methaemoglobin formation and oxidative damage to red blood cells, leading to a regenerative anemia and a recognized spectrum of tissue damage and changes secondary to erythrocyte injury, were the main adverse effects.

1-Chloro-4-nitrobenzene induced reverse mutations in bacteria. It was not mutagenic in mammalian cells *in vitro* (HPRT test) and in insects *in vivo*. A mouse lymphoma assay was positive. *In vitro* it induced chromosomal aberrations and sister chromatid exchanges at high doses; no UDS in rat hepatocytes was reported.

The chemical induced micronuclei in mouse bone marrow *in vivo* at a toxic dose. In rat bone marrow it did not induce chromosomal aberrations *in vivo*. An *in vivo* SCE test was weakly positive in bone marrow cells of Chinese hamsters. DNA strand breaks were observed in liver, kidney and brain of mice. 1-Chloro-4-nitrobenzene is consequently capable of expressing mutgenic activity *in vivo* with low potency.

A combined chronic toxicity/carcinogenicity study (OECD Guideline 453) with 1-chloro-4-nitrobenzene in rats produced an increased incidence in interstitial cell tumours of the testes which were within the range of the historical control data and evaluated as not compound related. These tumours were described in literature as common tumours in male Sprague-Dawley rats. In another rat study which doesn't meet the criteria of today and is reported in brief, no tumours were found. In the available study with mice which doesn't meet the criteria of today and is only reported in brief, vascular tumors (localization not specified) were found. This tumor type is not uncommon in the substance class of substituted amino- or nitrobenzenes. Overall, taking into consideration the results of the genotoxicity tests and the limitations in the available long term studies, a carcinogenic potential cannot be ruled out.

Toxicity to reproduction of 1-chloro-4-nitrobenzene has been examined in rats and mice by oral administration. In a two generation study with rats [OECD guideline 416] no impairment of fertility was observed up to 5 mg/kg bw (high dose group), nevertheless, at this dose histopathological effects in testes were observed. But the evaluation of the effect on the male reproductive tract is limited because the testes in the low and mid dose group were not examined histopathologically. Therefore a NOAEL (male reproductive organ toxicity) was not established. The NOAEL for general toxicity of adults was not achieved. A LOAEL (adults) of 0.1 mg/kg bw/day based on histopathological effects in the spleen of F1 adults is indicated. The NOAEL for general toxicity of offspring is 0.1 mg/kg bw/day. In mice a study was performed using the NTP continuous breeding protocol. The NOAEL (fertility) is 125 mg/kg bw/day, the LOAEL (offspring general toxicity) is 62.5 mg/kg bw/day. The NOAEL (adult general toxicity) is 125 mg/kg bw/day, but full evaluation is not possible because evaluation of the animals of the two lower groups were very limited. Two subchronic inhalation studies with rats and mice with histopathologic evaluations on reproductive organs are available. There was evidence of decreased spermatogenesis (24 ppm) and decrease in average estrous cycle length in rats exposed to 1-chloro-4-nitrobenzene (6 ppm and above). In female mice an increase in estrous cycle length was noted at the highest exposure group (24 ppm).

Developmental toxicity of 1-chloro-4-nitrobenzene has been examined in rats and rabbits by oral administration [OECD TG 414]. In rats, a NOAEL for maternal toxicity was not achieved, the LOAEL(maternal toxicity) is 5 mg/kg bw/day; the NOAEL (developmental toxicity) is 15 mg/kg bw/day. The study with rabbits suffered from methodology deficiencies. Due to high mortality rate at the highest dose level, only two doses could be evaluated: the LOAEL (maternal toxicity) is 5 mg/kg bw/day and the LOAEL (developmental toxicity) is 5 mg/kg bw/day. Thus, in both species developmental toxicity occurred in the presence of maternal toxicity.

There are indications of immunotoxic potency following single and repeated applications of 1-chloro-4-nitrobenzene.

Environment

1-Chloro-4-nitrobenzene has a melting point of 83 °C, a solubility in water of 243 mg/l at 20 °C, and a vapour pressure of 8.5 Pa at 20°C. The measured log Kow is 2.39. The flash point is ca. 127 °C.

According to Mackay fugacity model level I the main target compartments for 1-chloro-4-nitrobenzene are air (65%) followed by water (33%). A measured Henry constant of 0.5 $Pa \cdot m^3 \cdot mol^{-1}$ indicates a moderate potential for volatilization of 1-chloro-4-nitrobenzene from aqueous solution. It is expected that in the atmosphere a degradation of 1-chloro-4-nitrobenzene occurs due to indirect photolysis ($t_{1/2air}$: ca. 62 days) and direct photolysis. 1-Chloro-4-nitrobenzene is not readily biodegradable. Various tests showed adapted cultures to degrade 1-chloro-4-nitrobenzene. However, the degradation was inhibited at concentrations ≥ 8 mg/l. For *Pseudomonas putida* a O_2 consumption test resulted in a EC10 (30 min) of 59 mg/l. Bioconcentration factors determined for fish were in the range of 5.8– 20.9 and thus indicate no significant bioaccumulation potential of 1-chloro-4-nitrobenzene. A calculated Koc (Koc=309) suggests the substance to have a medium geoaccumulation potential.

Concerning the toxicity of 1-chloro-4-nitrobenzene towards aquatic species reliable experimental results of tests with fish, daphnia, and algae are available. The acute toxicity determined for fish (*Brachydanio rerio*) was of 14.36 mg/l (96 h LC50) and 2 mg/l (48 h) for *Leuciscus idus* and for daphnia (*Daphnia magna*) of 2.7 mg/l (48 h-EC50). In the growth rate tests with algae (*Scenedesmus subspicatus)* the values 4.9 mg/l (48 h-ErC10) and 16 mg/l (48 h-ErC50) were achieved while for *Chlorella pyrenoidosa* an effect value of 4.9 mg/l (96h-EC50) was found.

The prolonged toxicity to fish (*Brachydanio rerio)* for the endpoint sub-lethal effects (feeding, malposition) was evaluated through a 14 days test and a NOEC value of 1.53 mg/l was determined.

Two chronic tests with Daphnia (*Daphnia magna*) are available that were performed with analytical monitoring of the test substance concentration. In one test a 21 d-EC_{10} of 0.103 mg/l (effective concentration) was observed for the endpoint reproduction rate. The second test resulted in a 21d-NOEC of 0.19 mg/l (effective concentration) for the same endpoint. Calculating the geometric mean of these two values gives a NOEC of 0.14 mg/l. A PNECaqua = 2.8 µg/l is derived from this value, using an assessment factor of 50.

Exposure

About 220,900 tons 1-chloro-4-nitrobenzene were produced by about 30 producers worldwide in 1995 (excluding Eastern Europe). All 1-chloro-4-nitrobenzene is a basic chemical for the synthesis of intermediates which are further processed to pharmaceuticals, plant protection agents, auxiliaries in the rubber and plastics industry, dyestuffs/pigments, and others within the chemical industry. A direct use is not known.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical possesses properties indicating a hazard for human health and the environment. Based on data presented by the Sponsor country, exposure to humans and 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.