FOREWORD INTRODUCTION

1-Chloro-2-nitrobenzene

CAS: 88-73-3

SIDS Initial Assessment Report

For

SIAM 13

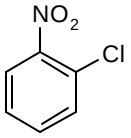
(Bern, Switzerland, 6-9 November 2001)

1. Chemical Name:	1-Chloro-2-nitrobenzene
2. CAS Number:	88-73-3
3. Sponsor Country:	Germany Name of lead organization: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Address: Postfach 12 06 29, D- 53048 Bonn- Bad Godesberg
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners: • Name of industry sponsor /consortium • Process used	
6. Sponsorship History • How was the chemical or category brought into the OECD HPV Chemicals Programme ?	
7. Review Process Prior to the SIAM:	
8. Quality check process:	
9. Date of Submission:	14. September 2001
10. Date of last Update:	Last literature search (up date): 16 August 2001 (Human Health): databases medline, toxline; searchprofile CAS-No. and special search terms 24 July 2001 (Ecotoxicology): databases CA, biosis; searchprofile CAS-No. and special search terms
11. Comments:	OECD/ICCA - The BUA Peer Review Process Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA

guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4) not assignable)
- Review o f validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
- In case of data gaps, review of testing plan or rationale for not testing.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	88-73-3
Chemical Name	1-Chloro-2-nitrobenzene
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

After single oral application 1-chloro-2-nitrobenzene is toxic to moderate toxic (LD_{50}, oral: rat, male: 144, 251or 560 mg/kg bw; rat, female: 263 mg/kg bw); the acute inhalative and dermal toxicity is moderate (LC_{50}, rat: 3200 mg/m^3 (= 495 ppm, vapor/aerosol mixture); LD_{50}, dermal, rat: female: 1320 mg/kg bw, male: 655 mg/kg bw; LD_{50}, dermal, rabbit: 400 mg/kg bw (male: 455 mg/kg bw, female: 355 mg/kg bw): Cyanotic appearance was the predominant symptom for all routes of application.

The documentation of the available studies on skin irritation is incomplete in one case and in two other cases the test substance was applied undissolved or respectively diluted. However, the studies gave no evidence of a skin irritating potential. 1-Chloro-2-nitrobenzene caused slight irritation effects to the eyes of rabbits, which were reversible within 24 hours. 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.

Target organs of repeated dose toxicity in rats and mice are blood, liver, kidney and spleen with methemogobinaemia as the most sensitive parameter. The repeated dose toxicity was examined in rats and in mice for a period of 13 weeks via whole body inhalation. The NOAEL in rats was not achieved, the LOAEL is 1.1 ppm (7 mg/m^3). In mice, increased liver and kidney weights were observed even at 1.1 ppm and respectively 2.3 ppm. The NOAEL for histopathological injury in mice is 4.5 ppm (28.8 mg/m^3). In a subacute feeding study with mice the NOAEL was 50 ppm (males: 16 mg/kg bw/day; females: 24 mg/kg bw/day).

1-Chloro-2-nitrobenzene showed weak mutagenic activity in bacterial test systems but not in mammalian cell test systems *in vitro*. It was not mutagenic in *Drosophila melanogaster*. In mammalian cells *in vitro*, it showed weak clastogenic activity. The substance induced increased rates of Sister Chromatid Exchanges, whereas the biological relevance of this effect is not yet clear. Intraperitoneal injection into mice resulted in DNA damage in the liver and kidney. The inconsistent results of the available genotoxic studies are typical for nitroaromatics. As a whole 1-chloro-2-nitrobenzene is suspected of being genotoxic, at least a weak clastogen.

1-Chloro-2-nitrobenzene induced tumours in different organs of rats and in the liver of mice. Based on the available studies, which have methodological deficiencies, there is a concern for a carcinogenic potential of 1-chloro-2-nitrobenzene. Following inhalative exposure of F344/N rats and B6C3F1 mice for 13 weeks, only in males 1-chloro-2-nitrobenzene affects the reproductive organs. Performance of a specific study on toxicity to reproduction (NTP continuous breeding protocol) reveals that 1-chloro-2-nitrobenzene was without reproductive toxicity in a different mice strain following oral treatment by gavage despite of significant changes in liver and spleen weight and despite of elevated methaemoglobin levels. Thus, the $NOAEL_{fertility}$ in Swiss CD-1 mice after oral application is 160 mg/kg bw/day whereas the dams showed general toxicity effects at this concentration. Because 1-choro-2-nitrobenzene affected the reproductive organs in systemic toxic doses in male rats and in males of one strain of mice

after subchronic inhalation there is a concern for a reproductive toxicity potential, even if an impairment of reproduction after oral administration in males of a second strain of mice could not be detected.

Developmental toxicity was examined by two studies with Sprague-Dawley rats which have methodology deficiencies. In one study, due to high mortality rate at the highest dose level, only two doses could be evaluated. NOAEL $_{\text{maternal toxicity}}$ is 25 mg/kg bw/day, a NOAEL $_{\text{developmental toxicity}}$ could not be conclusively derived since there was an increase in the number of litters exhibiting specific skeletal variations. In the second study only one dose was applied: NOAEL $_{\text{developmental toxicity}}$ is 100 mg/kg bw/day, a NOAEL maternal toxicity could not be derived. Based on the available studies the overall conclusion is, that there is no indication of developmental toxicity, although there are some limitations within the studies.

Environment

1-Chloro-2-nitrobenzene has a melting point of 32 °C, a solubility in water of 441 mg/l at 20 °C, and a vapour pressure of 4.0 Pa at 20°C. The log Kow was measured to 2.24.

According to Mackay fugacity model level I the main target compartments for 1-chloro-2-nitrobenzene are water (65.4 %) followed by air (32.9 %). 1-Chloro-2-nitrobenzene shows no ready biodegradation in aquatic compartments (OECD 301 C: 8.2% after 14d) but under the conditions of industrial waste water treatment plants removal to > 95 % was observed at one production/processing site. However, this elimination cannot be transferred to other sewage treatment plants. Special tests showed adapted cultures to be able to degrade 1-chloro-2-nitrobenzene in a cometabolic pathway. Bioconcentration factors determined for fish were in the range of 7.0 – 22.3 and thus indicate no significant bioaccumulation potential of 1-chloro-2-nitrobenzene. A calculated Koc suggests the substance to have a medium geoaccumulation potential. In the atmosphere the substance is photodegradable indirectly with a calculated half-life of 187 d.

The acute toxicity has been determined for: fish (*Cyprinus carpio*) with a 96 h-LC_{50} of 25.5 mg/l; daphnia (*Daphnia magna*) with a 24 h-$EC_{50}$of 12 mg/l and a 48 h-EC_{50} of 23.9 mg/l, and *Daphnia carinata* with a 48 h-EC_{50} of 21.3 mg/l; algae (*Chlorella pyrenoidosa*) with a 96 h-EbC_{50} of 6.9 mg/l. With another alga species (*Secendesmus subspicatus*) a 48h-ErC50 of 75 mg/l and a 48h-ErC10 of 19 mg/l was found.

Chronic toxicity has been tested for *Daphnia magna* with a 21 d-NOEC of 3 mg/l on reproduction (measured concentration) and for fish (*Pimephales promelas*) in an Early Life Stage Test with a 33 d-NOEC of 0.264 mg/l concerning the endpoint normal larvae (measured concentration). A PNECaqua of 0.026 mg/l is derived using an assessment factor of 10.

In a test with terrestrial plants a 14 d-EC50 in the range of 3.2 - 10 mg/kg soil dry weight was determined for Lactuca sativa regarding the endpoint of growth. APNECsoil of 3.2 µg/kg bw was derived from this value using an assessment factor of 1000.

Exposure

About 111,800 t/a 1-chloro-2-nitrobenzene are produced by about 30 producers worldwide. 1-Chloro-2-nitrobenzene is a basic chemical which is processed chemically to other intermediates in different fields of application. There is currently no information that there is consumer use.

NATURE OF FURTHER WORK RECOMMENDED

Human Health: The substance is a candidate for further work. Due to possible hazards (haemotoxicity, reproductive toxicity, genotoxicty, and carcinogenicity) the exposure situation in occupational settings and consumer settings should be clarified and, if then indicated, a risk assessment should be performed.

Environment: The substance is a candidate for further work. Environmental exposure at the sponsor company is adequately controlled. However, as there are no information on environmental releases from other production / processing sites, exposure assessment should be conducted and, if then indicated, a risk assessment may need to be considered. This is justified because the substance is not readily biodegradable and has a PNECaqua of 26 µg/l.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 88-73-3
IUPAC Name: 1-Chloro-2-nitrobenzene
Molecular Formula: $C_6H_4ClNO_2$

1.2 Purity/Impurities/Additives

The purity of the substance is given with > 99 % w/w.

1.3 Physico-Chemical properties

1-Chloro-2-nitrobenzene is a yellowish substance with a melting point of about 32 °C (Bayer AG 1989). With a density of 1.37 g/cm³ at 22 °C 1-chloro-2-nitrobenzene is heavier than water (Ullmann 1991). The substance is soluble in water with 441 mg/l at 20 °C (Eckert 1962). The vapour pressure has been tested to 4.0 Pa at 20 °C (Bayer AG 2001a). Log K_{ow} is measured with 2.24 (Leo et al. 1971).

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The world wide (excluding East Europe) production of 1-chloro-2-nitrobenzene amounted to 111,800 tons in 1995 (about 27,000 in West Europe, 19,000 t in USA, 9,000 t in Japan, 39,000 t in China, 15,500 t in India, and 2,300 t in South Korea) by approximately 30 producers. There is no information about production in East European countries (Bayer AG 2001).

1-Chloro-2-nitrobenzene is a basic chemical, used industrially for manufacturing of further intermediates by chlorination, nitration, sulfonation, reduction, and substitution. In the following an overview of further processing products and their percentage is given:

- 2-nitroaniline (31 %), an intermediate mainly for pesticides

- dichlorobenzidine (26 %), 2-nitroanisole (23 %), and 2-chloroaniline (8 %), processed mainly to dyestuffs and pigments

- others (12 %), including the manufacturing of nitrochlorobenzenesulphonic acid, dinitrodiphenyldisulphide, and nitrophenetole which are processed mainly to dyestuffs and pigments, of o-fluoronitrobenzene which is processed mainly to pharmaceuticals, and of nitrophenol an intermediate mainly for pesticides.

These data relate to the above cited world wide production demand in 1995 (Bayer AG 2001).

A direct use of 1-chloro-2-nitrobenzene is not known (Bayer AG 2001).

Production of 1-chloro-2-nitrobenzene takes place by mono-nitration of chlorobenzene in a continuously working closed system. Initially a mixture of chloronitrobenzenes is gained. This mixture is separated by distillation- and crystallisation procedures yielding 1-chloro-2-nitrobenzene with a purity above 99 % (Bayer AG 2001).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases into the environment may occur during production and processing.

Readily available information on exposure from production and processing to the chemical in the Sponsor country at Bayer AG is available.

The exhausts from production and processing of 1-chloro-2-nitrobenzene are connected to air washing units and thermal exhaust purification plants. Thus during normal operation no 1-chloro-2-nitrobenzene is emitted. Following the Official German Emission Declaration in year 2000, less than 25 kg/a 1-chloro-2-nitrobenzene were emitted into the atmosphere (Bayer AG 2001).

Waste water leaving the production and processing facilities are pretreated before reaching the industrial waste water treatment plant. 1-Chloro-2-nitrobenzene is monitored daily at the influent and the effluent of the waste water treatment plant.

Weekly, at changing days, the effluent is monitored on a fine analysis scale. All values of the fine analysis scale from January 2000 to May 2001 showed the substance to be eliminated to less than 5 µg/l. As worst case for the receiving water a PEC of < 0.007 µg/l is calculated from this effluent concentration taking the 10 perzentil of the river flow into account (Bayer AG 2001).

There is no information on releases into the environment from other production and processing sites.

Significant environmental releases from biological reformation of 1-chloro-2-nitrobenzene from end-products are not likely to occur. This is supported by monitoring data from German surface waters for the years 1991 – 2000. These data show that the environmental concentration of 1-chloro-2-nitrobenzene (90%ile) is in the range of < 0.005 µg/l to 0.58 µg/l.

A significant exposure to the terrestrial compartment could not be identified.

2.2.2 Other Information on Environmental Fate

With regard to its chemical structure 1-chloro-2-nitrobenzene is not expected to hydrolyze under environmental conditions. According to the Mackay Fugacity Model Level I (1991), the main target compartments for 1-chloro-2-nitrobenzene are the hydrosphere with 65.4 %, followed by air with 32.9 %. The Henry constant is calculated to be 1.43 Pa m^3 mol^{-1}.

Based on the available experimental data 1-chloro-2-nitrobenzene is not readily biodegradable. In a modified MITI I test according to OECD guideline 301 C a non adapted mixed microbial inoculum mineralized 8.2 % of the initial test substance concentration within 14 days (MITI 1992).

Using the model Simpletreat 3.0 the following distribution/elimination in sewage treatment plants can be estimated using a degradation rate constant of 0 h^{-1} (not readily biodegradable), a Henry constant of 1.43 Pa m^3 mol^{-1} and a log Kow of 2.24:

% to air	2.7
% to water	95.2
% to sludge	2.1
% degraded	0
% removal	4.8

The comparison of influent and effluent concentrations of an industrial sewage treatment plant showed the substance to be removed to > 95 % [Bayer AG 2001]. However, this elimination cannot be transferred to other sewage treatment plants due to possible different waste water composition and adaptation processes.

Examination of the degradation pathway of chloronitrobenzenes, showed these substances only to be biodegraded by isolated bacteria and adapted mixed sludge as long as the chloronitrobenzenes are not the only sole source for carbon and nitrogen (Kuhlmann 1999).

The indirect photochemical degradation in air by hydroxyl radicals is calculated with a half-life of 187.2 days.

Measured bioconcentration factors (BCF) determined for fish (Cyprinus carpio) according to OECD guideline 305 C, were in the range of 7.0 – 22.3. 1-Chloro-2-nitrobenzene concentrations of 0.25 and 0.025 mg/l had been tested. Thus no significant potential for bioaccumulation of 1-chloro-2-nitrobenzene in aquatic organisms is indicated (MITI 1992).

There is no test on geoaccumulation available. Binding to soil organic matter has been calculated with Koc = 315.5 [SRC-PcKocWIN v1.66, 2000]. According to Blume [1990] 1-chloro-2-nitrobenzene can be regarded as a substance with medium geoaccumulation properties.

2.3 Human Exposure

Note: In Germany/Europe no workplace limit concentration is laid down for 1-chloro-2-nitrobenzene as the substance is classified in Germany in Cancerogenicity Category 3 and Fertility Category 3. A technical limit concentration (TRK-Wert) is planned by German authorities according to "Bundesministerium für Arbeit und Sozialordnung: Übernahme von Luftgrenzwerten in die TRGS 900 Bundesarbeitsblatt 7-8/1998; S. 70-71".

2.3.1 Occupational Exposure

From information from the Swiss (July 2001) and Swedish product register (September 2001) there is no other use pattern of 1-chloro-2-nitrobenzene than intermediate confirmed. To protect workers from exposure to 1-chloro-2-nitrobenzene at workplace, several different precautionary and protective measures are undertaken.

Workplace monitoring is carried out periodically and appropriate personal protection equipment is prescribed in detail for different work situations.

During the past five years (1997 - 2001) 31 8-hour shift samples were taken. Thereof 25 measurements were < 0.05 mg/m³. One measurement was < 0.32 mg/m³, the higher determination limit was due to a smaller air volume taken. Four measurements, taken during filling operations showed values between 0.032 and < 0.6 mg/m³. Here masks were worn to protect the workers from inhalation of 1-chloro-2-nitrobenzene. One value of 0.11 mg/m³ was caused by not appropriate sampling within the production process. This source of exposure has been put right immediately [Bayer AG 2001].

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

1-Chloro-2-nitrobenzene, under appropriate conditions of exposure, is absorbed by the body both via the skin and the gastrointestinal tract as well as via the respiratory tract. Rat studies with labelled chemical show that 1-chloro-2-nitrobenzene absorption is 80 % following oral administration and at least 40 % after open dermal application. 0n 11 consecutive days, 65 mg 1-chloro-2-nitrobenzene/kg bw was administered by gavage to adult and to old rats. On d 1, 5, and 9 applied substance was labelled and urine and faeces were collected in the following 96 hours. The adult rats excreted 71-74 % of the dose in the urine and 20-27 % of the dose in the faeces. Excretion rate increased with the duration of treatment. Urinary excretion rate in the old rats consisted 71-85 % of the dose and did not increase with the duration of treatment. The radioactivity level in the tissues were determined 72 hours after d9-treatment and shown to be found 5 % of the dose in adult rats and 8 % in the old rats. At very high doses, e.g. 200 mg/kg bw given orally, urinary excretion is delayed and faecal excretion is markedly suppressed. There is evidence to suggest involvement of the enterohepatic cycle, but there are no signs of accumulation of 1-chloro-2-nitrobenzene or one of its metabolites (BG-Chemie 2000, Nomeir et al. 1992).

After oral administration of 100 mg 1-chloro-2-nitrobenzene/kg bw to rabbits 42 % of the dose was excreted in the urine as glucuronides, 24 % as sulfates, 7 % as mercapturic acids and 9 % as free 2-chloroaniline. Only 2-Chloroaniline (0.3%) could be detected in the faeces. 48 hours after administration elimination was complete (Bray et al. 1956).

In tissue, only a very small fraction of the administered radioactivity is recovered (BG-Chemie 2000).

The main metabolic routes for 1-chloro-2-nitrobenzene in the body consist in reduction of the nitro group to an amino group and hydroxylation of the benzene ring. Apart from 2-Chloroaniline, the corresponding nitrophenols and aminophenols are formed, which are excreted as conjugates of glucuronic acid and sulfuric acid. 2-Chloroaniline also appears in the urine and faeces in the unconjugated form (BG-Chemie 2000, Bray et al. 1956, Sabbioni 1994, Rickert and Held 1990).

During reduction of the nitro group to the amino group, the hydroxylamine compound is formed as a highly reactive intermediate which has been detected both in vivo in rats, and in vitro (BG-Chemie 2000, Sabbioni 1994)

3.1.2 Acute Toxicity

Inhalation

There are no studies according to the current OECD guideline but there are study reports with rats which give sufficient information to evaluate this endpoint: (Haskell Laboratory, 1992) LC_{50} ca. 3200 mg/m^3 for 4 hours (= 495 ppm, vapor/aerosol mixture) . Signs of intoxication during exposure were lethargy, slight to moderate cyanosis, slight to moderate corneal opacity, semi-prostration or prostration, reddish brown nasal discharge and tachypnoe. Signs of intoxication post exposure were pallor, reddish brown nasal discharge, semi-prostration and lethargy, corneal opacity.

Death occurred within 7 days but not dose-dependently. Thus LC_{50} value was calculated from statistically not significant regression.

Conclusion

The acute inhalative toxicity is moderate: LC_{50} (rat) ca. 3200 mg/m³ (= 495 ppm, vapor/aerosol mixture) for 4 hours. Cyanotic appearance was the predominant symptom.

Dermal

There are no studies according to the current OECD guideline but there are study reports with rats and rabbits which give sufficient information to evaluate this endpoint: (Bayer 1976): The dermal LD_{50} following a 24-hour occlusive application of the test material to the skin of rats is determined to be 1320 mg/kg bw in females and 655 mg/kg bw in males. The test material was applied as emulsion with the vehicle polyethylene glycole 400. Reduced general condition, difficulties in breathing and cyanotic appearance were the signs of intoxication starting 18 hours post application. Skin irritation was not reported. Deaths occurred within 4 days (males), and 7 days (females), respectively. A section was not performed. In rabbits (2/sex/dose, undissolved substance but warmed to make suitable for dosing, no further information on application procedure, 5 doses, exposure time: 24 hours, observation time: 14 d; Younger Labs. Inc. 1992) the LD_{50} was 400 mg/kg bw (male: 445 mg/kg bw; female: 355 mg/kg bw). Lethargy for up to three days, increasing weakness, collapse and deaths were reported. At gross autopsy, decedents showed haemorrhagic areas in the lungs, liver-, kidneys- and spleen-discoloration, gastrointestinal inflammation and enlarged gall bladder whereas in survivors the viscera appeared normal.

A further investigation on acute dermal toxicity with rabbits yielded a similar result (LD_{50} = 450 mg/kg bw, 5/dose). The sex of the animals used was not mentioned and a section was not performed (United States Testing Company 1976).

Conclusion

The acute dermal toxicity is moderate (LD_{50} (rat, male) = 655 mg/kg bw, LD_{50} (rat, female) = 1320 mg/kg bw; LD_{50}(rabbit) = 400 mg/kg bw (male: 445 mg/kg bw, female: 355 mg/kg bw)). Cyanotic appearance was the predominant symptom.

Oral

There are no studies according to the current OECD guideline but there are study reports with rats which give sufficient information to evaluate this endpoint: (Bayer, 1982 a; b) LD_{50} (Wistar, male) 251 mg/kg bw; LD_{50} (Wistar, female) 263 mg/kg bw. As signs of intoxication rats displayed reduced general condition, cyanotic appearance, rough fur, sedation, narcosis and females showed paralysis of the hind limb. Death occurred within 3 days. No macroscopic findings were recorded from decedents and from survivors 14 days post application. In another study the LD_{50} of male and female Sprague-Dawley rats was determined to be 560 mg/kg bw (Younger Labs 1991). As signs of intoxication reduced appetite and reduced activity (in survivors for at least 2-3 days), increasing weakness, ocular discharge, collapse and death were noted. Death occurred within one to four days post application of 1-chloro-2-nitrobenzene, with most death within 2 days. Hemorrhagic lungs, jaundiced liver, darkened kidneys and spleen and gastrointestinal inflammation were seen at gross autopsy of decedents. From survivors 7 days post application, lung congestion and darkened kidneys and spleen were reported.

An older study on male Wistar rats (Hoechst 1975) yielded an LD_{50} of 144 mg/kg bw. As signs of intoxication rats showed imbalance, tremor, rough fur and diarrhea. Section of the rats, that had died, could not be performed because of ongoing autolytic changes.

Conclusion

After single oral application 1-chloro-2-nitrobenzene is toxic to moderate toxic (LD_{50}, oral: rat, male: 144, 251 or 560 mg/kg bw; rat, female: 263 or 560 mg/kg bw). Cyanotic appearance was the predominant symptom.

3.1.3 Irritation

Skin Irritation

There are no studies according to the current OECD guideline but there are study reports with rabbits which give sufficient information to evaluate this endpoint:

In an older study, 0.5 ml of a 10 % sesame oil solution of 1-chloro-2-nitrobenzene was applied to the shaved (intact and abraded) skin of six rabbits for 24 hours covered by semi-occlusive dressing. When the dressing was removed (24 hour-reading) only mild erythema (score 1/0-4) was noted in both, intact and abraded skin of 4/6 rabbits. Erythema were not observed at 48 hour- and at 72 hour-reading. According to Fed. Reg. 38, No 187, p. 27109, §1500.41, 1973, the compound was evaluated as no irritant (Hoechst 1975).

In another study, 500 mg 1-chloro-2-nitrobenzene was applied undissolved to the inner surface of one ear of each of two rabbits for 24 hours covered by cellulose pads and plaster. To fix the plaster tightly a rolled gauze pad was put on it. Ear, substance, pad, plaster and rolled pad were then bandaged. No signs of irritation (sore 0/4) were observed neither when the pad, plaster, rolled pad were removed nor during the 7 day post exposure observation period (Bayer 1976). In addition, in the same report, the results of acute dermal testing in rats with the substance formulated in polyethylene glycole 400 are mentioned. Signs of irritation were not reported.

0.5 ml of warmed, undiluted 1-chloro-2-nitrobenzene was applied to the skin of six rabbits for 24 hours. No erythema or edema was observed till 168 hours after application (no information about the type of application and pretreatment of the skin) (Younger Labs. 1991).

No skin irritation was reported in an acute dermal toxicity study (see chapter 3.2.3; Bayer 1976).

Conclusion

The study documentation of the available studies is incomplete in one case and in the two other cases the test substance was applied undissolved or respectively diluted. However, the studies gave no evidence of a skin irritating potential of 1-chloro-2-nitrobenzene.

Eye Irritation

There are no studies according to the current OECD guideline but there are study reports with rabbits which give sufficient information to evaluate this endpoint:

In an older study, performed as described in Fed. Reg, Vol. 38, No.187, §1500.42, 1973, 100 mg of 1-chloro-2-nitrobenzene was applied undissolved into one eye of each of 6 rabbits (the other eye served as control). One hour post application slight conjunctival injections (score 1-2/0-3) were noted in the eyes of 6/6 rabbits, 7 hours post application in the eyes of only 2/6 rabbits (score 1/0-3) and 24 hours post application no irritational effects were observed. The compound was evaluated to be a mild irritant (Hoechst 1975).

In another study in the same report, a 10 % solution was applied into one eye of each of 6 rabbits which leads to slight irritational effects (score 1/0-3) in the eyes of 3/6 rabbits one hour post application. These effects had disappeared after 7 hours. The compound was evaluated as slightly irritating (Hoechst 1975).

In another study 50 mg 1-chloro-2-nitrobenzene was applied into the right eye of each of two rabbits. Slight redness (score 1/3) was observed in the eye of one rabbit, which disappeared within 24 hours. No signs of irritation were observed in cornea neither on the application day nor during the 7 day post exposure observation period (Bayer 1976).

Conclusion

1-Chloro-2-nitrobenzene caused slight irritational effects to the eyes of rabbits which were reversible within 24 hours.

3.1.4 Sensitisation

Skin

Skin sensitization potency was examined in tests with 10 guinea pigs using test methods which are no longer in use and which are incompletely documented (Rusakov 1973): In a modified Draize test induction was performed with an 1 % aceton-solution of the compound on the shaved back for 5 consecutive days. At day 7 challenge was performed with the same solution. As there was no skin reaction observed, a modified Freunds complete adjuvant test was performed: the same guinea pigs were treated with a 10 % solution of 1-chloro-2-nitrobenzene at day 22: 0.2 ml Freunds Adjuvans together with 0.5 mg 1-chloro-2-nitrobenzene/kg bw was injected into the hind paw. 6 days later one drop of a 10 % solution of 1-chloro-2-nitrobenzene was applied on the shaved untreated skin as challenge. The author reported that 50 % of the treated guinea pigs showed a positive reaction. Rats exposed via inhalation to 0.008 mg/m^3 for 5 months showed also positive reactions (see above; Rusakov et al. 1973).

Conclusion

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.

3.1.5 Repeated Dose Toxicity

Inhalation

The repeated dose toxicity was examined in male and female Fischer 344/N rats and in male and female B6C3F1 mice for a period of 13 weeks via whole body inhalation of vapor (NTP 1993).

During exposure rats and mice were observed twice daily and were weighed at the start of the study, weekly thereafter and at necropsy. Clinical observations were recorded weekly. After cessation of exposure, complete necropsies were performed on all animals. Histopathologic evaluations, especially on target organs identified (kidney, liver, nasal cavity, and spleen (rats); liver and spleen (mice)) and on reproductive organs (see also chapter 3.2.10) were performed on all animals in the control and the highest exposure groups and on all animals that died early. Target organs identified were also examined in all lower exposure groups.

Groups of 10 male and 10 female rats were exposed to 0, 1.1, 2.3, 4.5, 9, 18 ppm (approx. 0, 7, 14.7, 28.8, 57.6, or 115.2 mg/m^3), 6 hours per day, 5 days per week over a period of 13 weeks. Additional 10 male and 10 female rats per group were exposed for clinical pathology studies at d 1 (only methaemoglobin - data not shown), d 4, and d 23 consisting of hematology and clinical chemistry evaluations. Animals in the base study were evaluated at the end of the study. There were no clear clinical signs of toxicity. All rats survived till the end of the study. Body weight gain was similar to the respective controls. At necropsy, males of the 18 ppm group had significant increased spleen (absol. and rel.) and from 9 ppm increased right kidney (rel.) weights. Absolute liver weights were increased from 1.1 ppm and the relative liver weight from 2.3 ppm. In males exposed to 18 ppm, abs. and rel. lung weights were significant decreased. 2/10 males in the 18 ppm group showed

darkened spleen. Histopathologic evaluation of the kidney showed tubule pigments from 4.5 ppm and tubule regeneration from 1.1 ppm. In the liver, cytoplasmic basophilia was noted from 9 ppm. Spleenic congestion was observed in all exposed and in the control male rats with dose-dependent slight increase in severity. Females, at necropsy, had increased right kidney (absol. and rel.) in the 18 ppm-group and increased absolute liver weights from 2.3 ppm and increased relative liver weights from 4.5 ppm. Significant increased spleen weights (absol. and rel.) were noted from 4.5 ppm. 1/10 females in the 18 ppm group showed darkened spleen. Histopathologic evaluation yielded in the kidney tubule pigment and cytoplasmic basophilia of the liver from 9 ppm. Spleenic congestion was noted in exposed and in the control females with dose-dependent slightly increased incidences. Hyperplasia of the nasal cavity respiratory epithelium in all exposed male and female rats was considered as a toxic effect due to 1-chloro-2-nitrobenzene exposure.

Concentration-related increase in methaemoglobinaemia (males: significant from 1.1 ppm at d 23 and from 2.3 ppm at all time points with max. of 1.14 g/dl at 18 ppm; females: significant from 1.1 ppm at week 13 and from 2.3 ppm at all time points with max. of 1.04 g/dl at 18 ppm; data from d1 not shown) and oxidative damage to red blood cells occurred from the first days of exposure (males: significant at 1.1 ppm (d23), at 4.5 ppm (week 13), at 9 ppm (d4, week13), at 18 ppm (at all time points) when compared to the control values at the respective time point; females: significant in every exposure group at week 13 when compared to the control values at the respective time point). Decrease in haematokrit, haemoglobin and increase in leukocytes predominantly in the highest dose groups of male and female rats was recorded. The beginning regeneration could be recognized in the increase in reticulocyte count at all dose groups of male and female rats at week 13. Serum activities of alanine aminotransferase and sorbitol dehydrogenase were mildly increased in different male and female exposure groups at various time points. A NOAEL was not achieved, the LOAEL is 1.1 ppm (7 mg/m³).

Male and female mice were exposed to 0, 1.1, 2.3 , 9, 4.5, 18 ppm, 6 hours per day, 5 days per week over a period of 13 weeks. There were no clinical signs of toxicity. 2/10 male mice exposed to 18 ppm died. In females from 1.1 ppm body weight gain was greater than in the concurrent control females; in males, body weight gain was similar to the respective control. Exposed mice had treatment-related increased liver and kidney weights (males: abs. and rel. right kidney weights, rel. liver weights sign. increased from 2.3 ppm, abs. liver weights from 9 ppm; females: abs. right kidney weight from 2.3 ppm, abs. liver weights in all exposed groups, rel. liver weight from 9 ppm) . Pale discoloration in the liver was noted in 6/10 males and 1/10 females in the 18 ppm group. The spleen was grossly enlarged in 3 females in the 9 ppm group and 4 females in the 18 ppm group. Hepatocellular necrosis, cytomegaly, mineralization and chronic inflammation were seen in the liver, primarily in mice in the 18 ppm group but also in the 9 ppm-group. In addition, increased haematopoetic activity of the spleen was seen in both sexes of mice, particularily in females at 9 ppm and greater. The NOAEL for histopathologic injury is 4.5 ppm (28.8 mg/m³).

Oral

The repeated dose toxicity was also examined in a subacute feeding study with B6C3F1 mice according OECD Guideline 407 (Bayer 1991, 1993). The objective of the study was to recognize possible prae-neoplastic lesions by means of enzyme histochemistry.

12 mice/sex/dose received 0, 50, 500, 5000 ppm 1-chloro-2-nitrobenzene for 5 weeks. Additional 6 mice/sex/dose were used for interim kill and examination after one week of treatment. The calculated feed intake was 0, 16, 167, 1120 mg 1-chloro-2-nitrobenzene/kg bw/day for males and 0, 24, 220, 1310 mg/kg bw/day for females. Except of one male in the lowest dose group, no animal died during treatment. No clinical signs of toxicity up to and including 500 ppm were observed. At 5000 ppm narrowed palpebral fissures and corneal opacity in males were reported. From 5000 ppm reduced body weight gain and reduced food intake in both sexes and additionally in females from 500 ppm.

From 5000 ppm in both sexes reduced number of erythrocytes (change in morphology: anisocytosis, poikilocytosis and polychromasie), haematokrit- and haemoglobin-content and increased bilirubin-, methaemoglobin-(f: 2.8 %; m:1,7 %) MCV-, MCH- and MCHC-values. Increased spleen weights, dark red discoloration of the spleen and increased haemosiderin deposition could be seen.

No treatment related changes in the kidneys were observed.

From 500 ppm increase in cholesterin content in the blood, increased liver weights (differences of up to 89 % were noted in females) accompanied by hypertrophy of the centrolobular hepatocytes. From 5000 ppm gross changes in the liver, increase in the activity of ASAT and ALAT and alkaline phosphatase (male) was noted. In males, blood-urea was decreased.

Additional investigations demonstrate from 500 ppm increase in liver enzyme activities (EOD, ALD, EH, GSH-T,GLU-T) and disturbance of carbohydrate metabolism (decreased gluconeogenesis and glycogen, activated pentose phosphate cycle (at 5000 ppm), increased glycolysis (at 5000 ppm)).

At 5000 ppm males showed decreased testis weight without histopathological changes.

No other treatment-related functional disturbances or impairment of other organs were observed.

Thus, the NOAEL of 50 ppm (16 mg/kg bw/day for males and 24 mg/kg bw/day for females) could be derived.

Also in several other studies on rats and mice with oral or inhalational exposure for 2 and 4 weeks or 7 months, spleen, liver and kidneys were identified as target organs.

Effects on CNS function in rats were reported in a subchronic oral study with poor reliability (Davydova SG 1967). These effects cannot be evaluated because of the incomplete description of the results and the method used.

Conclusion

The repeated dose toxic ity was examined in rats and in mice for a period of 13 weeks via whole body inhalation. As target organs liver, kidney and spleen were identified in both species, and furthermore, in rats erythrocytes and the nasal cavity respiratory epithelium. The NOAEL in rats was not achieved, the LOAEL is 1.1 ppm (7 mg/m³). In mice, increased liver and kidney weights were observed even at 1.1 and 2.3 ppm, respectively. The NOAEL for histopathological injury in mice is 4.5 ppm (28.8 mg/m³).

In a subacute feeding study with mice target organs were blood, spleen and liver. The NOAEL was 50 ppm (males: 16 mg/kg bw/day ; females 24 mg/kg bw/day).

3.1.6 Mutagenicity

In vitro Studies

(A) Gene mutation

There are several Ames-tests which are mostly performed according to OECD Guideline 471 with and without metabolic activation. In every study at least the highest dose levels exhibit 100 % toxicity. For example 1-chloro-2-nitrobenzene was evaluated as mutagenic in the tests reported by Haworth et al. (1983) (doses: 6-600 resp. 10-1000 µg/plate) and by Bayer (1984) (doses: 833.3-2073.6 µg/plate). An additional Ames test, which was reported in JETOC (1996) (doses: 10-1000 µg/plate), yielded negative results. A repetition of the study (doses: 39.1-10000 µg/plate) showed

positive results in TA 100 and TA98. Investigations with E. coli yielded positive and negative results (JETOC 1997).

In a study with deficiencies in the description of results, 1-chloro-2-nitrobenzene showed mutagenic acitivity in *Salmonella typhimurium* TA98 with metabolic activation and norharman (Suzuki et al. 1983). In summary, the available tests with *Salmonella typhimurium* showed mostly negative results without the addition of a metabolic activation system in different strains. Only in strain TA98 and TA1538 there were obtained mostly negative and one resp. 2 positive results. In the presence of a metabolic activation system positive and negative results were obtained in TA 98 and TA 100 mostly at high but not bacteriotoxic concentrations.

In an HPRT Test which was performed with Chinese Hamster V79 lung cells according to OECD Guideline 476 1-chloro-2-nitrobenzene does not induce gene mutations. The doses used were 100-1200 ug/ml in the presence of S9-mix and 100-900 ug/ml without S9-mix. Cytotoxicity was noted in the highest concentration (TNO 1989).

Conclusion

1-Chloro-2-nitrobenzene yielded positive results only in 2 tester strains of Salmonella typhimurium and mostly at high but not bacteriotoxic concentrations. Therefore it can be regarded as a weak mutagen in bacterial test systems. It showed no mutagenic activity in mammalian cell test systems in vitro.

(B) Cytogenicity

There is a study on cytogenicity using Chinese Hamster Ovary (CHO) cells and doses ranging from 10-100 µg/ml without addition of a metabolic activation system (S9-mix) and from 25-250 µg/ml in the presence of S9-mix. Harvest times were 8, 12, 21 hours. The study was performed according to OECD Guideline 473 and yielded negative results (Huntingdon 1988).

NTP (1993) reported additional cytogenetic tests with Chinese Hamster Ovary cells using different harvest times: Without metabolic activation an equivocal result at the highest concentration was obtained when the harvest time was 14 hours (doses: 16-160 ug/ml) and a negative result with a harvest time of 18.5 hours (dose: 47-216 ug/ml). In the presence of an activation system negative results were obtained after a harvest time of 14 hours (doses: 50-500 µg/ml) and weak positive results at the highest concentration when the harvest time was 13.6 hours (doses: 101-465 and 125-500 µg/ml).

Conclusion

1-Chloro-2-nitrobenzene showed weak clastogenic activity in CHO cells in vitro at high concentrations only.

(C) Indicator Tests

1-Chloro-2-nitrobenzene did not increase Unscheduled DNA repair in rat hepatocytes using a dose range from 1.0 to 100 µg/ml DMSO. Cytotoxicity was determined in preliminary results (Monsanto 1984).

An increase in Sister Chromatid Exchange (SCE) rate was found in Chinese Hamster Ovary cells treated with 1-chloro-2-nitrobenzene in doses ranging from 5 to 500 µg/ml (NTP 1993). The biological relevance of SCE is not yet clear.

Conclusion

1-Chloro-2-nitrobenzene did not induce Unscheduled DNA repair. It induced increased rates of Sister Chromatid Exchanges, whereas the biological relevance of this effect is not yet clear.

In vivo Studies

(A) Gene mutation

There are several Drosophila SLRL tests which are performed using different application routes: intraperitoneal injection, adult and larval feeding. Both dosing methods lead to negative results (Zimmering 1985, 1989).

Conclusion

1-Chloro-2-nitrobenzene showed no mutagenic activity in *Drosophila melanogaster*.

(B) Cytogenicity

Intraperitoneal injection of 60 mg 1-chloro-2-nitrobenzene/kg bw of unknown purity into CD-1 mice (n=8) induced single DNA strand breaks in liver and kidneys which were identified by alkaline elution technique (Cesarone et al. 1982). Intraperitoneal injection, however, is not the recommended exposure route of the respective OECD guideline because it could expose the organs directly rather than via the circulatory system.

Conclusion

Intraperitoneal injection of 1-chloro-2-nitrobenzene into mice resulted in DNA damage in the liver and kidney.

Conclusion

1-Chloro-2-nitrobenzene showed weak mutagenic activity in bacterial test systems but not in mammalian cell test systems in vitro. It was not mutagenic in *Drosophila melanogaster*. In mammalian cells in vitro, it showed weak clastogenic activity. The substance induced increased rates of Sister Chromatid Exchanges, whereas the biological relevance of this effect is not yet clear. Intraperitoneal injection into mice resulted in DNA damage in the liver and kidney. The inconsistent results of the available genotoxic studies are typical for nitroaromatics. As a whole 1-chloro-2-nitrobenzene is suspected of being genotoxic, at least a weak clastogen.

3.1.7 Carcinogenicity

For evaluating carcinogenicity the only available studies in rats and mice don't meet the criteria of today (doses too high, number of animals too low, duration time too short) and are only reported in brief (Weisburger et al. 978).

25 male CD rats/group were given 1-chloro-2-nitrobenzene in the diet for 18 months (50 % of MTD, MTD): 0, 1000, 2000 mg/kg diet (approx. 0, 75, 150 mg/kg bw/day). After 6 months of treatment, dosage was reduced to 500, 1000 mg/kg diet (approx. 37.5, 75 mg/kg bw/day), because body weight gain was reduced by 10 % when compared to the control group or deaths occurred from toxicity (no further information). Reduced doses were given for the remaining 12 months. Following the 6-month-observation period, necropsy was performed and male rats with tumours were recorded: 1/22 in the simultaneous control group (pooled control: 14/111) and 7/22 resp 1/19 in the low resp. the high dose group. These tumours of the low dose group usually included

pituitary adenomas along with either a stomach papilloma, a tumour of the adrenals, a thyroid adenocarcinoma, a lymphosarcoma, a bile duct carcinoma or a subcutaneous fibroma.

25 male and female CD1 HaM/ICR mice/group were given 1-chloro-2-nitrobenzene in the diet for 18 months (50 % of MTD, MTD): 0, 3000, 6000 mg/kg diet (approx. 0, 450, 900 mg/kg bw/day). After 8 months of treatment dosage was reduced to 1500, 3000 mg/kg diet (approx. 225, 450 mg/kg bw/day) which was given for the remaining 10 months (see above). Following the 3-month-observation period, necropsy was performed and mice with tumours were recorded: 3/18 (m), 0/20 (f) in the simultaneous control group (pooled control: (m) 7/99, (f) 1/102) and 7/17 (m), 5/22 (f) resp 3/16 (m), 5/19 (f) in the low resp. the high dose group, identified as hepatocellular carcinomas.

The objective of a subacute **feeding** study with B6C3F1 mice was to recognize possible prae-neoplastic lesions by means of enzyme histochemistry.

12 mice/sex/dose received 0, 50, 500, 5000 ppm 1-chloro-2-nitrobenzene in the diet for 5 weeks. Additional 6 mice/sex/dose were used for interim kill and examination after one week of treatment. The calculated feed intake was 0, 16, 167, 1120 mg/kg bw/day for males and 0, 24, 220, 1310 mg/kg bw/day for females. Except of one male in the lowest dose group, no animal died during treatment.

The additional investigations demonstrate from 500 ppm increase in liver enzyme activities (EOD, ALD, EH GSH-T, GLU-T) and disturbance of carbohydrate metabolism (decreased gluconeogenesis and glycogen, activated pentose phosphate cycle (at 5000 ppm), increased glycolysis (at 5000 ppm)). These marked changes in the carbohydrate metabolism were evaluated as possible promotion activity of 1-chloro-2-nitrobenzene (Bayer 1991, 1993).

Conclusion

1-Chloro-2-nitrobenzene induced tumours in different organs of rats and in the liver of mice.
Overall taking into consideration the results of the genotoxicity tests, the analogy to other nitroaromatics and the results of the available limited studies in rats and mice, there is a concern for a carcinogenic potential of 1-chloro-2-nitrobenzene.

3.1.8 Toxicity for Reproduction

Effects on Fertility

There are no specific studies on toxicity to reproduction using inhalative exposure, but there is a 13 week inhalation study which also evaluated the reproductive organs and can therefore be taken into account for this exposure route.

Male and female F344/N rats were exposed to 0, 1.1, 2.3, 4.5, 9, 18 ppm (0, 7, 14.7, 28.8, 57.6, 115.2 mg/m^3), 6 hours per day, 5 days per week over a period of 13 weeks (NTP, 1993; see also chapter 3.2.7). At the end of the study sperm morphology and vaginal cytology evaluations were performed of animals in the 0, 4.5, 9 and 18 ppm groups (reproductive organs of animals of the two lower exposure groups were not evaluated).

There were no clear clinical signs of toxicity. All rats survived till the end of the study. Concentration-related increase in methaemoglobinaemia and oxidative damage to red blood cells occurred from the first days of exposure and resulted in a regenerative anaemia; target organs were kidneys, spleen, liver, erythrocytes and nasal cavity respiratory epithelium (for details see chapter 3.2.7). Males of the 18 ppm group showed decreases in cauda epididymis weights and in the spermatid count and spermatid heads/testis (NOAEL $_{\text{reproductive organs}}$ = 9 ppm). Females reproductive system was not affected by treatment (NOAEL $_{\text{reproductive organs}}$ = 18 ppm).

Male and female B6C3F1 mice were exposed to 0, 1.1, 2.3, 4.5, 9, 18 ppm (0, 7, 14.7, 28.8, 57.6, 115.2 mg/m^3), 6 hours per day, 5 days per week over a period of 13 weeks (NTP 1993). At the end of the study sperm morphology and vaginal cytology evaluations were performed of animals in the 0, 4.5, 9 and 18 ppm group (reproductive organs of animals of the two lower exposure groups were not evaluated): There were no clinical signs of toxicity. 2/10 male mice exposed to 18 ppm died; target organs were kidneys, spleen and liver (for further details see also Chapter 3.2.7). Male mice in all evaluated dose groups demonstrated a decrease in sperm motility (a $NOAEL_{reproductive\ organs}$ for male mice was not determined); in females no effects were observed ($NOAEL_{reproductive\ organs}$ = 18 ppm).

In a 5 week feeding study 12 B6C3F1 mice/sex/dose received 0, 50, 500 or 5000 ppm 1-chloro-2-nitrobenzene. Males of the highest dose group showed decreased testis weight without histopathological changes (Bayer 1991, 1993; for further details on general toxicity see chapter 3.2.7).

There is a carefully performed study on toxicity to reproduction in mice using oral treatment (NTP 1992):

Male and female Swiss CD-1 mice were exposed to 1-chloro-2-nitrobenzene dissolved in corn oil by gavage to assess reproduction and fertility using the NTP continuous breeding protocol:

Groups of 20 breeding pairs received 40, 80 or 160 mg/kg bw per day 2-chloronitrotoluene for 7 days prior to cohousing and for 98 days of continuous breeding. 40 breeding pairs received the corn oil vehicle only. The last litter born during the holding period following the continuous breeding phase from control and high dose groups was reared by the dam until weaning, after which time treatment of the F1 animals was initiated by the same route and at the same concentration as the F0 animals. These F1 animals were used for the assessment of second generation fertility.

Data from a 2-week dose-range-finding study were used to set exposure concentration. The highest dose used in the reproduction study was one-half of that caused mortality in the dose-range-finding study.

In the F0-generation mortality occurred in 2, 2, 2 and 3 mice in the control to the high dose groups, respectively, which was suggested not to be treatment related. There was a slight increase in male and post partum dam terminal weights. 3 females in the high dose group appeared cyanotic. No other clinical signs were observed. Necropsy of the high dose mice showed increased spleen weights by 50-100 % and 4-6 fold increased methemoglobin level. No other necropsy data were collected.

Reproductive performance and function of the F0-mice was not affected by treatment: number of litters, pup weight, and viability were all unchanged; live pups per litter and proportion of pups born alive were increased (15% resp. 10%) in the high dose group.

In the final litter of the holding period following the continuous breeding phase, pup weight gain during suckling was lower in the treated groups. At weaning, pups of the high dose group weighed 12% less than control. None of the pups showed clinical signs of toxicity.

Mating of the adult F1 mice (only control and high dose group) revealed no difference between the groups in terms of proportion of mated pairs, number of litters per group, number of live pups per litter and pup weight or viability. Treated F1 male and female mice had 3-fold increased methaemoglobin level compared to the control and were approximately 7 and 5 % heavier than their control counterparts. At necropsy, liver and spleen weights were increased by 40 to 60 %. In male mice, abs. right epididymis and kidney/adrenals weights were increased, seminal vesicle-to-body weight was reduced compared to controls. Sperm measured were unaffected by 1-chloro-2-nitrobenzene exposure (epididymal sperm motility, sperm count, percentage of abnormal sperm). In

females, oestrous cycle were unaffected by 1-chloro-2-nitrobenzene exposure. Thus, NOAEL for fertility is 160 mg/kg bw/day.

Conclusion

Following inhalational exposure of F344/N rats and B6C3F1 mice for 13 weeks, only in males 1-chloro-2-nitrobenzene affects the reproductive organs. Performance of a specific study on toxicity to reproduction (NTP Continuous Breeding Protocol) reveals that 1-chloro-2-nitrobenzene was without reproductive toxicity in a different mice strain following oral treatment by gavage despite of significant changes in liver and spleen weights and despite elevated methemoglobin levels. The $NOAEL_{fertility}$ in Swiss CD-1 mice after oral application is 160 mg/kg bw/day whereas the dams showed general toxicity effects at this concentration.

Because 1-chloro-2-nitrobenzene affected the reproductive organs in systemic toxic doses in male rats and in males of one strain of mice after subchronic inhalation there is a concern for a reproductive toxicity potential, even if an impairment of reproduction after oral administration in males of a second strain of mice could not be detected.

Developmental Toxicity

25 female Sprague-Dawley rats per group received 0, 25, 75 or 150 mg/kg bw/day 1-chloro-2-nitrobenzene dissolved in corn oil by gavage from d6 to d15 of gestation. Due to severe toxicity and high mortality rate of the dams in the 150 mg/kg bw/day group, all females of the 150 mg-group were terminated prior to scheduled sacrifice. One year later, in another laboratory, a third dose group was examined together with a concurrent control group (see later).

No evidence of maternal toxicity was exhibited at the 25 mg/kg level.

For gestation d 6-10 a slight, but not significant reduction in maternal body weight gain at the 75 mg/kg level, urinary staining and alopecia were noted in some dams when compared to the respective control groups. The difference in maternal body weight gain was accompanied by reductions in food consumption for d 6-10. The reductions noted at 75 mg/kg were recovered later in gestation.

Maternal reproductive parameters and fetal body weight in the treatment groups were similar to the respective control groups except for the mean number of early resorptions and postimplantation loss at the 75 mg/kg level. However, postimplantation loss in the respective control group was very low compared to the historical control value.

No differences in the number of the litters exhibiting malformations were evident in the treatment groups compared to the control group. Increased incidences of variations were seen in the 25 and 75 mg/kg group: cervical #7 rib (sign. at 75 mg/kg); and 13 full pairs of ribs with lumbar #1 rudimentary rib; in the 25 mg/kg group: 12 full pair ribs with #13 unilateral full rib and/or rudimentary rib(s). No historical control data were given. Thus, $NOAEL_{maternal\ toxicty}$ is 25 mg/kg bw/day, a $NOAEL_{developmental\ toxicity}$ could not be conclusively derived (Monsanto 1990).

In an additional study which was performed in a different laboratory one year later and which was intended to clarify the observation of the first study, mated female rats received 0, or 100 mg 1-chloro-2-nitrobenzene/kg bw in corn oil by gavage from d6 to d15 of gestation. For gestation d 6-10 slight reduction in maternal body weight loss accompanied by reduction in food consumption for days 6-16 was noted. Maternal reproductive parameters and fetal body weights in the treatment group was comparable to the respective control group. No teratogenic effect nor statistically significant increase of skeletal variations like in the first experiment were observed (IRDC 1984).

Conclusion

Developmental toxicity was examined by two studies with Sprague Dawley rats which both have methodological deficiencies. In one study, due to high mortality rate at the highest dose level, only two doses could be evaluated: $NOAEL_{maternal\ toxicity}$ is 25 mg/kg bw/day, a $NOAEL_{developmental\ toxicity}$ could not be conclusively derived since there was an increase in the number of litters exhibiting specific skeletal variations. In the second study only one dose was applied: $NOAEL_{developmental\ toxicity}$ is 100 mg/kg bw/day, a $NOAEL_{maternal\ toxicity}$ could not be derived. Based on the available studies the overall conclusion is, that there is no indication of developmental toxicity, although there are some limitations within the studies.

3.2 Initial Assessment for Human Health

All available reports relate to mixed exposure, frequently in combination with 4-chloronitrobenzene and/or nitrobenzene. A critical aspect in this context is that the chemical is rapidly absorbed via skin and the respiratory tract. The signs of acute intoxication include methaemoglobinaemia, vomiting, headache and, in severe cases, collapse (Gerbis 1932, Renshaw and Ashcroft 1926, Linch 1974, Sekimpi and Jones 1986)

No allergenic potential had been indicated although 1-chloro-2-nitrobenzene has been used for decades (BUA 1985, BG-Chemie 2000)

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute and Chronic Toxicity Test Results

The lowest valid test concentrations of acute and chronic testing are presented in the following.

Acute toxicity to fish (*Brachydanio rerio*) has been tested in a flow through system according to OECD Guideline 203 with analytical monitoring. The 96 h-LC_{50} was determined to be 34.8 mg/l (Röderer 1990). In a semi static test with *Cyprinus carpio* according to OECD Guideline 203 as well, the 96 h-LC_{50} was determined to be 25.5 mg/l (no information about analytical monitoring) (Zhao 1997). An Early Life Stage Test was conducted in an analytically monitored flow through system with Pimephales promelas. In a first step 50 embryos were tested on hatchability and development after 4 - 5 days of incubation. In a second step 15 randomly selected frys from the initial egg cups where observed on their further development for 33 days. The 33 d-NOEC was determined by the authors Call & Geiger (1992) to be 0.264 mg/l based on the endpoint 'normal larvae' related to the hatched larvae. The review of the raw data of the study shows that at the next higher test concentration of 0.530 mg/l a statistically significant effect compared to the control could be observed, however, there is no dose-effect relation for this endpoint at higher test concentrations. The highest test concentration of 3.9 mg/l shows less normal larvae after hatch with a deviation of 7 % compared to the control. Apart from that regarding the endpoint 'normal larvae related to initial embryos' no effect at any concentration can be seen. Regarding 'weight' and 'length' of the fry, at both endpoints a deviation to the control of > 5 % can be seen at a concentration of 2.04 mg/l. Also for this endpoint there is no dose-effect relationship seen at the next higher concentration. As statistically significant effects for the endpoint “normal larvae” were seen at concentrations above 0.264 mg/l, the NOEC derived by the authors is used for the hazard assessment for reasons of precaution.

With Daphnia three valid acute tests are available. A test according to a Dutch standard test showed a 48 h-EC_{50} of 23.9 mg/l for *Daphnia magna* (Deneer et al. 1989). A second test on *Daphnia carinata*, comparable to OECD guideline 202 part I, showed a 48 h-EC_{50} of 21.3 mg/l (Zhao 1997). For both tests there is no information about analytical monitoring given. The pretest to the reproduction test showed a lower 24 h-EC_{50} of 12 mg/l (nominal). The long-term study revealed a 21 d-NOEC of 3.0 mg/l (measured concentration) for reproduction of *Daphnia magna* (Kühn et al. 1988).

The lowest effect value for algae has been found for *Chlorella pyrenoidosa*. A 96 h-EC_{50} on biomass is reported with 6.9 mg/l (no information about analytical monitoring), but there is no EC_0 value given (Deneer 1989). With the green alga *Scenedesmus subspicatus* the following effect values were found:

48h-E_bC_{50}:	34 mg/l
48h-E_bC_{10}:	11 mg/l
48h-E_rC_{50}:	75 mg/l
48h-E_rC_{10}:	19 mg/l

The lowest available long-term test value without effects, a NOEC of 0.264 mg/l found in the early life stage test with *Pimephales promelas*, is used as basic value for the derivation of the PNECaqua. Since long-term tests with species from three trophic levels are available, an assessment factor of 10 is proposed.

Therefore: PNECaqua = 0.264 mg/l / 10 = 0.026 mg/l.

4.2 Terrestrial Effects

In a test according to OECD-Guideline 208 (Terrestrial plant growth test) a 14 d-EC50 in the range of 3.2 - 10 mg/kg soil dry weight was determined for *Lactuca sativa* regarding the endpoint of growth (Hulzebos 1993). The soil has an organic matter content of 1.8 %. In a second soil with an organic matter content of 1.4 % a 14d-EC50-value of 5.4 mg/kg soil dry weight was found. Both values are related to nominal concentrations.

With an assessment factor of 1000 a PNECsoil of 3.2 µg/kg dw can be derived from this test.

4.3 Other Environmental Effects

No data available.

5 CONCLUSIONS

Production and processing

The world wide production of 1-chloro-2-nitrobenzene amounted to 111,800 tons in 1995 by approximately 30 producers, excluding production in East European countries. 1-Chloro-2-nitrobenzene is a basic chemical for processing intermediates which are further processed mainly to dyestuffs, pigments, pesticides, and pharmaceuticals within the chemical industry. Direct use of 1-chloro-2-nitrobenzene is not known. Releases into the environment may occur during production and processing. Emission data are only available for Bayer AG. During normal operation no 1-chloro-2-nitrobenzene is emitted into the atmosphere. Following the Official German Emission Declaration in year 2000, less than 25 kg/a 1-chloro-2-nitrobenzene were emitted. Regular monitoring data at the industrial sewage treatment plant showed the substance to be eliminated to less than 5 µg/l. As worst case for the receiving water a PEC of < 0.007 µg/l is calculated taking the 10 percentile of the river flow into account. There is no information on releases into the environment from other production and processing sites. A significant exposure to the terrestrial compartment could not be identified.

Environmental behavior

The favourite target compartments for 1-chloro-2-nitrobenzene are water with 65.4 %, followed by air with 32.9 % according to a Mackay calculation level I. In air, the substance is indirectly photodegradable with $t_{1/2}$ = 187 days. 1-Chloro-2-nitrobenzene is not readily biodegradable. According to the model Simpletreat a removal in sewage treatment plants of 4.8 % can be estimated. Under the conditions of industrial waste water treatment plants removal to > 95 % was observed at one production/processing site. However, this removal cannot be transferred to other sewage treatment plants. Special tests showed adapted cultures to be able to degrade 1-chloro-2-nitrobenzene in a cometabolic pathway.

Measured bioconcentration factors in fish are in the range of 7.0 - 22.3 at a 1-chloro-2-nitrobenzene concentration of 0.25 to 0.025 mg/l. A calculated Koc suggests the substance to have a medium geoaccumulation potential.

The lowest valid acute test results of aquatic testing were determined for fish (*Cyprinus carpio*) with a 96 h-LC_{50} of 25.5 mg/l, for *Daphnia magna* with a 24 h-EC_{50} of 12 mg/l and 48 h-EC_{50} of 23.9 mg/l, and for algae (*Chlorella pyrenoidosa*) with a 96 h-EC_{50} of 6.9 mg/l. With another algae species (*Scendesmus subspicatus*) a 48h-ErC50 of 75 mg/l and a 48h-ErC10 of 19 mg/l was found. Chronic toxicity has been tested for fish (*Pimephales promelas*) in an Early Live Stage Test with a 33 d-NOEC of 0.264 mg/l (endpoint number of normal larvae; measured concentration), and for *Daphnia magna* with a 21 d-NOEC of 3.0 mg/l on reproduction (measured concentration). A PNECaqua of 0.026 mg/l is derived from the fish NOEC of 0.264 mg/l using an assessment factor of 10.

In a test with terrestrial plants a 14 d-EC_{50} in the range of 3.2 - 10 mg/kg soil dry weight was determined for *Lactuca sativa* regarding the endpoint of growth. A PNECsoil of 3.2 µg/kg dw was derived from this test.

Human health

After single oral application 1-chloro-2-nitrobenzene is toxic to moderate toxic (LD_{50}, oral: rat, male: 144, 251 or 560 mg/kg bw; rat, female: 263 or 560 mg/kg bw). The acute inhalative toxicity and dermal toxicity is moderate (LC_{50} (rat) ca. 3200 mg/m³ (= 495 ppm, vapor/aerosol mixture) for 4 hours; LD_{50}, dermal, rat: male: 655 mg/kg bw, female: 1320 mg/kg bw; LD_{50} dermal rabbit: 400 mg/kg bw (male: 445 mg/kg bw, female: 355 mg/kg bw)).

Cyanotic appearance was the predominant appearance for all three routes of application.

The documentation of the available studies on skin irritation is incomplete in one case and in the two other cases the test substance was applied undissolved or respectively diluted. However, the studies gave no evidence of a skin irritating potential of 1-chloro-2-nitrobenzene.

1-Chloro-2-nitrobenzene caused slight irritational effects to the eyes of rabbits which were reversible within 24 hours.

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 was examined in rats and in mice for a period of 13 weeks via whole body **inhalation**. As target organs liver, kidney and spleen were identified in both species, and furthermore, in rats erythrocytes and the nasal cavity respiratory epithelium. The NOAEL in rats was not achieved, the LOAEL is 1.1 ppm (7 mg/m³); In mice, increased liver and kidney weights were observed even at 1.1 ppm and 2.3 ppm, respectively. The NOAEL for histopathological injury in mice is 4.5 ppm (28.8 mg/m³).

In a subacute **feeding** study with mice target organs were blood, spleen and liver. The NOAEL was 50 ppm (males: 16 mg/kg bw/day ; females 24 mg/kg bw/day)

1-Chloro-2-nitrobenzene showed weak mutagenic activity in bacterial test systems but not in mammalian cell test systems in vitro. It was not mutagenic in Drosophila melanogaster. In mammalian cells in vitro, it showed weak clastogenic activity. The substance induced increased rates of Sister Chromatid Exchanges, whereas the biological relevance of this effect is not yet clear. Intraperitoneal injection into mice resulted in DNA damage in the liver and kidney. The inconsistent results of the genotoxic tests as described above are typical for nitroaromatics. As a whole 1-chloro-2-nitrobenzene is suspected of being genotoxic, or at least a weak clastogen.

1-Chloro-2-nitrobenzene showed tumours in different organs of rats and in the liver of mice. Overall taking into consideration the results of the genotoxicity tests,and the resulsts of the available limited studies in rats and mice, there is a concern for a carcinogenic potential of 1-chloro-2-nitrobenzene.

Following inhalative exposure of F344/N rats and B6C3F1 mice for 13 weeks, only in males 1-chloro-2-nitrobenzene affects the reproductive organs. Performance of a specific study on toxicity to reproduction (NTP Continuous Breeding Protocol) reveals that 1-chloro-2-nitrobenzene was without reproductive toxicity in a different mice strain following oral treatment by gavage despite of significant changes in liver and spleen weight and despite of elevated methemoglobin levels. Thus, the $NOAEL_{fertility}$ in Swiss CD-1 mice after oral application is 160 mg/kg bw/day whereas the dams showed general toxicity effects at this concentration. Because 1-choro-2-nitrobenzene affected the reproductive organs in systemic toxic doses in male rats and in males of one strain of mice after subchronic inhalation there is a concern for a reproductive toxicity potential, even if an impairment of reproduction after oral administration in males of a second strain of mice could not be detected.

Developmental toxicity was examined by two studies with Sprague-Dawley rats which have methodology deficiencies. In one study, due to high mortality rate at the highest dose level, only two doses could be evaluated. $NOAEL_{maternal\ toxicity}$ is 25 mg/kg bw/day, a $NOAEL_{developmental\ toxicity}$ could not be conclusively derived, since there was an increase in the number of litters exhibiting specific skeletal variations. In the second study only one dose was applied: $NOAEL_{developmental\ toxicity}$ is 100 mg/kg bw/day, a $NOAEL_{maternal\ toxicity}$ could not be derived. Based on the available studies the overall conclusion is, that there is no indication of developmental toxicity, although there are some limitations within the studies.

6 RECOMMENDATIONS

Environment: The substance is a candidate for further work. Environmental exposure at the sponsor company is adequately controlled. However, as there are no information on environmental releases from other production / processing sites, national or regional exposure information gathering and risk assessment may need to be considered. This is justified because the substance is not readily biodegradable and has a PNECaqua of 26 µg/l.

Human Health: The substance is a candidate for further work. Due to possible hazards (haemotoxicity, reproductive toxicity, genotoxicity, and carcinogenicity) the exposure situation in occupational settings and consumer settings should be clarified and, if then indicated, a risk assessment should be performed.

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I U C L I D D a t a S e t

Existing Chemical	ID: 88-73-3
CAS No.	88-73-3
EINECS Name	1-chloro-2-nitrobenzene
EC No.	201-854-9
TSCA Name	Benzene, 1-chloro-2-nitro-
Molecular Formula	C6H4ClNO2

Producer Related Part	
Company:	Bayer AG
Creation date:	08-JUN-1993
Substance Related Part	
Company:	Bayer AG
Creation date:	08-JUN-1993
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 13 (6-9 November 2001)

Printing date:	26-NOV-2003
Revision date:	02-JUN-1994
Date of last Update:	26-NOV-2003

Number of Pages:	96

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: cooperating company
Name: ACNA C.O.
Town: 17010 Cengio (SV)
Country: Italy

Type: cooperating company
Name: Chemie AG Bitterfeld-Wolfen
Town: 06749 Bitterfeld-Wolfen
Country: Germany

Type: cooperating company
Name: Hoechst AG
Town: 65903 Frankfurt/Main
Country: Germany

Type: cooperating company
Name: Monsanto
Town: 1150 Brussels
Country: Belgium

Type: cooperating company
Name: Rhone-Poulenc Chimie
Street: 25 quai Paul Doumer
Town: 92408 Courbevoie Cedex
Country: France

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

1.1.1 General Substance Information

Substance type: organic
Physical status: solid
Purity: > 99 - % w/w

Remark: cooperating companies for the Existing Chemical Regulation:
Hoechst AG, Germany
Chemie AG Bitterfeld-Wolfen, Germany
Monsanto Europe S.A., Belgium
Rhone-Poulenc Chimie, France
ACNA Chimica Organica, Italy
Flag: Critical study for SIDS endpoint
16-NOV-2000

1.1.2 Spectra

1.2 Synonyms and Tradenames

1-CHLORO-2-NITROBENZOL

Flag: Critical study for SIDS endpoint
27-JUL-2001

1-NITRO-2-CHLORBENZOL

Flag: Critical study for SIDS endpoint

2-CHLOR-1-NITROBENZOL

Flag: Critical study for SIDS endpoint

2-CHLORNITROBENZOL

Flag: Critical study for SIDS endpoint

2-NITRO-1-CHLORBENZOL

Flag: Critical study for SIDS endpoint

2-NITROCHLORBENZOL

Flag: Critical study for SIDS endpoint

BENZENE, 1-CHLORO-2-NITRO-

Flag: Critical study for SIDS endpoint

CHLOR-O-NITROBENZOL

Flag: Critical study for SIDS endpoint

O-CHLORNITROBENZOL

Flag: Critical study for SIDS endpoint

O-NITROCHLORBENZOL

Flag: Critical study for SIDS endpoint

OCNB

Flag: Critical study for SIDS endpoint

ONCB

Flag: Critical study for SIDS endpoint

1.3 Impurities

Remark: Dinitrochlorobenzene : max. 0.01 %
p-Nitrochlorobenzene : max. 0.2 %
water : max. 0.1 %

1.4 Additives

1.5 Total Quantity

1.6.1 Labelling

Labelling: provisionally by manufacturer/importer
Symbols: (T) toxic
(N) dangerous for the environment
R-Phrases: (24/25) Toxic in contact with skin and if swallowed
(40) Possible risks of irreversible effects
(43) May cause sensitization by skin contact
(51/53) Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
(62) Possible risk of impaired fertility
S-Phrases: (28) After contact with skin, wash immediately with plenty of water and soap, if possible with Polyethylenglykol 400, too
(36/37) Wear suitable protective clothing and gloves
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

Remark: Classification by EEC is required
Flag: Critical study for SIDS endpoint
18-JUN-2001

1.6.2 Classification

Classified: provisionally by manufacturer/importer
Class of danger: carcinogenic, category 3
R-Phrases: (40) Possible risks of irreversible effects

Flag: Critical study for SIDS endpoint
28-MAR-2000

Classified: provisionally by manufacturer/importer
Class of danger: dangerous for the environment
R-Phrases: (51/53) Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Flag: Critical study for SIDS endpoint
28-MAR-2000

Classified: provisionally by manufacturer/importer
Class of danger: harmful
R-Phrases: (62) Possible risk of impaired fertility

Remark: due to classification according to TRGS 905 (DE): risk of impaired fertility, category 3
Flag: Critical study for SIDS endpoint
25-JUN-2001

Classified: provisionally by manufacturer/importer
Class of danger: irritating
R-Phrases: (43) May cause sensitization by skin contact

Flag: Critical study for SIDS endpoint
03-APR-2000

Classified: provisionally by manufacturer/importer
Class of danger: toxic
R-Phrases: (24/25) Toxic in contact with skin and if swallowed

Remark: Classification by EEC is required

Flag: Critical study for SIDS endpoint
28-MAR-2000

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Use in closed system

Flag: Critical study for SIDS endpoint

Type: industrial
Category: Chemical industry: used in synthesis

Flag: Critical study for SIDS endpoint

Type: use
Category: Intermediates

Flag: Critical study for SIDS endpoint

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

Type of limit: MAK (DE)

Remark: carcinogenic category 3
risk of cutaneous absorption
risk of impaired fertility, category 3
Source: TRGS 905 (DE)
Flag: Critical study for SIDS endpoint
18-JUN-2001

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: KBwS (DE)
Labelled by: KBwS (DE)
Class of danger: 2 (water polluting)

1.8.4 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: yes

Remark: Appendix I, No. 2
16-JUL-2001

1.8.5 Air Pollution

Classified by: other: producer according to TA-Luft (DE)

Number: 3.1.7 (organic substances)
Class of danger: I

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

1.12 Last Literature Search

Type of Search: Internal and External

Remark: Environmental, ecotoxicology : November 2000
Toxicology: April 1999
25-JUN-2001

1.13 Reviews

Memo: BUA Report No. 2 (o-Chloronitrobenzene), VCH, Weinheim, Oct. 1985

25-JUN-2001

2.1 Melting Point

Value: 32 degree C

Remark: solidifying point
Flag: Critical study for SIDS endpoint
27-JUL-2001 (11)

Value: 31.7 degree C

Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (38)

Value: >= 31.7 degree C

Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (37)

Value: 33 degree C

25-JUN-2001 (103)

2.2 Boiling Point

Value: 245.5 degree C at 1000 hPa

Flag: Critical study for SIDS endpoint
25-JUN-2001 (103)

Value: 243 degree C at 1013 hPa

12-JUL-2001 (12)

Value: 245 degree C at 1013 hPa

Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (38)

Value: 370 degree C
Decomposition: yes

Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (38)

2.3 Density

Type: density
Value: 1.368 g/cm³ at 22 degree C

Flag: Critical study for SIDS endpoint
27-JUL-2001 (103)

Type: density
Value: 1.32 g/cm³ at 70 degree C

Source: Hoechst AG Frankfurt/Main (reference not available)
11-JUL-2001 (37)

Type: density
Value: 1.294 g/cm³ at 90.5 degree C

Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (38)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .04 hPa at 20 degree C
Decomposition: no

Method: Directive 84/449/EEC, A.4 "Vapour pressure"
Year: 2001
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: 0.07 hPa at 25 °C
Flag: Critical study for SIDS endpoint
27-JUL-2001 (10)

Value: .0575 hPa at 20 degree C

25-JUN-2001 (16)

Value: 6 hPa at 20 degree C

24-NOV-2000 (25)

Value: 2 hPa at 67.6 degree C

14-SEP-2000 (1)

Value: 49.8 hPa at 150 degree C

Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (38)

2.5 Partition Coefficient

log Pow: 2.24

Method: other (measured)

Flag: Critical study for SIDS endpoint
30-JUL-2001 (58)

log Pow: 2.46

Method: other (calculated)
Year: 2000

Remark: Calculation KOWWIN v1.66 (2001)
Flag: Critical study for SIDS endpoint
25-JUN-2001 (94)

2.6.1 Solubility in different media

Solubility in: Water
Value: .441 g/l at 20 degree C

Flag: Critical study for SIDS endpoint
27-JUL-2001 (27)

Solubility in: Water
Value: .43 g/l at 20 degree C

Source: Hoechst AG Frankfurt/Main, (Reference not available)
27-JUL-2001 (37)

Solubility in: Water
Value: .59 g/l at 20 degree C

27-JUL-2001 (16)

2.6.2 Surface Tension

2.7 Flash Point

Value: 127 degree C
Type: closed cup

Flag: Critical study for SIDS endpoint
25-JUN-2001 (103)

Value: 124 degree C

27-JUL-2001 (16)

Value: 124 degree C

Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (38)

Value: 128 degree C
Type: closed cup

Method: other: DIN 51758

12-JUL-2001 (12)

2.8 Auto Flammability

Value: 470 degree C

Method: other: DIN 51794

Remark: ignition temp.
Flag: Critical study for SIDS endpoint
12-JUL-2001 (12)

Value: > 450 degree C

Source: Hoechst AG Frankfurt am Main, (Reference not available)
25-JUN-2001 (37)

Value: 487 degree C

Remark: Zuendtemperatur
Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (38)

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Remark: Untere Explosionsgrenze: 1.15 Vol-%
Obere Explosionsgrenze: 13.1 Vol-%
Gefährliche Zersetzungsprodukte: Nitrose Gase, Chlorwasserstoff
Unverträgliche Substanz: Chlornitrobenzole reagieren mit Reduktionsmitteln.
Source: Hoechst AG Frankfurt/Main, (Reference not available)
25-JUN-2001 (38)

3.1.1 Photodegradation

Type: other: air, indirect photolysis

Method: Calculation of the atmospheric oxidation of 1-chloro-2-nitrobenzene by hydroxyl radicals (AOPWIN v1.90, 2001)
Result: OH rate constant: 0.1714 E-12 cm3/molecule x sec
Half-life : 187.2 days (12 h day; 0.5 E6 OH/cm3)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
12-JUL-2001 (93)

Type: water
Light source: other: mercury high pressure lamps
Light spect.: > 290 nm
DIRECT PHOTOLYSIS
Degradation: = 0 % after 180 minute(s)

Method: other (measured)
Year: 1987
GLP: no
Test substance: other TS: 1-chloro-2-nitrobenzene

Method: irradiation of TS in aqueous solution in the absence and in the presence of TiO2; HPLC analysis
Result: quantitative degradation of TS was observed only in the presence of TiO2
Reliability: (3) invalid

no detailed description of method, test conditions, and results
12-JUL-2001 (48)

3.1.2 Stability in Water

Remark: Based on the chemical structure of the compound hydrolysis is not expected under environmental conditions
Flag: Critical study for SIDS endpoint
25-JUN-2001

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level I
Year: 1991

Remark: Mackay, Calculation of the environmental distribution of 1-chloro-2-nitrobenzene according to fugacity model level I (1991)
Input parameter:
Temperature: 20°C
Vapor pressure: 4.0 Pa
Water solubility: 441 mg/l
log Kow: 2.24
Entry of chemical: 1 mol
Result: Calculated distribution between environmental compartments: water 65.4 %, air 32.9 %, soil 0.9 %, sediment: 0.8 %, susp. sediment: < 0.1 %, fish: < 0.1 %
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
26-NOV-2003

Media: water - air
Method: other (calculation): Henry constant

Result: H = 1.43 Pa m3 mol-1
Flag: Critical study for SIDS endpoint
27-JUL-2001 (61)

Media: water - soil
Method: other (calculation): SCR-PCKOCWIN v1.66
Year: 2000

Result: Koc = 315.5
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2001 (95)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: other: sludge samples from different sewage plants, rivers, bays and a lake, non adapted
Concentration: 30 mg/l related to Test substance
Degradation: 8.2 % after 14 day(s)

Method: other: Japanese Guideline by MITI of 1974; corresp. OECD 301 C Modified MITI Test I
GLP: no data
Test substance: other TS: no purity given

Remark: Inoculum added: 30 mg/l; BOD measurement
Difference to OECD 301C: Initial test substance concentration 30 mg/l instead of 100 mg/l
Reliability: (1) valid without restriction
Test procedure according to national standards
Flag: Critical study for SIDS endpoint
15-JUL-2002 (64)

Type: aerobic
Inoculum: activated sludge, industrial, non-adapted
Concentration: 200 mg/l related to DOC (Dissolved Organic Carbon)

Kinetic: 5 day(s) 80 %
10 day(s) > 90 %

Method: OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year: 1982
GLP: no

Remark: Elimination by Stripping
Source: Hoechst AG Frankfurt/Main
Reliability: (4) not assignable
Original reference not available
25-JUN-2001 (39)

Type: aerobic
Inoculum: activated sludge
Concentration: 200 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: < 10 % after 15 day(s)
Kinetic: 5 day(s) < 10 %
10 day(s) < 10 %

Method: other: Respirometer Test
Year: 1982
GLP: no

Source: Hoechst AG Frankfurt/Main
Reliability: (4) not assignable
Original reference not available
25-JUN-2001 (39)

Type: aerobic
Inoculum: predominantly domestic sewage, adapted
Degradation: 0 % after 20 day(s)
Result: under test conditions no biodegradation observed

Method: other: comparable to OECD Guide-line 301 D
Year: 1977
GLP: no

Remark: related to BOD
Reliability: (4) not assignable
Original reference not available
12-JUL-2001 (9)

Type: aerobic
Inoculum: other: activated sludge, non-adapted and adapted

Method: other: see remarks
GLP: no
Test substance: other TS: > 99.9 % purity

Method: 3 methods were applied:
1) Revised OECD test, 1971 (Determination of the Biodegradability of Anionic Surface Active Agents)
2) Repetitive Die Away Test: Blok, 1979 (A repetitive Die Away test combining several biodegradability test procedures; Int. Biodeterior. Bull. 15, 57-63)
3) Pitter test (Pitter (1976): Determination of biological degradability of organic substances, Water Res. 10, 231-235.)
Result: t1/2 >> 4 weeks

Reliability: (3) invalid
Insufficient documentation: no details on origin and density of inoculum, and on tested concentrations and test conditions
12-JUL-2001 (18)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 56 day(s) at 25 degree C
Concentration: .025 mg/l
BCF: = 7.4 - 22.3

Method: other: Japanese Guideline by MITI of 1974; corresp. OECD 305 C Bioaccumulation (1981)
GLP: no data
Test substance: other TS: o-chloronitrobenzene (CAS-No. 88-73-3)

Method: Flow-through system;
Weight/length of exposed fish: 30g / 10cm, lipid content: 2-6 %; water analyzed twice a week, fish every two weeks
Remark: At a o-chloronitrobenzene concentration of 0.25 mg/l and the same test conditions as already described, a BCF of 7.0 - 20.8 was determined
Test condition: flow-rate of test water: 200-800 ml/min
Reliability: (1) valid without restriction

Test procedure according to national standards
Flag: Critical study for SIDS endpoint
12-JUL-2001 (64)

Species: Poecilia reticulata (Fish, fresh water)
Exposure period: 3 day(s) at 22 degree C
Concentration: 6 mg/l
BCF: 11.6 - 19.4

Method: other: comparable to OECD 305B (Bioaccumulation: Semi Static Fish Test) (1981)
Year: 1986
GLP: no data
Test substance: other TS: > 99 %

Remark: Test temperature 21-23 °C
Mean fat content of fish: 8 +/- 2 %
Difference to Guideline 305 B: only 1 test concentration at 1/5 of 14 d-LC50 tested
Result: The test result in the publication is given on fat weight basis with BCFfat = 194. The BCF values of 11.6 - 19.4 are calculated from this data to the whole fish for reason of

comparability to other test results.
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions (see remark)
27-JUL-2001 (24)

Species: Oncorhynchus mykiss (Fish, fresh water)
Exposure period: 36 day(s)

Method: other: fish exposed to a mono- to pentachloronitrobenzene isomer mixture at the same time in a flow-through system
Year: 1989
GLP: no
Test substance: other TS: mono- to pentachloronitrobenzenes

Method: 30 fish exposed to 720 +/-130 mg TS/l in a flow-through system; acetone used as solvent; samples of 6 fish each analyzed at 5, 12, 20, 28 and 36 days of exposure; duplicate water samples taken every 3 or 4 days; GC analysis
Remark: significant differences among sample intervals: BCF decreasing from 134 mg/l (day 5) to 89 mg/l (day 20) and then increasing again to 179 mg/l (day 36)
Result: as the higher chlorinated nitrobenzenes are possibly dechlorinated by metabolism in fish a BCF for o-chloronitrobenzene cannot be derived within this test design
Reliability: (3) invalid
Unsuitable test system (more than one substance tested in the same test vessel)
27-JUL-2001 (78)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: 34.8 -

Method: other: OECD Guide-line 203 (1984)
Year: 1990
GLP: no data
Test substance: other TS: no purity given

Test condition: 10 fish per concentration step; fish length: 2 cm; temperature: 23 °C; pH (dilution water) 8.15; 16 h light / 8 h dark
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
02-AUG-2001 (86)

Type: other: static or semistatic, no details given
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 28 -

Method: other: Japanese Industrial Standard (JIS K 0102-1986-71) "Testing methods for industrial waste water" (1986)
GLP: no data
Test substance: other TS: o-chloronitrobenzene (CAS-No. 88-73-3)

Test condition: 25 +/- 2 degree C
Reliability: (2) valid with restrictions
Test procedure according to national standards but only basic data given
10-AUG-2001 (64)

Type: other: semistatic, renewal at 12 hours
Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 25.5 -

Method: other: comparable to OECD 203 (Fish: Acute Toxicity Test, 1992)
Year: 1996
GLP: no data
Test substance: other TS: purity not given (commercial TS)

Remark: Deviation to OECD 203: higher fish load in test vessel (about 50 g in 16 l test water)
Test condition: 60 fish used in each test; fish weight/length: 5 g/5 cm; temperature: 20°C
Reliability: (2) valid with restrictions
According to guideline study with acceptable restrictions
Flag: Critical study for SIDS endpoint
27-JUL-2001 (114)

Type: semistatic
Species: Poecilia reticulata (Fish, fresh water)
Exposure period: 14 day(s)
Unit: mg/l Analytical monitoring: yes
LC50: 30 -

Method: other: comparable to OECD 204 (fish, prolonged toxicity test, 1984)
Year: 1987
GLP: no data
Test substance: other TS: > 99 %

Reliability: (2) valid with restrictions
Basic data given: comparable to guideline
02-AUG-2001 (24)

Type: flow through
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 14 day(s)
Unit: mg/l Analytical monitoring: yes
NOEC: 2.9 -
LOEC: 5.9 -

Method: other: OECD 204: Fish, Prolonged Toxicity Test: 14-day Study (4 April 1984)
Year: 1990
GLP: no data

Remark: The 14 d-LOEC of 5.9 mg/l corresponds to the feeding behaviour of the fish. A 14 d-LOEC concerning lethal effect was determined to be 24.8 mg/l.
Reliability: (1) valid without restriction
Guideline study
27-JUL-2001 (86)

Type: static
Species: Poecilia reticulata (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 30 -

Method: other: according to OECD Proposal (1979:) Report on the Assessment of Potential Environmental Effects of Chemicals
Year: 1984
GLP: no data
Test substance: other TS: 1-chloro-2-nitrobenzene; purity > 99.9 %

Reliability: (3) invalid
Documentation insufficent for assessment
12-JUL-2001 (18)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: 5 -
LC100: 10 -

Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15

Year: 1974
GLP: no

Reliability: (3) invalid
Range-finding test with two fish only
Original report not available
12-JUL-2001 (9)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: other: Daphnia carinata
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 21.3 -

Method: other: comparable to OECD 202 part I (Daphnia, Acute Toxicity, 1984)
Year: 1996
GLP: no data
Test substance: other TS: purity not given

Reliability: (2) valid with restrictions
Basic data given: comparable to guideline
Flag: Critical study for SIDS endpoint
12-JUL-2001 (114)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: 5 -
EC50: 12 -

Method: other: Daphnien-Schwimmunfaehigkeits-Test, UBA-Verfahrensvorschlag Mai 1984, Bestimmung der Schwimmunfaehigkeit beim Wasserfloh Daphnia magna, EC0, EC50, EC100 24h, statisches System
Year: 1987
GLP: no data

Remark: Pretest to reproduction test
Reliability: (2) valid with restrictions
Basic data given
Flag: Critical study for SIDS endpoint
27-JUL-2001 (57)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 23.9 -

Method: other: according to the Protocol of the Dutch Standards Organisation, NEN 6501 (1980)
Year: 1988
GLP: no data
Test substance: other TS: no purity given

Test condition: Daphnids < 24 h old; temperature: 20 °C; illumination 12 h/day; hardness: 200 mg/l as CaCO3; pH 8.4; dissolved oxygen > 7.9 mg/l
Reliability: (2) valid with restrictions
Basic data given
Flag: Critical study for SIDS endpoint
27-JUL-2001 (23)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: 3.2 -
LC50 : 49 -

Method: other: OECD Proposal (1979: Report on the assessment of Potential Environmental Effects of Chemicals I)
Year: 1979
GLP: no data
Test substance: other TS: 1-chloro-2-nitrobenzene; purity > 99.9 %

Remark: no data on test conditions
Reliability: (3) invalid
Documentation insufficent for assessment
11-JUL-2001 (18)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Chlorella pyrenoidosa (Algae)
Endpoint: biomass
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 6.9 -

Method: other: According to Modified OECD 201 (Algae, growth inhibition test, 1984)
Year: 1988
GLP: no data
Test substance: other TS: purity not given

Reliability: (2) valid with restrictions
Basic data given: comparable to guideline
Flag: Critical study for SIDS endpoint
07-SEP-2001 (23)

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass

Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC10: 11 -
EC50: 34 -

Method: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen (1988)
Year: 1988
GLP: no data
Test substance: other TS: purity not given

Remark: modification of test procedure: bottles with ground glass stoppers were used

Result: Effect levels determined for the endpoint growth rate:
EC10: 19 mg/l
EC50: 75 mg/l
Reliability: (2) valid with restrictions
Test procedure according to national standards, but only basic data given
Flag: Critical study for SIDS endpoint
10-AUG-2001 (56)

Species: other algae: Scenedesmus obliquus
Endpoint: growth rate
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 18.1 -

Method: other: comparable to OECD 201 (Algae, Growth inhibition test, 1984)
Year: 1996
GLP: no data
Test substance: other TS: purity not given

Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
12-JUL-2001 (114)

Species: Scenedesmus pannonicus (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: = 24 -

Method: other: OECD Proposal (1979: Report on the Assessement of Potential Environmental Effects of Chemicals I
Year: 1984
GLP: no data
Test substance: other TS: 1-chloro-2-nitrobenzene; > 99.9 % purity

Reliability: (3) invalid
Documentation insufficent for assessment
12-JUL-2001 (18)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring: no
EC0: 100 -

Method: other: Bewertung toxischer Wasserinhaltsstoffe aus ihrer Inhibitorwirkung auf die Substratoxydation von Pseudomonas Stamm Berlin mit Hilfe polarographischer Sauerstoffmessungen. Robra, K.H.: gwf wasser/abwasser 117 (2), 80-86 (1976)
Year: 1983
GLP: no
Test substance: other TS: no purity given

Reliability: (4) not assignable
Original reference not available
12-JUL-2001 (9)

Type: aquatic
Species: anaerobic bact. from a domestic water treatment plant
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: ca. 80 -

Method: ETAD Fermentation tube method "Determination of damage to effluent bacteria by the Fermentation Tube Method"
Year: 1982
GLP: no
Test substance: other TS: no purity given

Source: Hoechst AG Frankfurt/Main
Reliability: (4) not assignable
Publication/report not available
27-JUL-2001 (39)

Type: other: phytopathogen
Species: other fungi: Pythium ultimum
Exposure period: 88 hour(s)
Unit: mg/l Analytical monitoring: no data
ED 50 : 157.6 -

Year: 1961
GLP: no
Test substance: other TS: recrystallized

Method: Growth inhibition test: test substance incorporated in agar medium which is filled into a growth tube; inoculation after solidification of agar with 8 mm plug of an 48 h fungi culture. Evaluation of linear growth.
Reliability: (2) valid with restrictions
Acceptable, well-documented publication/study report which meets basic scientific principles
12-JUL-2001 (27)

Type: other: phytopathogen
Species: other fungi: Rhizoctonia solani
Exposure period: 88 hour(s)
Unit: mg/l Analytical monitoring: no data
ED 50 : 48.9 -

Year: 1961
GLP: no
Test substance: other TS: recrystallized

Method: Growth inhibition test: test substance incorporated in agar medium which is filled into a growth tube; inoculation after solidification of agar with 8 mm plug of an 48 h fungi culture. Evaluation of linear growth.
Reliability: (2) valid with restrictions
Acceptable, well-documented publication/study report which meets basic scientific principles
13-JUL-2001 (27)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species: Pimephales promelas (Fish, fresh water)
Endpoint: other: weight and length of juveniles

Exposure period: 33 day(s)
Unit: mg/l Analytical monitoring: yes
NOEC: 1.02 -
LOEC: 2.04 -

Method: other: comp. to OECD 210 (Fish, Early-life Stage Toxicity Test, 1992)
Year: 1992
GLP: no data
Test substance: other TS: 99 %

Remark: In a first step 50 embryos were tested on hatchability and development after 4 - 5 days of incubation. In a second step 15 randomly selected frys from the initial egg cups where observed on their further development for 33 days. The 33 d-NOEC was determined by the authors Call & Geiger (1992) to be 0.264 mg/l based on the endpoint 'normal larvae' related to the hatched larvae. The review of the raw data of the study shows, that at the next higher test concentration of 0.530 mg/l a statistically significant effect compared to the control could be observed, however, there is no dose-effect relation for this endpoint at higher test concentrations. The highest test concentration of 3.9 mg/l shows less normal larvae after hatch with a deviation of 7 % compared to the control. Apart from that regarding the endpoint 'normal larvae related to initial embryos' no effect at any concentration can be seen. Regarding 'weight' and 'length' of the fry, at both endpoints a deviation to the control of > 5 % can be seen at a concentration of 2.04 mg/l. Also for this endpoint there is no dose-effect relationship seen at the next higher concentration. As statistically significant effects for the endpoint "normal larvae" were seen at concentrations above 0.264 mg/l, the NOEC derived by the authors is used for the hazard assessment for reasons of precaution.
Test condition: Flow through system
Photoperiod: 16 h light / 8 h dark
Temperature, mean: 24.81 degree C
O2, mean: 6.32 mg/l
pH, mean: 7.42
Total hardness: 54.35 mg/l CaCO3
Total alkalinity, mean: 45.09 mg/l CaCO3
Reliability: (2) valid with restrictions
Well-documented study, comparable to guideline
Flag: Critical study for SIDS endpoint
07-SEP-2001 (17)

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 21 day(s)
Unit: mg/l Analytical monitoring: yes
NOEC: = 3 -

Method: other: UBA-Verfahrensvorschlag (vorlaeufiger) "Verlaengerter Toxzitaetstest bei Daphnia magna" (Bestimmung der NOEC fuer Reproduktionsrate, Mortalitaet und den Zeitpunkt des ersten Auftretens von Nachkommen; 21d) (1984)
Year: 1987
GLP: no data
Test substance: other TS: no purity given

Remark: semistatic test system
Reliability: (1) valid without restriction
Test procedure according to national standards
Flag: Critical study for SIDS endpoint
27-JUL-2001 (57)

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 21 day(s)
Unit: mg/l Analytical monitoring: no data
LOEC: 9.9 -

Method: other: According to the Protocol of the Dutch Standards Organisation, NEN 6502 (1980)
Year: 1988
GLP: no data
Test substance: other TS: no purity given

Remark: semi static test system
Reliability: (2) valid with restrictions
Basic data given
27-JUL-2001 (23)

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Species:	other terrestrial plant: Lactuca sativa Ravel R2
Endpoint:	growth
Expos. period:	14 day(s)
Unit:	mg/kg soil dw
EC50:	= 3.2 - 10
Method:	other: OECD Guide-line 208 (1984)
Year:	1991
GLP:	no data
Test substance:	other TS: purity >= 95 % (summarized information for all test substances)
Remark:	Two different natural soils at different testing facilities were used. Both soil characteristics corr. to OECD advice of an Entisol soil (organic matter content 1.4 % and 1.8 % resp., and clay content 12 % and 24 % resp., pH 7.5). Nominal concentrations given
Test condition:	10 seeds per tray, trays covered with glas plates, temperature 21 °C, photoperiod 16 h light / 8 h dark; light intensity 6,500 Lux; humidity 40-80 %
Reliability:	(2) valid with restrictions Guideline study with acceptable restrictions; only one type of soil tested
Flag:	Critical study for SIDS endpoint

10-AUG-2001 (46)

Species:	other terrestrial plant: Cucumis sativus var. National Pickling
Endpoint:	growth
Expos. period:	6 day(s)
Unit:	mg/l
Method:	other: germination and growth of seedlings in sand
Year:	1961
GLP:	no
Test substance:	other TS: recrystallized
Remark:	A definite amount of test solution was added to sand. Three concentrations were tested (20, 50, and 100 ppm) by weight in to water.
Result:	A 6 d-ED 50 of 18.1 mg/l was determined for sand.
Reliability:	(3) invalid Unsuitable test system (no soil tested)

11-JUL-2001 (27)

Species:	Phaseolus aureus (Dicotyledon)
Endpoint:	growth
Expos. period:	6 day(s)
Unit:	mg/l
Method:	other: germination and growth of seedlings in sand
Year:	1961
GLP:	no
Test substance:	other TS: recrystallized

Remark: A definite amount of test solution was added to sand. Three concentrations were tested (20, 50, and 100 ppm) by weight in to water.
Result: A 6 d-ED 50 of 29.9 mg/l was determined for sand.
Reliability: (3) invalid
Unsuitable test system (no soil tested)
11-JUL-2001 (27)

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex: male
No. of Animals: 15
Vehicle: other: polyethylene glycol 400
Value: = 219 mg/kg bw

Method: other: 15 rats/dose group, 7 doses dissolved in polyethylenglycol 400, given by gavage, observation time: 14 d
Year: 1976
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark:

dosis mg/kg	conc. %	result m /s /n	signs of intoxication start	signs of intoxication end	time of death
50	1	0/ 0/15	-	-	-
100	2	0/15/15	49 min.	5 d	-
150	3	2/15/15	20 min	7 d	2 d
200	4	4/15/15	16 min	7 d	24 h
250	5	10/15/15	36 min	11 d	1-2 d
300	6	14/15/15	13 min	9 d	24 h
500	10	15/15/15	18 min	-	24 h

m: number of rats which died;
n: number of animals put in test
s: number of animals with signs of intoxication:
reduced general condition, cyanotic appearance
Reliability: (2) valid with restrictions
no histopathological examination performed, individual animal data and information on GLP is missing
21-MAR-2003 (6)

Type: LD50
Species: rat
Sex: female
No. of Animals: 15
Vehicle: other: polyethylene glycol 400
Value: = 457 mg/kg bw

Method: other: 15 rats/dose group, 8 doses dissolved in polyethylenglycol 400, given by gavage, observation time: 14 d
Year: 1976
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark:

dosis mg/kg	conc. %	result m /s /n	signs of intoxication start	signs of intoxication end	time of death
25	0.5	0/ 0/15	-	-	-
50	1	0/15/15	24 h	3 d	-
100	2	0/15/15	24 h	7 d	-
250	5	1/15/15	90 min	7 d	8 d
350	7	2/15/15	11 min	7 d	1-2 d
500	10	10/15/15	2 h	13 d	1-2 d
650	13	12/15/15	8 min	12 d	1-2 d
850	17	15/15/15	2 h	-	1-2 d

m: number of rats which died;
n: number of animals put in test
s: number of animals with signs of intoxication:
reduced general condition, cyanotic appearance

Reliability: (2) valid with restrictions
no histopathological examination performed, individual animal data and information on GLP is missing

21-MAR-2003 (6)

Type: LD50
Species: rat
Strain: Wistar
Sex: male
No. of Animals: 10
Vehicle: other: Lutrol
Value: = 251 mg/kg bw

Method: other: 10 rats/dose, 5 doses, test subst. dissolved in lutrol, gavage: application volume: 20 ml/kg bw., observation time: 14 d, some of the rats, that died, and some of the survivors were dissected
Year: 1982
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark:

dosis mg/kg	result m /s /n	signs of intoxication start	time of death
100	0/ 0/10	-	-
200	2/10/10	1 h	8 - 24 h
250	5/10/10	1 h	4 - 24 h
300	7/10/10	1 h	8 h - 3 d
400	10/10/10	1 h	4 h - 2 d

m: number of rats which died;
n: number of animals in test
s: number of animals with signs of intoxication:
reduced general condition, cyanotic appearance, rough fur, sedation, narcosis, no macroscopic effects in dissected animals

Reliability: (2) valid with restrictions
study meets criteria of today, but information on GLP is missing
Flag: Critical study for SIDS endpoint
21-MAR-2003 (7)

Type: LD50
Species: rat
Strain: Wistar

Sex: female
No. of Animals: 10
Vehicle: other: Lutrol
Value: = 263 mg/kg bw

Method: other: 10 rats/dose, 5 doses, test subst. dissolved in lutrol, gavage: application volume: 20 ml/kg bw., observation time: 14 d, some of the animals, that died, and some of the survivors were dissected
Year: 1982
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark:

dosis mg/kg	result m /s /n	signs of intoxication start	time of death
100	0/ 0/10	-	-
200	3/10/10	2 h	8 h - 3 d
300	5/10/10	2 h	24 h - 3 d
400	9/10/10	1 h	24 h - 3 d
500	10/10/10	1 h	4 h - 3 d

m: number of rats which died;
n: number of animals in test
s: number of animals with signs of intoxication:
reduced general condition, cyanotic appearance, rough fur, sedation, narcosis, paralysis of the hind limb

no macroscopic effects in dissected animals
Reliability: (2) valid with restrictions
study meets criteria of today, but information on GLP is missing
Flag: Critical study for SIDS endpoint
21-MAR-2003 (8)

Type: LD50
Species: rat
Strain: Wistar
Sex: male
No. of Animals: 10
Vehicle: other:sesame oil
Value: = 144 mg/kg bw

Method: other: 10 rats/dose, males were more sensitive in a pre-test, starved 16 hrs prior appl. and 2 hrs post appl., 4 doses, dissolved in sesame oil, single application by gavage, observation time: 14 d
Year: 1975
GLP: no
Test substance: other TS: no data on purity

Remark: doses and mortality rate (death occurred within 3 days):
63 mg/kg: 0/10; 100 mg/kg: 2/10;
160 mg/kg: 5/10; 250 mg/kg: 10/10
signs of intoxication: imbalance, rough fur, diarrhea, slight tremor
section of survivors: no findings
section of rats, that had died, was not possible because of autolytic changes.
Reliability: (2) valid with restrictions
individual animal data of signs of intoxication and information on GLP is missing

Flag: Critical study for SIDS endpoint
25-MAR-2003 (40)

Type: LD50
Species: rat
Sex: no data
Vehicle: no data
Value: = 350 mg/kg bw

Method: other: no information
Year: 1967
GLP: no data
Test substance: other TS: no data on purity

Reliability: (4) not assignable
lack of information
16-JUN-2003 (22)

Type: LD50
Species: rat
Sex: no data
Vehicle: no data
Value: = 339 mg/kg bw

Method: other: no information given
Year: 1982
GLP: no data
Test substance: other TS: no data on purity

Remark: clinical signs: central nervous system affected, methaemoglobin former (no further information)
Reliability: (4) not assignable
lack of information
16-JUN-2003 (50)

Type: LD50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
Vehicle: other: corn oil
Value: = 560 mg/kg bw

Method: other: 2 or 3 rats/dose, single oral dose as 10 % warm solution, observation time: 7 d
Year: 1983
GLP: no data
Test substance: other TS: purity: 99.71 %

Remark: doses and mortality:
398 mg/kg: males 1/2 females 0/3
501 mg/kg: males 1/3 females 1/2
631 mg/kg: males 2/2 females 2/3
794 mg7kg: males 3/3 females 2/2
signs of intoxication: reduced appetite and activity(2-3 days in survivors), increasing weakness, ocular discharge, collapse and death
time to death: 1-4 days with most deaths within 2 days
gross autopsy:
decedents: hemorrhagic lungs, jaundiced liver, darkened kidneys and spleen, and gastrointestinal inflammation
survivors: lung congestion and darkened kidneys and spleen

Reliability: (2) valid with restrictions
individual animal data and information on GLP is missing
Flag: Critical study for SIDS endpoint
21-MAR-2003 (68) (113)

Type: LD50
Species: rat
Sex: no data
Vehicle: no data
Value: = 288 mg/kg bw

Method: other: observation time: 14 d (no further information)
Year: 1972
GLP: no
Test substance: other TS: no data on purity

Reliability: (4) not assignable
lack of information
16-JUN-2003 (2)

Type: LD50
Species: rat
Value: = 510 mg/kg bw

Method: other: no details given

Reliability: (4) not assignable
lack of information
16-JUN-2003 (106)

Type: LD50
Species: rat
Sex: male
Value: = 270 mg/kg bw

Method: other: according to Smyth, Am. Ind. Hyg. Ass. J. 30, 470 (1962)
Year: 1977
GLP: no
Test substance: other TS: no data on purity

Reliability: (4) not assignable
lack of information
16-JUN-2003 (107)

Type: LD50
Species: rat
Sex: male
Value: = 300 mg/kg bw

Method: other: no further information given
Year: 1988
GLP: no data
Test substance: other TS: no data on purity

Reliability: (4) not assignable
lack of information
16-JUN-2003 (65)

Type: LD50
Species: rat
Sex: male

No. of Animals: 5
Vehicle: other: none
Value: ca. 630 mg/kg bw

Method: other: 3 rats/dose, single oral application of undiluted substance, observation time: 14 d
Year: 1975
GLP: no
Test substance: other TS: o-nitrochlorobenzene residue

Remark: dose / mortality / time of death:
50 mg/kg / 0/5 / -;
500 mg/kg / 2/5 / one day;
5000 mg/kg / 5/5 / one day
signs of intoxication: reduced appetite and activity (2-4 days in survivors, increasing weakness, collapse, and death
gross autopsy:
decedents: haemorrhagic areas of the lungs, slight liver discoloration, acute gastrointestinal inflammation
survivors: viscera appeared normal
Reliability: (4) not assignable
o-nitrochlorobenzene residue used, no information for o-nitrochlorobenzene itself
21-MAR-2003 (111)

Type: LD50
Species: mouse
Sex: no data
Vehicle: no data
Value: = 440 mg/kg bw

Method: other: no information given
Year: 1982
GLP: no data
Test substance: other TS: no data on purity

Remark: clinical signs: central nervous system affected, methaemoglobin former (no further information)
Reliability: (4) not assignable
lack of information
16-JUN-2003 (50)

Type: LD50
Species: mouse
Sex: no data
Vehicle: no data
Value: = 135 mg/kg bw

Method: other: observation time: 14 d (no further information)
Year: 1972
GLP: no
Test substance: other TS: no data on purity

Reliability: (4) not assignable
lack of information
16-JUN-2003 (2)

Type: LD50
Species: mouse
Value: = 340 mg/kg bw

Method: other: no details given

Reliability: (4) not assignable
lack of information
16-JUN-2003 (106)

Type: LD50
Species: mouse
Value: = 140 mg/kg bw

Method: other: according to Smyth, Am. Ind. Hyg. Ass. J. 30, 470 (1962)
Year: 1977
GLP: no
Test substance: other TS: no data on purity

Reliability: (4) not assignable
lack of information
16-JUN-2003 (107)

Type: LD50
Species: rabbit
Sex: no data
Vehicle: no data
Value: = 280 mg/kg bw
Method: other: no information given
Year: 1982
GLP: no data
Test substance: other TS: no data on purity
Remark: clinical signs: central nervous system affected, methaemoglobin former (no further information)
Reliability: (4) not assignable
lack of information
16-JUN-2003 (50)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Strain: other: CD
Sex: male
No. of Animals: 10
Exposure time: 4 hour(s)
Value: ca. 3200 mg/m³
Method: other: 10 male rats/conc., head-only exposure, 6 conc., heated vapour was diluted with humidified and O2-enriched air and thus converted to a mixture of vapour and liquid aerosol, post exposure observation time: 14 d
Year: 1981
GLP: no data
Test substance: other TS: purity: 99.8 %
Remark:

Concentration (mg/l)	Mortality	Time to death 0, 1, 2, 3, 5, 7 (d)
1.56	1/10	1
1.83	3/10	2 1
2.46	2/10	1 1
2.64	10/10	1 1 7 1
3.23	1/10	1
3.33	6/10	1 2 2 1

signs of intoxication during exposure: slight to moderate cyanosis, semi-prostration, lethargy and reddish brown nasal discharge to 24 hours, slight to moderate corneal opacity, tachypnea, some rats with partial hind-leg paralysis, abnormal arched-back posture
signs of intoxication post exposure: weight loss of 8 to 16 % from 1 to 3 days with normal gains thereafter, pallor, stained perineal area, lethargy, some rats with salivation, lacrimation and corneal opacity, chromodacryorrhea
gross autopsy not reported
LD50: 495 ppm
Mortalities were not strictly dose-dependant, stat. analysis showed a non significant regression

Result: value: LD50: 495 ppm
Reliability: (2) valid with restrictions
gross autopsy not reported, no information about GLP
Flag: Critical study for SIDS endpoint
21-MAR-2003 (31)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Strain: Wistar
Sex: male
No. of Animals: 10
Vehicle: other: polyethylene glycol 400
Value: = 655 mg/kg bw

Method: other: 10 rats/dose, 6 doses, subst.(solved in polyethylene glycol 400) appl. on the shaved back for 24 hours, covered by alu and a plaster, then rinsed with water and soap, post exposure observ.-time: 14 d
Year: 1976
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark:

dosis mg/kg	conc. %	result m /s /n	signs of intoxication start	signs of intoxication end	time of death
250	25	1/10/10	18 h	14 d	4 d
350	25	1/10/10	18 h	7 d	18 h
500	50	3/10/10	18 h	9 d	1-3 d
750	50	7/10/10	24 h	13 d	1-3 d
1000	50	7/10/10	18 h	4 d	18 h - 3 d
1500	75	9/10/10	18 h	14 d	18 h - 4 d

m: number of rats which died;
n: number of animals put in test
s: number of animals with signs of intoxication: reduced general condition, difficulties in breathing, cyanotic appearance, some animals showed lacrimation
Reliability: (2) valid with restrictions

no pathologic examination performed, individual animal data and information on GLP are missing
Flag: Critical study for SIDS endpoint
21-MAR-2003 (6)

Type: LD50
Species: rat

Strain: Wistar
Sex: female
Vehicle: other: polyethylene glycol 400
Value: ca. 1320 mg/kg bw
Method: other: 10 or 20 rats/dose, 3 doses, subst.(solved in polyethylene glycol 400) appl. on the shaved back for 24 hours, covered by alu and a plaster, then rinsed with water and soap, post exposure observ.-time: 14 d
Year: 1976
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark:

dosis mg/kg	conc. %	result m /s /n	signs of intoxication start	signs of intoxication end	time of death
750	50	0/10/10	24 h	6 d	-
1000	50	5/20/20	18 h	14 d	2 - 3 d
1500	75	6/10/10	18 h	10 d	2 - 6 d

m: number of rats which died;
n: number of animals in test
s: number of animals with signs of intoxication:
reduced general condition, difficulties in breathing, cyanotic appearance, some animals showed lacrimation

Reliability: (2) valid with restrictions
no pathologic examination performed, individual animal data and information on GLP are missing
Flag: Critical study for SIDS endpoint
21-MAR-2003 (6)

Type: LD50
Species: rat
Sex: female
No. of Animals: 6
Vehicle: other: diluted in sesame oil to give a concentration of 40 %
Value: = 1796 mg/kg bw

Method: other: 6 rats/dose, single application to the clipped intact skin, covered by alu and a plaster, exposure time: 24 h, then rinsing, postexposure observation time: 14 d
Year: 1975
GLP: no
Test substance: other TS: no data on purity

Remark: doses and mortality:
500 mg/kg: 0/6 ; 1000 mg/kg: 1/6 ; 1600 mg/kg: 3/6;
2000 mg/kg: 3/6
no signs of toxicity, necropsy of the survivors: no pathological findings
Reliability: (2) valid with restrictions
no data on purity and information on GLP is missing
21-MAR-2003 (42)

Type: LD50
Species: rabbit
Value: = 450 mg/kg bw

Method: other: 5 rabbits/dose, trunks were clipped free of hair, 3 doses (warm to melting point), exposure time 24 h (rabbits immobilized during exposure), then rinsing and wiping dry, observation time: 14 d
Year: 1975

GLP: no
Test substance: other TS: no data on purity

Remark: dose / mortality / individual reactions
330 mg/kg/ 20 % / slight discoloration of the skin and eyes; normal < 48 hrs
560 mg/kg/ 80 % / death 48 to 96 hours preceded by lethargy, loss of motor coordination, sometimes coma
750 mg/kg/ 80 % / death 2 to 5 days, other reaction similar

general reaction:
manifestation of methaemoglobinaemia symptoms evident in < 20 minutes
Reliability: (2) valid with restrictions
no data on purity, no pathologic examination, information on GLP is missing
16-JUN-2003 (104)

Type: LD50
Species: rabbit
Sex: male/female
No. of Animals: 2
Vehicle: other: undissolved
Value: = 400 mg/kg bw
Method: other: 2 rabbits/sex/dose, 5 doses, single dermal application (intact skin), undiluted (warmed to make suitable for dosing), no further information, exposure time: 24 hrs, post exp.observation time: 14 d
Year: 1983
GLP: yes
Test substance: other TS: purity: no data
Remark: Dose and mortality: 251 mg/kg: Males: 0/2; Females: 0/2
316 mg/kg: 0/2 1/2
398 mg/kg: 0/2 2/2
501 mg/kg: 2/2 1/2
631 mg/kg: 2/2 2/2

observations: toxic signs: lethargy (lasting up to 3 days); increasing weakness; collapse; death
Gross necropsy:
decedents: haemorrhagic areas of the lungs;
liver, kidney, spleen discoloration; enlarged gall bladder, gastrointestinal inflammation
survivors(14 d): viscera appeared normal
LD50 (male): 445 mg/kg bw
LD50 (female): 355 mg/kg bw
Reliability: (2) valid with restrictions
no data on purity, no individual pathologic data
Flag: Critical study for SIDS endpoint
21-MAR-2003 (69) (112)

Type: LD50
Species: rabbit
Sex: male/female
No. of Animals: 1
Vehicle: other: none
Value: > 79.4 mg/kg bw
Method: other:1 rabbit/dose, 6 doses, single application of undiluted, warmed substance, exposure time. 24 hrs, postexposure observation time: 14 d (no further information)
Year: 1975
GLP: no

Test substance: other TS: no data on purity

Remark: dose, sex, mortality, time to death:
31.6 mg/kg, male, 0/1, -; 50.0 mg/kg, female, 0/1, -;
79.4 mg/kg, male, 0/1, -; 126.0 mg/kg, female, 1/1, 2 d;
200.0 mg7kg, male, 1/1, 1 d; 398.0 mg/kg, female, 1/1, 1 d

signs of intoxication: slight lethargy (1-2 d in survivors), increasing weakness, collapse, death

gross autopsy: decedents: haemorrhagic areas of the lungs, slight liver discoloration, enlarged gall bladder, gastrointestinal inflammation;
survivors: viscera appeared normal

Reliability: (2) valid with restrictions
no data on purity, information on GLP is missing, only 1 animal/dose, no individual pathologic data

16-JUN-2003 (113)

Type: LDLo
Species: rabbit
Sex: male/female
No. of Animals: 1
Vehicle: other: none
Value: 316 mg/kg bw

Method: other: 1 rat /dose, single application of undiluted substance, exposure time: 24 hrs, post exposure observation time: 14 d
Year: 1975
GLP: no
Test substance: other TS: orthonitrobenzene residue

Remark: dose, sex, mortality, time to death:
126 mg/kg, male, 0/1, -; 200 mg/kg, female, 0/1, -;
316 mg/kg, male, 1/1, 2 days; 794 mg/kg, 1/1, 3 days
signs of intoxication: reduced appetite and activity (2-4 days in survivors), increasing weakness, collapse, death
gross autopsy: decedents: haemorrhagic areas of the lungs, mottled liver, slight enlarged gall bladder, blackened spleen, gastrointestinal inflammation
survivors: viscera appeared normal

Reliability: (4) not assignable
o-chloronitrobenzene residue used, no information of o-chloronitrobenzene itself

21-MAR-2003 (111)

5.1.4 Acute Toxicity, other Routes

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: 500 other: mg
Exposure Time: 24 hour(s)
No. of Animals: 2
Result: not irritating

Method: other: ear, dose: 500 mg/animal, undissolved TS, covered by cellulose pads and plaster, a rolled gauze pad was put on it, all together was bandaged, exposure time: 24 h, semi-occlusive, observation time 7 d
Year: 1976
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
only a few animals used, no information on GLP
Flag: Critical study for SIDS endpoint
21-MAR-2003 (6)

Species: rabbit
Concentration: 10 %
Exposure: Semiocclusive
Exposure Time: 24 hour(s)
No. of Animals: 6
Result: not irritating

Method: other: appl. to intact and abraded skin, flank, test substance diluted in sesame oil, dose: 0.5 ml/animal, observation time: 72 hrs, reading: 24, 48 and 72 hours, evaluated according Fed.Reg.38, No.187, p.27019, 1973, § 1500.41
Year: 1975
GLP: no
Test substance: other TS: no data on purity

Remark: intakt skin (score 0-4):
24 hrs: 4/6 erythema: score: 1; 0/6 oedema
48 hrs: 0/6 erythema: score: ; 0/6 oedema
72 hrs: 0/6 erythema: score: ; 0/6 oedema
abraded skin:
24 hrs: 4/6 erythema: score: 1; 0/6 oedema
48 hrs: 0/6 erythema: score: ; 0/6 oedema
72 hrs: 0/6 erythema: score: ; 0/6 oed
Reliability: (2) valid with restrictions
sesame oil as vehicle, no data on purity
16-JUN-2003 (41)

Species: rabbit
Concentration: undiluted
Exposure: no data
Exposure Time: 24 hour(s)
No. of Animals: 3
Result: corrosive

Method: other: 0.5 ml undiluted, exposure: 24 hrs
Year: 1974
GLP: no
Test substance: other TS: o-nitrochlorobenzene residue (not the original substance, no further information on chemical characteristics)

Reliability: (4) not assignable
o-chloronitrobenzene residue used, no information of o-chloronitrobenzene itself
21-MAR-2003 (111)

Species: rabbit
Concentration: other: undissolved
Exposure: no data

Exposure Time: 24 hour(s)
No. of Animals: 6
Result: not irritating

Method: other: 0.5 ml/rabbit, warmed, observation time: 168 hours (no further information)
Year: 1973
GLP: no
Test substance: other TS: purity: 99.71 %

Remark: time of reading up to 168 hours: no erythema or oedema
Reliability: (2) valid with restrictions
no GLP, no information on exposure
Flag: Critical study for SIDS endpoint
21-MAR-2003 (113)

5.2.2 Eye Irritation

Species: rabbit
Dose: 50 other: mg
No. of Animals: 2
Result: not irritating

Method: other: undissolved test substance, dose: 50 mg/animal,observation period: 7 d
Year: 1976
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Slight redness (score 1/3) observed in 1/2 animals, disappeared within 24 hours, the other animal was without effects
Reliability: (2) valid with restrictions
no GLP, only a few animals used
Flag: Critical study for SIDS endpoint

21-MAR-2003 (6)

Species: rabbit
Concentration: other: undissolved
Dose: 100 other: mg
Exposure Time: 24 hour(s)
Comment: no data
No. of Animals: 6
Result: slightly irritating

Method: other: according Fed.Reg.38, No.187, 1973: undissolved test substance, dose: 100 mg/animal, observation time: 24 hrs
Year: 1975
GLP: no
Test substance: other TS: no data on purity

Remark: 1 hr post appl: 4/6 with conjunctival injections, score: 1/0-3; and 2/6 with conjunctival injections, score: 2/0-3; 7 hr post appl: 2/6 with conjunctival injections, score: 1/0-3; 24 hr post appl: no findin
Reliability: (2) valid with restrictions
no data on purity, no GLP
Flag: Critical study for SIDS endpoint
16-JUN-2003 (41)

Species: rabbit

Concentration: undiluted
Dose: .1 ml
Exposure Time: 24 hour(s)
No. of Animals: 3
Result: corrosive

Method: other: 0.1 ml, undiluted, 24 hrs exposure
Year: 1974
GLP: no
Test substance: other TS: o-nitrochlorobenzene residue (not the original substance, no further information on chemical characteristics)

Reliability: (4) not assignable
o-chloronitrobenzene residue used, no information of o-chloronitrobenzene itself
21-MAR-2003 (111)

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Exposure Time: 24 hour(s)
No. of Animals: 6
Result: not irritating

Method: other: 0.1 ml/rabbit, warmed, observation time: 168 hours
Year: 1973
GLP: no
Test substance: other TS: purity: 99.71 %

Remark: Time of reading:
24 hrs: 6/6 slight erythema, Score 9.6/110
48 hrs: 5/6 slight erythema, Score 2.3/110
72 hrs: 1/6 slight erythema, Score 0.3/110
168 hrs: no findings
Reliability: (2) valid with restrictions
no GLP
21-MAR-2003 (113)

Species: rabbit
Concentration: 10 %
Dose: .1 ml
No. of Animals: 6
Result: slightly irritating
Method: other: according Fed.Reg.38, No.187, 1973: observation time: 24 hrs
Year: 1975
GLP: no
Test substance: other TS
Remark: 1 hr post appl: 3/6 conjunctival injection, score: 1/0-3; 7 and 24 hrs post appl: no findings
Reliability: (2) valid with restrictions
no data on purity, no GLP
21-MAR-2003 (41)

5.3 Sensitization

Type: no data
Species: human

Remark: experience with human exposure: o-chloronitrobenzene

has been used for decades, but there have been no indications of an allergenic potential in man

(16)

Type: other: modified Draize test
Species: guinea pig
Concentration 1st: Induction 1 %
2nd: Challenge 1 %
No. of Animals: 10
Vehicle: other: Aceton
Result: not sensitizing

Method: other: 3 drops of a 1 % solution to the clipped area of the skin for 5 d; on the 7th d 3 drops of the 1 % solution to an untreated area of the skin; reading time not mentioned
Year: 1973
GLP: no
Test substance: other TS: no data on purity

Remark: The study documentation is incomplete and the methology employed is no longer in use.
Reliability: (3) invalid
no data on purity, study documentation incomplete, no data on GLP
16-JUN-2003 (88)

Type: other: modified Freunds complete adjuvant test
Species: guinea pig
Concentration 1st: Induction 10 %
2nd: Challenge 10 %
No. of Animals: 10
Vehicle: other: aceton
Result: sensitizing

Method: other: 3 drops(10% sol.) to the clipped area of the skin;22nd inj.of Freund-adjuvans and TS into the hind paw (0.5 mg/kg bw), 28th d 3 drops(10 % sol.) to an untreated clipped area of the skin; reading time not mentioned
Year: 1973
GLP: no
Test substance: other TS: no data on purity

Remark: The allergenic activity of o-chloronitrobenzene is less marked than that of p-chloronitrobenzene; 2,4-dinitro-chlorobenzene provokes even stronger sensitization ef-fects than p-chloronitrobenzene
The study documentation is incomplete and the methology employed is no longer in use.
Reliability: (3) invalid
no data on purity, study documentation incomplete, no data on GLP
16-JUN-2003 (88)

Type: other: the rats were exposed via inhalation to o-chloronitrobenzene for 5 months
Species: rat
Result: sensitizing
Year: 1973
GLP: no
Test substance: other TS: no data on purity

Reliability: (3) invalid
no data on purity, study documentation incomplete, no data

on GLP
16-JUN-2003 (88)

5.4 Repeated Dose Toxicity

Species:	rat	Sex: male/female
Strain:	other: F344/N	
Route of administration:	inhalation	
Exposure period:	13 w	
Frequency of treatment:	6 h/d, 5 d/w	
Post exposure period:	no	
Doses:	0, 1.1, 2.3, 4.5, 9 or 18 ppm (approx. 0, 7, 14.7, 28.8, 57.6, 115.2 mg/m3)	
Control Group:	yes	
LOAEL:	ca. 1.1 ppm	
Method:	other: see freetext: method	
Year:	1993	
GLP:	yes	
Test substance:	other TS: purity: 99 %	

Method: 10 rats/sex/group, whole body expos., clin.chem., hematol., bw., org.weight, compl. histopathol. in all control rats and 18ppm gr. and rats that died, gross lesions and selec. organs of rats < 18-ppm-groups, add. 10 rats/sex/conc: clin. pathol. at d1, d4, d23

histopathol. evaluations on reproductive organs: see chapter 5.8

Remark: although a no-observed-effect level (NOEL) for his-topathological findings was not found in this study, observations among rats exposed to 4.5 ppm or less were limited to minimal effects on nasal tissues

Result: clinical signs:
no clear signs of toxicity (no other information), no deaths, no differences in body weight gain or terminal body weight compared to controls;
haematology, male and female:
concentration-related increase in methaemoglobinaemia (m sign: from 1.1 ppm at d23; from 2.3 ppm at all time points with max of 1.14 g/dl at 18 ppm; f sign.: from 1.1 ppm at week 13 and from 2.3 ppm at all time points with max of 1.04 g/dl at 18 ppm), reticulocyte count (sign. at all dose groups at week 13), nucleated erythrocytes, leucocyte count (predominantly at the highest dose groups of male and females); concentration-related decrease in haematocrit, haematoglobin, RBC (m. sign.: 1.1 ppm(d23), 4.4 ppm (week13), 9 ppm (d4,week13),18 ppm (at all time points); f. sign.: at every dose group at week13), MCH and MCHC (only in females)
clinical chemistry, male and female:
increase in serum activities of sorbitol dehydrogenase and alanine aminotransferase in different male and female exposure groups at various time points, decrease in alkaline phosphatase
pathology: dark spleen (1 female, 2 males, 18 ppm)
concentration-related increases in liver, spleen and right kidney weight
Histopathologic changes:
liver: basophilia of centrilobular hepatocytes, kidney: pigmentation and regeneration of the proximal convoluted

tubules, spleenic congestion was observed in all exposed and control rats: in males with dose-dependent increase in severity and in females with dose-dependent increase in incidences; nose: hyperplasia of the nasal cavity respiratory epithelium
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
21-MAR-2003 (45) (80) (102)

Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: 4 w
Frequency of treatment: 6 h/d, 5 d/w
Post exposure period: no
Doses: 0, 10, 30 or 60 mg/m3
Control Group: yes, concurrent no treatment
LOAEL: ca. .01 mg/l

Method: other: 15 rats/sex/group, whole body exposure, haematology, clinical chemistry, gross and microscopic examination, statistical analysis
Year: 1986
GLP: no data
Test substance: other TS: purity: 99.71%
Result: all concentration groups:
no deaths, mean body weights comparable to controls, microscopic changes of the spleen: increased degree of haemosiderosis
0.01 mg/l: slight, but statistically significant increase in relative liver weights in male rats
0.03 and 0.06 mg/l: increases in liver, kidneys and spleen weight, significant increase in blood methaemoglobin levels and decrease in haemoglobin, haematocrit and red blood cell count values; increases in liver, kidney, and spleen weights, microscopic changes of the spleen:
slight increase in degree of extramedullary haematopoiesis
Reliability: (2) valid with restrictions
Histopathologic evaluation not performed from all animals, no information on GLP
21-MAR-2003 (73) (74)

Species: rat Sex: male/female
Strain: other: F344/N
Route of administration: inhalation
Exposure period: 2 weeks
Frequency of treatment: 6 h/d, 5 d/w
Post exposure period: no
Doses: 0, 1.1, 2.3, 4.5, 9, 18 ppm (approx. 0, 7, 14.7, 28.8, 57.6, 115.2 mg/m3)
Control Group: yes
LOAEL: ca. 1.1 ppm

Method: other: 5 rats/sex/group, whole body exposure, complete necropsies on all rats, histopathologic evaluation of all rats in the controls and the highest exposure group
Year: 1993
GLP: yes
Test substance: other TS: purity: 99 %

```
Result:           clinical signs:
                  18 ppm, males: hypoactivity, ataxia, pallor
                  18 ppm, males, females: dehydration, nasal discharge,
                  decreased urination and defecation
                  all concentration groups:
                  no deaths, body weight gain was not affected
                  pathology:
                  males and females: exposure-related increases in liver
                  weights,
                  18 ppm, males, females: increased spleen weights
                  18 ppm-group, males: slight increased relative kidney
                  weights
                  histopathologic findings:
                  18 ppm, all rats:
                  hemosiderin deposition in liver (minimal) and spleen (mild
                  severity)
Reliability:      (2)  valid with restrictions
                  dose-finding study
21-MAR-2003                                                          (80)

Species:                  rat                          Sex: male/female
Strain:                   Sprague-Dawley
Route of administration: inhalation
Exposure period:          3 days
Frequency of treatment:   6 hours/day, daily
Post exposure period:     none
Doses:                    0.045 mg/l
Control Group:            yes
NOAEL:                    < .045 mg/l
LOAEL:                    = .045 mg/l

Method:           other: no information
  Year:           1982
   GLP:           yes
Test substance:   other TS: as prescribed in 1.1-1.4 of the Monsanto datasheet

Result:           0.045 mg/l blood, methaemoglobin (3%), incr.; m.f.
Source:           Monsanto
Reliability:      (3) invalid
                  information on method and no. of animals is missing
21-MAR-2003                                                          (70)

Species:                  rat                          Sex: male
Strain:                   other: Crl:CD
Route of administration: inhalation
Exposure period:          2 weeks
Frequency of treatment:   6 hrs/d, 5 d/week
Post exposure period:     13 d
Doses:                    0, 0.03, 0.15, 0.53 mg/l
Control Group:            yes, concurrent no treatment
NOAEL:                    ca. .03 mg/l

Method:           other
  Year:           1984
   GLP:           no data
Test substance:   other TS: purity: 99.8 %

Result:           haemolytic anemia, methaemoglobinemia
Reliability:      (2) valid with restrictions
                  no information of GLP
21-MAR-2003                                                          (32)
```

Species: rat Sex: no data
Strain: no data
Route of administration: oral unspecified
Exposure period: 20 d
Frequency of treatment: daily
Post exposure period: no data
Doses: 70 mg/kg bw/d
Control Group: other: no data

Method: other: 20 rats, no further information
Year: 1967
GLP: no
Test substance: other TS: no data on purity

Result: no deaths (thus, the test substance may be regarded as lacking any marked cumulative properties)
Reliability: (3) invalid
only one dose used, lack of information (e.g. unspecified route of oral administration)
16-JUN-2003 (22)

Species: rat Sex: no data
Strain: no data
Route of administration: oral unspecified
Exposure period: 7 months
Frequency of treatment: daily
Post exposure period: no data
Doses: 0.0025, 0.005, 0.025. 0.25 or 5 mg/kg bw/d
Control Group: yes
NOAEL: ca. .25 mg/kg bw

Method: other: CNS function evaluated according Cherkinskii, 1949: method of conditioned reflexes (time required for appearance, establishment,latent period,magnitude, frequency of occurrence), no further information
Year: 1967
GLP: no
Test substance: other TS: no data on purity
Remark: o-, m-, and p-chloronitrobenzene were tested: the para-isomer was found to be most toxic
Result: 0.0025, 0.005, 0.025, 0.25 mg/kg bw/d: no toxic effects

5 mg/kg bw/d:
hemapoetic system, last month of the experiment:
increase in the methaemoglobin content in the blood,
decrease of the haemoglobin content,
increase in the reticulocyte count (up to 78 %) and presence of Heinz bodies in the erythrocytes(up to 47 %);

liver function test: slight increase in blood alkaline phosphatase (no detail given)
effects on CNS function: some slowing down of fixation of the positive conditioned reaction and of the development of the differentiation reaction; liver function tests: increase in the blood alkaline phosphatase activity; rise in the level of bilirubin in the urine

urine: slight increase in bilirubin level
Reliability: (4) not assignable
lack of relevant information
16-JUN-2003 (22)

Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: 13 w
Frequency of treatment: 6 h/d, 5 d/w
Post exposure period: no
Doses: 0, 1.1, 2.3, 4.5, 9 or 18 ppm (0, 7, 14.7, 28.8, 57.6,115.2 mg/m3)
Control Group: yes

Method: other: 10 mice/sex/group, whole body exposure, body/organ weight, gross and microscopic pathology , statistical analysis; histopathological evaluations on reproductive organs: see chapter 5.8
Year: 1993
GLP: yes
Test substance: other TS: purity: 99 %

Result: No clinical signs related to 2-chloronitrobenzene exposure
Mortality: 18 ppm, week 12, 2/10 males (livers darkly discoloured, defuse, severe sinusoidal congestion with hepatocellular degeneration and necrosis);
males: no significant different in body weight gain between control and treated mice; females: from 2.3 ppm body weight greater than in control mice
pathology:
2.3, 4.5, 9 and 18 ppm: increases in right kidney weight and liver weight (all groups, females)
9 and 18 ppm: increase in liver weights(males), hepatocytomegaly in all males; spleen enlargement among females due to hematopoietic cell proliferation
18 ppm: incidence of mild hepatic mineralization and/or necrosis, pale discoloration of the liver (1/10 females, 6/10 males), chronic inflammation in the liver (especially males), incidence of hematopoietic cell proliferation in the spleens of the males; histopathologic changes in the liver, notably hepatocytomegaly observed among females
NOAEL: 4.5 ppm (histopathological injury)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
30-AUG-2001 (44) (80) (102)

Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: 2 weeks
Frequency of treatment: 6 h/d, 5 d/w
Post exposure period: no
Doses: 0, 1.1, 2.3, 4.5, 9, 18 ppm (approx. 0, 7, 14.7, 28.8, 57.6, 115.2 mg/m3)
Control Group: yes
NOAEL: ca. 2.3 ppm

Method: other: 5 mice/sex/group, whole body exposure, complete necropsy on all mice, histopathological evaluation on all mice
Year: 1993
GLP: yes
Test substance: other TS: purity: 99 %

Result: clinical signs:

18 ppm, esp. males: hypoactivity, abnormal posture, dyspnea
mortality, 18 ppm: 1/5 male on day 2 (diffusely dark, discoloured liver, severe centrilobular congestion, necrosis)
body weight gain was not affected,
pathology:
concentration-related increases in liver weights,
18 ppm, all rats: increased spleen and kidney weights
histopathologic findings:
18 ppm, all rats: liver: coagulative necrosis with associated inflammation; spleen: haemosiderin deposition
18 ppm, esp. males: haematopoietic cell proliferation, increased haematopoietic activity
9,18 ppm: hepatocytomegaly of the centrilobular cells
4.5, 9, 18 ppm, females: increasing incidence and severity of haematopoietic activity

Reliability: (2) valid with restrictions
dose-range finding study

21-MAR-2003 (80)

Species: mouse Sex: male/female
Strain: B6C3F1
Route of administration: oral feed
Exposure period: 5 weeks
Frequency of treatment: daily
Post exposure period: no
Doses: 0, 50, 500, 5000 ppm (calc. intake: (m):0,16,167,1120 mg/kg bw; (f):0,24,220,1310 mg/kg bw)
Control Group: yes, concurrent no treatment
NOAEL: ca. 50 ppm

Method: other: according to OECD Guideline 407, 1981; 12 mice/sex/group and additional 6 mice/sex/group for the interim sacrifice
Year: 1990
GLP: yes
Test substance: as prescribed by 1.1 - 1.4
Result: except one male in the low dose group no deaths,
5000 ppm(m)/500, 5000 ppm(f): reduced food intake,
sign. clin. findings only in the male 5000 ppm gr.: narrowed palpebral fissure and corneal opacity;
500/5000 ppm, m/f: centrilobular hepatocytomegaly
5000 ppm, m/f: reduced body weight gain, increased spleen weight, discolored spleen, deposition of hemosiderin in the spleen; increased liver weight (differences up to 89% were noted in females)
5000 ppm,m: reduced tested weight, decreased urea;
5000 ppm, m/f: reduced erythrocyte count(change in morphology: anisocytosis, poiklocytosis and polychromasie), reduced HK- and HB-content, increased MetHb (2.8 % f; 1.7% m), MCV, MCH, MCHC, bilirubin,
500 and 5000 ppm, after 1 week, m/f: increased cholesterin content, sign. changes in the activity of cytochrome 450-dependent EOD (7-Ethoxycoumarin deethylase), EH (Epoxide Hydroxylase) and ALD (Aldrin epoxidase) and Phase II enzymes: GSH-T(Glutathion-S-transferase), GLU-T (UDP-Glucuronyltransferase), and decreased gluconeogenesis and glycogen;
after 5 weeks:
f: normal ALD activity, increased activity of EOR, EH, Glu-T, slight increase in EOD, strong increase in GSH-T activity; m: increased activities of EOD, EOR, GLU-T, ALD,

GSH-T, EH
5000 ppm: increased activity of ASAT, ALAT, alkaline phosphatase(m), activated pentose phosphate cycle, increased glycolysis
no signs of nephrotoxicity
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
30-AUG-2001 (4) (5)

Species: mouse Sex: male/female
Strain: other: Swiss CD-1
Route of administration: gavage
Exposure period: 14 d
Frequency of treatment: daily
Post exposure period: no data
Doses: 0, 20, 40, 80, 160 or 320 mg/kg bw/d dissolved in corn oil
Control Group: yes, concurrent vehicle
NOAEL: ca. 40 mg/kg bw

Method: other: 8 mice/sex/dose, statistical analysis
Year: 1992
GLP: yes
Test substance: other TS: purity: > 99 %

Remark: type: dose-setting study
Result: mortality due to gavage trauma: control, f: 2/8, 20 mg-group, f: 1/8, 40-mg-group,f: 1/8
20 and 40 mg/kg bw/d: no clinical signs
80 mg/kg bw/d: all animals were inactive after the first two daily doses but appeared normal post-dosing throughout the rest of the exposure period
160 mg/kg bw/d: during the first week, animals were slightly weak and inactive; during the second week, these animals became slightly cyanotic, but remained active
320 mg/kg bw/d: during the first 2 days of treatment, all mice died or were moribund and sacrificed; clinical signs of toxicity: recumbency, trembling, inactivity, weakness and cyanosis
Reliability: (2) valid with restrictions
dose-setting study, histopathologic examination not performed
21-MAR-2003 (75) (80)

Species: rabbit Sex: no data
Strain: no data
Route of administration: inhalation
Exposure period: up to 18 d
Frequency of treatment: 8 h/d
Post exposure period: no
Doses: 0.1 mg/l
Control Group: other: no data

Method: other: no information
Year: 1910
GLP: no
Test substance: other TS: no data on purity

Result: deaths occurred after exposure for 8-18 d (no further data)
Reliability: (3) invalid
lack of information

16-JUN-2003 (26)

Species: cat Sex: no data
Strain: no data
Route of administration: inhalation
Exposure period: up to 14 d
Frequency of treatment: 8 h/d
Post exposure period: no
Doses: 0.1 mg/l
Control Group: other: no data

Method: other: no data
Year: 1910
GLP: no
Test substance: other TS: no data on purity

Result: deaths occurred after exposure for 8-14 d (no further data); 1 animal survived (total number of animals not mentioned)
Reliability: (3) invalid
lack of information

16-JUN-2003 (26)

Species: cat Sex: no data
Strain: no data
Route of administration: inhalation
Exposure period: all together 17.5 h during 3 consecutive d
Frequency of treatment: no data
Post exposure period: no
Doses: 0.05-0.18 mg/l
Control Group: other: no data

Method: other: no details given
Year: 1908

Result: mortality: 100 % (no further data)
Reliability: (3) invalid
lack of information: secondary literature

16-JUN-2003 (96)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Concentration: 0, 833.3, 1000.0, 1200.0, 1440.0, 1728.0, 2073.6 ug/plate in DMSO; from 1000 ug/plate bacteriotoxicity
Metabolic activation: with and without
Result: positive

Method: other: s. freetext
Year: 1984
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: suspensions of bacterial cells were incubated with the TS with and without S9-mix from rat liver for 48 hours at 37 celsius, the number of revertant colonies were counted; positive (2-aminoanthrazene, trypaflavine, endoxan) and negative controls

Remark: on strain TA 100, a marked dose-dependent increase in mutation rate (up to 4 times higher than in control) was found with metabolic activation
Reliability: (2) valid with restrictions
only 4 strains used
Flag: Critical study for SIDS endpoint
25-MAR-2003 (3)

Type: Ames test
System of testing: S. typhimurium TA 100
Concentration: no data
Metabolic activation: with
Result: positive

Method: other: no data
Year: 1981
GLP: no data
Test substance: other TS: no data on purity
Reliability: (4) not assignable
documentation insufficient for assessment
16-JUN-2003 (21)

Type: Ames test
System of testing: S. typhimurium TA 78, TA 100, TA 1535, TA 1538
Concentration: no data
Metabolic activation: with and without
Result: negative

Method: other: no data
Year: 1983
GLP: no data
Test substance: no data

Reliability: (4) not assignable
documentation insufficient for assessment
25-MAR-2003 (30)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Concentration: (1): 0.0, 6.0, 20.0, 60.0, 200.0, 600.0:
TA98,TA100,TA1535,TA1537
(2): 0.0, 6.0, 20.0, 60.0, 200.0, 600.0: TA100,TA98
(3): 0.0, 62.5, 125.0, 250.0, 500.0, 1000.0: TA100
see RM
Metabolic activation: with and without
Result: positive

Method: other: s. freetext
Year: 1983
GLP: no data
Test substance: other TS: purity 99 %
Method: preincubation method, solvent: DMSO, S9 prepared from rat liver and hamster liver, positive controls (2-AA, NOPD, 9-AAD), solvent control, performed in triplicate and repeated twice, highest dose: cytotoxic, statistical method according to Margolin et al. 1981

Remark: (4): 0.0, 10.0, 33.3, 100.0, 333.3, 1000.0 : TA98,TA100,TA1535,TA1587
(5): 0.0, 10.0, 33.3,100.0, 333.3, 1000.0: TA100
the test substance was mutagenic only in strain TA 100 with metabolic activation from hamster and rat
Reliability: (2) valid with restrictions
only 4 strains used, no information about GLP
Flag: Critical study for SIDS endpoint
25-MAR-2003 (33) (80)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration: no information
Metabolic activation: with and without
Result: negative

Method: other: preincubation method (only engl. abstract available)
Year: 1987
GLP: no data
Test substance: no data

Reliability: (4) not assignable
documentation insufficient for assessment
25-MAR-2003 (54)

Type: Ames test
System of testing: S. typhimurium TA 97, TA 98, TA 100, TA 102, TA 1535, TA 1537, TA 1538
Concentration: no data
Metabolic activation: with and without
Result: positive
Method: other: no data
Year: 1985
GLP: no data
Test substance: no data
Remark: the strain(s) on which the test substance induced an increase in the mutant count is (are) not mentioned in the description of the test results
Reliability: (4) not assignable
documentation insufficient for assessment
25-MAR-2003 (55)

Type: Cytogenetic assay
System of testing: Chinese Hamster Ovary cells
Concentration: without: 0, 16, 50, 160 ug/ml DMSO;
with: 0, 50, 160, 500 ug/ml DMSO
Metabolic activation: with and without
Result: ambiguous
Method: other: protocol in Galloway Environm. Mol. Mutagen. 10 [Suppl 10],1-175, 1987; solvent control, positive control, harvest time: 14 hours
Year: 1993
GLP: no data
Test substance: other TS: purity: 99 %

Remark: type: chromosomal aberration test
Result: without S9: equivocal, cell with aberrations (control, low to high doses): 2, 7, 8, 9%
with S9: negative
Reliability: (2) valid with restrictions
no information about GLP

Flag: Critical study for SIDS endpoint
25-MAR-2003 (77) (80)

Type: Sister chromatid exchange assay
System of testing: Chinese Hamster Ovary cells
Concentration: without S9:
(1) 0, 5, 16, 50 ug/ml DMSO
(2) 0,30, 40, 50, 60, 75ug/ml DMSO;
with S9:
0, 50,160,500 ug/ml DMSO
Metabolic activation: with and without
Result: positive

Method: other: s. freetext
Year: 1993
GLP: no data
Test substance: other TS: purity: 99 %

Method: protocol in Galloway Environm. Mol. Mutagen. 10 [Suppl 10],1-175, 1987; solvent control, positive control (mitomycin C, cyclophosphamide), S9-mix of induced rat liver, incubation time without S9: 26 hours, with S9: 2 hours, after removal of TS 26 hours
Remark: the test substance exhibited a mutagenic response only in the absense of S9-mix (up to 29% increase over solvent control)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
25-MAR-2003 (77) (80)

Type: other: mutation assay in Actinobacteria
System of testing: spores of Actinomyces sphaeroides
Concentration: 0, 0.63 g/l (= 0.004 M)
Metabolic activation: no data
Result: positive

Method: other: no details given
Year: 1971
GLP: no
Test substance: no data

Reliability: (4) not assignable
documentation insufficient for assessment
25-MAR-2003 (87)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration: 0, 25.6, 51.2, 102.4, 204.8, 409.6, 819.2, 1638.4, 3276.8 ug/plate in DMSO
Metabolic activation: without
Result: positive

Method: other: according to: OECD Guide-line 471: pour plate method, highest dose cytotoxic, performed in duplicate and repeated at least 2 times, solvent and positive control
Year: 1983
GLP: no data
Test substance: other TS: purity: 99 %

Remark: increased mutation rate only in strains TA 98 and TA 1538

Reliability: (2) valid with restrictions
study meets criteria of today but is only performed without metabolic activation, no information about GLP
25-MAR-2003 (92)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 100
Concentration: 0, 1, 5, 10, 15, 20 ug/plate in DMSO
Metabolic activation: with and without
Result: positive

Method: other: according to OECD Guide-line 471, preincubation method, without S9-mix, and with S9-mix and 200 ug/plate Norharman
Year: 1983
GLP: no data
Test substance: other TS: chromatographically pure

Remark: the test substance exhibited no mutagenicity to the tester strains in the absence of S9 mix, without norharman;
in the presence of S9 mix, without norharman, o-chloronitrobenzene was not mutagenic to S. typhimurium TA 98;
in the presence of norharman and S9-mix, the test substance exhibited mutagenicity only to S. typhimurium TA
Reliability: (3) invalid
special study, only performed in the presence of metabolic activation, cytotox concentration not determined, no information on GLP, no exact data on purity
25-MAR-2003 (98)

Type: Ames test
System of testing: S. typhimurium TA 98, TA 98 NR and TA 98/1,8-DNP6
Concentration: 0, 5, 10, 15, 20 ug/plate in DMSO
Metabolic activation: with
Result: positive

Method: other: according to OECD Guide-line 471, preincubation method, addition of S9-mix and norharman
Year: 1987
GLP: no data
Test substance: other TS: no dataon purity

Remark: the test substance exhibited weak mutagenicity towards TA 98 NR; the mutagenic activity, however, was much lower than that of o-chloronitrobenzene towards TA 98; the difference in the mutagenicities (test results: positive) of the test compound towards TA 98 and TA 98/1,8-DNP6 could not be regarded as significant
Reliability: (3) invalid
special study, only performed in the presence of metabolic activation, cytotox concentration not determined, no information on GLP, no exact data on purity
16-JUN-2003 (97) (99)

Type: other: SOS chromotest
System of testing: E. coli PQ 37
Concentration: 3-5 different concentrations (no further information)
Metabolic activation: with and without
Result: negative

Method: other
Year: 1988

GLP: no data
Test substance: other TS: no data on purity

Remark: o-chloronitrobenzene did not induce SOS-repair in the chromotest with and without S9 mix (without norharman); it was tried to increase the sensitivity of the SOS chromotest by addition of norharman to the S9 mix: a negative result was obtained again with the test substance
Reliability: (4) not assignable
documentation insufficient for assessment
25-MAR-2003 (108)

Type: HGPRT assay
System of testing: V 79 Chinese Hamster lung cells
Concentration: without S9-mix: 0,100,300,400,500,600,700,800,900 ug/ml DMSO;
with S9-mix: 0,100,200,450,600,750,900,1050,1200 ug/ml DMSO
Cytotoxic Concentration: without: 800 ug/ml; with: 750 ug/ml
Metabolic activation: with and without
Result: negative

Method: other: OECD Guide-line 476, rat liver S9-mix (induced), toxicity test prior to testing, exposure duration 5 hours, positive controls (EMS, DMN)
Year: 1989
GLP: yes
Test substance: other TS: purity: 99.8%

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
25-MAR-2003 (101)

Type: Cytogenetic assay
System of testing: Chinese hamster ovary cells
Concentration: without S9-mix: 0, 10, 50, 100 ug/ml DMSO; with S9-mix: 0, 25, 125, 250 ug/ml DMSO
Metabolic activation: with and without
Result: negative
Method: other: OECD Guide-line 473, harvest time: 8, 12, 21 hours, cytotoxicity was tested prior to testing, positive controls: mitomycin C, cyclophosphamide
Year: 1988
GLP: yes
Test substance: other TS: purity: 99.8 %

Remark: type: chromosomal aberration test
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
25-MAR-2003 (47)

Type: Ames test
System of testing: Salmonella typhimurium TA 100, TA 1535, TA 1537, TA 1538, TA 98, Escherichia coli WP2uvrA
Concentration: 0, 4, 20, 100, 500, 2500 ug/plate, dissolved in 100 ul DMSO, additionally:TA100 with S9-mix: 2000 ug/plate, dissolved in 100 ul DMSO
Metabolic activation: with and without
Result: positive
Method: other: OECD Guideline 471, rat S9-mix, positive controls
Year: 1984

```
   GLP:            yes
Test substance:    other TS: purity: 99 %
Remark:            mutagen with metabolic activation in TA100 and without in TA
                   1538
Source:            Hoechst AG  Frankfurt/Main
Reliability:       (1) valid without restriction
25-MAR-2003                                                              (43)

Type:                     Unscheduled DNA synthesis
System of testing:        Rat Hepatocytes
Concentration:            0, 1.0, 5.0, 10, 50, 75, 100 ug/ml DMSO, 500 ug/ml DMSO
                          was cytotoxic
Metabolic activation:     with and without
Result:                   negative
Method:            other: in accordance with OECD Guide-line 482, no detailed
                   data available
  Year:            1983
   GLP:            yes
Test substance:    other TS: as prescribed in 1.1-1.4 of the Monsanto dataset

Remark:            Cytotoxicity observed at 100 ug/ml in preliminary, but not
                   replicate assay
                   Cytotoxicity at 500 ug/ml
Source:            Monsanto
Reliability:       (2) valid with restrictions
                   no details on results given
25-MAR-2003                                                              (72)

Type:                     other: UMU test
System of testing:        Salmonella typhimurium TA1535/pSK1002
Concentration:            100 ug/ml
Metabolic activation:     with and without
Result:                   negative

Method:            other: incubation time: 4 hours; determination of
                   ß-galactosidase activity
  Year:            1992
   GLP:            no data
Test substance:    no data

Reliability:       (4) not assignable
                   documentation insufficient for assessment
25-MAR-2003                                                              (81)

Type:                     Bacterial reverse mutation assay
System of testing:        S. typhimurium TA98, TA100, TA1530, TA1532, TA1535,
                          TA1537, TA1538, TA1950, TA1975, G46
Concentration:            no data
Metabolic activation:     with and without
Result:                   negative

Method:            other: OECD guideline 471: plate incorporation method: aerobic
                   and anaerobic condition; fluctuation method
  Year:            1980
   GLP:            no data
Test substance:    other TS: purest grade available
Reliability:       (3) invalid
                   no details given, special study
25-MAR-2003                                                              (29)

Type:                     Sister chromatid exchange assay
System of testing:        Chinese Hamster Ovary cells
```

Concentration: without S9:
0,5,16,50 ug/ml DMSO;
with S9:
(1): 0, 50, 167, 500 ug/ml DMSO
(2): 0, 63, 125, 250 ug/ml DMSO
Metabolic activation: with and without
Result: positive

Method: other: s. freetext
Year: 1993
GLP: no data
Test substance: other TS: purity: 99 %

Method: protocol in Galloway Environm. Mol. Mutagen. 10 [Suppl 10],1-175, 1987; solvent control, positive control (mitomycin C, cyclophosphamide), S9-mix of induced rat liver, incubation time without S9: 26 hours, with S9: 2 hours, after removal of TS 26 hours
Result: without S9-mix: negative; with S9-mix: positive (up to ca. 40% increase over solvent control)
Reliability: (2) valid with restrictions
no information about GLP
Flag: Critical study for SIDS endpoint
25-MAR-2003 (80)

Type: Cytogenetic assay
System of testing: Chinese Hamster Ovary (CHO) cells
Concentration: without S9: 0,47,101,216 ug/ml DMSO; with S9: 0, 101,125,216,250,465,500 ug/ml DMSO
Metabolic activation: with and without
Result: positive

Method: other: protocol in Galloway Environm. Mol. Mutagen. 10 [Suppl 10],1-175, 1987; solvent control, positive control, harvest time: without S9: 18.5 hours, with S9: 13.6 hours
Year: 1993
GLP: no data
Test substance: other TS: purity: 99 %

Result: with S9-mix: poitive;
without S9-mix: negative
Reliability: (2) valid with restrictions
no information about GLP
Flag: Critical study for SIDS endpoint
25-MAR-2003 (80)

Type: HGPRT assay
System of testing: Chinese Hamster Ovary cells
Concentration: with S9-mix: 0, 10,30,100,300,400 ug/ml DMSO; without S9-mix: 0, 6.6, 20, 66.6, 200, 300 ug/ml DMSO
Metabolic activation: with and without
Result: negative
Method: other: in accordance with OECD Guide-line 476
Year: 1984
GLP: yes
Test substance: other TS: as prescribed in 1.1-1.4 of the Monsanto dataset
Reliability: (2) valid with restrictions
only summarized report available
16-JUN-2003 (71)

Type: Bacterial reverse mutation assay

System of testing: Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2uvrA
Concentration: 0, 10, 20, 50, 100, 200, 500, 1000 ug/plate dissolved in DMSO, highest dose cytotoxic
Metabolic activation: with and without
Result: negative

Method: other: OECD Guide-line 471, preincubation method, S9-mix from induced rat liver, solvent and positive controls (AF2, NaN3, 9AA)
Year: 1996
GLP: no data
Test substance: other TS: purity: 99 %

Reliability: (2) valid with restrictions
no information about GLP
Flag: Critical study for SIDS endpoint
25-MAR-2003 (51)

Type: Bacterial reverse mutation assay
System of testing: S. typhimurium TA100, TA1535, WP2uvrA, TA98, TA1537
Concentration: 0, 39.1, 78.1, 156, 313, 625, 1250, 2500, 5000, 10000 ug/plate dissolved in DMSO and TA100, TA1535, WP2uvrA: 500 ug/plate dissolved in DMSO
Metabolic activation: with and without
Result: positive

Method: other: OECD Guide-line 471, preincubation method, S9-mix from rat and from hamster, highest dose cytotoxic, solvent and positive controls
Year: 1997
GLP: no data
Test substance: other TS: purity: 99 %

Result: positive: TA100 with rat and hamster S9, TA98 with hamster S9
WP2uvrA: positive and negative with hamster S9-mix
Reliability: (2) valid with restrictions
no information about GLP
25-MAR-2003 (52)

Type: Ames test
System of testing: S. typhimurium TA100, TA98
Concentration: (1)0,10,33,100,133,166,250,333,666,1000,1666 ug/plate
(2)0,3,10,33,66,100,166,333,666 ug/plate
Metabolic activation: with and without
Result: positive

Method: other: praeincubation assay, S9-mix from hamster and rat liver
Year: 1983
GLP: no data
Test substance: other TS: purity: 98 %

Remark: TS was positive only in TA98 in presence of 30 % hamster S9-mix and in TA100 in presence of induced hamster or rat mix
Reliability: (2) valid with restrictions
no information on GLP only two strains used
25-MAR-2003 (80)

5.6 Genetic Toxicity 'in Vivo'

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Strain: other: Canton-S wild type
Route of admin.: i.p.
Exposure period: once
Doses: 0, 10000 ppm in peanut oil
Result: negative

Method: other: males(1-3d old), mated with 3x with Basc virgin females brood1: 3d, brood2: 2d, brood3: 2d;
Year: 1985
GLP: no data
Test substance: other TS: purity:>99 %

Reliability: (2) valid with restrictions
no information about GLP
25-MAR-2003 (80) (116)

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Strain: other: Canton-S wild type
Route of admin.: oral feed
Exposure period: 72 hours
Doses: 0, 125 ppm in 10 % ethanol and 5 % sucrose solution
Result: negative

Method: other: males(24 hrs old), mated with 3x with Basc virgin females brood1: 3d, brood2: 2d, brood3: 2d;
Year: 1985
GLP: no data
Test substance: other TS: purity: > 99 %

Reliability: (2) valid with restrictions
no information about GLP
Flag: Critical study for SIDS endpoint
25-MAR-2003 (80) (116)

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Strain: other: Canton S wild type
Route of admin.: oral feed
Doses: 0, 60 ppm in 4 % ethanol
Result: negative

Method: other: see ME
Year: 1989
GLP: no data
Test substance: other TS: purity: > 99 %

Method: In order to obtain individuals for larval treatment Canton-S females and males were mated and eggs exposed in vials with standard cornmealfood containing the chemical plus solvent alone. Adult males emerging from the treatrment were mated at approximately 24 hours of age with two successive harems of three to five Basc females to establish two single day broods. Males were then discarded and two conventional SLRL assay were carried out.

Reliability: (2) valid with restrictions
no information about GLP
25-MAR-2003 (80) (115)

Type: other: single-strand DNA-breaks
Species: mouse Sex: male
Strain: CD-1
Route of admin.: i.p.
Exposure period: single application
Doses: 60 mg/kg bw
Result: positive
Method: other: 8 mice, 4 h post appl. nuclei were isolated from liver and kidney cells, DNA damage was evaluated by alkaline elution technique was used, coupled with a microfluorometric method for DNA assay
Year: 1982
GLP: no data
Test substance: other TS: no data on purity
Result: effects: an increased elution rate in alkali of DNA from liver and kidney was obtained
Reliability: (2) valid with restrictions
no data on purity and GLP, only 1 dose used
Flag: Critical study for SIDS endpoint
25-MAR-2003 (19)

5.7 Carcinogenicity

Species: rat Sex: male
Strain: other: CD
Route of administration: oral feed
Exposure period: 18 months
Frequency of treatment: daily
Post exposure period: 6 months
Doses: 0, 500, 1000 or 2000 ppm (= ca. 0, 37.5, 75 or 150 mg/kg bw/d) ; see method
Control Group: yes, concurrent no treatment

Method: other: s. freetext
Year: 1978
GLP: no data
Test substance: other TS: purity: 97-99 %

Method: 25 rats/group,1000 or 2000 ppm for 6 mo., 500 or 1000 ppm for another 12 mo; complete gross necropsy and histology on certain organs (lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs, pituitaries), on all grossly abnormal organs and tumour masses, statistical methods: Fisher Exact Test, Bonferroni correction
Remark: pathological examination was not performed of animals that died within the first six months
Result: no information on body weight gain
multiple tumours at the low dose only and late in life: usually a pituitary adenoma along with either a stomach papilloma, adrenal tumour, thyroid adenocarcinoma, lymphosarcoma, choliangosarcoma of the liver or subcutaneous fibroma
incidences: low dose level:7/22, high dose level:1/19, simultaneous control: 1/22, pooled control: 14/111

Reliability: (2) valid with restrictions
study doesn't meet the criteria of today (number of animals too low, time of duration too short, doses too high), reported in brief
Flag: Critical study for SIDS endpoint
16-JUN-2003 (110)

Species: mouse Sex: male/female
Strain: CD-1
Route of administration: oral feed
Exposure period: 18 months
Frequency of treatment: daily
Post exposure period: 3 months
Doses: 0, 1500, 3000 or 6000 ppm (= ca.0, 225, 450 or 900 mg/kg bw/d)
Control Group: yes, concurrent no treatment

Method: other: s. freetext
Year: 1978
GLP: no data
Test substance: other TS: purity: 97-99 %

Method: 25 mice/sex/group,3000 or 6000 ppm for 8 mo., 1500 or 3000 ppm for another 10 mo; complete gross necropsy, histology on certain organs (lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs), on all grossly abnormal organs and tumour masses , statistical methods: Fisher Exact Test, Bonferroni correction
Remark: pathological examination was not performed of animals that died within the first six months
Result: no information on body weight gain
significant increase in hepatocellular carcinomas in female mice at both dose levels and in male mice at the low dose level
incidences of hepatocellular carcinomas:
male mice:
low dose level: 7/17, high dose level: 3/16, simultaneous control: 3/18, pooled control: 7/99;
female mice:
low dose level: 5/22, high dose level: 5/19, simultaneous control: 0/20, pooled control: 1/102
Reliability: (2) valid with restrictions
study doesn't meet the criteria of today (number of animals too low, time of duration too short, doses too high), reported in brief
Flag: Critical study for SIDS endpoint
16-JUN-2003 (110)

5.8.1 Toxicity to Fertility

Type: Two generation study
Species: mouse
Sex: male/female
Strain: other: Swiss CD-1
Route of administration: gavage
Exposure Period: see type and remarks
Frequency of treatment: daily
Premating Exposure Period
male: 7 d
female: 7d
Duration of test: 34 weeks

Doses: 0, 40, 80 or 160 mg/kg bw/d dissolved in corn oil
Control Group: yes, concurrent vehicle
NOAEL F1 Offspring: ca. 160 mg/kg bw
NOAEL F2 Offspring: ca. 160 mg/kg bw

Method: other: NTP Continuous Breeding Protocol, see also ME
Year: 1992
GLP: yes
Test substance: other TS: purity: > 99 %
Method: NTP Continuous Breeding Protocol: 20 ps/group, 40 ps (contr.), exposure period: F0: 7d prior to cohousing, 98d of continuous breeding. Last litter from F0, control and high dose groups were reared, weaned, and kept until mating. Siblings received the same treatment as their parents. At sexual maturity, 20 non-sibling males and females were cohabited for 7 days and housed singly through delivery, until sacrifice. Exam.: symtoms, bw gain, water consumption; F0,F1: contr,160 mg-gr.: spleen weight, methb; F0,F1:

fertility indices; F1(m): testes,epididymis, F1(f): vaginal cytolo
Result: Conclusion:
In the presence of altered somatic and selected organ weights 2-chloronitrobenzene (2CNB) did not alter reproductive function in either generation (NOEL 160 mg/kg bw); thus, 2CNB is not a selective reproductive toxicant.
F0 mice:
Mortality: 2,2,2,3 control to high dose gr., 160 mg-group: increased terminal bw and spleen weights; 80 mg-gr.(1m), 160 mg-gr.(3m): with hepatocellular degeneration;
160 mg-gr.: methaemoglobinaemic, during the first 10 d mice were slightly inactive post dosing, 3 lactating females were cyanotic for up to 2 weeks; no other signs of clin.l toxicity
F0-fertility and reproductive parameters were not affected
F1-pups:
in the final litter of the holding period following the continuous breeding phase, F1 pup weight gain during suckling was lower in all treated groups;
at weaning, F1 pups in the 160 mg/kg bw/d group weighed 10-13% less than controls, all other fertility and reproductive parameters were not affected;
F1 mice (only control and high dose group):
no signs of clin. tox. observed, 160 mg/kg bw/d: significantly lowered body weights at weaning but sign. heavier than controls at mating and at terminal necropsy; right epididymis, kidney/adrenals(m), spleen and liver weights increased, seminal vesicle-to-body weight ratio was sign. decreased, sign. methaemoglobinaemia;
none of the fertility and reproductive parameters examined were affected in F1 mice, i.e., epididymal sperm parameters (motility, count and percentage of abnormal sperms) and estrous cycle length and estrual cyclicity
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
27-AUG-2001 (20) (76) (80)

Type: other:
Species: rat
Sex: male/female
Strain: other: F344/N
Route of administration: inhalation

Exposure Period: 13 w
Frequency of treatment: 6 h/d, 5 d/w
Doses: 0, 4.5, 9 or 18 ppm (approx. 0, 28.8, 57.6, 115.2 mg/m3)
Control Group: yes, concurrent no treatment

Method: other: 10 rats/sex/group, reproduct. system evaluation: vaginal cytology, sperm morphology, necropsy body and reproductive tissue weights, speremato zoal data, spermatogenesis, oestrous cycle length, percent of cycle spent in various
Year: 1993
GLP: yes
Test substance: other TS: purity: 99 %

Remark: see chapter 5.4.
Result: females: no effects observed
males, 18 ppm: decreases in cauda epididymis weights (6.8%), and in the spermatid count and spermatid heads/testis (ca. 13%)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
25-MAR-2003 (44) (80)

Type: other:
Species: rat
Sex: male
Strain: Fischer 344
Route of administration: gavage
Exposure Period: single application
Frequency of treatment: once
Doses: 150 mg/kg bw
Control Group: yes

Method: other: 5or 6 rats, sacrifice on d1 and d25 post application, evaluation of testes weight, testicular histopathology, sperm production
Year: 1988
GLP: no data
Test substance: other TS: no data

Result: no effect on testicular histopathology (at 1 d) or testes weight and daily sperm production (at 25 d)
Reliability: (4) not assignable
lack of information
25-MAR-2003 (65)

Type: other:
Species: mouse
Sex: male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure Period: 13 w
Frequency of treatment: 6 h/d, 5 d/w
Doses: 0, 4.5, 9 or 18 ppm (approx. 0, 28.8, 57.6, 115.2 mg/m3)
Control Group: yes, concurrent no treatment

Method: other: 10 rats/sex/group, reproductive system evaluation: vaginal cytology, sperm morphology, necropsy body and reproductive tissue weights, spermatozoal data, spermatogenesis, estrous cycle length, percent of cycle spent in various
Year: 1993
GLP: yes
Test substance: other TS: purity: 99 %

Remark: see chapter 5.4
Result: male, 4.5, 9, 18 ppm: decreased sperm motility
females: increased terminal body weight; no reproductive effects observed
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
03-SEP-2001 (20) (44) (80)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: days 6-15 of gestation
Frequency of treatment: daily
Duration of test: 21 d
Doses: 0, 25, 75, or 150 mg/kg bw/d dissolved in corn oil
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: ca. 25 mg/kg bw

Method: other: 25 females/group, due to severe mat. tox. and mortality the 150 mg-level was terminated prior to scheduled sacrifice
Year: 1986
GLP: yes
Test substance: other TS: purity: commercial

Result: mortality:
150 mg-gr.: due to severe toxicity and high mortality rate of the dams, all females were terminated prior to sheduled sacrifice, 75 mg-group: 1/25;
general toxicity:
75 mg/kg bw/d: gest.-d. 6-10: reduced body weight gain (slight but not significant) and
reduced food consumption; recovery later in gestation;
urinary staining, alopecia; maternal reproductive parameters comparable to controls, mean number of early resorptions and post implantation loss slightly increased (post implantation loss in the respective control very low when compared to historical control; values range: 0-0.9)
25 mg/kg bw/d: no evidence of maternal toxicity
developmental toxicity:
fetal body weight comparable to control
variations: cervical #7 ribs at 25 mg-gr (1.1%) and sign. at 75 mg-gr (2%); 13 full pair of ribs with lumbar #1 rudimentary ribs in controls, at 25 mg-, 75 mg-gr increased, but not sign.;
12 full pair of ribs with #13 unilateral full rib and/or rudimentary rib(s) in controls and in 25 mg-gr. increased, but not sign.
Reliability: (2) valid with restrictions
highest dose was too high
Flag: Critical study for SIDS endpoint
25-MAR-2003 (67) (105)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: d6-d15
Frequency of treatment: daily
Doses: 0, 100 mg/kg bw in corn oil
Control Group: yes, concurrent vehicle
other: NOAEL developmental toxicity : ca. 100 mg/kg bw

Method: other: 25 females/group, only one dose
Year: 1984
GLP: yes
Test substance: other TS: purity: commercial

Remark: The study was intended to clarify the observations of the study of Monsanto,1986
Result: d6-10: slight maternal body weight loss accompanied by reduction in food consumption for d6-16, maternal reproductive parameters were not affected, fetal body weight comparable to the respective controls; no teratogenic effects were observed
Reliability: (2) valid with restrictions
only one dose used
Flag: Critical study for SIDS endpoint
25-MAR-2003 (49)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Remark: based on clinical and laboratory evaluation of cyanosis cases during a 10-year period a number of cyanogenic aromatic nitro compounds were ranked in descending order of relative hazard relating to their cyanogenic potential observed in exposed industrial workers (rank 1 = most potent, rank 13 = least potent): o-chloronitrobenzene was classified in rank 7; laboratory evaluation showed that total oxygenatable haemoglobin in some cases, notably after be expected from methaemoglobin analysis (unspecified route of absorption)
Flag: Critical study for SIDS endpoint
(59)

Remark: experience with human exposure: a number of the more important aromatic nitrocompounds were ranked showing their commparative hazard ratings for cyanosis, anaemia and overall toxicity (the degree of hazard ranges from 1 = slight hazard to 6 = severe hazard): for o-chloronitro-benzene, the degree of hazard is 4 concerning cyanosis hazard, 2 concerning anaemia hazard and 3 concerning over-all toxic hazard (no further data)
(60)

Remark: all 325 records of industrial chemical cyanosis poisoning in Britain notified to the inspectorate from 1961 to 1980 were scrutinised: the cases occurred mainly during chemical or dyestuff manufacture; a total of 50 cases of chemical cyanosis syndrome due to chloronitrobenzene were reported; 23 (46 %) cases were "early cases", i.e., the symptoms developed while at work on the same day of exposure, and 27 (54 %) cases were "delayed cases", i.e., the symptoms developed insidiously or some definite time after the "working" day on which the poisoning occurred (the route of absorption is not described in detail for each test compound, the most cases resulted from skin absorption and/or inhalation; in this study, the isomer(s) of chloronitro-benzene is/are not clearly specified)
Flag: Critical study for SIDS endpoint
14-AUG-2001 (91)

Remark: experience with human exposure: in chloronitrobenzene poisoning cardiac complications appear to be more frequent and more serious than in aniline poisoning and gastro-intestinal irregularities (anacidity) also appear to be quite common (no further data, isomer(s) of chloro-nitrobenzene not specified)
(13) (14)

Remark: experience with human exposure: four workmen were reported who were hospitalized as the result of exposure to a mixture of o- and p-chloronitrobenzene; these cases resulted from two to four days exposure and all were cyanotic; headache and weakness accompanied the cyanoses
Flag: Critical study for SIDS endpoint
(84)

Remark: The exposition against a mixture of 2-chloro- and 4-chloronitrobenzene caused severe intoxications which exceeds the signs of intoxication during repair of a unit for isolation of the isomers. As symtoms cyanotic appearance and collapse were described. Hb-content was decreased up to 65 % of the normal value. During the recovery period the patients suffered from difficulty in breathing and sensation of dizziness. Within 7 weeks Hb content increased to 80 % of the normal value.
Flag: Critical study for SIDS endpoint
14-AUG-2001 (28)

5.11 Additional Remarks

Type: other

Remark: the level of lipid peroxidation, content of vitamine E and its metabolites as well as antioxidative activity in the blood serum, liver and spleen of white rats were studied. Toxicological efects of nitrochlorobenzenes were decreased by vitamine E (no further information) .

23-FEB-1998 (82) (83)

Type: other: Haematotoxizitaet

Remark: Ergebnis: 10 mg/kg Kgw. zeigte (2 Katzen): keine Letalitaet, leichte Veraenderungen im weissen Blutbild, leichten Anstieg der Zahl der Heinz'schen Innenkoerper und leichte Methaemoglobinaemie, nach 48 Stunden p.a. weitgehend reversibel.
Source: Hoechst AG Frankfurt/Main
Test substance: technisch rein

(36)

Remark: an attempt to vaporize o-chloronitrobenzene by passing air (2 l of air/min. for 1 h) through a tower of dust was not successful in that no weighable amounts of the test substance were vaporized; rats and mice in an inhalation chamber were exposed to the generated atmosphere for 1 h: no symptoms of toxicity were observable and no deaths occurred at the end of the exposure period or within an observation period of 7 d

(6)

Remark: 48 h after a single oral administration of 100 mg/kg bw of o-chloronitrobenzene to rabbits, 0.3 % of the administered dose was found in faeces as unabsorbed material which was completely reduced to the chloroaniline; in the urines collected each 24 h for 48 h the following metabolites of o-chloronitrobenzene were detectable (expressed as percentages of the administered dose): ether glucuronide (42 %), ethereal sulphate (24 %), mercapturic acid (7 %), free chloroaniline (9 %) (total accounted for: 82 %)
Flag: Critical study for SIDS endpoint

(15)

Remark: metabolism in vitro: radiolabelled (14 C) o-chloronitrobenzene (concentration not specified) was incubated with isolated rat hepatocytes for up to 90 min.: after 90 min., 71 % of the o-chloronitrobenzene had been metabolized; the primary metabolic pathway for o-chloronitrobenzene was reduction to o-chloroaniline (19.2 % of the total radioactivity after 90 min.); o-chloronitrobenzene was also conjugated with glutathione; two other very polar metabolites, com- prising 14.2 % of the total 14 C from o-chloronitrobenzene, have not been identified

23-FEB-1998 (34) (35)

Remark: in order to identify the specific enzymes involved in the metabolism of o-chloronitrobenzene by isolated rat hepatocytes, hepatic subcellular fractions were isolated from rats; microsomes incubated with radiolabelled (14 C) o-chloronitrobenzene in the presence of NADPH produced o-chloroaniline under aerobic conditions and SKF 525 A and metyrapone had no effect on the metabolism to o-chloroaniline: these findings suggest that cytochrome P-450 reductase is responsible for o-chloronitrobenzene reduction; radiolabelled o-chloronitrobenzene was also incubated with or without microsomes, cytosol and/or glutathione: o-chloronitrobenzene was converted to S-(2-nitrophenyl)glutathione in the presence of cytosol and glutathione suggesting that cytosolic glutathione transferase is involved in this conjugation (concentration of the test substance un-

specified)

(34)

Remark: the effect of o-chloronitrobenzene on heme synthesis was determined in vitro by studying its influence on delta-aminolevulinic acid synthetase (ALAS) and ferrochelatase (FC) activities in rat liver homogenates; at 0.001 mol/l concentration, o-chloronitrobenzene did not significantly affect the enzyme activities

(53)

Remark: o-chloronitrobenzene was administered by gavage to adult and geriatric rats at 65 mg/kg bw/d for 11 d; 14 C-o-chloronitrobenzene was administered on days 1, 5 and 9; 14 C was determined in urine and faeces up to 96 h after each 14 C-dose and in tissues at 72 h after the day 9 dose: in adult rats, at all treatment intervals, 71-74 % of each dose was excreted in urine and 20-27 % in faeces and the rates of excretion increased with pretreatment; 5 % of the day 9 dose was in tissues, the highest concentrations were in liver and kidney; 24 urinary metabolites were found; pattern, rate and extent of excretion of 14 C were similar in geriatric and adult rats, except that urinary excretion by unpretreated geriatrics was more extensive (85 %) and the rates of urinary and faecal excretion did not increase with pretreatment; tissue distribution of 14 C was also similar and 8 % of the day 9 dose was in tissues

Flag: Critical study for SIDS endpoint

27-AUG-2001 (62)

Remark: 14 C-o-chloronitrobenzene was administered by gavage to rats at 2, 20 or 200 mg/kg bw (single administration); radioactivity was determined in urine and faeces up to 72 h and in tissues at 24 and 72 h: at 2 and 20 mg/kg bw 58-60 % of the dose was excreted in urine, 26-28 % in faeces, primarily during the first 24 h, 6 % was in 24-h and 3 % in 72-h tissues; at 200 mg/kg bw 74 % was in urine and only 7 % in faeces and it was excreted more slowly with 21 % in 24-h and 4 % in 72-h tissues; at 2 and 20 mg/kg bw o-chloronitrobenzene equivalent concentrations in tissues

were proportional to dose, whereas at 200 mg/kg bw they were disproportionately higher in all tissues, especially in fat, and disproportionately lower in liver; at all doses the highest concentrations were in liver and kidney and at 200 mg/kg bw in fat; up to 23 metabolites were in urine

Flag: Critical study for SIDS endpoint

27-AUG-2001 (63)

Remark: After a single non-occlusive, protective dermal application of 14 C-o-chloronitrobenzene at doses of ca. 0.65, 6.5 or 65 mg/kg bw to male rats, 33-40 % of the doses of o-chloronitrobenzene was absorbed from the skin within 72 h; the absorbed 14 C was excreted in urine (21-28 %) and faeces (11-15 %). The extent absorption increased with an increase in dose from 0.65 to 6.5 mg/kg bw but increased only neglibly when the dose was increased to 65 mg/kg bw.

The extent of urinary excretion of radioactivity was not significantly affected by dose over the range studied. The initial rate of urinary excretion was also unaffected by dose. The initial rate of faecal exretion increased with dose over the 0.65 to 6.5 mg/kg range, but decreased notably at the high dose.

Flag: Critical study for SIDS endpoint

27-AUG-2001 (66) (79)

Remark: metabolism of o-chloronitrobenzene by hepatic subcellular fractions from rats: to determine the enzyme systems involved in the metabolism of o-chloronitrobenzene by rat isolated hepatocytes, radiolabelled (14 C) o-chloronitrobenzene (100 uM) was incubated with hepatic microsomes (incubation mixture containing microsomes and NADPH, some incubations also containing UDP-glucuronic acid) or with cytosol (incubation mixture containing GSH and cytosolic protein): reduction of o-chloronitrobenzene to o-chloroaniline occurred readily in microsomal incubations; substitution of NADH for NADPH or incubation of microsomes under a carbon monoxide atmosphere significantly inhibited nitroreduction, boiling the microsomes completely abolished reduction of o-chloronitrobenzene; addition of SKF 525-A or metyrapone significantly inhibited the microsomal reduction of o-chloronitrobenzene to o-chloroaniline (the inhibition of nitroreduction by carbon monoxide, SKF 525 A and metyrapone suggests that cytochrome P-450 catalyzes this reaction); incubation of o-chloronitrobenzene with rat hepatic cytosol and glutathione resulted in the formation of S-(2-nitrophenyl)glutathione

Flag: Critical study for SIDS endpoint

(85)

Remark: in vitro study of metabolism: after 90 min. incubation of isolated rat hepatocytes with radiolabelled (14 C) o-chloronitrobenzene (100 uM final concentration), 46.7 % of the added o-chloronitrobenzene was metabolized; the calculated half-life for disappearance of o-chloronitrobenzene from the incubations was 84 min.; a major metabolic pathway for o-chloronitrobenzene was reduction to o-chloroaniline (19.2 % of the total radioactivity after 90 min. incubation); o-chloroaniline was further metabolized to form the N-glucuronide accounting for 14.2 % of the total radioactivity; o-chloronitrobenzene was conjugated with glutathione and S-(2-nitrophenyl)glutathione accounted for 13.3 % of the total radioactivity

Flag: Critical study for SIDS endpoint

(85)

Remark: in vitro assay: the reduction of chloronitrobenzenes was investigated in purified milk xanthine oxidase-xanthine system: o-chloronitrobenzene was less readily reduced by the enzyme than the corresponding para and meta isomers, indicating the steric hindrance effect at ortho position

Flag: Critical study for SIDS endpoint

(100)

Remark: in an in vivo study, 100 umoles/kg bw (= 15.7 mg/kg bw) of o-chloronitrobenzene was given i.p. to male rats, the animals were killed 5 h after the injection to examine methaemoglobin levels: formation of methaemoglobin was observable (methaemoglobin level: 20.6 %)
Flag: Critical study for SIDS endpoint

(109)

Remark: in vitro methaemoglobin formation was studied by incubating haemolyzate (obtained from rats and containing 0.1 umole of haemoglobin) with 0.5 umole of o-chloronitrobenzene at pH 6.6 and 37 degrees centigrade for 5 h: formation of methaemoglobin (concentration: 4.8 %) was not significantly increased compared with the control

(109)

Remark: Single oral administration of 0.1 ml/100 g bw of a 0.5 M tricaprylinsolution of 1-chloro-2-nitrobenzene (o-CNB) to female Wistar rats resulted in hemoglobin binding: 2.1 (mmol TS/mol Hb)/(mmol TS/kg bw)
Flag: Critical study for SIDS endpoint

23-FEB-1998 (89) (90)

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