

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, cholangiosarcoma 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 cohoused for 7 days and housed singly through delivery, until sacrifice. Exam.: symptoms, bw gain, water consumption; F0, F1: contr, 160 mg-gr.: spleen weight, methb; F0, F1:

fertility indices; F1(m): testes, epididymis, F1(f): vaginal cytology

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 clinical 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 clinical toxicity observed, 160 mg/kg bw/d:

significantly lowered body weights at weaning but significantly 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 significantly decreased, significant 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 sperm) and estrous cycle length and estrual cyclicity

Reliability:

Flag: (1) valid without restriction
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

5. TOXICITY

DATE: 26-NOV-2003

SUBSTANCE ID: 88-73-3

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, sperematozoal 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: 5 or 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 comparative hazard ratings for cyanosis, anaemia and overall toxicity (the degree of hazard ranges from 1 = slight hazard to 6 = severe hazard): for o-chloronitrobenzene, 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 chloronitrobenzene is/are not clearly specified)

Flag: Critical study for SIDS endpoint (91)
14-AUG-2001

Remark: experience with human exposure: in chloronitrobenzene poisoning cardiac complications appear to be more frequent and more serious than in aniline poisoning and gastrointestinal irregularities (anacidity) also appear to be quite common (no further data, isomer(s) of chloronitrobenzene 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 symptoms 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 (28)
14-AUG-2001

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 effects 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, comprising 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)

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 (34)

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 (53)

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 (63)

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 negligibly 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 excretion 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 tricaprilynsolution 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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