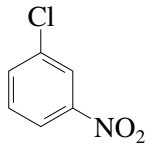
m-Chloronitrobenzene H

Classification/MAK value:	**not yet established see Section IIb MAK List 1991**
Synonyms:	*m*-nitrochlorobenzene 3-chloronitrobenzene 3-chloro-1-nitrobenzene
Chemical name (CAS):	1-chloro-3-nitrobenzene
CAS number:	121-73-3
Structural formula:	
Molecular formula:	$C_6H_4ClNO_2$
Molecular weight:	157.56
Melting point:	46 °C
Boiling point:	236 °C
Vapour pressure at 20 °C:	8 hPa
1 ml/m^3 (ppm) = 6.54 mg/m^3	**1 mg/m^3 = 0.153 ml/m^3 (ppm)**

1 Toxic Effects and Modes of Action

m-Chloronitrobenzene is obtained together with *o*-chloronitrobenzene and *p*-chloronitrobenzene by nitration of chlorobenzene.

In a study of the metabolism of the substance, metabolites hydroxylated on the ring and products with a reduced nitro group have been identified.

The toxic effects of *m*-chloronitrobenzene in man have not yet been described.

The main symptoms of intoxication in animals are methaemoglobinaemia and Heinz body formation; one report also describes testicular toxicity. The results of tests for skin irritation and sensitization were negative.

There are no known studies of reproductive toxicity of *m*-chloronitrobenzene. A weak positive result was obtained in only one of the available genotoxicity tests. There are no carcinogenicity studies with this substance.

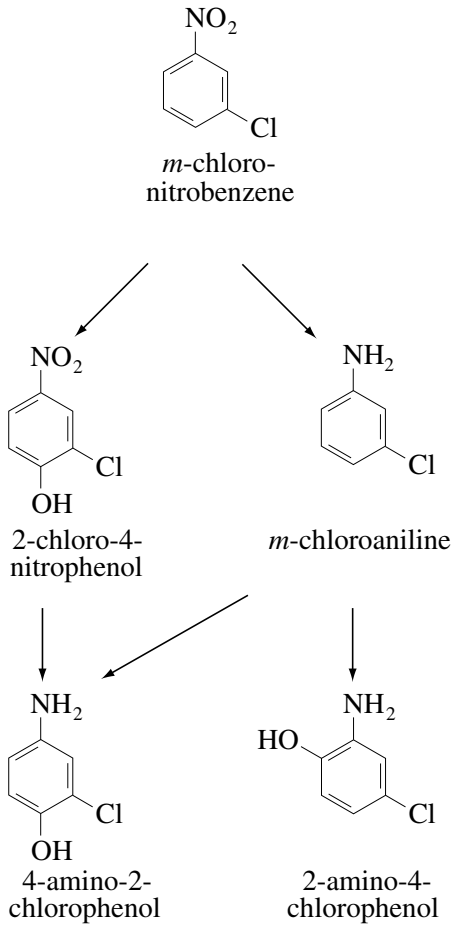


Figure 1. Metabolites identified in free and conjugated form in the urine of rabbits given oral doses of m-chloronitrobenzene [1]

1.1 Pharmacokinetics and metabolism

After oral administration of a *m*-chloronitrobenzene dose of 200 mg/kg to rabbits, 33 % of the dose was excreted in the urine as glucuronides, 18 % as sulfates, 1 % as mercapturic acids, 11 % as free m-chloroaniline and 0.6 % as free m-chloronitrobenzene. In the faeces only m-chloroaniline was detected. Elimination was complete within 48 hours. The urinary metabolites are shown in Figure 1 [1].

2 Effects in Man

The effects of *m*-chloronitrobenzene in man have not been described.

3 Effects on Animals

3.1 Acute toxicity

3.1.1 Oral and intraperitoneal administration

The LD_{50} values obtained after administration of single oral doses of *m*-chloronitrobenzene to experimental animals are shown below:

mouse: 380 mg/kg [2],
mouse: 390 mg/kg (278–575 mg/kg) [3],
rat: 470 mg/kg [2].

There are two acute toxicity studies in which methaemoglobin levels were determined after administration of *m*-chloronitrobenzene to cats and rats by intraperitoneal injection. The results are shown in Table 1.

The results of a study of the testicular toxicity of *m*-chloronitrobenzene have been reported only as an abstract. Five or six male Fischer 344 rats were given a single oral *m*-chloronitrobenzene dose of 200 mg/kg. In the testes of the animals killed 1 day later (number not specified) degenerative changes were observed (condensed nuclei, cytoplasmic vacuolization in spermatocytes). In the rats killed on day 25 after treatment, testis weights were reduced to 73 % of the control values and the daily production of spermatozoa to 17% [6].

3.1.2 Percutaneous absorption

The acute toxicity of *m*-chloronitrobenzene was studied by dermal application of the substance to groups of 5 rats per sex and dose. 24 hours after shaving the area with an electric razor, *m*-chloronitrobenzene doses of 0, 500, 1000, 1500 or 2000 mg/kg dissolved in polyethylene glycol were applied to the skin occlusively for 24 hours. All the

Table 1. Acute toxicity of *m*-chloronitrobenzene after intraperitoneal administration to experimental animals

Species	Number	Dose mg/kg	Methaemoglobin level in blood	Mortality	Ref.
cat	5	5*	after *c* 10 h: 10% (0–35%)	2/5	[4]
	4	7.5*	after *c* 10 h: 41.3% (19–70%)	11/13	
	9	10*	after *c* 10h: 43% (7–75%)		
			(after 20 h: maximum level of Heinz body formation – 90%)		
rat (Wistar)	?	15.7**	after 5 h: 31.9%		[5]

* solvent poppy-seed oil
** solvent propylene glycol

rats treated with the two lowest doses survived; the only observed effect was slight sedation. In the 1500 mg/kg group, 4/5 males and 1/5 females died; autopsy revealed discoloured reddish brown lungs. Autopsy of the survivors yielded no treatment-related findings. The observed symptoms included sedation, slight spasms, ruffled fur and a slight decrease in body weights. Of the animals treated with 2000 mg/kg, 5/5 males and 4/5 females died. Autopsy revealed red to dark red discoloured lungs in all animals except in those of the surviving female. In one of the females, the mucosa of the jejunum and ileum was also red. The preterminal symptoms of toxicity included marked sedation and spasms, ruffled fur and reduced body weights [7].

3.1.3 Local effects on skin and mucous membranes

Irritative effects of *m*-chloronitrobenzene were studied by semi-occlusive application of 0.5 g of the substance (moistened with polyethylene glycol) for 4 hours to the skin of 2 male and 1 female rabbits (New Zealand White), 24 hours after shaving the site with an electric razor. Neither signs of skin irritation nor other symptoms were detected during the 3 days after treatment [8].

3.2 Subchronic and chronic toxicity

In an early inhalation study, groups of 16 to 18 rats (strain and sex not specified) were exposed continuously for 100 days to *m*-chloronitrobenzene vapour concentrations of 0.0006, 0.0012 or 0.0122 ml/m^3 (0.004, 0.008 or 0.08 mg/m^3). At the medium and high concentrations from day 22 of the study, the chronaxy ratio of antagonistic muscles was shown to be greater than 1 (the control ratio is less than 1, i.e. the chronaxy of the extensors is greater than that of the flexors). The animals recovered by day 20 of the post-exposure observation period. In the 0.008 and 0.08 mg/m^3 groups, marked sulf-haemoglobinaemia without methaemoglobinaemia was seen from exposure day 40 (no other details). No effects were seen at the lowest concentration [9].

A group of 20 albino rats (sex and strain not specified) were given 20 daily oral *m*-chloronitrobenzene doses of 60 mg/kg body weight; 4 of the animals died [10].

In an early chronic toxicity study, a total of 42 albino rats (no other details) were each given an oral dose of 5.00, 0.025, 0.005 or 0.0025 mg/kg of one of the three chloro-nitrobenzene isomers, daily for a period of 6 months. The toxicity of *m*-chloronitro-benzene was between that of *o*-chloronitrobenzene and *p*-chloronitrobenzene; the 5.00 and 0.025 mg/kg doses produced the following symptoms: increase in the methaemo-globin level, increase in the number of reticulocytes and formation of Heinz bodies in the erythrocytes. In addition, at the highest dose (5 mg/kg) increased blood alkaline phosphatase activity and increased urine bilirubin levels were detected [10].

3.3 Sensitization

To investigate the sensitization potential of *m*-chloronitrobenzene, groups of 10 guinea pigs of each sex were given 3 intradermal injections into the shaved dorsal skin in the scapular area: Freund's adjuvant in ethanol (1:1), 0.1% *m*-chloronitrobenzene in ethanol,

and 0.1 % *m*-chloronitrobenzene in a 1:1 mixture of Freund's adjuvant with ethanol. One week later, a 25 % solution of *m*-chloronitrobenzene in ethanol was applied occlusively to the shaved dorsal skin of the same animals for 2 days. Two weeks later the first provocation was carried out with 25 % *m*-chloronitrobenzene in ethanol applied for 24 hours to the left flank. In the treated animals, there were no reactions which differed from those in the controls. Similarly, a second provocation carried out another two weeks later under the same conditions but on the right flank revealed no signs of sensitization [11].

4 Genotoxicity

In the Ames test in the *Salmonella typhimurium* strains TA98, TA1537, TA1538, TA100 and TA1535, *m*-chloronitrobenzene concentrations up to 3000 µg/plate produced no mutagenic effects even after metabolic activation and addition of norharman [12–15].
m-Chloronitrobenzene was not mutagenic either with or without S9 mix in the SOS chromotest [16].

m-Chloronitrobenzene with and without S9 mix produced neither sister chromatid exchange nor chromosome aberrations in CHO cells [17].

In a study of point mutations at the HGPRT locus of V79 cells, *m*-chloronitrobenzene concentrations between 27 and 400 µg/ml were ineffective both with and without S9 mix from Aroclor-induced rats [18].

Tested in V79 cells in concentrations between 15 and 400 µg/ml, *m*-chloronitrobenzene induced a slight but significant increase in chromosome aberrations only at the highest concentration and with metabolic activation [19].

5 Manifesto (MAK value, classification)

There is much less data available for *m*-chloronitrobenzene than for the other two chloronitrobenzene isomers.

In animal studies, *m*-chloronitrobenzene causes methaemoglobin production. In long-term studies, the toxicity of the substance lies between that of the other two isomers. All except one of the tests for genotoxic activity yielded negative results, even when carried out by investigators who obtained positive results with the other isomers. Any genotoxic potency of the substance must therefore be markedly less than that of *o*-chloronitrobenzene or *p*-chloronitrobenzene. Carcinogenicity studies have not been carried out to date. A MAK value cannot be established because neither sufficient data on the effects in man nor appropriate results of animal studies are available. *m*-Chloronitrobenzene is given the designation "H" for reasons of analogy.

Classification in one of the pregnancy groups is also not possible because studies of the embryotoxic or foetotoxic effects of the substance have not been carried out.

6 References

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