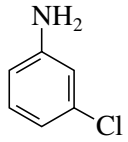
m-Chloroaniline H

Classification/MAK value:	**not yet established see Section IIb MAK List 1990**
Synonyms:	3-chloroaniline *m*-aminochlorobenzene 1-amino-3-chlorobenzene 3-chlorobenzeneamine *m*-chlorophenylamine 3-chlorophenylamine
Chemical name (CAS):	3-chlorobenzenamine
CAS number:	108-42-9
Structural formula:	
Molecular formula:	C_6H_6NCl
Molecular weight:	127.58
Melting point:	–10 °C
Boiling point:	231 °C
Vapour pressure at 20 °C:	not specified
1 ml/m³ (ppm) = 5.29 mg/m³	**1 mg/m³ = 0.189 ml/m³ (ppm)**

1 Toxic Effects and Modes of Action

m-Chloroaniline occurs as an intermediate in the synthesis of herbicides, colourants and Pharmaceuticals.

The main symptoms of intoxication in man and animals are methaemoglobinaemia and an increase in Heinz bodies. *m*-Chloroaniline is a local irritant on skin and mucous membranes.

Its known metabolites comprise compounds hydroxylated on the benzene ring and their conjugates.

Studies of the reproductive toxicology of *m*-chloroaniline have not been published. *m*-Chloroaniline yields negative results in the Ames test. Studies on its carcinogenic effects are not available.

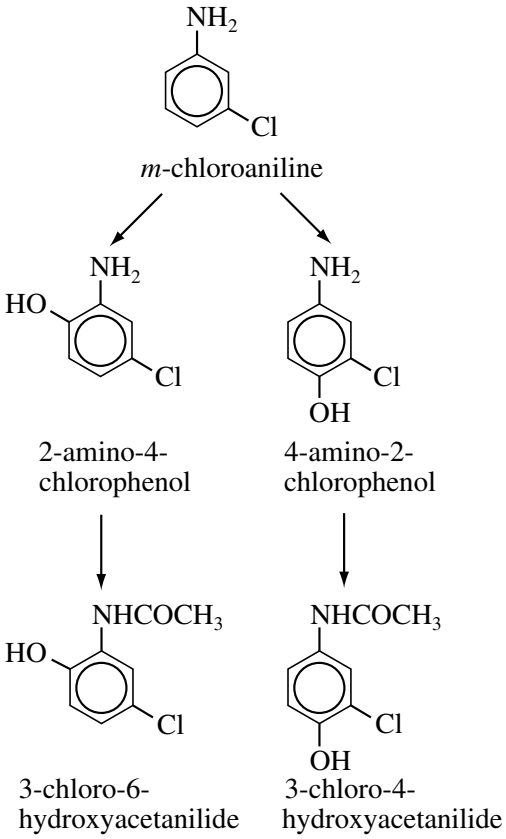


Figure 1. *In vivo* urinary metabolites of *m*-chloroaniline according to [1, 2]

1.1 Pharmacokinetics

The analysis of the 24 hour urine from rats which had been given a single intragastric dose of 150 mg *m*-chloroaniline/kg body weight revealed only metabolites hydroxylated on the benzene ring (mostly in *para* position to the amino group) and their acetylated and conjugated derivatives (see Figure 1); 3-chlorophenylhydroxylamine was not found. At longer intervals after dosing, no metabolites were found [1]. In the 24 hour urine collected after oral administration of 100 mg *m*-chloroaniline/kg to rabbits, 2-amino-4-chlorophenol and 4-amino-2-chlorophenol were found in free and conjugated form [2].

In *in vitro* studies with rabbit hepatic microsomes, 4-amino-2-chlorophenol was shown to be a metabolite of *m*-chloroaniline [3].

2 Effects in Man

2.1 Acute toxicity

There are two early reports of acute intoxications with *m*-chloroaniline. In one case a 35 year old worker spilled *m*-chloroaniline onto his clothing and gloves and, although he then washed his hands, he went on wearing the contaminated clothing and using the

gloves. 5 hours after the accident cyanosis had developed. On that same evening the worker was admitted to hospital with the following symptoms: cyanosis, headache, respiratory distress and rapid pulse. The patient was treated with oxygen, blood-letting and later with an infusion; methaemoglobin (metHb) was no longer detectable. Two days later the only abnormal findings were increased leukocytes in urine and lymphocytosis (41 %) [4].

In the second case a 49 year old worker in the chemical industry spilled a little *m*-chloroaniline on his trousers while filling an autoclave. One hour later he felt weak and dizzy and was cyanotic. The cyanosis reached its peak after 4 hours. Heinz bodies were present in 8 % of erythrocytes. The patient was treated with oxygen in hospital and was then only slightly cyanotic with 18 % Heinz bodies. On the 3rd day 28% Heinz bodies were determined and on the 7th day 20%. The man was not anaemic. He went back to work on the 4th day [5].

In a study of 187 cases of occupational cyanosis in the period between 1956 and 1966 the most severe cyanosis-inducing effects among 13 amino and nitro compounds were ascribed to the three chloroanilines [6].

2.2 Chronic toxicity

In a chemical works a series of examinations was carried out on 36 men (average age: 28.2 years) who were exposed to *m*-chloroaniline and had worked in the factory for an average of 41.2 months. 9 of the workers had already suffered from cyanosis once or several times. A physical examination and blood and urine analyses were carried out. All results were in the normal range. In 28 of the workers the erythrocytes contained < 1 % Heinz bodies; in the other 8 men the value was in the range 1 % to 4% [5].

3 Effects on Animals

3.1 Acute toxicity

LD_{50} values determined after single doses of *m*-chloroaniline are shown in Table 1.

In an acute toxicity study, rats (no further details given) were exposed to *m*-chloroaniline by inhalation or via the shaved skin by exposing either the trunk or the head of

Table 1. LD_{50} values after single doses of *m*-chloroaniline

Species	Application route	LD_{50} (mg/kg)	Ref.
mouse	intragastric	334	[7]
mouse	intragastric	1104	[8]
rat	intragastric	1104	[8]
rabbit	intragastric	750	[8]
cat	dermal	223	[7]

Table 2. Acute toxic effects of single doses of *m*-chloroaniline and its hydrochloride

Substance	Species	Application route (Solvent)	Dose	Observations	Ref.
m-CA	cat	oral (n.s.)	0.25 mmol/kg (~ 32 mg/kg)	metHb: 24.8 % after 1 h 39.9 % after 2 h 46.3 % after 3 h 53.1 % after 4 h 58.0 % after 5 h	[10]
m-CA	rat	i.p. (propylene glycol)	0.1 mmol/kg (~ 13 mg/kg)	metHb: 15.9 % after 5 h	[11]
m-CA	dog (anaesthetized)	i.v. (acetone)	25 mg/kg	metHb: 24 % after 2 h 28 % after 3 h 17 % after 6 h	[12]
m-CA	dog (anaesthetized)	i.v. (acetone)	50 mg/kg	LD_{low}	[12]
m-CA	cat	s.c. (n.s.)	125 mg/kg	LD_{low}	[9]
m-CA. HCl	mouse	i.p. (n.s.)	83 mg/kg	metHb: 39.6 % after 10 min 43.3 % after 30 min 6.5 % after 90 min	[13]

m-CA *m*-chloroaniline
n.s. not specified

the animal to the vapour in an exposure chamber. Threshold toxic concentrations for the increase of Heinz bodies in blood (no further details given) were determined for four hour exposures as 62 mg/m^3 for the skin and 130.3 mg/m^3 for intake by inhalation [7].

In an early study cyanosis, dilation of the pupils, increased respiration rate and unsteady gait were seen in cats after subcutaneous injection or dermal application of *m*-chloroaniline. The animals did not survive a subcutaneous dose of 310 mg/kg. Applied dermally, a dose of 3–6 g *m*-chloroaniline was lethal. Autopsy revealed discoloured brown lungs; metHb was not always detectable [9].

After intragastric administration of *m*-chloroaniline to mice or dermal application of lethal doses to cats the animals died within 3 days with blood metHb levels of 60–80% [7].

The metHb levels determined after administration of single doses of *m*-chloroaniline to animals are shown in Table 2. The maximum metHb levels were attained in 30 minutes to 3 hours, depending on the application route.

Table 3. Subchronic and chronic toxicity of *m*-chloroaniline after administration by gavage to rats [14]

Number	Dose mg/kg	Exposure duration	Observations
30	50	1 × /d 30 d	inhibition of erythropoiesis and leukopoiesis; reticulocytes ↑, metHb ↑, blood cholinesterase activity ↓, albumin ↓, α-globulin ↑; *histological changes:* degenerative changes in liver and kidneys, in some animals spleen enlargement, haemosiderin in the spleen
10	0	8 months	–
10	0.25	(no other	–
10	2.5	details)	– CNS excitability ↑, glycogen level in the liver ↓
10	25		– *blood count changes:* Hb level and erythrocyte number ↓, neutrophils ↓, reticulocytes ↑, metHb level ↑, α-globulin ↑, albumin ↓, glycogen level in the liver ↓, CNS excitability ↑; *histological findings:* fatty and granular degeneration of liver and kidney, iron-containing protein in spleen

↑ increase(d)
↓ decrease(d)

3.2 Local effects on skin and mucous membranes

A single application of 100–900 mg *m*-chloroaniline/kg to the skin of cats or rabbits (no other details given) caused inflammation of the skin in some animals after 3 to 5 days. In the survivors the inflammation healed within 15 to 20 days [7].

One drop of *m*-chloroaniline (no other details given) in the conjunctival sac of the rabbit eye caused suppurative conjunctivitis which healed in 5 to 10 days [7].

3.3 Subchronic and chronic toxicity

The results of a study on the subchronic and chronic toxicity of *m*-chloroaniline are shown in Table 3 and demonstrate that the main effects are on the blood and haematopoietic organs.

3.4 Nephrotoxicity

The possibility of a nephrotoxic effect of the chloroanilines has been mentioned in only one study. Groups of at least 4 male Fischer 344 rats were given single intraperitoneal doses of 0.4, 1 or 1.5 mmole *m*-chloroaniline per kg body weight and then observed for 2 days. The treated animals ate and drank less than the controls and in consequence gained weight more slowly. In the 1.5 mmole/kg dose group 8 of 12 animals died; in the control group there were no deaths. For the animals in the 1.5 mmole/kg group the following

observations were made: reduced urine volume with haematuria and proteinuria, increased blood urea and in slices of renal tissue from exposed animals reduced basal and lactate-stimulated accumulation of *p*-aminohippuric acid. In *in vitro* studies incubation of renal slices from untreated animals with 10^{-3} M *m*-chloroaniline reduced the uptake of tetraethylammonium. Histological examination revealed degenerative changes in the proximal and distal tubulus cells [15].

4 Reproductive and Developmental Toxicity

There are no studies available on the reproductive toxicology of *m*-chloroaniline.

5 Genotoxicity

m-Chloroaniline was not mutagenic in the Ames test in the *Salmonella typhimurium* strains TA92, TA94, TA97, TA98, TA100, TA1535, TA1537, TA1538 and G46 with or without metabolic activation with S9 mix [16–21]. In the presence of both S9 mix and norharman, *m*-chloroaniline (250–2500 µg/plate in the plate incorporation test or 10–250 µg/plate in the preincubation test) was mutagenic in the strains TA98 and TA1535 [22].

m-Chloroaniline yielded negative results with or without addition of S9 mix in a test for reversion in *Escherichia coli* WP2 and WP2uvrA$^-$ [19].

200 µg *m*-chloroaniline/ml caused reverse mutation at the methionine locus in *Aspergillus nidulans* [23].

The results of a UDS test in rat hepatocytes were negative [19].

m-Chloroaniline induced 8-azaguanine resistance in V79 Chinese hamster cells but not g-strophanthin resistance [23].

A micronucleus test in NMRI-SPF mice which had been given a single intraperitoneal dose of 100 mg *m*-chloroaniline/kg body weight yielded negative results [18].

m-Chloroaniline (25 – 400 mg/kg) was unable to induce sperm head anomalies in male (CBA × BALB/c)F_1 mice [24].

6 Carcinogenicity

There are no studies available on carcinogenic effects of *m*-chloroaniline.

7 Manifesto (MAK value, classification)

The acute toxicity of *m*-chloroaniline in animals is characterized by cyanosis; this is less severe than with *p*-chloroaniline but more severe than with *o*-chloroaniline. It is comparable with that induced by aniline. There are no data available on the effects in

man so that no MAK value for *m*-chloroaniline can be established. Numerous tests for genotoxic effects have produced negative results but there are also some tests with positive results. The carcinogenicity of *m*-chloroaniline has not yet been studied.

Because of the inadequate database *m*-chloroaniline is included in Section IIb of the List of MAK Values. The demonstrated dermal toxicity of *m*-chloroaniline requires the designation "H".

8 References

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