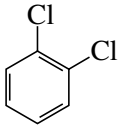
1,2-Dichlorobenzene H

Classification/MAK value:	**50 ml/m^3 (ppm)** **300 mg/m^3**
Classification/MAK value dates from:	**1958**
Synonyms:	o-dichlorobenzene 1,2-DCB
Chemical name (CAS):	1,2-dichlorobenzene
CAS number:	95-50-1
Structural formula:	
Molecular formula:	$C_6H_4Cl_2$
Molecular weight:	147
Melting point:	– 17 °C
Boiling point:	180.5 °C
Vapour pressure at 20 °C:	1.33 hPa
1 ml/m^3 (ppm) = 6.12 mg/m^3	**1 mg/m^3 = 0.164 ml/m^3 (ppm)**

1 Toxic Effects and Modes of Action

1,2-Dichlorobenzene (1,2-DCB) may be sorbed through the lungs, the gastrointestinal tract and the skin. It is metabolized oxidatively to dichlorophenol derivatives and excreted mostly in urine in the conjugated form. Brief exposures to 1,2-DCB in the air result in irritation of mucous membranes, hyperactivity, cyanosis and weight loss as well as damage to the liver (centrilobular necrosis) and kidneys (swelling of the tubular epithelium).

1,2-DCB, unlike 1,4-DCB, does not increase the production of hyaline droplets in the kidneys of male rats even on prolonged exposure.

1,2-DCB induces acquired porphyria. Repeated oral administration to rats results in the typical symptoms of porphyria and increases liver and kidney weights. Chronic administration to male rats and mice increases renal tubular regeneration; tumour formation has not been observed.

1,2-DCB is not genotoxic and has neither foetotoxic nor teratogenic effects.

In man after exposure to airborne 1,2-DCB, mucous membrane lesions and, very occasionally, adverse effects on the haematopoietic system have been described. There is also one report of a single case of sensitization.

1.1 Pharmacokinetics

Relatively soluble in lipids, 1,2-DCB readily penetrates membranes and can therefore be taken up through the lungs, the gastrointestinal tract and the skin. Together with the other two DCB-isomers, 1,2-DCB has been identified in the blood of residents of the city of New Orleans (USA) [1].

Male albino rats were given in their diet a mixture of chlorocarbons containing tetrachloroethene, hexachloro-1,3-butadiene, γ-hexachlorocyclohexane, 1,2-DCB, 1,3,5-trichlorobenzene, 1,2,3,4-tetrachlorobenzene and hexachlorobenzene. Groups of seven animals received daily doses of 2 or 4 mg/kg body weight of each component of the mixture for 4, 8 or 12 weeks. At the end of treatment the animals were killed and the chlorocarbon levels in adipose tissue were measured. In the animals of both dosage groups the 1,2-DCB level measured after 4 weeks on the diet was 20 mg/kg adipose tissue; after 12 weeks it was ca. 60 mg/kg. In animals who were not killed at the end of the treatment period, the 1,2-DCB level in the adipose tissue was unchanged after 1 week without any chlorocarbons in the diet and after 3 weeks 1,2-DCB could no longer be detected [2].

After oral administration of 500 mg 1,2-DCB/kg body weight, the following metabolites were detected in the urine of rabbits: 2,3-dichlorophenol (8.9 %), 3,4-dichlorophenol (30 %), catechols (3.90 %), glucuronides (48 %), ethereal sulfates (21 %) and mercapturic acids (5.0 %). The excretion rate was relatively slow; excretion of the metabolites was completed 5–6 days after 1,2-DCB administration [3].

Rats were given a single i.p. injection of 7.35 mg ^{14}C-1,2-DCB/kg body weight and were killed 6 or 24 hours later. The 1,2-DCB level in the liver sank from 10.4 µg/g liver to 2.4 µg/g, and the covalent binding to liver protein from 34 ng/mg to 20 ng/mg protein. 17 % and 42 % of the dose was excreted in the urine. Pretreatment of the animals with phenobarbital alone accelerated the excretion and increased the covalent binding to liver protein (45 ng/mg) whereas combined pretreatment with phenobarbital and SKF 525-A reduced the excretion rate markedly and reduced the binding to liver protein (27.3 ng/mg). It is concluded from these results and from data obtained for other halogenated benzene derivatives that there is a causal relationship between covalent binding to liver proteins and hepatotoxicity of 1,2-DCB [4].

In metabolism studies with rats, one of the exhaled metabolites of 1,2,4-trichlorobenzene was identified as 1,2-DCB, evidently produced by reductive dechlorination in intestinal bacteria [5, 6].

1.2 Other Effects

Incubation of isolated rat liver mitochondria with 1,2-DCB (35 µg/ml) decoupled oxidative phosphorylation and caused release of potassium ions [50].

2 Effects in Man

A case of sensitization to 1,2-DCB was reported in 1939 [7]. A worker who handled windows treated with 1,2-DCB developed severe erythema on the exposed skin areas and finally blisters. Later a brown skin pigmentation developed and persisted for 3 months.

Sewerage workers who inhaled fumes from the effluent of a dry cleaning establishment suffered from irritation of the eyes and respiratory tract as well as nausea [8]. A woman ironer in a dry cleaning business who was continually exposed to fumes containing 95 % 1,2-DCB and 5 % 1,4-DCB developed haemolytic anaemia with leukocytosis and polynucleosis [9]. Another report [10] describes 3 cases of leukemia after chronic exposure to mixtures containing 2 %, 37 % or 80 % 1,2-DCB and one case of anaemia; a causal relationship with the 1,2-DCB exposure was not proved. In contrast, no indication of organ damage or damage to the haematopoietic system was found in workers who had been exposed for many years to 1,2-DCB levels of 6–264 mg/m^3 air (average level 90 mg/m^3) [11].

Applied for 1 hour to the anterior surface of the forearm in volunteers 1,2-DCB produced after about 15 minutes a severe burning sensation which disappeared when the 1,2-DCB was removed. A diffuse erythema developed initially at the application site which after 24 hours became dark red and covered with blisters. Later a brownish pigmentation appeared and was still visible after 3 months [12].

An analytical study investigated 1,2-DCB levels in human adipose tissue and in mothers' milk and found 9 µg/kg milk or 230 µg/kg milk fat and 13 µg/kg fat in adipose tissue [13].

3 Effects on Animals

3.1 Acute toxicity

The data available on the acute toxicity of 1,2-DCB are shown in Table 1.

The symptoms of toxicity during a 6 hour inhalative exposure of rats to 1,2-DCB levels between ca. 6000 and 18000 mg/m^3 were hypotonia, somnolence and lacrimation. Deaths occurred mainly during the exposure and the subsequent 24 hours.

Table 1. Acute toxicity of 1,2-dichlorobenzene

Species	Application route		Ref.
rat	oral	500 mg/kg bw	[14]
rabbit	oral	500 mg/kg bw	[15]
guinea pig	oral	800–2000 mg/kg bw	[16]
rat	inhalation (6 h)	9192 mg/m^3	[17]
mouse	inhalation (6 h)	7416 mg/m^3	[17]
rat	i.p.	840 mg/kg bw	[18]
mouse (NMRI)	i.p.	1228 mg/kg bw	[19]

bw: body weight

Body weight gain of the survivors was still delayed at the last examination after 14 days. Autopsy of the survivors revealed no macroscopic lesions of the lungs, liver or kidneys [17]. In the other studies of acute toxicity the symptoms were not described in detail.

Subcutaneous injection of 0.5 ml 1,2-DCB/kg body weight produced macroscopically visible liver lesions in rabbits; occasionally these effects were obtained with a dose of only 0.0056 ml/kg body weight [20].

Rabbits died within 24 hours of an i.v. injection of 330–660 mg 1,2-DCB/kg body weight and within 20 seconds of an i.v. dose of 1310 mg 1,2-DCB/kg body weight [20].

A single exposure of rats, mice and guinea pigs to 1,2-DCB concentrations of 0.005 % to 0.08 % in air for various periods induced liver necroses in most animals and sometimes renal damage as well. Irritation of eyes and nose was observed during the exposure and some animals died after a protracted period in a comatose state [20].

Groups of 6 male Swiss OF1 mice were exposed briefly (ca. 5 minutes) to one of four concentrations of 1,2-DCB in the range from ca. 420 to 1200 mg/m^3 air and the RD50 value according to Alarie (irritant response in the airways) was determined as 1092 mg/m^3 [21].

In an earlier study a dog (Alsatian) was exposed for 1 hour to an atmosphere into which 2 ml 1,2-DCB/m^3 had been sprayed at a room temperature of 26 °C. When the experiment was repeated using twice the concentration (4 ml/m^3) the dog became somnolent [12].

In further inhalation studies mice, rats and guinea pigs were exposed for 1 hour to 2 ml 1,2-DCB/m^3. Agitation, which was immediately apparent in the mice, regressed in about 20 minutes. At the end of exposure the animals were severely cyanotic and they died within 24 hours. In the rats and guinea pigs, agitation was also observed but the animals recovered within a few hours [12].

Male rats were exposed to various concentrations of 1,2-DCB (3234–5862 mg/m^3 air) for 1–10 hours. During the exposure the animals were seen to suffer from agitation, irritation of the mucous membranes and respiratory difficulties. Transient weight loss was seen in the survivors. Deaths occurred within three days [16]. Organ damage was studied in 4 dosage groups each with 20 male rats—5862 mg/m^3/1 hour, 5862 mg/m^3/0.5 hour, 3234 mg/m^3/6.5 hours and 3234 mg/m^3/3 hours. Half of the animals in each group were killed one day after the exposure. No lesions were found in the animals from the 5862 mg/m^3/0.5 hour group. In the other groups the liver and kidney weights were increased, there was marked centrilobular necrosis in the liver and swelling of the renal tubular epithelium [16].

Fasting male Holtzman rats were given a single i.p. injection of 735 mg 1,2-DCB/kg body weight. 24 hours after the injection, the bile duct/pancreas secretion was increased by about a factor of ten and the protein level of the bile was reduced to about 25 % of the control value [22].

Inhalation hazard tests were carried out at various temperatures (exposure of the whole animal to a saturated atmosphere produced by active evaporation). The results are shown in Table 2. Abnormal behaviour, respiratory difficulties, agitation, sedation and irritation of the mucous membranes were observed [23].

Table 2. Acute inhalation studies with rats exposed to air saturated with 1,2-dichlorobenzene

Sex	Temperature °C	Exposure time in h	Result*
♂	20	3	0/5/5
♂/♀	20	7	3/10/10
♂/♀	30	3	0/10/10
♂	30	7	3/5/5
♀	30	7	0/5/5
♂/♀	95	0.5	0/10/10
♂/♀	95	1	5/10/10
♂	95	3	5/5/5
♀	95	3	4/5/5
♀	95	7	5/5/5

* mortalities/animals with symptoms/initial number of animals

24 hours after male F344 rats had received a single i.p. injection of 397 mg 1,2-DCB/kg body weight, an increase in plasma alanine aminotransferase activity was observed. Simultaneous injection of 154 mg CCl_4/kg body weight prevented this increase and, at the same time, reduced the excretion of 1,2-DCB metabolites in the urine and faeces. Exhaled 1,2-DCB was increased. The results indicate that CCl_4 inhibits 1,2-DCB metabolism [24].

In male Sprague-Dawley rats who were exposed for 4 hours to 1,2-DCB concentrations of 1830, 2556, 3654 or 4644 mg/m^3 in air, increased activities of the serum enzymes glutamate dehydrogenase, aspartate aminotransferase, alanine aminotransferase and sorbitol dehydrogenase were found 24 hours after the exposure. A four hour exposure to 1224 mg 1,2-DCB/m^3 air had no effect [25].

Male Sprague-Dawley rats were exposed for 4 hours to 1,2-DCB levels of 1476, 2214, 3660 or 4434 mg/m^3 air. At concentrations of 2214 mg/m^3 or more, the activities of serum glutamate dehydrogenase and serum sorbitol dehydrogenase were increased and liver glucose-6-phosphatase was decreased [26].

Male Sprague-Dawley rats which had been pretreated with sodium chloride or phenobarbital were given an i.p. injection of 0.03 ml 1,2-DCB. There were indications of glycogen loss from the liver. Histological investigation revealed an increased frequency of centrilobular necrosis in the liver of animals pretreated with phenobarbital [27].

A single oral dose of 500 mg 1,2-DCB/kg body weight did not induce a detectable increase in arylhydrocarbon hydroxylase activity in the livers or intestines of rats [28].

A single oral dose of 120 or 300 mg 1,2-DCB/kg body weight caused no increase in formation of hyaline droplets in the renal cortex of rats of either sex. A slight, reversible ^{14}C-labelling of $\alpha_{2\mu}$-globulin was detected after oral administration of 500 mg ^{14}C-1,2-DCB/kg body weight [29].

3.2 Effects on skin and mucous membranes, percutaneous absorption

1,2-DCB is a mild irritant on intact rabbit skin (exposed for 24 hours) and is weakly irritating in the rabbit eye [23]. Two drops of 1,2-DCB in the rabbit eye produced mild conjunctivitis. The inflammation regressed within 7 days [16].

1,2-DCB was applied dermally to rats by painting the shaved abdominal skin (ca. 10 cm^2) twice daily. The animals did not tolerate the treatment at all well. One rat died with signs of severe systemic effects after 5 applications. Macroscopic examination of another animal which died after nine applications revealed a pale mottled liver and kidney changes. The skin of the application site was unaffected [12].

Female rabbits were treated dermally with 0.1 ml undiluted 1,2-DCB applied to the inner surface of the ear on each of 5 consecutive days and were then killed 12 days after the last application. 1,2-DCB did not have an acnegenic effect, nor were signs of systemic toxicity observed [30].

3.3 Subacute and subchronic toxicity

It has been demonstrated in several studies that 1,2-DCB can induce acquired porphyria in rats. Male albino rats were given daily doses of 455 mg 1,2-DCB/kg body weight by gastric intubation for 15 days and then a 24 hour urine sample was collected and the porphyrin content determined. 1,2-DCB caused a 10 times increase in the urine levels of coproporphyrin, uroporphyrin and porphobilinogen and a decrease in urine δ-aminolaevulinic acid. At the end of 15 days treatment with 450 mg 1,2-DCB/kg body weight/day the liver porphyrin levels were also increased — by a factor of about 1.5 for coproporphyrin, 2.5 for protoporphyrin and 10 for uroporphyrin. The 1,2-DCB treatment decreased the catalase activity in the liver by about 50 % [31].

In another study rats were given an oral dose of 250 mg 1,2-DCB/kg body weight on each of three consecutive days and then were killed 24 hours after the last dose. The relative liver weights, the microsomal protein levels and the activities of aminopyrine-N-demethylase and δ-aminolaevulinate synthetase were increased as a result of the 1,2-DCB treatment [32]. Female Wistar rats were given daily subcutaneous injections of 100 mg phenobarbital/kg body weight and daily doses of 500 mg 1,2-DCB/kg body weight by gastric intubation for1–5 days. 24 hours after the last dose, the Harderian gland was removed to determine the levels of porphyrins and the activity of aminolaevulinate synthetase and aminolaevulinate dehydratase. On the first day after the first 1,2-DCB administration the porphyrin level was increased but on day 5 after 5 daily applications it had returned to normal whereas the enzyme activities remained unchanged. The relative liver weights increased after 1,2-DCB treatment [33]. Female rats received a total of 138 daily doses of 18.8,188 or 376 mg 1,2-DCB/kg body weight by oral intubation on 5 days each week during a period of 192 days. Weight gain and mortality of the animals were normal. In the medium and high dose groups the organ weights of liver and kidney were increased; the spleen weight was decreased only in the 376 mg/kg group. The low dose (18.8 mg/kg) was tolerated without symptoms [16].

Oral administration of 1,2-DCB to female Wistar rats for 60 or 120 days caused an increase in triglyceride levels in comparison with the controls. The liver ATP levels were reduced in the treated animals [34].

After repeated whole animal exposure of male rats to 1854 mg 1,2-DCB/m^3 air (6 hours/day, 2 or 4 days) increased glutamate dehydrogenase (only after two exposures) and sorbitol dehydrogenase activities were found. The effect, however, was markedly less than that of a single 4 hour exposure [26].

No symptoms of toxicity were seen in a dog (Alsatian) which was exposed to a 1,2-DCB level of 2 ml/m^3, 2 hours daily for 16 days [12].

F344/N rats of both sexes received daily oral doses of 0, 60, 125, 200 (females only), 250 (males only), 500 or 1000 mg 1,2-DCB/kg body weight for 14 days by gavage. All animals in the 1000 mg/kg group died during the study. There was a dose-dependent reduction in body weight gain in all animals [35].

In a 13 week study [35] F344/N rats of both sexes received daily oral doses (gavage) of 0, 30, 60,125, 250 or 500 mg 1,2-DCB/kg body weight on 5 days a week for 13 weeks. In the highest dose group the mortality of the females was increased, centrilobular necrosis and hepatocellular degeneration developed in the liver and lymphocyte deficiency in the thymus and spleen. In addition, there was a slight decrease in haemoglobin and haematocrit and, only in the males from this group, degeneration of the renal tubuli and reduction in erythrocyte count. In the animals from the 250 mg/kg group, necrosis of individual hepatocytes could be seen. In the 125 mg/kg group slight hepatocellular necrosis developed in just a few animals.

B6C3F_1 mice of both sexes were given daily doses of 0, 250, 500, 1000, 2000 or 4000 mg 1,2-DCB/kg body weight by gavage on 14 consecutive days. Most animals died after the 1,2-DCB treatment. Liver necrosis was found at doses of 250 mg/kg body weight or more. Because of the high mortality, the study was repeated using lower doses —0, 30, 60,125, 250 or 500 mg/kg body weight and day. One male from the 500 mg/kg group and one female from the 125 mg/kg group died. At the end of the study no macroscopically visible pathological changes were found in the survivors [35].

In another 13 week study with B6C3F_1 mice of both sexes, the animals were given daily oral (gavage) doses of 0, 30, 60, 125, 250 or 500 mg 1,2-DCB/kg body weight on 5 days per week. Many animals from the 500 mg/kg group died with centrilobular necrosis in the liver, hepatocellular degeneration, lymphocyte deficiency in the thymus and spleen as well as multifocal mineralization of the myocardial fibres and the skeletal muscles. Necrosis of individual hepatocytes developed in males from the 250 mg/kg group. No liver changes were found after 125 mg/kg body weight [35].

Male Wistar rats received daily doses of 500 mg 1,2-DCB/kg body weight for 7 days by gavage. No hyaline droplet formation was observed in the kidneys [36].

3.4 Chronic toxicity and carcinogenicity

Rats received daily oral doses of 0.001, 0.01 or 0.1 mg 1,2-DCB/kg body weight for 9 months. No symptoms developed in the animals of the 0.001 mg/kg group; in the other two groups there were changes in the conditioned reflexes, reduction in haematopoiesis and liver changes [37].

Rats, mice and guinea pigs were exposed to 1,2-DCB concentrations of 294 or 558 mg/m^3 air 7 hours daily on 5 days per week for 6–7 months. In addition 2 female monkeys were exposed to 558 mg 1,2-DCB/m^3. No symptoms of toxicity developed [16].

One carcinogenicity study with rats and mice has been published [35]. Groups of 50 male and 50 female F344/N rats received daily doses of 0, 60 or 120 mg/kg body weight on 5 days per week for 103 weeks by gavage. Survival was reduced in the males from the 120 mg/kg group . Body weight gain was unaffected even at the highest dose. The 120 mg/kg dose caused frequent renal tubular regeneration in the males. The spectrum of tumours obtained for the treated animals gave no evidence for a carcinogenic effect of 1,2-DCB. Thus 1,2-DCB was classified according to the NTP criteria as not carcinogenic in F344/N rats of either sex at doses of 60 or 120 mg/kg body weight and day.

Groups of 50 male and 50 female B6C3F$_1$ mice received daily doses of 0, 60 or 120 mg 1,2-DCB/kg body weight on 5 days per week for 103 weeks by gavage. There were no differences between control and treated animals with respect to body weight gain and mortality. A treatment-related increase in renal tubular regeneration was seen in the male mice of both dosage groups. The spectrum of tumours obtained for the treated animals yielded no evidence for a carcinogenic effect of 1,2-DCB in mice. Thus 1,2-DCB was classified according to the NTP criteria as not carcinogenic in B6C3F$_1$ mice of either sex at doses of 60 or 120 mg/kg body weight and day [35].

1,2-DCB was also tested for tumour-promoting effects in a rat liver foci bioassay. 18–24 hours after a 2/3 partial hepatectomy, rats of both sexes were given a single oral dose of 51 mg diethylnitrosamine/kg body weight followed by an i.p. injection of 147 mg 1,2-DCB/kg body weight after 1 and 5 weeks. The animals were killed two weeks after the second 1,2-DCB injection. 1,2-DCB did not cause an increase in γ-glutamyltranspeptidase positive foci in the rat livers after induction with diethylnitrosamine [38].

4 Genotoxicity

1,2-DCB was not mutagenic in numerous Ames tests, with or without S9 mix [39–44]. 1,2-DCB was also not mutagenic in the point mutation assay with *Escherichia coli* WP2 [42] or *Aspergillus nidulans* [45]. A test for 1,2-DCB-induced DNA damage in a polymerase I deficient strain of *E. coli* gave positive results; a similar test with a recombination deficient strain of *Bacillus subtilis* was negative [42]. 1,2-DCB was inactive in an assay for DNA damage in the eukaryote, *Saccharomyces cerevisiae* D3 [42].

With human lymphocytes in cell culture, in the absence of S9 mix and in the concentration range 1.47–147 µg/ml, 1,2-DCB produced a marked reduction in the rate of ^{3}H-thymidine incorporation into DNA and at 147 µg/ml cell survival was 15 %. In the presence of S9 mix the ^{3}H-thymidine incorporation rate was not decreased and cell survival at 147 µg 1,2-DCB/ml was about 50 % [46].

HeLa cells were incubated for 30 minutes with 350 µg 1,2-DCB/ml and the incorporation of ^{3}H-uridine into RNA and of ^{14}C-labelled amino acids into protein was measured. 1,2-DCB inhibited both synthetic processes almost completely [47].

In a micronucleus test, male NMRI mice received two i.p. injections 24 hours apart with 93.5, 187.5, 281 or 375 mg 1,2-DCB/kg body weight and were killed 30 hours after the first injection. A dose-dependent increase in the number of micronuclei was found [19].

5 Reproductive and Developmental Toxicity

In a teratology study [48] pregnant rats and rabbits were exposed to 1,2-DCB concentrations of 600,1200 or 2400 mg/m^3 air for 6 hours per day from day 6 to day 15 (rats) or day 6 to day 18 (rabbits) of gestation. In rats of all dose groups maternal toxicity was evident in reduced body weight gain and, in the highest dose group, in increased liver weights. In rabbits only the highest concentration, 2400 mg/m^3, produced a transitory reduction in body weight gain. In spite of the high concentrations, no indications of embryotoxic, foetotoxic or teratogenic effects were found in either rats or rabbits.

In another study [49] rats were given daily doses of 50, 100 or 300 mg 1,2-DCB/kg body weight from day 6 to day 15 of gestation by gavage. No teratogenic effects were seen (no other details were given in the abstract).

6 Manifesto (MAK value, classification)

In most studies on the toxicity of 1,2-dichlorobenzene, the substance was administered orally. High doses have been shown to cause necrosis of the liver and kidney and haematotoxic effects. Appropriate inhalation studies are not available. Thus a MAK value must be derived indirectly.

Several assays for point mutations and DNA damaging effects gave negative results with 1,2-dichlorobenzene which, however, proved to be clastogenic when administered by i.p. injection in a micronucleus test. In long-term studies with rats and mice there was no evidence for a carcinogenic potential even at high doses. Inhaled or orally administered, 1,2-dichlorobenzene was neither foetotoxic nor teratogenic.

The long-established MAK value for 1,2-dichlorobenzene, 50 ml/m^3 (300 mg/m^3), will be retained for the present since there is no evidence of adverse effects at this concentration. However, there is no appropriate documentation available of industrial experience with persons exposed to the substance or of animal studies which would allow the direct deduction of a MAK value. Such studies are necessary to substantiate or discredit the current MAK value.

1,2-Dichlorobenzene is classified in the peak limitation category II,1 because of its pharmacokinetics and because systemic toxicity is the critical parameter in the range of the MAK value. Since it is readily absorbed through intact skin it receives the designation H.

Since the studies of reproductive toxicology in rats and rabbits produced no indication of embryotoxic or foetotoxic effects even at 2400 mg/m^3 (400 ml/m^3) and because no reports of adverse effects in man are known, the substance is classified in group C.

7 References

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