

Dichloroacetic acid and its salts

MAK Value Documentation, supplement– Translation of the German version from 2020

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated the developmental toxicity of dichloroacetic acid [79-43-6] and its salts. In 2019, a maximum concentration at the workplace (MAK value) of 0.2 ml/m³, corresponding to 1.1 mg/m³, was set for dichloroacetic acid. Accordingly, a MAK value of 1.1 mg/m³ for the inhalable fraction, measured as the acid, has been set for the salts. The critical effects are irritation, carcinogenicity in the liver of rats and mice as well as neurotoxicity. In prenatal toxicity studies with neutralized dichloroacetic acid, elevated incidences of visceral malformations, mostly of cardiovascular origin, were seen in rats after administration of 140 mg/kg body weight and day via gavage. At higher, maternally toxic doses, hydronephrosis and eye malformations were observed. The NOAEL for developmental toxicity is 14 mg/kg body weight and day for rats, corresponding to 24.5 mg/m³ after scaling to a concentration at the workplace. In mice, perinatal death and delayed birth occurred at 722 mg/kg body weight. The NOAEL for developmental toxicity is 477 mg/kg body weight for mice, corresponding to 477 mg/m³ after scaling to a concentration at the workplace. Damage to the embryo or foetus would therefore be unlikely when the MAK value for dichloroacetic acid is not exceeded. However, after treatment with 16 mg/kg body weight and day, juvenile rats developed gait disturbance and reduced grip strength. Juvenile rats were more sensitive than adults. Thus, a NOAEL could not be determined for developmental neurotoxicity and dichloroacetic acid and its salts are assigned to Pregnancy Risk Group D.

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MAK value (2018)	dichloroacetic acid: 0.2 ml/m³ \triangleq 1.1 mg/m³ dichloroacetates: 1.1 mg/m³ I (inhalable fraction) as acid
Peak limitation (2018)	Category I, excursion factor 1
Absorption through the skin (2018)	dichloroacetic acid: – dichloroacetates: H
Sensitization	–
Carcinogenicity (2018)	Category 4
Prenatal toxicity (2019)	Pregnancy Risk Group D
Germ cell mutagenicity	–
BAT value	–
CAS number	79-43-6
1 ml/m³ (ppm) \triangleq 5.26 mg/m³	1 mg/m³ \triangleq 0.19 ml/m³ (ppm)

Note: Dichloroacetic acid can occur simultaneously as vapour and aerosol.

In 2018, dichloroacetic acid and its salts were classified in Carcinogen Category 4 and a MAK value of 0.2 ml/m³ (\triangleq 1.1 mg/m³) was set (Hartwig and MAK Commission 2021). In this supplement, the data for developmental toxicity are presented and the substance is assigned to a pregnancy risk group.

The dichloroacetate anion is responsible for the systemic effects. Therefore, also studies with sodium dichloroacetate or neutralized dichloroacetic acid are considered in this supplement. The evaluation applies to the acid and its salts.

Toxicokinetics

Experiments have demonstrated that the oral absorption of dichloroacetic acid in rats is almost 100% (BG Chemie 2006; Hartwig 2010, available in German only)

Effects in Humans

Developmental toxicity studies with exposure to dichloroacetic acid and its salts alone are not available.

Studies with dichloroacetic acid as a component of disinfection by-products

Dichloroacetic acid is one of the by-products of water disinfection by chlorination. It is to be assumed that in all studies there was exposure also to other haloacetic acids and chlorinated compounds; this means that the effects cannot be attributed to exposure to dichloroacetic acid alone.

Analysis of 112 stillbirths and 398 live births in Nova Scotia and Eastern Ontario, Canada, in the years 1999 to 2001 did not reveal an association between haloacetic acid exposure and stillbirths after adjustment for trihalomethane exposure (King et al. 2005). In three locations in the USA with different concentrations of disinfection by-products in drinking water, no association between exposure to disinfection by-products and 258 pregnancy losses between 2000 and 2004 was found (Savitz et al. 2006).

In a population-based case-control study in Quebec, Canada, from 2006 to 2008, there was no association between exposure to disinfection by-products and small-for-gestational-age status in the third trimester in a comparison of 330 cases with 1100 controls (Ileka-Priouzeau et al. 2015).

In three communities in the USA, no association was found in 2039 women in early pregnancy in the years 2000 to 2004 between exposure to haloacetic acids or organic halogen compounds and foetal growth or preterm birth (Hoffman et al. 2008 a, b) and very early pregnancy losses (measured as time to pregnancy) (MacLehose et al. 2008).

In the so-called “Bradford” birth cohort of 7438 women in the USA between 2007 and 2010, no association was found between haloacetic acid exposure and reduced birth weights (Smith et al. 2016).

Likewise, in two other communities in the USA, no association between exposure to haloacetic acid and foetal growth could be demonstrated in 1667 women in the years 2000 to 2004. On the other hand, there was an association between exposure to total haloacetic acids, including dichloroacetic acid, and preterm births ($n = 2201$) (Horton et al. 2011).

In studies in Massachusetts from 1996 to 2004 comprising 672 120 births, an association was found between the reduction in adjusted mean birth weight by 28 to 36 g, but not for newborns small for gestational age, and the exposure to haloacetic acids. No association between reduced birth weights and exposure to dichloroacetic acid was determined using multivariate models (Rivera-Núñez and Wright 2013).

In four regions of Maryland, USA, a slightly increased, statistically not significant risk of intrauterine growth retardation after exposure to total trihalomethanes and five haloacetic acids was observed in 15 315 mothers in the second and third trimesters from 1998 to 2002. For dichloroacetic acid, the risk (odds ratio: 1.23; confidence interval (CI): 1.03–1.48 for 14 $\mu\text{g}/\text{l}$ and 1.04–1.45 for 15 $\mu\text{g}/\text{l}$) of intrauterine growth retardation was increased in the third trimester at exposure concentrations of 14 to 15 $\mu\text{g}/\text{l}$ drinking water. The increase was statistically significant. However, there was no dose-response relationship either for trihalomethanes or for haloacetic acids or for the sum of the two. The authors suggested that these findings might have also been the result of chance due to multiple comparisons (Porter et al. 2005).

In a community served by three water treatment facilities, the associations between the sum of the concentrations of trihalomethanes and haloacetic acids in drinking water and low birth weights at term, intrauterine growth retardation and preterm births (< 37th week of pregnancy) were investigated for 48 119 births between 1998 and 2002. The concentrations ranged from 7 to 81 $\mu\text{g}/\text{l}$ drinking water. Adjustment was carried out for maternal smoking habits, educational level, age, ethnicity and adequate prenatal care (Kessner index). After exposure to dichloroacetic acid concentrations of > 8 $\mu\text{g}/\text{l}$ drinking water (relative risk 1.27; 95% CI: 1.02–1.59), a critical window for intrauterine developmental retardation in week 37 to 40 of pregnancy was observed in all live births and foetal deaths. No increased risk was observed for reduced birth weights and preterm births (Hinckley et al. 2005).

Neurophysiological development

In a population-based mother-child cohort study conducted in four Spanish regions between 2003 and 2008 in 1855 mothers and children, a positive association was found in children aged one year between exposure to dichloroacetic acid during pregnancy and the assessment of mental development (“Bayley scales of infant development”). However, this effect was no longer detectable at the age of 4 to 5 years (“McCarthy scales of children’s abilities”) (Villanueva et al. 2018).

Summary

From the described exposures to haloacetic acid mixtures, isolated associations between exposure to disinfection by-products or dichloroacetic acid and growth retardation in the second and third trimester of pregnancy as well as preterm birth and reduced birth weights were obtained. However, due to the exposure to a mixture of substances, the data are not sufficient to demonstrate that dichloroacetic acid causes developmental toxicity or neurotoxicity in humans.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Oral administration

In the supplement of 2019 (Hartwig and MAK Commission 2021), a 13-week drinking water study by Moser et al. (1999) with weanling and adult Long Evans rats was described. From this, a NOAEL (no observed adverse effect level) of 23 mg/kg body weight and day can be derived for the end point neurotoxicity (Table 1) in adult rats, since a decrease in grip strength and deficits in righting reflex were observed at 122 mg/kg body weight and day and above. In weanling and adult F344 rats, altered gait occurred at the lowest dose tested of 16 to 18 mg/kg body weight and day, which can be considered the first sign of a neurotoxic effect. A BMD (benchmark dose) cannot be calculated because no incidences are given. A dose of 16 mg/kg body weight corresponds after toxicokinetic extrapolation to a concentration of 10 mg/m³ in workplace air (taking into account the species-specific correction factor of 4 for the rat, the demonstrated oral absorption in the rat of 100% (BG Chemie 2006; Hartwig 2010), the body weight of 70 kg and the respiratory volume during the working day of 10 m³ of the person and the assumed 100% absorption by inhalation, exposure over 5 days at the workplace in comparison with 7 days per week in animal experiments, a factor of 2 each for subchronic exposure and the extrapolation from experimental studies with animals to humans).

Tab. 1 Neurotoxic effects of dichloroacetic acid after drinking water administration to weanling and adult Long Evans and F344 rats (Moser et al. 1999)

Strain	Age (days)	Duration (weeks)	Dose [mg/kg body weight]: effects
groups of 10 Long Evans	29–30	13	17: altered gait 88: decrease in grip strength of fore and hind limbs (no dose–response relationship) 192: tremor, hypotension, inhibition of pupil reflex
groups of 10 F344	29–30	13	16 and above: altered gait 173: decrease in grip strength of fore and hind limbs, tremor, hypotension, inhibition of pupil reflex
groups of 10 Long Evans	68–69	8	23: NOAEL 122 and above: decrease in grip strength of fore and hind limbs, no effects on foot splay, righting reflex deficits in 33%
groups of 10 F344	68–69	8	18: altered gait 91 and above: decrease in grip strength of fore and hind limbs, increase in landing foot splay, righting reflex deficits in 40%, unique chest-clasping response on being lifted by the tail

Reproductive and developmental toxicity

Fertility

The studies of effects on fertility in the rat were described in detail in the documentation of 2010 (Hartwig 2010).

Oral 90-day studies with sodium dichloroacetate (as salt or neutralized acid) given in the drinking water (Bhat et al. 1991) or by gavage (Katz et al. 1981) in rats and with gelatine capsules with administration by gavage in dogs (Cicmanec et al. 1991; Katz et al. 1981) are available, in which the reproductive organs were examined. Dose levels were in the range from 125 to 2000 mg sodium dichloroacetate/kg body weight and day for the rat and 12.5 to 100 mg sodium dichloroacetate/kg body weight and day for the dog. For the rat, a NOAEL for the effects on the reproductive organs of 125 mg sodium dichloroacetate/kg body weight and day can be derived. At sodium dichloroacetate doses of 500 mg/kg body weight and day and above, the testes were reduced in size and degenerative changes in the germinal epithelium with giant cell formation, enlarged Sertoli cells, aspermatogenesis and atrophic seminiferous tubules were found (Bhat et

al. 1991; Katz et al. 1981). In dogs, histopathological changes and atrophy of the testes were observed even at the lowest dose tested of 12.5 mg sodium dichloroacetate/kg body weight and day. These effects increased in a dose-dependent fashion (Cicmanec et al. 1991; Katz et al. 1981).

In a study of the effects on fertility after gavage administration of sodium dichloroacetate to male Long Evans rats for 10 weeks, the absolute weights of the preputial gland and epididymis were reduced at the lowest dose tested of 31.25 mg/kg body weight and day and above with reduced body weight gains and increased relative liver weights. At sodium dichloroacetate doses of 62.5 mg/kg body weight and day and above, the sperm count, motility and the proportion of intact sperm were reduced. At the sodium dichloroacetate dose of 125 mg/kg body weight and day, spermatogenesis was inhibited and fertility reduced (Toth et al. 1992).

In another study of the effects of dichloroacetic acid on male fertility with gavage administration for up to 14 days, significant effects on the sperm of Sprague Dawley rats were observed at 160 mg/kg body weight and day and above (Linder et al. 1997).

Taking all the data into account, a NOAEL for the male reproductive organs cannot be derived for rats and dogs; the LOAEL (lowest observed adverse effect level) for testicular effects is 12.5 mg sodium dichloroacetate/kg body weight and day in dogs and 31.25 mg sodium dichloroacetate/kg body weight and day in rats (Hartwig 2010).

Developmental toxicity

The following studies of developmental toxicity are described in the documentation of 2010 (Hartwig 2010).

In a study of prenatal developmental toxicity with gavage administration of neutralized dichloroacetic acid to Long Evans rats from gestation days 6 to 15, the body weight gains were reduced in the dams at 140 mg/kg body weight and day and above. In the offspring, the total incidence of visceral malformations was increased. Significantly increased incidences of cardiovascular malformations such as defects between the aorta and the right ventricle, malpositioning of the large vessels around the heart or interventricular septal defects were observed at 400 mg/kg body weight and day and above, and statistically significantly increased incidences of hydronephrosis at 1400 mg/kg body weight and day and above. Occasionally, also eye defects (microphthalmia, anophthalmia) were found. The NOAEL for prenatal developmental toxicity and maternal toxicity is 14 mg dichloroacetic acid/kg body weight and day (Smith et al. 1992).

In another study, Long Evans rats were treated with neutralized dichloroacetic acid doses of 1900 mg/kg body weight and day on gestation days 6 to 8, 9 to 11, 12 to 15 or 6 to 15 or with 2400 mg/kg body weight and day on gestation days 10, 11, 12 or 13. Heart malformations occurred after administration on gestation days 9 to 11, 12 to 15 and on days 10 and 12. When treated with 3500 mg/kg body weight on gestation days 9, 10, 11, 12 or 13, the cardiovascular effects were characterized as high interventricular septal defects, which were induced in particular by administration on gestation days 9, 10 or 12 (Epstein et al. 1992).

In CD-1 mice, parturition was delayed at 722 mg/kg body weight and day after prenatal administration of gavage doses of neutralized dichloroacetic acid from gestation days 6 to 15; this resulted in an increased incidence of perinatal mortality. The NOAEL for developmental and maternal toxicity in mice was 477 mg dichloroacetic acid/kg body weight and day (Narotsky et al. 1996).

In Table 2, two studies are listed that were not included in the 2010 documentation, which examined the heart and eyes.

After oral administration of neutralized dichloroacetic acid in a dose of 300 mg/kg body weight and day from gestation days 6 to 15, no heart malformations were found according to the method of Dawson et al. (1993) (Fisher et al. 2001). Statistically significant reductions were determined in the lens area, globe area, and interocular distance. Due to the minimal extent of the changes, the specificity of the effects is questionable, especially since these could also be caused by the reduced foetal body weights or size (Warren et al. 2006).

Tab.2 Developmental toxicity studies of the heart and eyes with neutralized dichloroacetic acid

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley CrI:CDR (SD) BR, 18–21 ♀ positive control all-trans retinoic acid	GD 6–15, 0, 300 mg/kg body weight and day in water, neutralized, gavage; examina- tion on GD 21	only heart examined	Fisher et al. 2001
		300 mg/kg body weight: dams: body weights ↓, uterus weights ↓, foe- tuses: body weights ↓ by 8–9%, no cardiac malformations (3.0% (9/298 foetus- es) compared with 2.6% (7/273 foetuses) in the controls or 30% (6/20 litters) compared with 31.6% (6/19 litters) in the controls, heart examined according to the method of Dawson et al. (1993)	
		only eyes examined	Warren et al. 2006
		300 mg/kg body weight: <u>foetuses/litter</u> : body weights ↓ (4.76 ± 0.28 compared with 5.21 ± 0.30 g/litter in the con- trols), effects in the eyes: lens area/litter ↓ (1.57 ± 0.11 compared with 1.67 ± 0.08 mm ² / litter in the controls), globe area/litter ↓ (2.92 ± 0.18 compared with 3.10 ± 0.13 mm ² /litter in the controls), interocular distance/litter ↓ (3.69 ± 0.13 compared with 3.81 ± 0.11 mm/litter in the controls)	

GD: gestation day

Studies with dichloroacetic acid as a component of disinfection by-products

In the screening test for developmental toxicity according to Chernoff and Kavlock, dichloroacetic acid was administered in combination with four other haloacetic acids (neutralized pH; 0, 44, 88, 176 mg/kg body weight and day, of which 0, 18, 36, 72 mg dichloroacetic acid/kg body weight) by gavage daily from gestation days 6 to 20. Due to severe toxicity, the treatment was terminated on gestation day 11. The offspring were examined on postnatal days 1 and 6. No visceral or skeletal examinations were carried out. This mixture of the five haloacetic acids caused an increase in pre-implantation losses and eye defects in the offspring or litters at the high dose level. Maternal toxicity occurred in the middle and high dose groups in the form of reduced body weights on gestation days 6 and 7, with signs of piloerection and kyphosis. In the high dose group, the body weight loss was significant (Narotsky et al. 2011).

In a 2-generation study, Sprague Dawley rats were given drinking water with a mixture of 9 trihalomethanes and haloacetic acids from the beginning of gestation in the parent generation up to postnatal day 6 of the F2 generation. The sums of trihalomethanes and haloacetic acids were equivalent to 0, 500, 1000 and 2000 times the U.S. Environmental Protection Agency's maximum contaminant levels permitted for drinking water. This corresponds to dichloroacetic acid concentrations of 0, 13.52, 27.03 and 54.06 mg/l drinking water at neutral pH and dose levels of about 0, 1.6, 3.2 and 6.5 mg/kg body weight and day with a conversion factor of 0.12 for the F0 generation and about 0, 1.2, 2.4 and 5.0 mg/kg body weight and day with a conversion factor of 0.09 for the F1 generation (conversion factors for subacute (F0) and subchronic (F1) exposure in accordance with EFSA (2012)). The F1 offspring were examined on postnatal days 6, 13, 21, 26 and 66, the F2 offspring on postnatal day 6. No effects on prenatal or postnatal survival or on weights at birth were found for the haloacetic acids. Perinatal toxicity was not observed in the low dose group. In the F1 offspring, body weights were reduced at the middle dose from postnatal day 21, and at the high dose from postnatal day 6 onwards. Water consumption was reduced in all treated groups. In addition, retained nipples and reduced sperm motility were observed in the male F1 offspring in the high dose group, as well as a delayed onset of puberty in both sexes of the middle and high dose groups. However, these effects could also be secondary to the reduced water consumption and reduced body weights. Maternal toxicity at the high dose level consisted in reduced body weights. Histologically, in the F0 dams of the high dose group, nephropathy and adrenal cortical pathology were observed (Narotsky et al. 2015). Up to the highest dichloroacetic acid dose levels of 6.5 and 5.0 mg/kg body weight and day, respectively, no perinatal

toxicity was observed in the offspring of the F0 and F1 generation up to postnatal day 4 in the 2-generation study with exposure to a mixture of substances.

Developmental neurotoxicity

There are no studies available.

In vitro

In in vitro tests with explanted mouse embryos, dichloroacetic acid induced defects in the neural tube and in the heart, eyes and pharynx (BG Chemie 2006; Hartwig 2010).

Summary

In a prenatal developmental toxicity study in Long Evans rats with gavage administration of neutralized dichloroacetic acid from gestation days 6 to 15, a dose-dependent increase in the total incidence of visceral malformations, mostly of cardiovascular nature, was observed in the foetuses at 140 mg/kg body weight and above. At higher dose levels, which caused severe maternal toxicity, also hydronephrosis and occasional ocular malformations were found, but no skeletal malformations. The NOAEL for developmental toxicity was 14 mg neutralized dichloroacetic acid/kg body weight and day. The relative liver weights of the dams were increased (Smith et al. 1992). The results with regard to heart malformation were confirmed when rats were treated during three gestation periods or on individual gestation days with doses of neutralized dichloroacetic acid of 1900 and 2400 mg/kg body weight and day (GD 9 to 11, 12 to 15, 6 to 15 and GD 10 and 12, respectively) and when a neutralized dichloroacetic acid dose of 3500 mg/kg body weight was administered on gestation day 9, 10 or 12 (Epstein et al. 1992).

In contrast, in a prenatal developmental toxicity study with Sprague Dawley rats, no increased incidence of heart malformations was found at a neutralized dichloroacetic acid dose of 300 mg/kg body weight and day administered from gestation days 6 to 15 (Fisher et al. 2001).

In a prenatal developmental toxicity study in CD-1 mice with gavage administration of dichloroacetic acid in a dose of 722 mg/kg body weight and day from gestation days 6 to 15, perinatal mortality was increased and birth was delayed. The NOAEL for developmental and maternal toxicity in mice is 477 mg dichloroacetic acid/kg body weight and day (Narotsky et al. 1996).

Manifesto (classification)

Prenatal toxicity. Since the epidemiological studies in humans always involved exposure to a mixture of substances, these data do not provide conclusive evidence of developmental toxicity or developmental neurotoxicity caused by dichloroacetic acid.

A prenatal developmental toxicity study in Long Evans rats with gavage administration of neutralized dichloroacetic acid from gestation days 6 to 15 revealed a dose-dependent increase in the total incidence of visceral malformations, mostly in the cardiovascular system, in the foetuses at 140 mg/kg body weight and day and above (Smith et al. 1992). However, these effects were not found in Sprague Dawley rats up to 300 mg/kg body weight and day (Fisher et al. 2001). At higher dose levels, which caused severe maternal toxicity, also hydronephrosis and occasional eye malformations were observed in Long Evans rats. The NOAEL for developmental toxicity was 14 mg neutralized dichloroacetic acid/kg body weight and day (Smith et al. 1992).

In CD-1 mice, a prenatal developmental toxicity study revealed perinatal mortality and delayed births after gavage of dichloroacetic acid of 722 mg/kg body weight and day from gestation days 6 to 15. The NOAEL for developmental and maternal toxicity in mice was 477 mg dichloroacetic acid/kg body weight and day (Narotsky et al. 1996).

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL for developmental toxicity of 14 mg neutralized dichloroacetic acid/kg body weight and day in the rat or 477 mg dichloroacetic acid/kg body weight and day in the mouse to a concentration in workplace air: the species-specific correction values for the rat and the mouse (1:4 and 1:7), the demonstrated oral absorption in rats of 100% (BG Chemie 2006; Hartwig 2010), the body weight (70 kg) and respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The concentrations calculated from this are 24.5 and 477 mg/m³, corresponding to 4.5 and 86.7 ml/m³, respectively. Since the 23-fold and 434-fold margin between the calculated NOAEC (no observed adverse effect concentration) and the MAK value of 0.2 ml/m³ (1.1 mg/m³) is sufficiently large and the anion is responsible for the systemic effects, dichloroacetic acid and its salts could be assigned to Pregnancy Risk Group C. However, dichloroacetic acid led to gait disturbances in juvenile F344 rats at neutralized dichloroacetic acid doses of 16 mg/kg body weight and day after 3 weeks of treatment, and to reduced grip strength after 13 weeks of treatment. Moreover, juvenile animals were more sensitive than adults (Hartwig and MAK Commission 2021; Moser et al. 1999). Thus, a NOAEL could not be determined for developmental neurotoxicity and dichloroacetic acid and its salts are assigned to Pregnancy Risk Group D.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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