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Monochloroacetic acid, sodium monochloroacetate

MAK Value Documentation, supplement – Translation of the German version from 2019

A. Hartwig[1,*] MAK Commission[2,*]

1 Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany

2 Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

* E-Mail: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated monochloroacetic acid [79-11-8] together with sodium monochloroacetate [3926-62-3] considering all toxicological endpoints. Monochloroacetic acid is a strong acid and dissociates in biological media. Therefore, also data for sodium monochloroacetate are used to evaluate the systemic toxicity. Monochloroacetic acid is corrosive to the eyes but there are no inhalation studies from which a NOAEC for local effects can be derived. Therefore, a maximum concentration at the workplace (MAK value) of 2 mg/m³ (0.5 ml/m³), which has been set for the better investigated phosphoric acid, is also established for monochloroacetic acid. As irritation is the critical effect, monochloroacetic acid is classified in Peak Limitation Category I. By analogy with phosphoric acid, an excursion factor of 2 is set. In chronic studies in rats, a NOAEL for sodium monochloroacetate of 3.5 mg/kg body weight and day for males was found for depressed body weight gain and diminished liver and kidney weights. After toxicokinetic scaling, extrapolation to humans and application of the preferred value approach, a MAK value of 2 mg/m³ for the inhalable fraction is set. Since systemic effects of sodium monochloroacetate are critical, it is assigned to Peak Limitation Category II. From the half-life of 3 hours in rat plasma, an excursion factor of 2 is derived. In a study with monochloroacetic acid in rats, the NOAEL for developmental toxicity was 70 mg/kg body weight. This dose corresponds to a concentration of 121 mg/m³ at the workplace, which is about 60 times as high as the MAK value of 2 mg/m³. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and monochloroacetic acid and its sodium salt are classified in Pregnancy Risk Group C. Monochloroacetic acid is DNA damaging in vitro at concentrations which are also cytotoxic, but it is not in alkylating agent. Overall, the acid and its sodium salt are not regarded as genotoxic and they are not carcinogenic in rats and mice. Monochloroacetic acid at concentrations which are not irritating to the skin is not taken up by the skin in toxicologically relevant amounts. The sodium salt, however, is expected to penetrate the skin in amounts contributing to toxicity and is therefore designated with “H”. Both compounds are not expected to be sensitizers.

MAK value (2018)	**monochloroacetic acid:** **0.5 ml/m³ (ppm) ≙ 2.0 mg/m³** **sodium monochloroacetate:** **2 mg/m³ I (inhalable fraction) as acid**
Peak limitation (2018)	**monochloroacetic acid:** **Category I, excursion factor 2** **sodium monochloroacetate:** **Category II, excursion factor 2**
Absorption through the skin (2018)	**monochloroacetic acid: –** **sodium monochloroacetate: H**
Sensitization	**monochloroacetic acid: –** **sodium monochloroacetate: –**
Carcinogenicity	**monochloroacetic acid: –** **sodium monochloroacetate: –**
Prenatal toxicity (2018)	**monochloroacetic acid: Pregnancy Risk Group C** **sodium monochloroacetate: Pregnancy Risk Group C**
Germ cell mutagenicity	**monochloroacetic acid: –** **sodium monochloroacetate: –**
BAT value	**–**
Vapour pressure	acid: at 20 °C: 0.0214 hPa (ECHA 2017 a), 0.2–1 hPa (ECHA 2017 a) Na salt: at 25 °C: 4.2×10^{-8} hPa (calculated; ECHA 2017 b), at 20 °C: < 1.47×10^{-6} hPa (ECHA 2017 c)
log K_{OW}	acid: 0.49 (calculated; ECHA 2017 a) Na salt: −3.47 (calculated; ECHA 2017 b), −3.8 (ECHA 2017 c)
Solubility at 20 °C	acid: > 1000 g/l water (ECHA 2017 a) Na salt: 850 g/l water (ECHA 2017 b), 822 g/l water (ECHA 2017 c)
pH	acid: 0.86 at 1000 g/l (ECHA 2017 a) Na salt: 5.4 at 822 g/l (ECHA 2017 c)
pKa value	acid: 2.8 (ECHA 2017 a)
1 ml/m³ (ppm) ≙ 3.92 mg/m³	**1 mg/m³ ≙ 0.26 ml/m³ (ppm)**

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

For monochloroacetic acid, documentation from 1998 in German only (Greim 1998) is available. The systemic toxicity is attributed to the monochloroacetate ion and in many studies monochloroacetic acid neutralized with sodium hydroxide or its sodium salt was used. Therefore, in this supplement, sodium monochloroacetate is also assessed.

For monochloroacetic acid and sodium monochloroacetate, publicly available REACH registration data are accessible (ECHA 2017 a, b, c). For workers, a systemic DNEL (derived no effect level) of 0.488 mg/m³ and a DNEL of 8 mg/m³ for local effects were obtained (ECHA 2017 a). For the sodium salt, systemic DNELs of 0.061 mg/m³ (ECHA 2017 b) and 0.6 mg/m³ (ECHA 2017 c) were derived by two registrants.

At room temperature, monochloroacetic acid is a solid with a relatively high vapour pressure. The data for vapour pressure given in the REACH dossier are contradictory, and range up to 1 hPa at 20 °C (see above). From the experimentally determined vapour pressure of 0.021 hPa in the key study of the REACH dossier, a vapour saturation concentration of 78 mg/m³ at 20 °C is calculated. In an acute inhalation toxicity study with monochloroacetic acid in vapour form, however, an atmosphere of 255 mg vapour/m³ was generated and it was stated that this corresponds to 48% of the theoretical vapour saturation concentration (ECHA 2017 a).

1 Toxic Effects and Mode of Action

Monochloroacetic acid is almost completely absorbed after oral administration and is subject to enterohepatic circulation. Absorption is high also after dermal application of undiluted monochloroacetic acid because of the destruction of the skin barrier. The half-life in the plasma of rats is 3 hours. Monochloroacetic acid is both systemically toxic and corrosive to the skin and eyes of rabbits. Irritation occurred in rats at and above the lowest concentration tested of 225 mg/m³. In rabbits, sodium monochloroacetate is not irritating to the skin, but to the eye. The acute dermal toxicity of monochloroacetic acid in rabbits is higher than that of sodium monochloroacetate.

As a mechanism for the systemic toxicity of monochloroacetic acid, it is assumed that the inhibition of glyceraldehyde-3-phosphate dehydrogenase inhibits gluconeogenesis and the citric acid cycle, which in turn causes a deficiency in adenosine triphosphate (ATP) and pyruvate as well as oxidative stress. Cytotoxic effects, neurotoxicity, endoplasmic reticulum (ER) stress and apoptosis are produced by reactive oxygen species. In addition, monochloroacetic acid causes glutathione depletion. These systemic effects are caused by the anion, as demonstrated by the similarly high toxicity of neutralized monochloroacetic acid.

In a carcinogenicity study with gavage administration of monochloroacetic acid in rats, mortality was increased at dose levels of 15 mg/kg body weight and above. After chronic administration of neutralized monochloroacetic acid with the drinking water in rats, body, liver and kidney weights were decreased at 25 mg/kg body weight. No tumours occurred in either study.

The DNA damage observed in indicator tests with monochloroacetic acid in vitro is caused by oxidative stress.

Data for skin sensitization caused by monochloroacetic acid in humans are not available. In two local lymph node assays with mice, sodium monochloroacetate was not sensitizing. Data for sensitizing effects of monochloroacetic acid on the airways are not available.

In a prenatal toxicity study in rats with gavage administration of monochloroacetic acid, an increased incidence of malformations of the cardiovascular system occurred at the highest dose tested of 140 mg/kg body weight and day.

2 Mechanism of Action

The toxicity of monochloroacetic acid was attributed to inhibition of the citric acid cycle and gluconeogenesis, whereby ATP synthesis is suppressed, producing an energy deficiency in various organs (Greim 1998). In rats, mitochondrial aconitase was inhibited in the heart, but not in the liver. This agrees with the finding in a 90-day study that the heart is a target organ (Bryant et al. 1992).

Monochloroacetic acid inhibited glyceraldehyde-3-phosphate dehydrogenase in vitro and gluconeogenesis in isolated perfused rat liver. As the levels of citrate and 2-oxoglutarate were similarly reduced, it was concluded that the aconitase of the citric acid cycle in the liver was not inhibited. The other enzymes involved in gluconeogenesis were likewise not inhibited. At the lethal dose of 80 mg/kg body weight, the activity of glyceraldehyde-3-phosphate dehydrogenase in the liver of rats was reduced to 19% of the control values (Sakai et al. 2005).

Monochloroacetic acid inhibited glyceraldehyde-3-phosphate dehydrogenase in the transgenic CHO (Chinese hamster ovary) cell line AS52 after 20-minutes incubation at concentrations of 1 mM and above (Pals et al. 2011).

Sodium monochloroacetate inhibited glyceraldehyde-3-phosphate dehydrogenase, reduced the glutathione content and was cytotoxic in primary rat astrocytes with half-maximal effects at concentrations in the range of 0.3 to 3 mM. Dichloroacetate and trichloroacetate did not have these effects. Unlike iodine acetate, sodium monochloroacetate did not react directly with glutathione (Schmidt et al. 2011), so that the alkylating potency of monochloroacetate is expected to be low.

The inhibition of glyceraldehyde-3-phosphate dehydrogenase as a target cytosolic enzyme causes the depletion of ATP and consequently a reduction in pyruvate, which can result in mitochondrial stress and genomic DNA damage due to reactive oxygen species. This was demonstrated by the reduction in the ATP concentration in the CHO cell line AS52 after incubation with monohalogenated acetic acids. The extent of ATP depletion followed the pattern: iodoacetic acid > bromoacetic acid > monochloroacetic acid, which correlated with the potency of the cytotoxic and genotoxic effects of the acids and also with their alkylating potency. Supplementation with pyruvate increased the ATP level and reduced DNA damage in the comet assay (Dad et al. 2013).

The inhibition of glyceraldehyde-3-phosphate dehydrogenase occurs at relatively high concentrations, contrary to what would be expected from the high toxicity. For this reason, it has not yet been sufficiently confirmed as the only mechanism.

Possible mechanisms of the neurotoxicity of monochloroacetic acid were investigated in Neuro-2a cells (neuroblastoma cells of mice). It was concluded that oxidative stress induces the p38-MAPK-activated signal pathways, which increases mitochondria-dependent apoptosis in the cells (Chen et al. 2013). At concentrations between 0.5 and 2 mM, monochloroacetic acid increased the release of lactate dehydrogenase, was cytotoxic, induced apoptotic events and triggered ER stress. Pretreatment with acetylcysteine reduced the extent of these effects. It was concluded that monochloroacetic acid triggers cellular apoptosis via an ER stress signalling pathway induced by reactive oxygen species (Lu et al. 2015).

Addition of the antioxidants *tert*-butyl-4-hydroxyanisol or catalase reduced the monochloroacetic acid-induced DNA damage in the comet assay and the formation of micronuclei in human lymphocytes. For this reason, it was assumed that oxygen radicals play a role in causing DNA damage and micronuclei (Ali et al. 2014).

Oxidative stress/gene activation

In the ARE-geneBLAzer assay using the HepG2 cell line, monochloroacetic acid (not further specified) induced the gene expression of different enzymes associated with oxidative stress. The concentration producing the 1.5-fold induction of gene expression in this test ($EC_{1.5}$) was 0.0086 mM (Pals et al. 2013).

Monochloroacetic acid (not further specified) produced oxidative stress in the AREc32 test with the MCF cell line, and positive results in the cell sensor p53RE-bla test using HCT-116 cells on agonists and antagonists of the p53 pathway (evidence of DNA damage). In these tests, the $EC_{1.5}$ was 7 mM and 0.086 mM, respectively. The EC_{10} for cytotoxicity was 0.5 mM. In the AREc32 test, the effects of iodoacetic acid and bromoacetic acid were markedly stronger. In the p53 test they were not used. The data are available only in tabular form annexed to the publication. The high $EC_{1.5}$ in the AREc32 test compared with that in the ARE-geneBLAzer assay (Pals et al. 2013) was attributed

to using the MCF cell line, which is not metabolically competent, unlike the HepG2 cell line, in which the ARE-bla reporter gene is integrated (Yeh et al. 2014).

In another study with monochloroacetic acid (not further specified), the $EC_{1.5}$ in the ARE-bla assay using the HepG2 cell line and in the P53RE-bla test using HCT116 cells was 0.071 mM and 0.1 mM, respectively. In both tests, iodoacetic acid and bromoacetic acid were around 10 to 18 times more effective (Procházka et al. 2015).

These studies confirm that reactive oxygen species are responsible for the neurotoxicity and probably also for other cytotoxic/organotoxic effects, and for the DNA damage in the indicator tests for genotoxicity.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

After intravenous injection of rats with radiolabelled neutralized monochloroacetic acid at doses of 10 or 75 mg/kg body weight, the peak concentrations were 30 and 130 mg/l plasma, respectively. The half-lives of the total radioactivity in plasma were 3.25 hours at the low dose, 3.03 hours for monochloroacetate and 5.4 or 4.9 hours for the high dose. 73% and 59% of the low and the high dose, respectively, was excreted with the urine, 55% and 68% of which was eliminated in unchanged form. In the first two hours, biliary excretion of 71% of the dose was found. The fact, however, that less than 1.5% of the dose was excreted in the faeces means that the amount excreted into the intestine was almost completely reabsorbed (Saghir et al. 2001).

After gavage administration of radiolabelled monochloroacetic acid doses of 10 or 225 mg/kg body weight to rats, less than 1.5% in total was excreted with the faeces 32 hours after administration, despite the detected presence of metabolites in the gastrointestinal tract. This suggests enterohepatic circulation, and oral absorption is practically complete (at least 98.5%). The maximum concentration was 1.9 mg/l plasma at the low dose and 46 mg/l at the high dose. These values were attained after 1.48 and 0.27 hours, respectively. The half-life of the total radioactivity in plasma was about 2 hours. Bioavailability was 100% at 10 mg/kg body weight, but could not be calculated for the higher dose (Saghir and Rozman 2003).

Male Sprague Dawley rats were given a dose of 0.1 mmol radiolabelled monochloroacetic acid/kg body weight by gavage. The highest concentrations were determined in the intestines and kidneys 4 and 8 hours after administration. Monochloroacetic acid was bound to plasma albumin. During the first 24 hours, 90% of the dose was excreted with the urine. After 48 hours, significant amounts of radioactivity were still found in the tissues (Kaphalia et al. 1992).

After occlusive dermal application of 125 mg radioactively labelled monochloroacetic acid/kg body weight in acetone to the skin of rats for up to 4 hours, the bioavailability of the substance was determined to be 90%. The maximum concentration was 60.6 mg/l in the plasma, and was attained after 1.41 hours. The half-life of the total radioactivity in the plasma was about 3.7 hours. A skin depot developed, from which the monochloroacetic acid was continuously absorbed, and the skin erosion occurring at the site of application due to the acidity of the substance presumably increased its uptake (Saghir and Rozman 2003).

As before, no data are available for the dermal absorption of monochloroacetic acid at non-irritating concentrations.

The permeation of neutralized monochloroacetic acid through human skin (n = 3) was studied using diffusion chambers at 40 °C. The exposure lasted for 24 to 48 hours, the lag time was 3.7 hours. The receptor phase was phosphate-buffered saline solution. At a concentration of 1000 mg neutralized monochloroacetic acid/l, the permeation coefficient was 1.1×10^{-3} cm/hour. In addition, the study found that at 40 °C the permeability of the simultaneously investigated halogen ketones was three times as high as that at 20 °C (Xu et al. 2002). From the permeation coefficient for monochloroacetic acid, a flux of 1.1 µg/cm² and hour at 40 °C can be calculated. A threefold increase in permeability at 40 °C compared with at 20 °C can be assumed also for monochloroacetic acid, so that a flux of 0.37 µg/cm²

and hour for a 0.1% solution at a temperature of 20 °C is assumed. At a pH of the skin of 5.5, monochloroacetic acid, with a pKa value of 2.8, is present in an almost completely ionized form, so that adjustment to a pH of 7 did not cause a relevant change in the dissociation equilibrium. The flux therefore applies for monochloroacetic acid and monochloroacetate. According to ECHA (2017 a) monochloroacetic acid is corrosive to the skin. For such substances, according to the regulation on classification, labelling and packaging, skin irritation is to be assumed at concentrations of 1% and above. After linear extrapolation of the flux of 0.37 µg/cm² and hour to a non-irritating solution of 0.5%, the uptake would be 3.7 mg after one-hour exposure of 2000 cm².

According to ECHA (2017 b), sodium monochloroacetate is classified as a skin irritant. For such substances, according to the regulation on classification, labelling and packaging, skin irritation is to be assumed at concentrations of 10% and above. After linear extrapolation of the flux of 0.37 µg/cm² and hour to a non-irritating solution of 5%, the uptake would be 37 mg after one-hour exposure of 2000 cm².

As the toxicity of monochloroacetic acid after oral administration in rats is clearly lower than that of monochloroacetate after intravenous administration, it was assumed that a hepatic first-pass effect may have contributed. However, after oral administration of toxic doses of monochloroacetic acid it is more probable that reduced absorption of the substance from the gastrointestinal tract resulting from a reduction in the movement of the stomach contents plays a more important role. The authors point out that extrapolation of the kinetics of toxic doses from one route of administration to another is difficult (Saghir and Rozman 2003).

From the data for acute toxicity (Section 5.1) it can be concluded that, at the same absorbed doses, the systemic toxicity after inhalation exposure to a vapour/aerosol mixture of monochloroacetic acid is not higher than after oral administration.

3.2 Metabolism

Monochloroacetic acid is metabolized by mice to *S*-carboxymethylcysteine and thiodiacetic acid, which are excreted with the urine. Further metabolites are glycolic acid, oxalic acid and CO_2 (Greim 1998). The biliary metabolites found in rats after intravenous administration of neutralized monochloroacetic acid were assumed to be glutathione conjugates. About 60% of the administered dose was metabolized (Saghir et al. 2001).

4 Effects in Humans

4.1 Single exposures

There are numerous reports available of accidental poisoning with monochloroacetic acid after oral or dermal exposure, some with a fatal outcome (Greim 1998).

4.2 Repeated exposure

A value of 5.7 mg/m³ was given as the irritation threshold for monochloroacetic acid at the workplace (Greim 1998). In view of the limited documentation, this publication from Russia is, however, not suitable for inclusion in the evaluation.

4.3 Local effects on skin and mucous membranes

Monochloroacetic acid is corrosive to the skin (Greim 1998).

4.4 Allergenic effects

In a chemical laboratory assistant who had poured a solution of monochloroacetic acid of about 14% in 94% ethanol over his hand, erythema and blisters appeared in spite of rinsing the affected skin with water for 10 minutes; these healed after 10 days. After 14 days, small itching blisters developed. A patch test was carried out on day 28. The patient produced a markedly positive reaction to a 1% ethanolic monochloroacetic acid solution in 70% methanol. The authors assumed sensitization to ethyl monochloroacetate. On day 49, a second patch test using 1% ethyl monochloroacetate both in acetone and in ethanol and 1% monochloroacetic acid in water was carried out. This time the patient produced a markedly positive reaction only to ethyl monochloroacetate and not to monochloroacetic acid (Braun and van der Walle 1987).

4.5 Reproductive and developmental toxicity

In a case–control study involving 40 subjects, the risk of hypospadias was not statistically significantly associated with maternal exposure to monochloroacetic acid during pregnancy (Luben et al. 2008).

4.6 Genotoxicity

No data are available.

4.7 Carcinogenicity

No data are available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

An unpublished study from 2007 carried out in accordance with OECD Test Guideline 403 is described in the REACH registration data. Wistar rats were exposed nose-only for 4 hours to monochloroacetic acid concentrations of 512 or 1268 mg/m^3 at slight overpressure. Due to the hygroscopic property of solid monochloroacetic acid, it was difficult to generate a respirable aerosol. For this reason, an aqueous solution of 50% monochloroacetic acid was nebulized to generate a vapour/aerosol mixture. The concentration in the breathing zone of the animals was determined as the sum of vapour and aerosol by passing the air through two wash bottles with receiver solutions connected in series. The particle sizes were between 3 and 20 µm. In range-finding tests, the exposure tubes were installed in a plethysmograph. Shortly after the exposure, the animals' respiration rate was reduced and their tidal volume increased (no other details). Also during the 4-hour exposure in the main study, a reduced respiration rate was found during clinical observation. No deaths occurred, the body weights were unaffected and no abnormalities were found at the gross-pathological examination/necropsy at the end of the 14-day recovery period. The 4-hour LC_{50} for rats was thus higher than 1268 mg/m^3 (ECHA 2017 a). With a respiratory minute volume of 0.8 l/min/kg body weight and 100% absorption, the concentration of 1268 mg/m^3 would correspond to about 230 mg/kg body weight. Due to the reduced respiration rate, the dose was, however, probably somewhat lower.

In another unpublished study from 1987, no deaths occurred in 6 F344 rats after whole-body exposure for 1 hour to monochloroacetic acid in vapour form at a concentration of 66 ml/m^3 (225 mg/m^3). The animals were lethargic, and irritation was evident in the rats blinking their eyes. There was a slight loss in body weights, which was reversible

during the 14-day recovery period. The limit test was planned with a nominal concentration of 1000 ml/m³. This concentration was not attained due to the recrystallization of the compound at room temperature (ECHA 2017 a).

No inhalation studies with the sodium salt are available.

5.1.2 Oral administration

The LD_{50} for monochloroacetic acid after oral administration in rats was between 400 and 450 mg/kg body weight. At 225 mg/kg body weight, about 20% of the animals died (Saghir and Rozman 2003).

Lower LD_{50} values were also obtained: according to another report, an LD_{50} of 90.4 mg/kg body weight was determined in female rats (ECHA 2017 a).

The LD_{50} for neutralized monochloroacetic acid was 76.2 mg/kg body weight in rats (ECHA 2017 b) and 165 to 255 mg/kg body weight in mice (ECETOC 1999).

5.1.3 Dermal application

The LD_{50} for monochloroacetic acid after patch testing was 145 mg/kg body weight in rats. After the application of 125 mg/kg body weight, 21% of the animals died (Saghir and Rozman 2003). An LD_{50} of 178 mg/kg body weight was given for rabbits (ECETOC 1999).

The dermal LD_{50} of sodium monochloroacetate was 3250 mg/kg body weight in male rats and above 2000 mg/kg body weight in females (ECHA 2017 b, c).

5.1.4 Intravenous and intraperitoneal injection

The dose–response relationship for mortality in rats is very steep, as no signs of intoxication (coma) were observed after intravenous injection of 50 mg neutralized monochloroacetic acid/kg body weight, whereas 43% of the animals died at 60 mg/kg body weight (Saghir et al. 2001).

The intraperitoneal LD_{50} of monochloroacetic acid in rats was 154 mg/kg body weight (Bakishev 1978 in ECETOC 1999). In NLM (2017), however, an LD_{50} of 16.6 mg/kg body weight is given for the same study. In the study by Siddiqui et al. (2006), the doses for the genotoxicity tests were selected on the basis of this lower LD_{50}. The low LD_{50} was probably wrongly calculated, as the LD_{50} values for other parenteral routes of administration, such as intravenous and subcutaneous administration, were about 60 mg/kg (see above) and about 100 mg/kg body weight, respectively (Greim 1998).

The intraperitoneal LD_{50} for neutralized monochloroacetic acid was 269 mg/kg body weight in mice (ECETOC 1999).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

No valid study is available.

According to a study with rats and guinea pigs exposed to monochloroacetic acid concentrations of 20.8 mg/m³ for 4 months, reduced body weight gains, inflammatory changes in the respiratory tract, a drop in haemoglobin values and changes in clinico-chemical parameters occurred. At 5.8 mg/m³, only transient changes in the clinico-chemical parameters and no morphological changes in the respiratory organs were observed. In view of the limited documentation, this publication from Russia is, however, not suitable for inclusion in the evaluation (Greim 1998).

5.2.2 Oral administration

After the administration of monochloroacetic acid with the drinking water at concentrations of 1 to 3 g/l for 14 days, the liver weights of B6C3F1 mice were not increased and those of Sprague Dawley rats were decreased. Peroxisome proliferation was not increased, unlike after exposure to equimolar doses of dichloroacetic acid and trichloroacetic acid (DeAngelo et al. 1989).

In 90-day studies carried out within the National Toxicology Program (NTP), the NOAELs (no observed adverse effect levels) given were 30 mg/kg body weight and day for F344 rats and 100 mg/kg body weight and day for B6C3F1 mice after gavage administration of monochloroacetic acid on 5 days per week (Bryant et al. 1992; Greim 1998). On the other hand, in the Risk Assessment Report (EU 2005), 30 mg/kg body weight and day is interpreted to be the LOAEL (lowest observed adverse effect level) for rats as, at this dose, reduced relative heart weights in female animals, increased relative liver weights (< 20%), increased relative kidney weights in male animals and changed clinico-chemical parameters (reduced cholinesterase activity after 4 and 8 weeks) were observed. Thus, on a dose per kg body weight basis, rats are more sensitive than mice.

The heart lesions in this study were, in a retrospective evaluation, not characterized as increased spontaneous lesions but as independent substance-induced degeneration (Jokinen et al. 2005).

Five male Sprague Dawley rats were given neutralized monochloroacetic acid in drinking water for 90 days. The estimated dose was about 18.6 mg/kg body weight and day. At the end of the study, compared with the findings in the 5 controls, slight collagenic deposits and slight dilation of the portal vein in the liver as well as sporadic small inflammatory foci in the lungs were found in the treated animals. Body weight gains and liver weights were not statistically significantly changed (Bhat et al. 1991; Greim 1998).

In another 90-day study in Sprague Dawley rats with daily administration of neutralized monochloroacetic acid by gavage, the levels of creatinine, calcium and blood urea nitrogen as well as of liver enzymes in blood were increased at the lowest dose tested of 15 mg/kg body weight and above, so that the LOAEL was 15 mg/kg body weight. In view of the severity of the histopathological lesions in the liver, kidneys, heart and spleen at the higher doses, the male animals were more sensitive than the females in this study (Daniel et al. 1991; Greim 1998).

In the 2-year study of the NTP with gavage administration of monochloroacetic acid doses of 15 and 30 mg/kg body weight and day on 5 days per week, mortality in the female F344 rats was statistically significantly, but not dose-dependently, increased even at 15 mg/kg body weight and above, so that the LOAEL was 15 mg/kg body weight. In the males, the mortality was statistically significantly increased at 30 mg/kg body weight. It was due to an increase in the incidence of spontaneous tumours, which was not dose-dependent, and increased incidences of unknown causes of death. The latter were dose-dependent both in the males (1, 4, 12) and in the females (0, 4, 12). There was no increase in the incidence of histopathological findings, however. At the lowest dose tested in B6C3F1 mice of 50 mg/kg body weight and above, the body weights were reduced in the females. Therefore, for the mice, the LOAEL was 50 mg/kg body weight (Greim 1998; NTP 1992). The rats were more sensitive than the mice also in this study.

In a 2-year study, male F344 rats were given daily doses of neutralized monochloroacetic acid with the drinking water of 3.5, 26.1 or 59.9 mg/kg body weight and day. At the middle and high dose, water consumption, body weights, the absolute kidney weights, and the absolute and relative liver weights were reduced. The relative weights of the testes were increased, probably as a result of the lower body weights. The relative and absolute spleen weights were increased only in the animals of the low dose group, so that this is not regarded as a substance-related effect (DeAngelo et al. 1997; Greim 1998). The fact that mortality was not increased in this study at daily doses higher than those in the NTP study could be due to the continuous intake with the drinking water, compared with the bolus administration in the NTP study, which leads to high peak concentrations in the body that cannot be detoxified.

In summary, for rats, as the most sensitive species, a NOAEL of 3.5 mg/kg body weight and day and a LOAEL of 15 mg/kg body weight and day were obtained after chronic administration.

5.2.3 Dermal application

No studies with dermal application are available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Monochloroacetic acid is corrosive to the skin (ECHA 2017 a; Greim 1998).

In a study carried out according to OECD Test Guideline 404, sodium monochloroacetate was not irritating to the skin of rabbits. However, according to the Globally Harmonized System (GHS) it is classified as irritating to the skin (ECHA 2017 b, c).

5.3.2 Eyes

Monochloroacetic acid is corrosive to the eyes of rabbits. The findings were so severe that the animals had to be killed after 24 hours (ECHA 2017 a; Greim 1998).

In a study carried out according to OECD Test Guideline 405, sodium monochloroacetate was irritating to the eyes of rabbits. The findings were reversible after 7 days. Although it is not legally classified according to the GHS, the term "causes severe irritation to the eyes" has been used to describe the substance (ECHA 2017 b, c).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In two local lymph node assays (LLNAs) in female CBA mice, sodium monochloroacetate (purity 98.7% and 99.12%, respectively) was not sensitizing in concentrations of 5%, 10%, 25% and 50% (ECHA 2017 b) and 5%, 10% and 25% (ECHA 2017 c) in 1% aqueous poloxamer solution. The stimulation indices in these LLNAs were 1.0, 1.0, 2.3, 1.4 and 1.4, 0.8 and 0.7, respectively. No data are available for monochloroacetic acid.

5.4.2 Sensitizing effects on the airways

No data are available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no fertility studies available. In the 90-day studies of the NTP in mice and rats, no effects on reproductive organs were observed (Greim 1998).

In an in vitro study, the growth of murine antral follicles and the concentration of oestradiol in the medium was reduced by incubation with concentrations of 0.25 to 1 mM monochloroacetic acid, which was interpreted as ovarian toxicity in mice (Jeong et al. 2016).

5.5.2 Developmental toxicity

5.5.2.1 In vivo

An aqueous monochloroacetic acid solution was administered by gavage to Long Evans rats from gestation days 6 to 15 at dose levels of 0, 17, 35, 70 or 140 mg/kg body weight and day. Body weight gains were reduced in the

dams of the high dose group, organ weights were not affected. Only in the foetuses of the high dose group was there a statistically significant increase in malformations of the cardiovascular system, mainly of the left cardiac ventricle. Skeletal malformations were not observed (Greim 1998; Smith et al. 1990).

Throughout the entire gestation period, 10 Sprague Dawley rats were given drinking water with 1570 mg neutralized monochloroacetic acid/l, which corresponded to 193 mg/kg body weight and day. Neither maternal nor developmental toxicity were observed, and, in particular, there was no statistically significant increase in the incidence of cardiac malformation. The frequency of cardiac malformations in the control group was 2.15%, that in the monochloroacetic acid group 4.55% (Johnson et al. 1998 a, b). The findings in the study by Smith et al. (1990) could therefore not be reproduced. A possible explanation for such effects can be found in the high peak concentration following bolus administration.

5.5.2.2 In vitro

The in vitro studies in mouse embryos (Greim 1998; Hunter et al. 1996) were also used to compare the teratogenic potency of different halogen acids. Monochloroacetic acid was in this case more potent than all dihalogenic acids, but less potent than bromoacetic and iodoacetic acid (Richard and Hunter 1996).

5.6 Genotoxicity

With monochloroacetic acid, no genotoxic effects were found in prokaryotes in various test systems in the presence and absence of a metabolic activation system. Without S9 mix, monochloroacetic acid induced sister chromatid exchange (SCE) in CHO cells. At higher concentrations with S9 mix, and in CHL cells (a cell line derived from Chinese hamster lung) without S9 mix, the results were negative. No DNA strand breaks could be induced in human leukaemia cells. In primary rat or mouse hepatocytes, DNA strand breaks were induced only in the cytotoxic range. Chromosomal aberration studies with CHO and CHL cells as well as a hypoxanthine guanine phosphoribosyl transferase (HPRT) test with V79 cells likewise yielded negative results. In thymidine kinase gene mutation tests with mouse lymphoma cells, a statistically significant increase in the mutation frequency occurred only at concentrations which were already cytotoxic and produced a shift in the pH. In Drosophila, there were no X-chromosomal recessive lethal mutations after feeding, the result was equivocal after injection. The results of an in vivo test for DNA strand breaks were negative in rats and mice (Greim 1998).

Monochloroacetic acid is a by-product of the disinfection of water with chlorine and for this reason has been investigated in a large number of in vitro genotoxicity tests since the publication of the last documentation. Non-neutralized acid with a purity of ≥ 97% was used in all cases, in so far as purity data were reported in the publications.

5.6.1 In vitro

5.6.1.1 Bacteria

Both with and without metabolic activation, monochloroacetic acid did not cause SOS repair in Escherichia coli PQ37 at concentrations up to 3000 mg/l. Cytotoxicity occurred at 300 and 1000 mg/l (10.6 mM) and above, respectively (Giller et al. 1997).

In an umu test for SOS repair with Salmonella typhimurium TA1535/pSK1002, monochloroacetic acid (not further specified) yielded negative results at the concentration tested of 485.4 mg/l (5.1 mM) (Ono et al. 1991).

In another SOS/umu test in Salmonella typhimurium TA1535/pSK1002, monochloroacetic acid was weakly genotoxic. Concentrations between 0.2 and 15.9 mM were tested. Toxicity occurred at around 1 mM and above. Bromoacetic acid and dichloroacetic acid were markedly genotoxic and trichloroacetic acid was weakly genotoxic (Zhang et al. 2016).

A further umu test in Salmonella typhimurium TA1535/pSK1002 with monochloroacetic acid (not further specified) yielded a positive result. The concentration which produced a 1.5-fold increase in the SOS response was 13.5 mM.

The EC_{10} for cytotoxicity was 0.5 mM. Iodoacetic acid and bromoacetic acid were markedly more effective in the umu test. The data are available only in tabular form annexed to the publication (Yeh et al. 2014; http://ars.els-cdn.com/content/image/1-s2.0-S0043135414002851-mmc1.pdf).

A fluctuation test with Salmonella typhimurium TA100 yielded negative results for monochloroacetic acid both with and without metabolic activation. Without metabolic activation, concentrations up to 300 mg/l were tested, with activation, concentrations up to 10 000 mg/l (106 mM). The highest concentrations tested were cytotoxic (Giller et al. 1997).

Monochloroacetic acid (not further specified) was found to be mutagenic in TA98 in a preincubation test without metabolic activation in the range of 20 to 28 mM (1890 to 2650 mg/l), but not with metabolic activation, as well as in TA100 both without and with metabolic activation in the range of 12 to 25 mM. No mutagenic activity was observed with Salmonella typhimurium RSJ100. In the TA100 strain, the number of revertants was almost doubled compared with that in the controls (no data for TA98). Taking the cytotoxicity into account, the mutagenic effect, measured as the number of revertants per µmol monochloroacetic acid, increased by 40 to 70% with TA98 (6/µmol) and TA100 (with and without activation 44 and 63/µmol, respectively). Bromoacetic acid was 100 times as effective as monochloroacetic acid (Kargalioglu et al. 2002). It can be concluded from the very high concentrations used, which were also cytotoxic, that monochloroacetic acid, unlike bromoacetic and iodoacetic acid, is only weakly mutagenic.

5.6.1.2 Mammalian cells

Monochloroacetic acid (not further specified) yielded a positive result in a comet assay (end point: tail moment) with the transgenic CHO cell line AS52. Concentrations between 0.1 and 1 mM were tested. Tests with dichloroacetic and trichloroacetic acid produced negative results (Plewa et al. 2002, 2004, 2010). Monochloroacetic acid was cytotoxic in the range of 0.3 to 2 mM (Plewa et al. 2004). The corresponding EC_{50} values were 0.85 mM (Plewa et al. 2004) and 0.8 mM (Plewa et al. 2010).

With the transgenic CHO cell line AS52, monochloroacetic acid (no further details) yielded a positive result in a comet assay (end point: % DNA in the tail) at the only concentration tested of 6 mM. Bromoacetic acid produced the same extent of DNA damage at a concentration of 0.06 mM. The DNA damage caused by monochloroacetic acid was, however, repaired more rapidly than that caused by bromoacetic acid. In view of this, the authors deduced that different mechanisms are in action or the two acids cause a different distribution of DNA damage (Komaki et al. 2009). The effects could be reduced with 10 mM pyruvate (Dad et al. 2013).

In a comet assay (end points: tail moment and % DNA in the tail) with the HepG2 cell line, monochloroacetic acid did not cause damage to DNA up to the highest tested cytotoxic concentration of 10 mM. In contrast, bromoacetic and dibromoacetic acid, and dichloroacetic and trichloroacetic acid yielded positive results, in some cases even at concentrations as low as 0.1 µM (bromoacetic acid) (Zhang et al. 2012).

Monochloroacetic acid (not further specified) yielded a positive result in a comet assay (end point: % DNA in the tail) carried out with primary lymphocytes from 3 male donors and at concentrations of 0.001 to 2.94 mM. The human lymphocytes were half as sensitive to DNA damage as the CHO cell line AS52. However, after 6 hours, half of the DNA damage had been repaired; after this no more repair was observed, whereas the damaged parts of the CHO cell line AS52 were completely repaired. Monochloroacetic acid produced a reduction in the mitotic index by 50% at 0.722 mM. Iodoacetic acid and bromoacetic acid were markedly more genotoxic and cytotoxic (Escobar-Hoyos et al. 2013).

A comet assay with 25 mM monochloroacetic acid (not further specified) (end points: tail moment and % DNA in the tail) with human lymphocytes from 12 male and female non-smokers yielded positive results. This concentration was determined as the most effective in range-finding studies. Under the same conditions, the results of a comet assay with sperms from 4 donors were likewise positive. The addition of 10, 50 or 100 µM *tert*-butyl-4-hydroxyanisol

or catalase as antioxidants reduced the DNA damage. In view of this, the authors concluded that oxygen radicals participate in the DNA damage caused by monochloroacetic acid (Ali et al. 2014).

A comet assay (end point: % DNA in the tail) with non-transformed human epithelial cells from the small intestine, FHs 74, yielded positive results at concentrations of 1.04 mM monochloroacetic acid and above (no other details). At 3.42 mM, the expression of genes regulating DNA repair, cell cycle control and apoptosis was changed (Attene-Ramos et al. 2010).

A chromosomal aberration test was carried out with monochloroacetic acid (not further specified) in the primary lymphocytes of 3 male donors. Concentrations of 0.001, 0.18 and 1.47 mM were used. At 0.18 mM and above, the increase in the frequency of chromatid aberrations was statistically significant, but not that of chromosomal aberrations (Escobar-Hoyos et al. 2013).

In a cytokinesis-block micronucleus test with human TK6 cells, monochloroacetic acid was neither clastogenic nor aneugenic up to the highest tested cytotoxic concentration of 1 mM. Also iodoacetic acid and bromoacetic acid were negative up to cytotoxic concentrations, whereas mitomycin C produced the expected positive result. The authors concluded that DNA damage in the TK6 cells is efficiently repaired, preventing the manifestation of clastogenic effects (Liviac et al. 2010).

In a cytokinesis-block micronucleus test with fresh blood samples from 6 male and female donors who were non-smokers, monochloroacetic acid (not further specified) yielded positive results both in mononuclear and in binuclear lymphocytes at the only concentration used of 0.0625 mM. In range-finding studies, this was the most effective non-cytotoxic concentration. Iodoacetic and bromoacetic acid were markedly more effective. By the addition of 0.1, 0.5 or 1 µM *tert*-butyl-4-hydroxyanisol or catalase, the frequency of micronuclei could be reduced; therefore, the authors concluded that oxygen radicals participate in the formation of micronuclei with all three acids (Ali et al. 2014).

In an HPRT test with the CHO cell line K1, monochloroacetic acid (not further specified) was mutagenic at concentrations of 1 mM and above. The concentrations tested were between 0.1 and 3 mM. In this range, from 97% down to about 50% of the cells survived compared with the number of control cells. Bromoacetic acid had a stronger effect than monochloroacetic acid, which in turn had a stronger effect than dichloroacetic acid, whereas trichloroacetic acid was not mutagenic (Zhang et al. 2010).

5.6.2 In vivo

Male rats (strain and origin of the animals not specified) received single intraperitoneal injections of 0, 8, 10 or 12 mg monochloroacetic acid/kg body weight. Bone marrow cells were extracted 12, 24 or 48 hours after the injection. Only the high dose produced a statistically significant increase in the number of chromosomal aberrations after 24 hours (only including gaps, not without gaps) and micronuclei (Siddiqui et al. 2006). As the gaps are not chromosomal aberrations, monochloroacetic acid was not clastogenic in this test. In this micronucleus test, 12 mg monochloroacetic acid/kg body weight was half as effective as 20 mg cyclophosphamide/kg body weight. However, in rats, no tumours were found in the chronic study with about 60 mg neutralized monochloroacetic acid/kg body weight. For this reason, there are doubts concerning the validity of this study. Dose-finding was not carried out by means of a range-finding study, but established on the basis of an intraperitoneal LD_{50} of 16.6 mg/kg body weight in the literature. This value is, however, not plausible (see Section 5.1.4).

Conclusions

In the documentation of 1998 (Greim 1998) monochloroacetic acid was assessed as non-genotoxic: studies of gene mutations in bacteria and mammalian cells and of clastogenicity yielded negative results. A SCE test in CHO cells yielded a positive result. Positive DNA strand break and TK test results were obtained only in the cytotoxic range. In Drosophila, no X-chromosomal recessive lethal mutations were produced after feeding, the results were equivocal after injection. An in vivo test for DNA strand breaks yielded negative results in rats and mice.

In more recent in vitro studies, DNA-damaging effects of monochloroacetic acid were detected; these were attributed to oxidative stress (see also Section 2; Pals et al. 2013; Procházka et al. 2015; Yeh et al. 2014). The induction of micronuclei in human lymphocytes and a positive result in an HPRT test can probably likewise be attributed to reactive oxygen species, as an alkylating effect of monochloroacetic acid is unlikely, as suggested by the negative results in the Salmonella mutagenicity tests at non-cytotoxic concentrations. DNA damage occurs at cytotoxic concentrations in which the reactive oxygen species can no longer be completely detoxified by natural defence mechanisms. There is thus a NOAEL for this effect. No DNA strand breaks were produced in rats and mice, so that in vivo DNA damage is apparently of minor importance. The positive result in the micronucleus test in rats would suggest a very high clastogenic potency which, however, was not found in vitro in chromosomal aberration studies. For this reason, the test is of doubtful validity.

5.7 Carcinogenicity

5.7.1 Short-term studies

No data are available.

5.7.2 Long-term studies

No new data are available.

In a carcinogenicity study in F344 rats and B6C3F1 mice with gavage administration carried out by the NTP, there was no evidence of carcinogenicity up to the highest doses tested of 30 and 100 mg monochloroacetic acid/kg body weight, respectively (Greim 1998; see Section 5.2.2).

Also, in another 2-year study, in which neutralized monochloroacetic acid was administered with the drinking water, no increase in tumour incidences was found in male F344 rats up to highest dose tested of 59.9 mg/kg body weight (DeAngelo et al. 1997; Greim 1998; see Section 5.2.2).

6 Manifesto (MAK value/classification)

The critical effects are the irritation caused by monochloroacetic acid and sodium monochloroacetate and, after chronic exposure, decreased body, liver and kidney weights after the administration of neutralized monochloroacetic acid with the drinking water and mortality after gavage administration of monochloroacetic acid. With regard to systemic effects, rats are more sensitive than mice.

MAK value. A 2-year drinking water study in male rats with neutralized monochloroacetic acid revealed a LOAEL for systemic toxicity of 26 mg/kg body weight and day (given as acid); decreased body weight gains, and liver and kidney weights were found (DeAngelo et al. 1997). The NOAEL was 3.5 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7 : 5), the corresponding species-specific correction value (1 : 4) for the rat, the experimentally determined almost complete absorption (98.5%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 8.4 mg/m^3. As, at this concentration, monochloroacetic acid can be present in vapour form, the corresponding value is 2.2 ml/m^3. As this value was derived from a NOAEL from animal experiments (1 : 2) and after applying the preferred value approach, the MAK value providing protection against systemic effects would be 1 ml/m^3.

From the LOAEL of 15 mg/kg body weight and day in the 2-year NTP study with administration of monochloroacetic acid on 5 days per week by gavage to female rats, a NAEL (no adverse effect level) of 5 mg/kg body weight and day

is assumed. Extrapolation of the NAEL to a concentration in air yields a value of 8.6 mg/m³ and thus an identical MAK value for systemic effects is obtained.

Monochloroacetic acid is corrosive to the skin and eyes. However, a study with repeated inhalation is not available and irritation of the respiratory tract can thus not be evaluated. The acidity of monochloroacetic acid (pKa value 2.8) is somewhat lower than that of phosphoric acid (pKa value 2.12) with a MAK value of 2 mg/m³ I (corresponding to 0.5 ml/m³). For this reason, in analogy to phosphoric acid, a MAK value of 0.5 ml/m³ (2 mg/m³) has been established for monochloroacetic acid, in order to protect also against its local effects.

On the basis of its systemic toxicity, a MAK value of 2 mg/m³ I has been established for sodium monochloroacetate, determined as the acid, obtained by extrapolation of the concentration of 8.4 mg/m³ given above to humans (1 : 2) and using the preferred value approach. This value also provides protection against its irritant effect, which is less pronounced than that of monochloroacetic acid.

Peak limitation. Since irritation is the critical effect, monochloroacetic acid is assigned to Peak Limitation Category I. In analogy to phosphoric acid, the excursion factor is 2.

The MAK value for sodium monochloroacetate is based on systemic effects, for which reason it is assigned to Peak Limitation Category II. The half-life for monochloroacetate in the plasma of rats is about 3 hours. This corresponds to an excursion factor of 2 (Hartwig and MAK Commission 2017).

Prenatal toxicity. In a prenatal toxicity study in rats with gavage administration of monochloroacetic acid, there was an increased incidence of malformations in the cardiovascular system at the highest dose tested of 140 mg/kg body weight and day (Smith et al. 1990). The NOAEL was 70 mg/kg body weight and day. These findings could not be reproduced after the administration of neutralized monochloroacetic acid with the drinking water at a dose level of 193 mg/kg body weight. It is possible that the different toxicokinetics of the two administration methods contribute to this difference in the NOAELs.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 70 mg/kg body weight to a concentration in workplace air: the species-specific correction value (1 : 4) for the rat, the experimentally determined almost complete absorption (98.5%), the body weight (70 kg) and respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 121 mg/m³, which is about 60 times as high as the MAK value of 2 mg/m³ (0.5 ml/m³). Monochloroacetic acid and its sodium salt have therefore been assigned to Pregnancy Risk Group C.

Carcinogenicity. As, in rats and mice, no evidence of carcinogenicity was found, monochloroacetic acid and its sodium salt have not been assigned to one of the categories for carcinogens.

Germ cell mutagenicity. In more recent in vitro studies, DNA-damaging effects of monochloroacetic acid have been detected. These can be attributed to oxidative stress. Clastogenic effects were found in the form of double strand breaks in primary rat and mouse hepatocytes in vitro only at cytotoxic concentrations, but not in vivo. The induction of micronuclei in human lymphocytes in vitro and positive results in the HPRT test are probably also attributable to reactive oxygen species, as an alkylating effect of monochloroacetic acid is unlikely, as suggested by the negative results in the Salmonella mutagenicity tests at concentrations which are not cytotoxic. The induction of micronuclei in vivo at 12 mg/kg body weight in rats (Siddiqui et al. 2006) is not plausible, as the potency of monochloroacetic acid would be half as high as that of the positive control cyclophosphamide, although, in rats, no tumours occurred up to about 60 mg neutralized monochloroacetic acid/kg body weight in a chronic study. The study is therefore of doubtful validity. Apart from this, clastogenicity was found neither in vitro nor in vivo. Taking all the data into account, monochloroacetic acid and its sodium salt have not been assigned to one of the categories for germ cell mutagens.

Absorption through the skin. For humans (assuming the exposure of 2000 cm² of skin for 1 hour), the dermal absorption of 3.7 mg monochloroacetate can be estimated from an in vitro study (Xu et al. 2002) after exposure

to a non-irritating 0.5% solution of monochloroacetic acid. From the above extrapolation from the NOAEL of the oral studies in rats, a systemically tolerable concentration of about 4 mg/m³ for humans and, at 100% absorption by inhalation and a 10 m³ respiratory volume, a tolerable uptake of 40 mg is obtained. Dermal absorption thus accounts for less than 25% of the systemically tolerable amount. Monochloroacetic acid has therefore not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

On the basis of an absorbed amount of 3.7 mg for 0.5% monochloroacetic acid, as calculated above, after linear extrapolation the absorption of 37 mg would be expected for a non-irritating 5% monochloroacetate solution. For monochloroacetate, the same tolerable amount of about 40 mg, as derived above, applies. Dermal absorption thus accounts for more than 25% of the systemically tolerable amount, and sodium monochloroacetate has been designated with an "H".

Sensitization. As before, no positive clinical findings in humans are available for skin sensitization caused by monochloroacetic acid. The results of two local lymph node assays with sodium monochloroacetate in mice were negative. Data for respiratory sensitization caused by monochloroacetic acid are not available. Therefore, monochloroacetic acid and sodium monochloroacetate are designated neither with "Sh" nor with "Sa" (for substances causing sensitization of the skin and airways).

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