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Trichloroacetic acid and sodium trichloroacetate

MAK Value Documentation, supplement – Translation of the German version from 2016

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Keywords

trichloroacetic acid; sodium trichloroacetate; irritation; eye; respiratory tract; developmental toxicity; skin absorption; maximum workplace concentration; MAK value; peak limitation

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated trichloroacetic acid [76-03-9] and sodium trichloroacetate [650-51-1] to derive a maximum concentration at the workplace (MAK value), considering all toxicity endpoints. Available publications are described in detail. After oral application of trichloroacetic acid or the sodium salt, the target organ is the liver with mice being more susceptible than rats. Trichloroacetic acid can be regarded as non-genotoxic. Trichloroacetic acid is only carcinogenic in the liver of mice, not in other organs or in rats. Humans are much less sensitive to mechanisms regarded to be causative for effects in the liver of male mice. Therefore, trichloroacetic acid and its sodium salt, which acts in vivo like trichloroacetic acid, are not classified as carcinogens or germ cell mutagens. The systemic NOAEL in rats is 32.5 mg/kg bw and day in a 2-year study, which would correspond to a MAK value of 20 mg/m^3. However, trichloroacetic acid and sodium trichloroacetate are corrosive to the eye of rabbits. As no inhalation studies are available to judge possible irritating effects on the respiratory tract, phosphorous acid, which is also corrosive to the eye, is used as a read-across. The irritation strength of the three substances is very similar. Since the MAK value of phosphorous acid is 2 mg/m^3, and the critical effect of trichloroacetic acid and sodium trichloroacetate is local toxicity, a MAK value of 2 mg/m^3 is also assigned to sodium trichloroacetate. As trichloroacetic acid is a vapour at this concentration range, a corresponding MAK value is set in ml/m^3. Applying the preferred value approach, a MAK value of 0.2 ml/m^3 corresponding to 1.4 mg/m^3 is derived for trichloroacetic acid, which also takes into account the slightly higher acidity compared to phosphorous acid. As the local effect is critical, both substances are assigned to Peak Limitation Category I with an excursion factor of 1. The NOAEL for developmental toxicity in rats is 100 mg sodium trichloroacetate/kg bw and day, corresponding to 100 mg/m^3. Thus, damage to the embryo or foetus is unlikely when the MAK value is observed and both substances are classified in Pregnancy Risk Group C. For sodium trichloroacetate, but not for trichloroacetic acid, skin contact may contribute significantly to systemic toxicity; sodium trichloroacetate is designated with an "H" notation. Sensitization is not expected from the available data.

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MAK value (2015)	**trichloroacetic acid: 0.2 ml/m³ ≙ 1.4 mg/m³**
	sodium trichloroacetate: 2 mg/m³ I (inhalable fraction)
Peak limitation (2015)	**trichloroacetic acid: Category I, excursion factor 1**
	sodium trichloroacetate: Category I, excursion factor 1
Absorption through the skin (2015)	**trichloroacetic acid: –**
	sodium trichloroacetate: H
Sensitization	**trichloroacetic acid: –**
	sodium trichloroacetate: –
Carcinogenicity	**trichloroacetic acid: –**
	sodium trichloroacetate: –
Prenatal toxicity (2015)	**trichloroacetic acid: Pregnancy Risk Group C**
	sodium trichloroacetate: Pregnancy Risk Group C
Germ cell mutagenicity	**trichloroacetic acid: –**
	sodium trichloroacetate: –
BAT value	**–**
BAR	**–**
BAR for trichloroethylene (2010)	**0.07 mg trichloroacetic acid/l urine**
CAS number	trichloroacetic acid: 76-03-9 sodium trichloroacetate: 650-51-1

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

Trichloroacetic acid is used as a textile auxiliary, polymerization initiator, caustic agent and mordant, lubricating oil additive, swelling agent and solvent. Sodium trichloroacetate is used in textile, leather and fur processing. The anion is responsible for the systemic effects, the acid for the irritation. A large number of studies were carried out with the neutralized acid; for this reason both the acid and its sodium salt are assessed in this supplement. For trichloroacetic acid, documentation from 1981 (Henschler 1981, available in German only) is available. Since then, data have been published for all end points, making a re-evaluation necessary.

Mechanism of Action

Various mechanisms have been suggested for the formation of hepatocarcinomas in mice, such as increased lipid peroxidation, peroxisome proliferation and cell proliferation. But also DNA hypomethylation and the inhibition of intercellular communication contribute to the hepatocarcinogenicity of trichloroacetic acid (US EPA 2011). Table 1 gives an overview of the studies of the mechanisms of action in rats and mice.

Tab. 1 Studies of the mechanisms of action of trichloroacetic acid in the liver in vivo

Species, strain, number per group	Exposure	Findings	References
Liver enzymes			
rat, Sprague Dawley, 6 ♀	**50 days,** 0, 2000 mg/l (about 180 mg/kg body weight[a]), drinking water	**180 mg/kg body weight:** AST, ALT, creatine phosphokinase, acid phosphatase, catalase, superoxide dismutase ↑, **unchanged:** glutathione, glutathione reductase, glutathione *S*-transferase	Çelik 2007
rat, F344, 30 ♂	**104 weeks,** 0, 50, 500, 5000 mg/l (0, 3.6, 32.5, 364 mg/kg body weight), drinking water	**3.6 mg/kg body weight: NOAEL** **32.5 mg/kg body weight:** AST ↓ (not dose-dependent) **364 mg/kg body weight:** ALT ↑	DeAngelo et al. 1997
mouse, B6C3F1, 6–18 ♂	**14 days,** 0, 1000 mg/l (228 mg/kg body weight), drinking water	**228 mg/kg body weight:** CYP4A ↑, no induction of CYP2E1 and total P450	Austin et al. 1995
mouse, B6C3F1, 3–6 ♂	**3 and 10 weeks,** 0, 100, 500, 2000 mg/l **3 weeks:** about 18, 90, 360 mg/kg body weight[b], **10 weeks:** about 15, 75, 300 mg/kg body weight[c], drinking water	**15/18 mg/kg body weight and above:** laurate hydroxylase ↑	Parrish et al. 1996
Oxidative stress/lipid peroxidation			
rat, Sprague Dawley, 6 ♀	**50 days**, 0, 2000 mg/l (about 180 mg/kg body weight[a]), drinking water	**180 mg/kg body weight:** catalase, superoxide dismutase ↑	Çelik 2007
rat, F344, 3 ♂	**single dose,** 0, 100, 300, 1000, 2000 mg/kg body weight, gavage; positive control: 1600 mg CCl_4/kg body weight, intraperitoneal	**1000 mg/kg body weight and above:** TBARS after 9 hours ↑	Larson and Bull 1992
mouse, B6C3F1, 6 ♂	**single dose,** 0, 30, 100, 300 mg/kg body weight, drinking water	**300 mg/kg body weight:** 8-OHdG in the liver ↑	Austin et al. 1996
mouse, B6C3F1, 2–4 ♂	**single dose,** 0, 100, 300, 1000, 2000 mg/kg body weight, gavage, positive control: 1600 mg CCl_4/kg body weight, intraperitoneal	**300 mg/kg body weight and above:** TBARS ↑ after 24 hours back to control level	Larson and Bull 1992
mouse, B6C3F1, 8 ♂	**single dose,** 300 mg/kg body weight, gavage	**300 mg/kg body weight:** **6 hours:** no increase **12 hours:** superoxide anions ↑, lipid peroxidation ↑	Hassoun and Dey 2008
mouse, B6C3F1, 6–18 ♂	**14 days,** 1st group: 1000 mg/l (228 mg/kg body weight), on day 15: water, (control) 2nd group: 1000 mg/l (228 mg/kg body weight), on day 15: 300 mg trichloroacetic acid/kg body weight, drinking water	**228 mg/kg body weight:** 1st group: TBARS, palmitoyl coenzyme A oxidase, catalase, CYP ↑ 2nd group: increase less pronounced	Austin et al. 1995

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 6 ♂	**3 and 10 weeks,** 0, 100, 500, 2000 mg/l **3 weeks:** about 18, 90, 360 mg/kg body weight[b], **10 weeks:** about 15, 75, 300 mg/kg body weight[c], drinking water	**360/300 mg/kg body weight: 3 and 10 weeks:** no increase in 8-OHdG in the liver	Parrish et al. 1996
mouse, B6C3F1, 7 ♂	**4 and 13 weeks,** 0, 7.7, 77, 154, 410 mg/kg body weight, gavage	**7.7 mg/kg body weight: 4 weeks:** **NOAEL** lipid peroxidation **13 weeks:** **NOAEL** relative liver weight **7.7 mg/kg body weight and above:** lipid peroxidation ↑, superoxide anions ↑ **77 mg/kg body weight:** myeloperoxidase ↑, TNFα ↑	Hassoun et al. 2010
mouse, B6C3F1, 11–35 ♂	**52 weeks,** 0, 1000, 2000 mg/l (about 125, 250 mg/kg body weight and day, calculated using the data from DeAngelo et al. (2008)), drinking water	**250 mg/kg body weight:** accumulation of lipofuscin in the liver	Bull et al. 1990
Peroxisome proliferation			
rat, Sprague Dawley, 6 ♂	**14 days,** 0, 6, 12, 31 mM 0, 980, 1960, 5060 mg/l (0, 212, 327, 719 mg/kg body weight), drinking water	**212 mg/kg body weight:** palmitoyl coenzyme A oxidase not increased **327 mg/kg body weight and above:** carnitine acetyl coenzyme A transferase ↑	DeAngelo et al. 1989
rat, Wistar, 3–5 ♂	**10 days,** 10–200 mg/kg body weight, gavage	**50 mg/kg body weight and above:** palmitoyl coenzyme A oxidase ↑ **100 mg/kg body weight and above:** catalase activity ↓	Elcombe 1985
rat, F344, 6 ♂	**10 days,** 500 mg/kg body weight, gavage	**500 mg/kg body weight:** palmitoyl coenzyme A oxidase ↑	Goldsworthy and Popp 1987
rat, Sprague Dawley, 10 ♂	**90 days,** 0, 4.1, 36.5, 355 mg/kg body weight, drinking water	**355 mg/kg body weight:** palmitoyl coenzyme A oxidase ↑	Mather et al. 1990
rat, F344, 30 ♂	**104 weeks,** 0, 50, 500, 5000 mg/l (0, 3.6, 32.5, 364 mg/kg body weight), drinking water	**32.5 mg/kg body weight: NOAEL** **364 mg/kg body weight:** palmitoyl coenzyme A oxidase ↑	DeAngelo et al. 1997
mouse, B6C3F1, 6 ♂	**10 days,** 500 mg/kg body weight, gavage	**500 mg/kg body weight:** palmitoyl coenzyme A oxidase ↑, significant increase in relative and absolute liver weights	Nelson et al. 1989
mouse, B6C3F1, 8 ♂	**10 days,** 500 mg/kg body weight, gavage	**500 mg/kg body weight:** palmitoyl coenzyme A oxidase of kidneys ↑	Goldsworthy and Popp 1987
mouse, B6C3F1, 4–5 ♂	**10 days,** 10–200 mg/kg body weight, gavage	**50 mg/kg body weight and above:** palmitoyl coenzyme A oxidase ↑ **200 mg/kg body weight:** catalase activity ↑	Elcombe 1985

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 6 ♂	**14 days,** 0, 6, 12, 31 mM (980, 1960, 5060 mg/l) (0, 131, 261, 442 mg/kg body weight), drinking water	**131 mg/kg body weight and above:** dose-dependent increase in palmitoyl coenzyme A oxidase **442 mg/kg body weight:** carnitine acetyl coenzyme A transferase ↑	DeAngelo et al. 1989
mouse, B6C3F1, 6 ♂	**3 and 10 weeks,** 0, 100, 500, 2000 mg/l **3 weeks:** about 18, 90, 360 mg/kg body weight[b)], **10 weeks:** about 15, 75, 300 mg/kg body weight[c)], drinking water	**15/18 mg/kg body weight and above:** cyanide-insensitive acyl coenzyme A oxidase ↑	Parrish et al. 1996
mouse, B6C3F1, 30 ♂	**60 weeks,** 0, 50, 500, 5000 mg/l (0, 8, 68, 602 mg/kg body weight), drinking water	**8 mg/kg body weight: NOAEL** **68 mg/kg body weight and above:** palmitoyl coenzyme A oxidase ↑ at every time point in the examination	DeAngelo et al. 2008
Cell proliferation			
rat, F344, 30 ♂	**104 weeks,** 0, 50, 500, 5000 mg/l (0, 3.6, 32.5, 364 mg/kg body weight), drinking water	**364 mg/kg body weight: NOAEL**	DeAngelo et al. 1997
mouse, B6C3F1, 5 ♂	**5 and 15 days,** 5000 mg/l (about 900 mg/kg body weight[b)]), drinking water	**900 mg/kg body weight: 5 days:** [^{3}H]thymidine labelling index ↓ **15 days:** DNA content ↑, [^{3}H]thymidine labelling index in the control range	DeAngelo and Chavis 1991
mouse, B6C3F1, 5 ♂	**5, 10 and 15 days,** 5000 mg/l (about 900 mg/kg body weight[b)]), drinking water	**900 mg/kg body weight: 5/10 days:** cell density ↑, liver weights ↓, enlarged cell nuclei, multiple nuclei **15 days:** cell density ↓, enlarged cell nuclei, multiple nuclei ⇨ hypertrophy	Carter et al. 1991
mouse, B6C3F1, 30 ♂	**60 weeks,** 0, 50, 500, 5000 mg/l (0, 8, 68, 602 mg/kg body weight), drinking water	**only at 68 mg/kg body weight:** [^{3}H]thymidine labelling index ↑	DeAngelo et al. 2008
	78 weeks, 0, 50, 500, 4500 mg/l (0, 6, 81, 572 mg/kg body weight), drinking water	**only at 6 mg/kg body weight:** significant increase in BrdU labelling index	DeAngelo et al. 2008
mouse, B6C3F1, 10 ♀	**5, 12, 33 days,** 0, 2, 6.67, 20 mM (0, 327, 1090, 3270 mg/l) (about 40, 130, 400 mg/kg body weight; calculated using the data from De Angelo et al. (1989)), drinking water	**40 mg/kg body weight: 5 days:** significant increase in BrdU labelling index **12/33 days:** no longer significantly increased	Pereira 1996
mouse, B6C3F1, 12 ♂	**50 weeks,** 2000 mg/l (about 250 mg/kg body weight; calculated using the data from DeAngelo et al. (2008)), drinking water	**250 mg/kg body weight: 28 days:** significant increase in BrdU labelling index **50 weeks:** BrdU labelling index ↓	Stauber and Bull 1997

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
LDH activity			
mouse, B6C3F1, 30 ♂	**60 weeks,** 0, 50, 500, 5000 mg/l (0, 8, 68, 602 mg/kg body weight), drinking water	**68 mg/kg body weight and above:** **30 weeks:** LDH activity in the serum ↑ **60 weeks:** no increase	DeAngelo et al. 2008
DNA single strand breaks			
mouse, B6C3F1, 8 ♂	**single dose,** 300 mg/kg body weight, gavage	**300 mg/kg body weight: 6 hours:** no increase, **12 hours:** increased	Hassoun and Dey 2008
mouse, B6C3F1, 7 ♂	**4 and 13 weeks,** 0, 7.7, 77, 154, 410 mg/kg body weight, gavage	**7.7 mg/kg body weight: 4 and 13 weeks: NOAEL**	Hassoun et al. 2010

[a] conversion factor for subchronic exposure in the rat 0.09 according to EFSA (2012)
[b] conversion factor for subacute exposure in the mouse 0.18 according to EFSA (2012)
[c] conversion factor for subchronic exposure in the mouse 0.15 according to EFSA (2012)
ALT: alanine aminotransferase; AST: aspartate aminotransferase; BrdU: bromodeoxyuridine; CYP: cytochrome P450; 8-OHdG: 8-hydroxydeoxyguanosine; LDH: lactate dehydrogenase; TBARS: thiobarbituric acid-reactive substances; TNFα: tumour necrosis factor α

Oxidative stress / lipid peroxidation

In male mice, after the administration of doses of 228 mg/kg body weight and above with the drinking water, increased lipid peroxidation and the formation of superoxide anions were observed (Austin et al. 1995). The accumulation of lipofuscin—an indication of oxidative stress and increased lipid peroxidation—in the proliferating area of the liver was found in male mice after the administration of 250 mg/kg body weight with the drinking water (Bull et al. 1990). After gavage administration of 77 mg/kg body weight and above for 4 and 13 weeks, the formation of thiobarbituric acid-reactive substances (TBARS, as evidence of lipid peroxidation) and of superoxide anions were increased in a dose-dependent manner in male mice. The amounts formed after administration for 13 weeks were higher than after administration for 4 weeks. Following treatment with 7.7 mg/kg body weight, the formation of TBARS or superoxide anions was slightly, but significantly increased (Hassoun et al. 2010). The results show that at dose levels producing liver carcinomas in male mice (81 mg/kg body weight), lipid peroxidation and oxidative stress are detectable.

An increase in 8-hydroxydeoxyguanosine (8-OHdG, a marker for DNA damage) in the liver of mice could be found only after a comparably high single dose of 300 mg/kg body weight. After administration for 3 and 10 weeks, no increase in 8-OHdG in the liver was measured up to doses of 360 mg/kg body weight (Austin et al. 1996; Parrish et al. 1996).

Peroxisome proliferation

Trichloroacetic acid induced peroxisome proliferation in the liver of mice and rats after single and repeated administration. Induction of the marker enzyme palmitoyl coenzyme-A oxidase occurred after the treatment of male mice for 60 weeks at dose levels of 68 mg/kg body weight and above (Table 1). No increase in peroxisome proliferation was found after the administration for 60 weeks of 8 mg/kg body weight and after the administration for 104 weeks of 6 mg/kg body weight (Table 6). The number of tumours per animal correlated with the peroxisome proliferation in male mice in the 60 and 104-week study (correlation coefficient: 60 weeks: $r^2 = 0.984$; 104 weeks: $r^2 = 0.984$) (DeAngelo et al. 2008). In in vitro studies, activation of the peroxisome proliferator-activated receptor alpha (PPARα) was detectable in the mouse at concentrations of 1 and 5 mM (Zhou and Waxman 1998).

Cell proliferation

Trichloroacetic acid produced an increase in cell proliferation in the liver of male B6C3F1 mice only after five days at 40 mg/kg body weight and above. After 12 and 33 days, the values were again within the range of the control animals (Pereira 1996). After the administration of 68 mg/kg body weight for 60 weeks and of 572 mg/kg body weight for 45 weeks, cell proliferation in male B6C3F1 mice was significantly increased. After 78 weeks, cell proliferation was significantly increased only at the lowest dose tested of 6 mg/kg body weight but not at 81 mg/kg body weight (DeAngelo et al. 2008).

Activation of proto-oncogenes and tumour suppressor genes

In about 45% of the liver tumours (adenomas plus carcinomas) in male B6C3F1 mice treated with trichloroacetic acid, mutations were found in the *H-ras* proto-oncogene. Here, codon 61 was almost exclusively affected. The study shows that the frequency of *H-ras*-61 mutations did not differ from that in liver tumours of the study and historical controls. Generally, mutations in *ras* proto-oncogenes are not essential for the hepatocarcinogenic effects of trichloroacetic acid, as *H-ras*-61 mutations are not found in all liver tumours. Furthermore, the liver tumours do not seem to be based on genotoxic mechanisms, as the frequency of *H-ras*-61 mutations was not increased compared with that in controls (Ferreira-Gonzalez et al. 1995).

Tumour promotion

In initiation–promotion studies in rats and mice, trichloroacetic acid was found to be a weak tumour promoter in the liver (BUA 1995; Herren-Freund et al. 1987; Pereira et al. 1997). An initiating effect was not observed.

Summary

Lipid peroxidation and peroxisome proliferation are considered responsible for the hepatocarcinogenicity in mice. At dose levels producing hepatocarcinomas in male mice (at and above 81 mg/kg body weight), a marked increase in TBARS and superoxide anions has been demonstrated. At higher doses, the accumulation of lipofuscin in the proliferating area of the liver is observed. The dichloroacetic acid radical produced could be responsible for the formation of reactive oxygen species. The extent of peroxisome proliferation correlates with the total number of tumours per animal (DeAngelo et al. 2008). Trichloroacetic acid was found to be a strong peroxisome proliferator and activates PPARα. Concurrent with the occurrence of liver carcinomas, centrilobular and cytoplasmic changes in the liver, and liver necrosis were found. These findings indicate a cytotoxic mechanism of action.

The oxidative DNA damage occurring at high doses (Austin et al. 1996) can be explained by the formation of reactive oxygen species, as also lipid peroxidation and peroxisome proliferation are increased in this dose range. No data are available that indicate a genotoxic mechanism of action.

In addition, it has been suggested that during the initial stages of cell division, inhibiting growth factors are increasingly produced as a possible compensation. Cells with mutations are resistant to these inhibiting growth factors. Liver foci and liver tumours thus have a selective growth advantage (Stauber and Bull 1997).

A dose or time-dependent increase in cell proliferation could not be unequivocally identified, and is thus of less significance for the carcinogenic effect.

Toxicokinetics and Metabolism

Absorption, distribution, elimination

Humans

Trichloroacetic acid

No information is available for absorption after inhalation exposure.

The oral and dermal absorption of trichloroacetic acid is rapid in both humans and various animal species. The results in humans are based on drinking water studies and studies in swimming pools in which disinfectants, including trichloroacetic acid, had been added to the water. Here, the concentration of trichloroacetic acid in the urine was increased with increasing exposure to trichloroacetic acid (IARC 2013).

As they can all be possible components in chlorinated drinking and bathing water, the two haloacetic acids trichloroacetic acid and dichloroacetic acid were investigated in addition to trihalomethanes and haloketones in a chamber diffusion study with human skin samples (n = 3). In this study, the penetration of the substances was determined at different temperatures between 20 °C and 40 °C. The exposure duration was between 24 and 48 hours, the lag time was 4.5 hours. The receptor phase consisted of phosphate-buffered saline solution. At a concentration of 1000 mg neutralized trichloroacetic acid/l, a permeability coefficient of 1.9×10^{-3} cm/hour was found. It was further demonstrated that the permeability of the investigated haloketones was three times as high at 40 °C as at 20 °C (Xu et al. 2002). From the permeability coefficient of trichloroacetic acid, a flux of 1.9 µg/cm² and hour at 40 °C can be calculated. As a threefold increase in permeability at 40 °C compared with at 20 °C can be expected also for trichloroacetic acid, a flux of 0.6 µg/cm² and hour for a 0.1% solution at the usual temperatures is assumed. At a pH of 5.5 for the skin, trichloroacetic acid is available in almost completely ionized form with a pKa of 0.7, so that adjustment to a pH of 7 did not change the dissociation equilibrium to any relevant extent. The flux therefore applies to trichloroacetic acid and trichloroacetate. According to ECHA (2015 b), trichloroacetic acid is regarded as irritating at 1% and above. Linear extrapolation of the flux of 0.6 µg/cm² for a 0.1% solution results in the absorption of 6 mg after the exposure of a surface area of 2000 cm² for one hour to a non-irritating solution of 0.5%.

After the addition of ^{14}C-labelled trichloroacetic acid to blood samples of 4 male volunteers, 4 male beagles and 4 male F344 rats, in humans 74.8% to 84.3% of the radioactivity, in rats 38.3% to 53.5% and in dogs 54.2% to 64.8% was recovered bound to plasma proteins (Templin et al. 1995).

In an in vitro study, the plasma of humans, rats and mice was incubated with neutralized trichloroacetic acid at concentrations between 0.01 mg/l (0.61 µM) and 1000 mg/l (6130 µM). The ratio between bound and free trichloroacetic acid was greatest in humans, decreasing in all three species up to a concentration of 307 µM. This concentration is taken to be the saturation concentration. Plasma protein binding in humans remained almost constant at 81% to 87% over a concentration range of a factor of 3.7. The maximum level of plasma protein binding in the rat was 67% and in the mouse 47%, with levels of 39% and 19% in the steady state, respectively. Different models were used to determine the binding capacity (N × P, N: number of binding sites per protein molecule, P: protein concentration in µM) and the dissociation constant (µM). The highest albumin concentrations, the highest number of binding sites per protein molecule and thus the greatest binding capacity were found in humans. Related to the number of binding sites per protein molecule, the value in humans was twice that in the rat and 17 times as high as that in the mouse. Differences in the dissociation constant between the species were not biologically significant (Lumpkin et al. 2003).

Sodium trichloroacetate

There are no studies available for the inhalation and dermal absorption of sodium trichloroacetate. The irritating effects on the skin are slight. After dermal exposure of rabbits to gels containing between 10% and 90% sodium trichloroacetate or to the pure substance, no or only slight skin irritation was found (see Section "Skin"). A 10% solution is thus not expected to be irritating to the skin. On the basis of an absorbed amount of 6 mg calculated above for 0.5% trichloroacetic acid, absorption of 120 mg would be expected for a 10% sodium trichloroacetate solution after linear extrapolation.

After 3 healthy volunteers were given a single oral sodium trichloroacetate dose of 3 mg/kg body weight, dissolved in water, the plasma half-life of the substance was given as about 50 hours and the distribution volume as 115 ml/kg. The long half-life is a result of the extensive plasma protein binding of trichloroacetic acid (IARC 2013; Müller et al. 1974).

Animals

No data are available for absorption after inhalation exposure.

Male F344 rats and male B6C3F1 mice were given single gavage doses of [^{14}C] trichloroacetic acid of 0, 5, 20 or 100 mg/kg body weight neutralized in water. Blood samples were taken after 0.25, 1, 3, 5, 10, 16, 24 and 48 hours. Urine, faeces and exhaled air were collected during and 48 hours after exposure. Both the rats and the mice exhaled 3.6% to 7.8% as CO_2. Between 1.8% and 3.7% was excreted unchanged with the faeces and between 48% and 65% unchanged with the urine (Table 2).

Tab. 2 Toxicokinetic data in rats and mice after single gavage administration of trichloroacetic acid (Larson and Bull 1992)

	Rat			Mouse	
Dose [mg/kg body weight]	**5**	**20**	**100**	**20**	**100**
CO_2 [%]	6.4 ± 0.8	7.8 ± 0.5	6.3 ± 0.3	3.6 ± 0.9	3.6 ± 0.2
faeces [%]	3.1 ± 0.8	3.3 ± 0.2	1.4 ± 0.3	3.7 ± 0.8	1.8 ± 0.2
TCA in the urine [%]	49.7 ± 2.3	58.0 ± 4.7	64.6 ± 0.9	47.8 ± 2.8	54.6 ± 4.0
DCA in the urine [%]	0.9 ± 0.1	1.3 ± 0.3	2.5 ± 0.6	1.1 ± 0.4	2.1 ± 0.5
GOG in the urine [%]	8.7 ± 1.3	10.8 ± 0.6	4.9 ± 0.5	6.7 ± 1.2	5.8 ± 1.6
C_{max} TCA [nmol/ml]	n. i.	230 ± 10	1200 ± 100	230 ± 10	790 ± 60
$t_{½}$ [hours]	n. i.	7.0	5.8	4.2	5.8
V_d [ml/kg]	n. i.	365	485	335	555
Cl [ml/kg/hour]	n. i.	36	58	55	66

Cl: clearance; C_{max}: plasma peak concentration; DCA: dichloroacetic acid; GOG: unspecified non-chlorinated acids; n. i.: not investigated; $t_{½}$: terminal half-life; TCA: trichloroacetic acid; V_d: distribution volume

In addition, 0.9% to 2.5% dichloroacetic acid was found in the urine. Dichloroacetic acid was detected also in the blood. After the administration of 20 mg trichloroacetic acid/kg body weight, the concentration of dichloroacetic acid in the blood of the mouse was higher than that in the blood of the rat. In contrast, after the administration of 100 mg trichloroacetic acid/kg body weight, the concentration of dichloroacetic acid in the blood was markedly higher in the rat (30 nmol/ml) than in the mouse (5 nmol/ml). Non-chlorinated acids that were not further defined were given as in the range of 4.9% to 10.8%. The recovery was therefore in the range from 60% to 85%. The remaining radioactivity in the carcass was reported as varying up to a factor of five. It is to be assumed that the remaining radioactivity was retained in the animal body due to the high protein binding of trichloroacetic acid. The distribution volume and clearance were within the same order of magnitude in rats and mice (see Table 2). The half-lives of trichloroacetic acid were somewhat longer in rats than in mice. The highest concentration of trichloroacetic acid in blood was determined in rats after the administration of 100 mg/kg body weight, and was about one third higher than that in mice (Larson and Bull 1992).

Groups of 4 to 6 male F344 rats were given 25 µmol trichloroacetic acid/kg body weight by gavage or intravenous injection. The concentrations in blood were analysed within 36 hours. Four to six rats were pretreated with 0.2 g dichloroacetic acid/l drinking water for 7 days in order to inhibit glutathione *S*-transferase zeta (GSTzeta). The aim was to investigate whether the inactivation of GSTzeta has an effect on the toxicokinetic parameters of trichloroacetic acid and other chlorinated acetates. After intravenous injection, the plasma half-life of the substance in the pretreated rats was 7.58 hours compared with 12 hours in the control animals, and was thus significantly reduced. 24% of the administered dose was excreted with the urine. After oral administration, trichloroacetic acid was rapidly absorbed and detected in the plasma after just one minute. The bioavailability was 82% (Table 3). In the pretreated animals, only the plasma half-life of the substance was significantly reduced compared with that in the control animals, the other parameters were not affected (Saghir and Schultz 2005).

Tab. 3 Toxicokinetic parameters after intravenous or gavage administration of trichloroacetic acid to rats (Saghir and Schultz 2005)

Parameter	i.v., controls	i.v., GSTzeta-inactivated	Gavage, controls	Gavage, GSTzeta-inactivated
AUC [nmol × hours/ml]	1561 ± 85	1289 ± 78	1247 ± 113	1061 ± 40
V_{ss} [ml/kg]	287 ± 23	200 ± 10	no data	no data
Cl [ml/kg/hour]	17.1 ± 1.4	19.7 ± 1.2	no data	no data
MRT [hours]	17.2 ± 0.9	10.2 ± 0.2	15.3 ± 1.0	12.6 ± 1.1
K_a [hours^{-1}]	–	–	1.55 ± 0.22	1.95 ± 0.29
$t_{½}$ [hours]	12.03 ± 0.36	7.49 ± 0.15	10.24 ± 0.85	7.58 ± 0.61
bioavailability (%)	100	100	82	82

AUC: area under the plasma concentration curve; Cl: total clearance; K_a: oral absorption rate; MRT: mean residence time; $t_{½}$: plasma elimination half-life; V_{ss}: distribution volume at steady state

Male B6C3F1 mice were given a single gavage dose of 100 mg ^{14}C-labelled trichloroacetic acid/kg body weight. Urine, faeces, exhaled CO_2 and exhaled organic metabolites were collected for 24 hours. The proportion of unmetabolized trichloroacetic acid in the urine was about 57%, that in the faeces about 6%, about 30% remained in the animal, about 5% was exhaled and only about 2% was metabolized (Xu et al. 1995).

Male F344 rats were given intravenous injections of 0, 1, 10 or 50 mg ^{14}C-labelled trichloroacetic acid/kg body weight. Within 24 hours, the concentrations were highest in the plasma, followed by kidneys, erythrocytes, liver, skin, small intestine, large intestine, muscle and fat. After 24 hours, the highest concentrations were determined in the liver (IARC 2013; Yu et al. 2000).

Male B6C3F1 mice were given gavage doses of trichloroacetic acid of 0.03, 0.12 or 0.61 mmol/kg body weight (about 5, 20 and 100 mg/kg body weight), neutralized in distilled water. Blood samples were taken after 1, 2, 4, 6, 9, 12, 18 and 24 hours. The half-lives were 6 (5 mg trichloroacetic acid/kg body weight), 5.4 (20 mg trichloroacetic acid/kg) and 6.4 (100 mg trichloroacetic acid/kg) hours, respectively. The plasma protein binding and the ratio between the liver and blood concentration correlated well above a blood concentration of 306 nmol trichloroacetic acid/ml. At blood concentrations of 306, 612 and 1224 nmol trichloroacetic acid/ml, 41%, 34% and 23% were present in bound form, respectively. Below 306 nmol trichloroacetic acid/ml, the plasma protein binding was between 50% and 57%. The ratio between the concentration in the liver and that in the blood at the peak concentrations was between 0.31 and 0.38, that of the AUC in liver and blood below 300 nmol/ml was 0.7. The clearance was 0.05 ml/min (Templin et al. 1993).

For 3 or 14 days, groups of 5 to 6 male F344 rats received 0, 100, 500 or 2000 mg trichloroacetic acid/l drinking water and male B6C3F1 mice 0, 80, 800 or 2000 mg trichloroacetic acid/l drinking water (neutralized). The control animals were given water with the same concentrations of NaCl. The body weights were determined on the first and third days in the 3-day study and on days 1, 7 and 14 during the 14-day exposure. The body weights were significantly reduced after 3 days in the male mice at and above 800 mg trichloroacetic acid/l drinking water, as was the drinking water consumption after 3 and 14 days compared with that in the control group (14 days). In the male rats, the drinking

water consumption was significantly reduced only at the high dose. The concentrations of trichloroacetic acid were determined 8 hours after the exposure in the blood and in the liver. After both the 3 and 14-day administration, the blood and liver concentrations were of the same order of magnitude and dependent on the dose, both in mice and in rats. Only in the mice of the high dose group were the concentrations in the liver higher (by 32%) after the 14-day administration than after the 3-day administration, which indicates accumulation of trichloroacetic acid in the liver (Table 4) (US Air Force Research Laboratory 1999).

Tab. 4 Toxicokinetic parameters after the administration of trichloroacetic acid in drinking water in male mice and rats (US Air Force Research Laboratory 1999)

♂ mouse	3 days			14 days			
concentration in the drinking water [mg/l]	**80**	**800**	**2000**	**0**	**80**	**800**	**2000**
dose [mg/kg body weight day]	13	111.5	272.1	0	11.6	110	268
body weight – start [g]	26.6 ± 1.2	28.1 ± 1.3	27.1 ± 1.2	25.3–27.4	26.7 ± 1.1	28.4 ± 1	27.4 ± 1.2
body weight – end [g]	27.7 ± 1.2	28.4 ± 1.6*	27.3 ± 1.3*	27.5–30.4	29.7 ± 1.8	28.7 ± 1.6	29.1 ± 1.6
change in body weight [g]	1.1 ± 0.5	0.4 ± 0.9	0.2 ± 1.5	1.3–3.8	3.0 ± 1.5	0.2 ± 1.4	1.7 ± 0.8
H_2O consumption [ml/day]	3.9 ± 0.8	3.5 ± 1.2*	3.4 ± 1.2*	4.0–4.3	4.2 ± 0.7	3.8 ± 0.8*	3.6 ± 0.5*
concentration/blood [µg/ml]	10.3	72.9	79.9	0	10.3	72.9	79.9
concentration/liver [µg/ml]	about 0.8[a)]	about 45[a)]	about 48[a)]	0	6.2	48.2	61.6
♂ rat	**3 days**			**14 days**			
concentration in the drinking water [mg/l]	**100**	**500**	**2000**	**0**	**100**	**500**	**2000**
dose [mg/kg body weight day]	9.8	49.1	149.7	0	6.8	36.4	108.3
body weight – start [g]	225.9 ± 8.9	230.8 ± 8.4	232.1 ± 6.5	282.8–296.9	232.8 ± 7.4	231.9 ± 6.8	224.7 ± 9.5
body weight – end [g]	242.4 ± 16.4	237.3 ± 7.1	235.2 ± 6.9	299.9–315.4	263 ± 9.8	263.8 ± 10.3	251.2 ± 11
change in body weights [g]	16.5 ± 16.4	6.5 ± 2.1	3.2 ± 3.5	17.2–18.5	30.1 ± 2.6	31.9 ± 6.4	26.5 ± 2.8
H_2O consumption [ml/day]	22.5 ± 3.5	22.5 ± 2.5	21.9 ± 9.8	21.2–23.9	21.3 ± 6.1	21.0 ± 6.1	17.1 ± 3.4
concentration/blood [µg/ml]	3.5	30.4	96.4	0	4.3	30.6	93.6
concentration/liver [µg/ml]	0.8 ± 0.32	7.3 ± 0.25	13.0 ± 2.6	0	1.4 ± 0.1	6.2 ± 1.2	11.6 ± 3.8

*statistically significant
[a)] estimated from figure

Summary

Data for inhalation exposure are not available. After oral administration, trichloroacetic acid and its sodium salt are almost completely absorbed in humans, rats and mice. The half-life in humans (3 mg/kg body weight: 50 hours) is about seven times longer than that in the rat (20 mg/kg body weight: 7 hours) due to the higher plasma protein binding.

Metabolism

Humans

Six patients received trichloroacetic acid in aqueous solution at a dose of between 1.5 and 3 g via an intravenous drip for 1 hour (no other details). After 10 days approximately 75% of the dose had been excreted unchanged in the urine, indicating little metabolism. Urinary metabolites were not investigated (IARC 2013).

Rat and mouse

As dichloroacetic acid could be detected in the urine after oral administration of trichloroacetic acid, it is assumed that dichloroacetic acid is formed by reductive dehalogenation at cytochrome P450 (CYP) via a reactive intermediate, namely the dichloroacetate radical. Dichloroacetic acid is metabolized very rapidly and eliminated from the blood, for which reason dichloroacetic acid is present in only very small amounts after the administration of trichloroacetic acid or is not detectable at all (Larson and Bull 1992).

The liver microsomes of male B6C3F1 mice, either untreated or treated with pyrazole, an inducer of CYP2E1, were incubated with trichloroacetic acid. After incubation for 10 or 15 minutes, the amounts of lipid peroxidation products, such as malondialdehyde, formaldehyde, acetaldehyde, acetone and propionaldehyde in the pretreated animals were two to three times as high as the amounts in the untreated animals (Ni et al. 1996).

The liver was removed from male B6C3F1 mice and liver slices were prepared. The liver slices were incubated with 0 or 14 mg trichloroacetic acid/ml for 3, 6 or 8 hours. Cytotoxicity was investigated via the release of lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase. No cytotoxicity occurred after either 6 or 8 hours. To determine the metabolic activity on the basis of the deethylation and glucuronidation/sulfation of 7-ethoxycoumarin, the liver slices were preincubated for 30 and 150 minutes with 0, 25 or 1000 µg trichloroacetic acid/ml and subsequently for 2 hours with 50 µM 7-ethoxycoumarin. A significant increase in 7-hydroxycoumarin (phase I) was found only after incubation with 1000 µg trichloroacetic acid/ml. No increase in glucuronidation or sulfation (phase II) was found. After the 2-hour exposure, the liver slices were exposed to between 0 and 5000 µg trichloroacetic acid/ml for up to 4 hours. The metabolism was not saturable at non-cytotoxic concentrations. Metabolites were not determined, but the decrease in trichloroacetic acid per mg protein per minute was measured (Pravecek et al. 1996).

After the incubation of rat and mouse liver microsomes with trichloroacetic acid, a phenyl-*tert*-butylnitroxide/dichloroacetate radical adduct could be detected using gas chromatography/mass spectrometry in a Fenton reaction system, which confirms the reductive dehalogenation of trichloroacetic acid to dichloroacetic acid. Investigations of other metabolites and of relevant enzymes are not available. It is to be assumed that the dichloroacetic acid formed from trichloroacetic acid is further metabolized in exactly the same way as after direct administration of dichloroacetic acid (Merdink et al. 2000).

Effects in Humans

No new data are available.

Clinical reports of allergic reactions after contact with trichloroacetic acid or of allergenic effects on the airways are not known. Also when used as a caustic, the substance apparently caused no cases of allergic contact eczema.

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

A total of 15 female Sprague Dawley rats, 15 female guinea pigs, 6 female rabbits and 6 male and female cats were exposed to sodium trichloroacetate concentrations of 3460, 11 460 or 32 540 mg/m^3 for 4 hours and observed during a 7-day recovery period. There were no signs of intolerance reactions in any of the animals tested up to 32 540 mg/m^3. Necropsy did not yield any specific pathological findings (no other details) (BUA 1995).

Subacute, subchronic and chronic toxicity

Inhalation

There are no data available.

Oral administration

Several studies in rats and mice with drinking water or gavage administration are available, as shown in Table 5. Only the studies with the lowest tested dose levels in rats and mice are described in detail below.

Tab. 5 Toxicity after repeated oral administration of trichloroacetic acid or sodium trichloroacetate

Species	Exposure	Findings	References
rat			
Sprague Dawley 5 ♂ per group	**90 days,** 0, 45.8 mM (7500 mg/l) (825 mg/kg body weight), drinking water (neutralized)	**825 mg/ kg body weight:** **liver:** absolute liver weights ↓, collagenic deposits in portal veins and central vein in 4/5 animals, extension of portal veins (5/5) slight to moderate **lungs:** perivascular inflammation	Bhat et al. 1991
Sprague Dawley 10 ♂ per group	**90 days,** 0, 50, 500, 5000 mg/l (0, 4.1; 36.5; 355 mg/kg body weight), drinking water (neutralized)	**36.5 mg/kg body weight: NOAEL** **355 mg/kg body weight:** relative liver weights ↑, hepatomegaly, relative kidney weights ↑	Mather et al. 1990
Wistar 5–6 ♂ per group	**10 weeks**, 0, 25 mg/l (about 2 mg/kg body weight, calculation based on the data of Mather et al. (1990)), drinking water (no data regarding neutralization)	**2 mg/kg body weight**: body weight ↓, SDH ↑, triglycerides ↑, glucose ↑, **liver:** centrilobular necrosis, vacuolation and hypertrophy of hepatocytes, loss of hepatic architecture, triglycerides ↓, glycogen ↑, cholesterol ↓, **kidneys:** degeneration of renal tubules and basement membrane of Bowman's capsule, diffuse glomeruli, vacuolation and renal tubular proliferation, GSH ↓	Acharya et al. 1995, 1997
F344 50 ♂ per group	**104 weeks,** 0.05, 0.5, 5.0 g/l (0, 3.6, 32.5, 364 mg/kg body weight), drinking water (neutralized)	**32.5 mg/kg body weight:** NOAEL for liver weight increase and peroxisome proliferation **364 mg/kg body weight:** slight hepatocellular necrosis, ALT ↑, peroxisome proliferation ↑, no increased cell proliferation	DeAngelo et al. 1997
mouse			
B6C3F1 7 ♂ per group	**4 or 13 weeks,** 0, 7.7, 77, 154, 410 mg/kg body weight, gavage (neutralized)	**7.7 mg/kg body weight: 4 weeks: NOAEL** for lipid peroxidation, superoxide anion production, DNA single strand breaks, liver weight **13 weeks: NOAEL** for DNA single strand breaks, liver weight **LOAEL:** lipid peroxidation ↑, superoxide anion production ↑	Hassoun et al. 2010

ALT: alanine aminotransferase; GSH: glutathione; SDH: succinate dehydrogenase

Groups of 5 to 6 male Wistar rats were exposed to 0 or 25 mg trichloroacetic acid/l drinking water (calculation based on the data of the 90-day study by Mather et al. (1990): about 2 mg/kg body weight and day) for 10 weeks. Data regarding neutralization were not given. The body weights and the cholesterol levels were reduced. Centrilobular necrosis, vacuolation, hypertrophy of the hepatocytes, loss of hepatic architecture, and reduced triglyceride and increased glycogen levels were found in the liver. Degeneration of the renal tubules and the basement membrane of the Bowman's capsule were observed in the kidneys. The renal glomeruli were diffuse, in addition to which vacuolation and renal tubular proliferation occurred (Acharya et al. 1997). There is no verification of the concentration of trichloroacetic acid in the drinking water in this study. Furthermore, no details of drinking water consumption are given. The description of histopathological findings is purely qualitative, incidences or a graduation of the findings are not reported.

No investigation of clinical signs and clinico-chemical parameters was carried out. As only one concentration was tested, the dose-dependency of the findings could not be demonstrated. For these reasons, the study is not used for the derivation of a MAK value.

In a 2-year study with 50 male F344 rats per group, these effects, in particular those on the kidneys, could not be found even at considerably higher doses. The concentrations in the drinking water were 0, 50, 500, 5000 mg/l (0, 3.6, 32.5, 364 mg/kg body weight and day). Effects were described only in the liver. At the highest dose tested of 364 mg/kg body weight and day, slight hepatocellular necrosis was observed and peroxisome proliferation was increased. In serum the levels of alanine aminotransferase activity were increased. Cell proliferation was not increased. The middle dose of 32.5 mg/kg body weight and day can be considered as the NOAEL (no observed adverse effect level) in this study (DeAngelo et al. 1997). Thus, F344 rats are considerably less sensitive to trichloroacetic acid than Wistar rats. This difference in sensitivity cannot be explained mechanistically. It is, however, known that the Wistar rat reacts more sensitively to peroxisome proliferators than the mouse (Elcombe 1985).

From the 2-year study in male B6C3F1 mice, a NOAEL (liver, peroxisome proliferation) of 6 mg/kg body weight and day can be derived (Table 6) (DeAngelo et al. 2008). This means that trichloroacetic acid has stronger effects in the male mouse than in the male F344 rat.

Tab. 6 60 and 104-week drinking water studies with trichloroacetic acid in B6C3F1 mice (30 ♂) (DeAngelo et al. 2008)

[mg/kg body weight and day]	60 weeks exposure
8	**LOAEL:** hepatocellular adenomas increased (not significant), centrilobular cytoplasmic changes in the liver: low level of degeneration of hepatocytes, characterized by eosinophilic cytoplasm with basophilic granularity, slight cytomegaly, **NOAEL:** carcinomas, liver weights, peroxisome proliferation, cell proliferation, serum LDH activity
68	adenomas increased (not significant), palmitoyl CoA oxidase ↑ at every time point in the study, 30 weeks: serum LDH activity ↑, 60 weeks: no increase, relative liver weights ↑, increased incidence of liver necrosis 30% (controls 0%), [^{3}H]thymidine labelling index ↑, testes: tubular degeneration
602	adenomas significantly increased, palmitoyl CoA oxidase ↑ at every time point in the study, [^{3}H]thymidine labelling index ↑, increased incidence of liver inflammation, increased incidence of liver necrosis 50% (controls 0%)
6	**NOAEL:** liver weights, peroxisome proliferation, LDH activity, carcinomas, adenomas, **LOAEL:** centrilobular cytoplasmic changes in the liver: low level of degeneration of hepatocytes, characterized by eosinophilic cytoplasm with basophilic granularity, slight cytomegaly, 78 weeks: BrdU labelling index significantly ↑
81	palmitoyl CoA oxidase ↑, serum LDH activity ↑
572	78 weeks: relative liver weights ↑, 50 weeks: [^{3}H]thymidine labelling index ↑

BrdU: bromodeoxyuridine; LDH: lactate dehydrogenase

Summary: The study in male Wistar rats (Acharya et al. 1995, 1997) is not used for the derivation of a NOAEL due to a lack of data to verify the trichloroacetic acid concentration in the drinking water and water consumption and because of insufficient documentation of the effects. From a 2-year drinking water study, a NOAEL (liver, peroxisome proliferation) of 6 mg/kg body weight (DeAngelo et al. 2008) can be derived for male B6C3F1 mice, and a NOAEL of 32.5 mg/kg body weight for male F344 rats (DeAngelo et al. 1997). The increase in peroxisome proliferation and the resultant increased formation of reactive oxygen species are thought to be responsible for the effects in the liver. The species differences in the activation of PPARα, especially the lower sensitivity of humans as regards the induction of peroxisome proliferation, have been investigated a number of times and have also been confirmed in more recent studies (IARC 2012). According to present-day knowledge, the PPARα activated peroxisome proliferation in the liver of rodents is not relevant for humans as, in humans, PPARα is present in considerably lower concentrations (1% to 10% compared with those in the liver of rats and mice) and the response activated by PPARα is weaker. In the case of other genes activated by PPARα, for example those for the regulation of proliferation or of apoptosis, very few data are available, so that no quantitative relationships can be deduced (Klaunig et al. 2003).

Dermal application

There are still no data available.

Local effects on skin and mucous membranes

Skin

Trichloroacetic acid is corrosive to the skin and mucous membranes. It is used as a caustic agent in dermatology and ear, nose and throat (ENT) therapy in the form of a 50% solution. After application of such a solution on human skin or mucosa, the epidermis is destroyed. The damaged tissue is regenerated in the course of two to three weeks (Henschler 1981).

Groups of 6 male and 6 female rabbits were treated on the shaved skin for 24 hours with 0.5 ml of a 10%, 30% or 90% **sodium trichloroacetate** solution (vehicle: 1% aqueous methylhydroxyethyl cellulose gel) using occlusive patches. The skin of 3 animals per group was scarified. The rabbits were observed over a 14-day recovery period. There was no evidence of irritation (ECB 2000; ECHA 2015 a).

Sodium trichloroacetate (0.5 g/animal) was applied semi-occlusively to the shaved left side of the dorsal skin (6 cm^2) of 3 male rabbits for 4 hours. The right side served as the control. The effects on the skin were examined after 30 to 60 minutes and after 24, 48 and 72 hours. No oedema occurred in any of the 3 animals, and only very slight erythema was found, which was reversible after 7 days (ECHA 2015 a).

Eyes

As **trichloroacetic acid** is corrosive to the skin, it is assumed that it is corrosive also to the eyes. After direct contact of the cornea with a 10%–25% trichloroacetic acid solution, immediate whitening occurs in humans. In rabbits, severe damage to the eyes was found at a concentration not specified (Grant and Schuman 1993).

An amount of 3.5 mg **trichloroacetic acid** caused severe irritation to the eyes in rabbits (Henschler 1981).

Sodium trichloroacetate (0.1 g) was applied to the conjunctival sac of one eye of 3 male rabbits, the untreated eye served as a control. After one hour, the eye was rinsed for 30 seconds. In all three animals, the cornea was opaque with necrotic areas after 24 and 72 hours, the dimensions of the pupil were no longer clearly recognizable and the iris exhibited moderate inflammation and a delayed reaction to light. Furthermore, slight oedema, but marked erythema were found in the conjunctiva. All effects were reversible after 14 days. Sodium trichloroacetate was thus found to produce strong irritation in the rabbit eye (ECHA 2015 a).

In groups of 6 male and 6 female rabbits, 0.1 ml of a 25%, 50% or 90% **sodium trichloroacetate** solution (vehicle: 1% aqueous methylhydroxyethyl cellulose gel) was instilled into the conjunctival sac of one eye and the eye was held closed for one minute. The untreated eye served as a control. Pain reactions occurred between one and two minutes after instillation of the 90% solution. Diffuse conjunctival reddening (individual blood vessels could not be differentiated) and slight swelling were found, which were reversible after 72 hours. No irritation was observed after instillation of the 25% or 50% solution (ECB 2000; ECHA 2015 a).

Summary

Trichloroacetic acid is corrosive to the skin and therefore also to the eyes. On direct contact with the cornea immediate whitening occurs in humans and in rabbits.

Sodium trichloroacetate is only slightly irritating to the skin. Strong irritation with corneal opacity, inflammation of the iris and conjunctival erythema was found in the rabbit eye.

Allergenic effects

Sensitizing effects on the skin

In a maximization test with albino guinea pigs (no other details), intradermal and epicutaneous induction was carried out with 0.5% trichloroacetic acid in water or 5% trichloroacetic acid in olive oil. After the occlusive challenge treatment using 2% trichloroacetic acid in olive oil, slight to moderate erythema without infiltration was found in 7 of 12 animals. At the challenge, the control animals were apparently not treated with the test substance, but only with the vehicle. In addition, determination of the maximum non-irritant concentration was carried out in animals not pretreated with FCA (Tang et al. 2002). For this reason, the suitability of the test preparation used for the challenge is questionable.

A maximization test carried out according to OECD Test Guideline 406 (induction: intradermal with 1%, topical and challenge treatment: 10% trichloroacetic acid in ethanol) did not lead to reactions regarded as allergic or irritating in any of the 15 animals at the challenge (ECHA 2015 b).

A mouse ear swelling test in which 100 µl of a 10% preparation of trichloroacetic acid in 70% ethanol was applied to the ear of 10 CF-1 mice on four consecutive days likewise yielded negative results, as only an average ear thickness of 101% of the control value was determined at the challenge with 20 µl of the same preparation carried out after a 7-day interval. Treatment with oxazolone (5%; 0.1%), the positive control, produced a marked increase in ear thickness (134% of the control value) (ECHA 2015 b).

A Buehler test with 10 female and 10 male guinea pigs per group, in which three occlusive induction treatments were carried out for 6 hours once a week followed by challenge treatment after one week with 0.5 g undiluted sodium trichloroacetate, likewise yielded negative results (ECHA 2015 b).

Sensitizing effects on the airways

There are no data available.

Reproductive and developmental toxicity

Fertility

In vitro

Oocytes and sperms of B6D2F1 mice were treated in vitro with trichloroacetic acid concentrations of 0, 100, 250 or 1000 µl/l in the medium (0, 0.98, 2.4 or 9.8 mM) for 24 hours. The percentage of fertilized oocytes decreased from 82% to 77.3% after treatment in the 2.4 mM medium. At a concentration of 9.8 mM, only 53.1% were fertilized (Cosby and Dukelow 1992). It is not reported whether the trichloroacetic acid was neutralized.

In vivo

Total doses of 125, 250 or 500 mg trichloroacetic acid/kg body weight, distributed over five single injections, were administered intraperitoneally on five consecutive days to groups of 3 male Swiss mice. The sperms were prepared 35 days after the first injection. Sperm head abnormalities were increased at and above 125 mg/kg body weight, the lowest dose tested, and the increase was dose-dependent at 250 and 500 mg/kg body weight (Bhunya and Behera 1987).

Developmental toxicity

Only studies with gavage administration of neutralized trichloroacetic acid and sodium trichloroacetate and one study with drinking water administration in rats are available.

The studies of developmental toxicity are summarized in Table 7.

Tab. 7 Developmental toxicity studies after oral administration of trichloroacetic acid or sodium trichloroacetate

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 55 controls, 11 ♀ treated	**GD 1–22**, 0, 291 mg/kg body weight and day, TCA neutralized, **drinking water; examination on GD 22**	**291 mg/kg body weight**: dams: body weights ↓, number of resorptions per litter and in total ↑, number of implantations ↑, foetuses: number of foetuses with cardiac malformations ↑ (10.5% TCA-exposed, 2.15% controls) (3 atrial septal defects, one pulmonary valve stenosis, 4 perimembranous ventricular septal defects, one muscular ventricular septal defect, one hypoplasia of the aorta, 2 cases of hypoplasia of the pulmonary artery, one hypoplasia of the mitral valves), cardiac examination according to the method of Dawson et al. (1993)	Johnson et al. 1998
rat, Long Evans, 20–21 ♀	**GD 6–15**, 0, 330, 800, 1200, 1800 mg/kg body weight and day in distilled water, TCA neutralized, **gavage; examination on GD 20**	**330 mg/kg body weight and above**: dams: body weights ↓, slight, but significant increase in absolute spleen and kidney weights, foetuses: body weights ↓, body length ↓, urogenital and cardiovascular malformations (laevocardia) **800 mg/kg body weight and above**: dams: body weights ↓, number of absorbed litters ↑, foetuses: cardiovascular (ventricular septum defects), soft tissue and orbital malformations **1200 mg/kg body weight and above**: dams: number of living litters ↓, foetuses: orbital and skeletal malformations	Smith et al. 1989
rat, CD® / Crl: CD (SD), 20 ♀	**GD 6–19**, 0, 100, 300, 1000 mg/kg body weight and day in water, sodium trichloroacetate pH 7.2–7.6, **gavage; examination on GD 20**	**100 mg/kg body weight and above**: dams: food consumption (GD 7–8) ↓ by 7.3% (10.9% at 300 mg/kg body weight) without biological relevance, foetuses: body weights ↓, (at 0, 100, 300, 1000 mg/kg body weight: 3.6 ± 0.2; 3.4 ± 0.2; 3.3 ± 0.3; 2.8 ± 0.2 g per litter ± SD) for 100 and 300 mg/kg body weight by comparison: foetal weights in the historical laboratory controls: mean value (3.5 ± 0.2 g per litter ± SD) and range (3.2–4.0 g litter); variations and ossification delays within the ranges of historical controls **300 mg kg/body weight**: NOAEL for developmental toxicity and maternal toxicity; effects up to 300 mg/kg body weight without biological relevance **1000 mg/kg body weight**: dams: body weights ↓ by 2.7% and 2.6% on GD 7 and 8, food consumption ↓ on GD 6–12 (by 27.7% on GD 7), 6/20 enlarged spleen, foetuses: body weights ↓ (by 22.2%), number of foetuses or litters with delayed ossification of metatarsals, ischium and pubic bone and the thoracic or caudal vertebrae ↑; number of foetuses or litters with dilated cerebral ventricles (variation) ↑ no heart, soft tissue or skeletal malformations	CABB GmbH 2014
rat, Sprague Dawley, 19 ♀, 12 ♀ positive control (all-trans retinoic acid)	**GD 6–15**, 0, 300 mg/kg body weight and day in water, TCA neutralized, **gavage; examination on GD 21**	only heart examined dams: body weights ↓, uterus weights ↓, foetuses: body weights ↓ by 8%–9%, **no cardiac malformations** cardiac examination according to the method of Dawson et al. (1993)	Fisher et al. 2001
rat, Sprague Dawley Crl:CDR (SD) BR, 18–21 ♀ positive control (all-trans retinoic acid)	**GD 6–15**, 0, 300 mg/kg body weight and day in water, TCA neutralized, **gavage; examination on GD 21**	only eyes examined **300 mg/kg body weight**: foetuses: body weights ↓, no effects in the eyes	Warren et al. 2006

Tab. 7 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Inbred Charles Foster, 6–12 ♀	**GD 6–15,** 0, 1000, 1200, 1400, 1600, 1800 mg/kg body weight and day in distilled water, TCA neutralized **gavage; examination on GD 19**	only testes, ovaries and brain examined **1000 mg/kg body weight and above**: dams: postimplantation losses ↑, foetuses: body weights ↓, brain weights ↓, apoptotic cells in the brain ↑, vacuolation in the neuropil of the brain ↑, number of hydrocephali ↑ **1200 mg/kg body weight and above**: dams: body weights ↓, foetuses: body weights ↓, decrease in diameter of seminal vesicles, apoptosis of gonocytes and Sertoli cells ↑, haemorrhage in the brain ↑ **1400 mg/kg body weight and above**: foetuses: ovarian weights ↓, number of oocytes and ovaries ↓	Singh 2005 a, b, 2006

GD: gestation day; SD: standard deviation; TCA: trichloroacetic acid

At the only dose tested of 291 mg/kg body weight and day (2730 mg neutralized trichloroacetic acid/l drinking water) and the lowest dose tested of 330 mg/kg body weight and day (gavage), reduced body weights and in particular cardiovascular malformations (see Table 7) were found in the foetuses (Johnson et al. 1998; Smith et al. 1989).

These effects on the heart were not observed after gavage administration in two other studies with doses of 300 mg/kg body weight and day (CABB GmbH 2014; Fisher et al. 2001).

In a developmental toxicity study carried out according to OECD Test Guideline 414 with gavage administration of 0, 100, 300, 1000 mg sodium trichloroacetate/kg body weight and day to Sprague Dawley rats, the body weights of the foetuses were reduced and the number of foetuses or litters with delayed ossification and dilated cerebral ventricles (variation) were increased at 1000 mg/kg body weight and day. In the dams, food consumption and body weights were decreased several days after starting treatment. The decrease in foetal weights and the number of foetuses or litters with variations or ossification delays found at 100 and 300 mg/kg body weight and day were within the range of the historical controls of the investigating laboratory and were not considered adverse. The reduction in food consumption of the dams by a maximum of 7.3% and 10.9% at 100 and 300 mg/kg body weight and day, respectively, on gestation days 7 and 8 was slight and regarded as not biologically relevant. A NOAEL of 300 mg sodium trichloroacetate/kg body weight and day was derived for developmental toxicity and maternal toxicity. No cardiac, soft tissue or skeletal malformations were found, thus indicating the absence of teratogenicity (CABB GmbH 2014).

In the study by Johnson et al. (1998), a detailed method for heart examination according to Dawson et al. (1993) was used. In the study by Fisher et al. (2001), no cardiac malformations were found using this method after gavage administration of 300 mg neutralized trichloroacetic acid/kg body weight and day. Likewise, no such malformations were observed after 300 mg sodium trichloroacetate/kg body weight and day in the study by CABB GmbH (2014) which was carried out according to OECD Test Guideline 414 without going into particular detail in the heart examination.

After gavage administration of 300 mg neutralized trichloroacetic acid/kg body weight and day to rats, the development of the eyes was not affected. Other dose levels or organs were not investigated (Warren et al. 2006).

Genotoxicity

In the tables of the IARC (2013) evaluation, the studies of genotoxicity are given in detail; a description of the large number of individual studies is therefore not included here. When evaluating the studies of genotoxicity, the cytotoxicity and the acidity of trichloroacetic acid must be taken into account. Especially in the in vitro studies, protein precipitation can occur if the acid is not neutralized.

In vitro

Trichloroacetic acid was found to be not mutagenic in all Salmonella strains both with and without the addition of metabolic activation. DNA strand breaks in hamster ovary cells (Plewa et al. 2002), in hepatocytes of B6C3F1 mice and F344 rats (neutralized) (Chang et al. 1992) and in human CCRF-CEM lymphoblasts (neutralized) (Chang et al. 1992) were not increased without metabolic activation (with metabolic activation was not tested).

A test for chromosomal aberrations in human lymphocytes with and without the addition of metabolic activation yielded negative results at concentrations between 1.6 and 5000 µg/l (neutralized) (Mackay et al. 1995).

In an HPRT (hypoxanthine-guanine phosphoribosyl transferase) gene mutation test with CHO (Chinese hamster ovary) cells (1630 µM) without metabolic activation (with metabolic activation was not tested), no increase in mutations could be found (Zhang et al. 2010). Furthermore, only a non-dose-dependent increase in mutation frequency (doubling to tripling at concentrations at which more than 10% of the cells survived) (not neutralized) was found in the $TK^{+/-}$-mutation test with L5178Y mouse lymphoma cells with and without the addition of metabolic activation (Harrington-Brock et al. 1998). A statistical analysis was not carried out. The mutation frequency increased with increasing cytotoxicity.

In vivo

DNA strand breaks

After single oral doses of trichloroacetic acid of 0.6 mmol/kg body weight (94.8 mg/kg body weight) and above were given to groups of 5 male Sprague Dawley rats or 0.006 mmol/kg body weight (1 mg/kg body weight) and above to groups of 5 male B6C3F1 mice, an increase in single strand breaks in the liver was detected after four hours using the alkaline elution assay (Nelson and Bull 1988). The effects were dose-dependent. No evidence of hepatotoxicity was found, as the activities of aspartate and alanine aminotransferase in the serum were not increased.

In another experiment using the same method, an increased incidence of single strand breaks was detected between one and four hours after treatment in the liver DNA of 5 to 6 male B6C3F1 mice after a single oral trichloroacetic acid dose of 500 mg/kg body weight (in 1% Tween 80). The values returned to the control level after 8 hours. At this early stage, peroxisome proliferation was not detectable. After 10-day oral administration of 500 mg trichloroacetic acid/kg body weight (in 1% Tween 80), peroxisome proliferation and the relative liver weights were significantly increased, whereas single strand breaks were no longer increased (Nelson et al. 1989).

Groups of 7 B6C3F1 mice were given gavage doses of trichloroacetic acid (neutralized) of 0, 7.7, 77, 154 or 410 mg/kg body weight for 4 or 13 weeks. The formation of superoxide anions, lipid peroxidation and DNA single strand breaks was investigated in the liver. After exposure for both 4 and 13 weeks, an increase in single DNA strand breaks was found at 77 mg/kg body weight and above. Lipid peroxidation increased slightly after 4-week administration of 77 mg/kg body weight and above. The effect was considerably more pronounced and statistically significant at 77 mg/kg body weight and above after 13-week administration. The superoxide anion concentration after 4-week administration was only markedly increased at 154 mg/kg body weight and above, and after 13-week administration at 77 mg/kg body weight and above. The liver weight was unaffected (Hassoun et al. 2010).

In contrast, in another study a dose-dependent induction of DNA single strand breaks in the liver of B6C3F1 mice could not be found one or four hours after far higher single oral trichloroacetic acid doses of 1, 5 or 10 mmol/kg body weight (163, 817, 1634 mg/kg body weight) (neutralized). In addition, the induction of single strand breaks was not found in epithelial cells from the stomach and duodenum. However, the amount of double strand DNA was significantly reduced after 4 hours at the high dose compared with that in the controls. Analogous experiments with F344 rats yielded negative results (Chang et al. 1992).

Male B6C3F1 mice received 1, 2 or 3 daily doses of 500 mg/kg body weight and day of neutralized trichloroacetic acid solution (sodium salt); they were killed one hour after the final dose. Some mice were given a single dose of 500 mg/

kg body weight and were killed 24 hours thereafter. No increase in single strand breaks in the liver DNA was found (Styles et al. 1991).

Micronuclei and chromosomal aberrations

Groups of 3 Swiss mice were given intraperitoneal or oral trichloroacetic acid doses of 0, 125, 250 or 500 mg/kg body weight. There was an increase in the number of chromosomal aberrations (chromatid breaks and gaps, chromosome breaks) in the bone marrow after 24 hours both after intraperitoneal and oral administration, which was, however, not dose-dependent. In the micronucleus test, the animals received the same intraperitoneal dose twice at an interval of 24 hours. The bone marrow of the animals was examined 6 hours after the second injection. At the lowest dose tested of 125 mg/kg body weight and above, the incidence of polychromatic erythrocytes and micronuclei was significantly increased compared with that in the controls, but not in a clearly dose-dependent manner (Bhunya and Behera 1987). Only three animals per group were used. Data for cytotoxicity (ratio between PCE and NCE) and neutralization are not available. The quality of the presentation of metaphases is very inadequate. Overall, due to the shortcomings described, the study is not suitable to demonstrate whether trichloroacetic acid has genotoxic effects.

Neutralized trichloroacetic acid was administered intraperitoneally twice at an interval of 24 hours to groups of 10 male and female C57BL/6JBL10/Alpk mice in doses of 0, 337, 675 or 1080 mg/kg body weight (male) and 0, 405, 810 or 1620 mg/kg body weight (female). Trichloroacetic acid was not found to induce micronuclei (Mackay et al. 1995).

Sperm morphology test

Groups of 3 male mice, were given total intraperitoneal doses of 0, 125, 250 or 500 mg trichloroacetic acid/kg body weight distributed over five single injections on 5 consecutive days. The sperms were prepared 35 days after the first injection. Sperm head abnormalities were increased at 125 mg trichloroacetic acid/kg body weight and above, and in a dose-dependent manner at 250 mg/kg body weight and above (Bhunya and Behera 1987). Changes in sperm morphology are not reliable indicators of mutagenic activity and the relevance of effects with regard to germ cell mutagenicity is doubtful (ICPEMC 1983; Salamone 1988; Wild 1984); the results can be interpreted only as a cytotoxic effect.

Summary

In studies with neutralized acid, trichloroacetic acid was not mutagenic or clastogenic in vitro. No in vivo data for the induction of gene mutations are available. In mice, single DNA strand breaks were found in a test with neutralized acid together with the dose-dependent induction of lipid peroxidation in the liver. However, in other tests at higher doses, no increase in single DNA strand breaks was found. In an in vivo micronucleus test, trichloroacetic acid was found to be neither clastogenic nor aneugenic. Due to methodological shortcomings, a second study of the induction of chromosomal aberrations or micronuclei in vivo is not included in the evaluation. All in all, trichloroacetic acid is not regarded as genotoxic.

Carcinogenicity

Short-term studies

Initiation–promotion studies

The available initiation–promotion studies are shown in Table 8.

Tab. 8 Preneoplastic and neoplastic liver lesions in initiation–promotion studies with neutralized trichloroacetic acid (TCA)

Author:	Parnell et al. 1986	
Substance:	TCA (purity > 99%), neutralized	
Species:	**rat**, Sprague Dawley, 4–6 ♂ per group	
Administration route:	drinking water	
Concentration:	initiation study: group A: initiation: partial hepatectomy, 10 mg DEN/kg body weight (gavage), 1, 10, 20 and 30 days group B: initiation: partial hepatectomy, 1500 mg TCA/kg body weight (gavage) single, or 5000 mg TCA/l (about 600 mg/kg body weight[a]), 10, 20 and 30 days promotion after 2 weeks: 500 mg phenobarbital/l or 50, 500, 5000 mg TCA/l (about 4.5, 45, 450 mg/kg body weight[b])	
Duration:	promotion: 3 and 6 months	
Toxicity:	no effects on body and liver weights	
Exposure [mg/kg body weight]	number of GGT-positive foci/cm^2	
	3 months	6 months
Initiation study		
PH/DEN/PB	2.05 ± 0.18	9.93 ± 0.71
PH/one day TCA/PB	0.05 ± 0.18	0.32 ± 0.71
PH/10 days TCA/PB	0.08 ± 0.18	0.28 ± 0.71
PH/20 days TCA/PB	0.07 ± 0.18	0.30 ± 0.71
PH/30 days TCA/PB	0.06 ± 0.18	0.33 ± 0.71
30 days TCA/PB	0.10 ± 0.18	0.49 ± 0.71
PH/PB	0.07 ± 0.22	0.14 ± 0.86
Promotion study[c]		
PH/DEN/PB	1.65 ± 0.23	7.61 ± 0.72
PH/DEN/4.5 TCA	0.71 ± 1.16*	1.83 ± 0.32*
PH/DEN/45 TCA	0.39 ± 0.16	1.63 ± 0.32*
PH/DEN/450 TCA	0.70 ± 0.16*	2.45 ± 0.32*
450 TCA	0.23 ± 0.16	0.03 ± 0.32
PH	0.23 ± 0.20	0.41 ± 0.39
PH/DEN	0.05 ± 0.20	0.30 ± 0.39
Author:	Herren-Freund et al. 1987	
Substance:	TCA (purity > 99%), neutralized	
Species:	**mouse**, B6C3F1, 22–33 ♂ per group	
Administration route:	drinking water	
Concentration:	controls: 2000 mg NaCl/l; 5000 mg TCA/l (625 mg/kg body weight) initiation: single doses of 2.5 or 10 mg ENU/kg body weight (intraperitoneal) promotion: 0, 2000, 5000 mg TCA/l (about 0, 250, 625 mg/kg body weight and day; calculation using the data from DeAngelo et al. (2008); pH 6.5–7.5)	
Duration:	promotion: 61 weeks	
Toxicity:	body and absolute kidney weights ↓, liver weights ↑	

*$p < 0.05$; DEN: diethylnitrosamine; GGT: gamma-glutamyl transpeptidase; PB: phenobarbital; PH: partial hepatectomy
[a] conversion factor for subacute studies 0.12 according to EFSA (2012)
[b] conversion factor for subchronic studies 0.09 according to EFSA (2012)
[c] for controls PH/4.5 TCA; PH/45 TCA; PH/450 TCA no data

Tab. 8 *(continued)*

Exposure [mg/kg body weight]	animals with hepatocellular adenomas	animals with hepatocellular carcinomas
NaCl control	2/22 (9%)	0
2.5 ENU control	1/22 (5%)	1/22 (5%)
10 ENU control	9/23 (39%)	9/23 (39%)
625 TCA[d)]	8/22 (36%)*	7/22 (32%)*
2.5 ENU + 250 TCA	11/33 (33%)*	16/33 (48%)*
2.5 ENU + 625 TCA	6/23 (26%)*	11/23 (48%)*
10 ENU + 250 TCA	11/28 (39%)	15/28 (54%)

*$p < 0.01$ (compared with the NaCl controls); ENU: ethylnitrosourea
[d)] no data for control value 250 mg ENU per kg body weight

Author:	Pereira et al. 1997
Substance:	TCA
Species:	**mouse**, B6C3F1, 20–30 ♀ per group
Administration route:	drinking water
Concentration:	initiation: 25 mg MNH/kg body weight intraperitoneal (single) promotion: 6, 25 mmol/l (about 115, 480 mg/kg body weight and day; calculation using the data from DeAngelo et al. (2008); pH 6.5–7.5)
Duration:	promotion: 44 weeks
Toxicity:	body weights after 7 months reduced by less than 10%

Exposure [mg/kg body weight]	foci/mouse	adenomas/mouse	lesions/mouse	carcinomas
MNH control	0.21 ± 0.09	0.07 ± 0.05	0.28 ± 0.1	none
MNH + 115 mg TCA/kg body weight	0.20 ± 0.09	0.15 ± 0.08	0.35 ± 0.11	none
MNH + 480 mg TCA/kg body weight	0.31 ± 0.11	0.52 ± 0.11	0.82 ± 0.21*	4/30

*statistically significant compared with controls; MNH: *N*-methyl-*N*-nitrosourea

The initiating and promoting properties of trichloroacetic acid were investigated in a short-term carcinogenicity test with male Sprague Dawley rats. Twenty-four hours following the removal of two-thirds of the liver, the animals received either a single oral dose of 1500 mg/kg body weight or 5000 mg trichloroacetic acid/l in the drinking water for 10, 20 or 30 days (about 600 mg/kg body weight, conversion factor for subacute studies 0.12 according to EFSA (2012)). Two weeks after termination of the treatment, the animals received 500 mg phenobarbital/l drinking water as a promoter for 3 or 6 months. Trichloroacetic acid was not initiating, as it did not induce gamma-glutamyl transpeptidase (GGT)-positive foci in the rat liver. In another study after a two-thirds hepatectomy, male Sprague Dawley rats (6 animals per group) were given a single oral dose of 10 mg/kg body weight of the initiator diethylnitrosamine after which they were treated with 50, 500 or 5000 mg trichloroacetic acid/l drinking water (about 4.5, 45 or 450 mg/kg body weight, conversion factor for subchronic studies 0.09 according to EFSA (2012)) for 3 or 6 months. In all dose groups, there was a significant increase in GGT-positive foci in the rat liver after 6 months. At the same time, a slight stimulation (10%–20% above the control level) of peroxisome proliferation was observed in the high dose group. Hepatomegaly was not found. In the authors' opinion, trichloroacetic acid seems to have weak promoting properties and is therefore possibly a weak, epigenetic carcinogen (Parnell et al. 1986, 1988).

In another initiation–promotion study in male mice, trichloroacetic acid was carcinogenic in the liver (Herren-Freund et al. 1987) after the administration of 5000 mg trichloroacetic acid/l (the only concentration tested) (about 625 mg/kg body weight and day, as calculated using the data from DeAngelo et al. (2008)).

After initiation with *N*-methyl-*N*-nitrosourea and promotion with 25 mmol trichloroacetic acid/l drinking water (about 480 mg trichloroacetic acid/kg body weight, as calculated using the data from DeAngelo et al. (2008)), the number of foci, liver adenomas and lesions in the liver per female mouse were increased. Thus, also in another initiation–promotion study, the tumour-promoting effect of trichloroacetic acid in the liver was confirmed (Pereira et al. 1997).

Long-term studies

The results of carcinogenicity studies are given in Table 9.

Tab. 9 Studies of the carcinogenicity of trichloroacetic acid (TCA)

Author:	DeAngelo et al. 1997				
Substance:	TCA (purity > 99%), neutralized				
Species:	**rat**, F344/N, 50 ♂ per group; of these 30 for 104 weeks				
Administration route:	drinking water				
Concentration:	0 (2000 mg NaCl/l), 50, 500, 5000 mg/l (0, 3.6, 32.5, 364 mg/kg body weight and day)				
Duration:	104 weeks (interim killing: after 15, 30, 45, 60 weeks; 5/group)				
Toxicity:	significant decrease in body weights, relative liver weights ↓				
	Dose [mg/kg body weight and day]				
	0	3.6	32.5	364	
survivors after 80–104 weeks	23/30	24/30	19/30	22/30	
Liver:					
hyperplastic nodules	1/23 (4.4%)	1/24 (4.2%)	2/19 (10%)	0/22	
adenomas	1/23 (4.4%)	1/24 (4.2%)	3/19 (15%)	1/22 (4.6%)	
carcinomas	0/23	0/24	0/19	1/22 (4.6%)	
Author:	DeAngelo et al. 2008				
Substance:	TCA (purity > 99%), neutralized				
Species:	**mouse,** B6C3F1 ♂				
Administration route:	drinking water				
Concentration:	**1st study:** 0 (2000 mg NaCl/l), 50, 500, 5000 mg/l (8, 68, 602 mg/kg body weight and day) **2nd study:** 1500 mg/l neutralized acetic acid (57 animals); 4500 mg TCA/l (572 mg/kg body weight) **3rd study:** 0 (deionized water), 50, 500 mg TCA/l (6, 81 mg/kg body weight)				
Duration:	**1st study**: 60 weeks, interim killing after 4, 15, 31, 45 weeks, 5 animals/group, 60 weeks: 30 animals **2nd study**: 104 weeks, interim killing after 15, 30, 45, 60, 75, 90 weeks; 5/group **3rd study**: 104 weeks, interim killing after 26, 52, 78 weeks; 8/group				
Toxicity:	see Table 6				
	Dose [mg/kg body weight and day]				
1st study	0 (2000 mg NaCl/l)	8	68	602	
survivors after 60 weeks	30/30	27/30	29/30	29/30	
Liver:					
large foci with cellular alterations	0/30	0/27	0/29	7/29 (24%)**	
adenomas	2/30 (7%)	4/27 (15%)	6/29 (21%)	11/29 (38%)**	$p \leq 0.01$; trend test
carcinomas	2/30 (7%)	1/27 (4%)	6/29 (21%)	11/29 (38%)**	$p \leq 0.01$; trend test

Tab. 9 *(continued)*

2nd study	0 (1500 mg neutralized acetic acid/l)		572
survivors after 104 weeks	25/30		36/58
Liver:			
large foci with cellular alterations	0/25		1/36 (3%)
adenomas	0/25		21/36 (59%)**
carcinomas[a)]	3/25 (12%)		28/36 (78%)**
3rd study	0 (deionized water)	6	81
survivors after 104 weeks	42/57	35/58	37/58
Liver:			
large foci with cellular alterations	3/42 (7%)	10/35 (29%)*	11/37 (30%)**
adenomas	9/42 (21%)	8/35 (23%)	19/37 (51%)**
carcinomas[a)]	23/42 (55%)	14/35 (40%)	29/37 (78%)*
Author:	Bull et al. 1990		
Substance:	TCA (purity > 99%), neutralized		
Species:	**mouse**, B6C3F1, 5–35 ♂ per group, 10 ♀ per group		
Administration route:	drinking water		
Concentration:	♂: 0 (2000 mg NaCl/l), 1000, 2000 mg/l (about 125, 250 mg/kg body weight and day, calculation using the data from De Angelo et al. (2008)) ♀: 0 (2000 mg NaCl/l), 2000 mg/l (0, 250 mg/kg body weight and day)		
Duration:	♂: 15, 24, 37, 37 + 15 weeks recovery period, 52 weeks ♀: 52 weeks		
Toxicity:	at and above 125 mg/kg body weight: significant increase in liver weights, accumulation of lipofuscin, only liver and kidneys examined, no neoplastic lesions in the ♀, no data for survivors		

		Dose [mg/kg body weight and day]			
		0	125	250 (37 weeks)	250 (52 weeks)
Liver:					
proliferative lesions	♂	0/35	5/11 (45%)**	4/11 (36%)**	19/24 (79%)**
hepatocellular nodules	♂	1/35 (3%)	3/11 (27%)*	2/11 (18%)	10/24 (42%)**
adenomas	♂	0/35	2/11 (18%)	0/11	1/24 (4%)
carcinomas	♂	0/35	2/11 (18%)	3/11 (27%)*	4/24 (17%)*
Author:	Bull et al. 2002				
Substance:	TCA, neutralized				
Species:	**mouse**, B6C3F1, 20 ♂ per group				
Administration route:	drinking water				
Concentration:	0, 500, 2000 mg/l (about 62.5, 250 mg/kg body weight and day, calculation using the data from DeAngelo et al. (2008))				
Duration:	52 weeks				
Toxicity:	only liver examined				

Tab. 9 *(continued)*

		Dose [mg/kg body weight and day]		
		0	62.5	250
Liver:				
hepatocellular nodules	♂	0/20	1/20 (5%)	2/20 (10%)
adenomas	♂	0/20	5/20 (25%)*	6/20 (30%)**
carcinomas	♂	0/20	3/20 (15%)	3/20 (15%)
Author:		Pereira 1996		
Substance:		TCA, neutralized		
Species:		**mouse**, B6C3F1, 38–134 ♀ per group		
Administration route:		drinking water		
Concentration:		0 (NaCl), 2, 6.67, 20 mmol/l (327, 1090, 3270 mg/l) (about 40, 130, 400 mg/kg body weight and day; calculation using the data from DeAngelo et al. (2008)); pH 6.5–7.5		
Duration:		360, 576 days		
Toxicity:		400 mg/kg body weight: body weights ↓, dose-dependent increase in relative liver weights		

	Dose [mg/kg body weight]			
	0 (NaCl)	40	130	400
Tumours and preneoplasms (only liver examined):				
360 days				
foci of cellular alterations	0/40	3/40 (7.5%)	0/19	0/20
adenomas	1/40 (2.5%)	3/40 (7.5%)	3/19 (16%)	2/20 (10%)
carcinomas	0/40	0/40	0/19	5/20 (25%)**
576 days				
foci of cellular alterations	10/90 (11%)	10/53 (19%)	9/27 (33%)**	11/18 (61%)**
adenomas[b)]	2/90 (2%)	4/53 (8%)	3/27 (11%)	7/18 (39%)**
carcinomas[c)]	2/90 (2%)	0/53	5/27 (19%)**	5/18 (38%)**

*$p < 0.05$; **$p < 0.01$ (subsequently calculated according to Fisher's exact test)
[a)] hepatocellular carcinomas in historical controls: ♂ 36% (28%–48%) (NTP 2009; drinking water) or ♂ 38% (24%–52%) (NTP 2013; drinking water)
[b)] historical control: incidence 17.3%, range 2%–50% (Haseman et al. 1998)
[c)] historical control: incidence 8.4%, range 0%–20% (Haseman et al. 1998)

After the administration of trichloroacetic acid with the drinking water for 104 weeks, the incidence of liver tumours was not increased in the male rats up to the highest dose tested of 364 mg/kg body weight and day. In the high dose group, the body weights and relative liver weights were significantly decreased. In the middle dose group, no adverse effects were found in the animals, so that a NOAEL of 32.5 mg/kg body weight can be derived (DeAngelo et al. 1997).

The incidences of liver adenomas and carcinomas were increased in a dose-dependent manner in male mice at 68 mg/kg body weight and day and above after administration with the drinking water for 60 weeks and at 81 mg/kg body weight and day after 104 weeks (DeAngelo et al. 2008). In the female mouse, trichloroacetic acid was carcinogenic in the liver at 130 mg/kg body weight and above (Pereira 1996). No tumours were found in other organs. Liver tumours occur in the B6C3F1 mouse very frequently. At the lowest dose level tested of 6 mg/kg body weight, administered for 104 weeks, the liver tumour incidences were within the range of the study controls and within that of the historical control data of the NTP published in 2009 (NTP 2009) and 2013 (NTP 2013). For the male mouse, therefore, a dose level without carcinogenic effects of 6 mg/kg body weight and day can be given (DeAngelo et al. 2008; Table 9). Increased lipid peroxidation and peroxisome proliferation are regarded as responsible for the hepatocarcinogenic effects in the B6C3F1 mouse. As regards both of these end points, the mouse is markedly more sensitive than the rat. Further mechanisms under discussion are cell proliferation, DNA hypomethylation and the inhibition of intercellular communication. It can be assumed that a combination of these effects is responsible for the tumour induction in the B6C3F1

mouse, which is particularly sensitive to hepatocarcinogenic effects. At concentrations at which no lipid peroxidation and no peroxisome proliferation occurred, no tumours were found. As this mechanism of action in the formation of liver carcinomas has no relevance for humans, and the B6C3F1 mouse is in addition highly sensitive as regards the induction of liver tumours, the liver carcinomas in the mouse have no relevance for humans.

Manifesto (MAK value/classification)

Trichloroacetic acid is corrosive to the skin and eyes. Sodium trichloroacetate is a strong eye irritant. The target organ of systemic toxicity is the liver. Trichloroacetic acid or its anion is carcinogenic in the liver of male and female mice.

MAK value.

Systemic toxicity

No data are available for trichloroacetic acid or sodium trichloroacetate after repeated inhalation in humans or in animals.

Both for the acid and the sodium salt, the 2-year drinking water study with F344 rats is used to evaluate the systemic effects in the liver. From this study, a NOAEL of 32.5 mg/kg body weight can be derived for effects in the liver. The studies in mice are not used for the derivation of the MAK value due to the greater sensitivity of the mouse as regards effects in the liver compared with that of rats and humans.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 32.5 mg/kg body weight in F344 rats 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 toxicokinetic correction value (1:7) corresponding to the measured difference in the half-life between rats (7 hours) and humans (50 hours), the measured oral absorption (100%), 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 45 mg/m^3. According to the procedures of the Commission this would result in a MAK value of 20 mg/m^3, which includes the extrapolation of the data from experimental studies with animals and is in accordance with the preferred value approach. However, irritation of the respiratory tract is to be assumed at this value, as trichloroacetic acid is a strong acid.

Irritation

Trichloroacetic acid: For an evaluation of irritation, the MAK value for the likewise corrosive phosphoric acid of 2 mg/m^3 is used. Trichloroacetic acid has a higher acidity than phosphoric acid. In the eyes, phosphoric acid in the same dilution (24%) as trichloroacetic acid causes inflammation and swelling of the conjunctiva and corneal opacity lasting 7 days, whereas whitening of the cornea and coagulation occur with trichloroacetic acid. Trichloroacetic acid therefore does not have a considerably more pronounced effect in spite of its higher acidity. A 70% solution of phosphoric acid results in complete ocular destruction (ECHA 2016). Similar effects are also to be assumed for trichloroacetic acid at the same concentration.

For phosphoric acid, which causes strong local irritation, there are no data available for sensory irritation in humans. Initial effects in the lungs were found in the 90-day inhalation study with rats at a concentration of 135 mg aerosol/m^3, which is about 68 times the MAK value of phosphoric acid, and no effects were found in the nasal cavity. It is therefore to be assumed that no sensory irritation occurs at 2 mg/m^3. In analogy to phosphoric acid, the sensory irritation caused by trichloroacetic acid is expected to be similar.

As trichloroacetic acid can be present in vapour form at 2 mg/m^3 (vapour saturation at 500 mg/m^3 due to the vapour pressure), the limit value is given in ml/m^3. In order to account for the higher acidity and using the preferred value approach, a MAK value of 0.2 ml/m^3 (1.4 mg/m^3) has been established. This is markedly below the above calculated threshold limit value in air for systemic effects.

Sodium trichloroacetate: Sodium trichloroacetate is only slightly irritating to the skin. Strong eye irritation with corneal opacity, inflammation of the iris and conjunctival erythema was observed in rabbits. Severe eye irritation was caused by the application of 119 mg phosphoric acid and also after 100 mg sodium trichloroacetate. This means that also the salt, sodium trichloroacetate, causes equally as strong irritation to the eyes as phosphoric acid. As no data for a concentration without local irritation is available for sodium trichloroacetate, the MAK value has likewise been established at 2 mg/m^3 I (inhalable fraction) in analogy to that for phosphoric acid.

Peak limitation. As trichloroacetic acid and sodium trichloroacetate cause strong local irritation, they are both assigned to Peak Limitation Category I. Due to the greater acidity and higher solubility in water of trichloroacetic acid compared with phosphoric acid, an excursion factor of 1 has been set for both substances.

Prenatal toxicity. In developmental toxicity studies with drinking water and gavage administration of 291 and 330 mg neutralized trichloroacetic acid/kg body weight and day, respectively, the only and lowest dose tested, malformations of the heart occurred in rats. At these dose levels, slight maternal toxicity was observed (Johnson et al. 1998; Smith et al. 1989). In the study by Johnson et al. (1998) the detailed method of cardiac examination according to Dawson (Dawson et al. 1993) was used. With this method, no cardiac malformations were found after gavage administration of 300 mg neutralized trichloroacetic acid/kg body weight and day in the study by Fisher et al. (2001), nor at 300 mg sodium trichloroacetate/kg body weight and day in the study by CABB GmbH (2014). The latter was carried out in accordance with OECD Test Guideline 414 but without going into particular detail in the cardiac examination. At 1000 mg sodium trichloroacetate/kg body weight and day, the body weights of the foetuses were reduced, but no teratogenicity was observed (CABB GmbH 2014). Due to the cardiac effects found at 291 mg neutralized trichloroacetic acid/kg body weight and day, the only dose tested in the study by Johnson et al. (1998), the lowest tested dose of 100 mg/kg body weight and day from the study of CABB GmbH (2014) is used as the starting point for toxicokinetic extrapolation.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 100 mg/kg body weight and day in the rat to a concentration in workplace air: the toxicokinetic correction value (1:7) corresponding to the measured difference in the half-life between rats (7 hours) and humans (50 hours), the measured oral absorption of 100%, 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 100 mg/m^3. As the 50-fold difference between the calculated NAEC (no adverse effect concentration) and the MAK value of 2 mg/m^3 is sufficient for sodium trichloroacetate, and as the anion is responsible for the systemic effects, trichloroacetic acid and sodium trichloroacetate are assigned to Pregnancy Risk Group C.

Carcinogenicity. After drinking water administration, no increased incidence of liver tumours was found in male F344 rats up to the highest dose level tested of 364 mg/kg body weight. At 81 mg/kg body weight and above, after drinking water administration for 104 weeks, a dose-dependent, statistically significant increase in the incidence of liver adenomas and carcinomas was found in male B6C3F1 mice. At 68 mg/kg body weight and day, after administration for 60 weeks, the incidence of liver adenomas and carcinomas was three times as high as that in the control group (DeAngelo et al. 2008). In the female mouse, trichloroacetic acid was carcinogenic in the liver at a dose level of 130 mg/kg body weight and above. Liver tumours occur very frequently in the B6C3F1 mouse with a high spontaneous incidence. At the lowest dose tested of 6 mg/kg body weight, administered over 104 weeks, the liver tumour incidences were within the range of the controls and also within the range of historical control data of the NTP (NTP 2009, 2013). This means that the dose level of 6 mg/kg body weight can be assumed not to cause carcinogenic effects in male B6C3F1 mice. Among other factors, the pronounced lipid peroxidation and peroxisome proliferation are considered to be responsible for the hepatocarcinogenic effects in B6C3F1 mice. As regards both end points, the mouse is more sensitive than the rat. Further mechanisms under discussion are cell proliferation, DNA hypomethylation and the inhibition of intercellular communication. It can be assumed that a combination of these effects is responsible for hepatocarcinogenicity in the B6C3F1 mice which are susceptible to the induction of liver carcinomas. No tumours are found at concentrations at which no lipid peroxidation and no peroxisome proliferation occur. As this mechanism of action has no relevance for the formation of liver carcinomas in humans, and since the B6C3F1 mouse is highly sensitive as regards the induction of liver tumours, the liver carcinomas in the mouse are considered of no relevance for humans.

Trichloroacetic acid is not mutagenic in vitro; in vivo data are not available. In valid studies both in vitro and in vivo, trichloroacetic acid was shown not to be clastogenic. Trichloroacetic acid is not considered to be genotoxic. Liver carcinomas occur only in the B6C3F1 mouse, a strain with particular sensitivity and a high spontaneous incidence as regards this end point. In other organs and in the rat, no carcinogenicity was found. The increased liver tumour incidences in the B6C3F1 mouse and the liver toxicity are not used in the evaluation of the carcinogenicity in humans. The substance is therefore not classified in one of the categories for carcinogens.

Germ cell mutagenicity. In studies with neutralized acid, trichloroacetic acid is not mutagenic or clastogenic in vitro. Data for the induction of gene mutations in vivo are not available. In mice, DNA single strand breaks were found in a study with the neutralized acid with the simultaneous dose-dependent induction of lipid peroxidation in the liver; however, in further tests at higher doses, no increase in DNA single strand breaks was found. In vivo, no micronuclei were induced. Data for germ cells are not available. All in all, trichloroacetic acid is not considered to be genotoxic and has not been classified in one of the categories for germ cell mutagens.

Absorption through the skin. For humans, assuming the exposure of a 2000 cm^2 skin surface to a 0.5%, non-irritating, solution of trichloroacetic acid for one hour, dermal absorption of 6 mg trichloroacetate can be estimated from the data from an in vitro study (Xu et al. 2002). The extrapolation of the NOAEL of 32.5 mg/kg body weight obtained in a feeding study with rats after long-term oral administration, to a concentration in air for humans (see MAK value derivation for systemic toxicity) results in a systemically tolerable amount of 225 mg (45 mg/m^3/2 (extrapolation of the data for animals to humans) × 10 m^3). Absorption through the skin is thus less than 25% of the systemically tolerable amount. Trichloroacetic acid is therefore not 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 6 mg calculated above for 0.5% trichloroacetic acid, the uptake of 120 mg would be expected after linear extrapolation to a non-irritating 10% sodium trichloroacetate solution. For trichloroacetate, the same tolerable amount of 225 mg derived above applies. The absorption through the skin is therefore more than 25% of the systemically tolerable amount, so that sodium trichloroacetate is designated with an "H".

Sensitization. No clinical findings are available for contact sensitization. Contact sensitizing potential cannot be derived from the results of a questionably valid maximization test for either trichloroacetic acid or sodium trichloroacetate, as negative findings were obtained in another maximization test, a Buehler test and a mouse ear swelling test. Data for respiratory sensitization are not available. Trichloroacetic acid and sodium trichloroacetate have therefore not been designated with either "Sh" or with "Sa" (for substances which cause sensitization of the skin and airways).

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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