Social Europe

# Recommendation from the Scientific Committee on Occupational Exposure Limits for 1,2,3-trichloropropane

SCOEL/SUM/170

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European Commission

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| | |
|---|---|
| 8-hour TWA: | not assigned |
| STEL (15 min): | not assigned |
| Notation: | "skin" |
| BLV: | not assigned |
| SCOEL carcinogen group: | A (genotoxic carcinogen, no threshold) |
| Recommendation: | Occupational contact should be avoided |

Substance identification: 1,2,3-trichloropropane

Synonyms: allyl trichloride, glycerol trichlorohydrin, trichlorohydrin

Structural formula: Cl-$CH_2$-$CH_2$Cl-$CH_2$-Cl

CAS no.: 96-18-4
Molecular formula: $C_3H_5Cl_3$
Molecular weight: 147.44
Melting point: -14.7°C
Boiling point: 156.8°C
EU-Classification:

| | | |
|---|---|---|
| Carc. 1B | H350 | May cause cancer |
| Repr. 1B | H360F *** | May damage fertility |
| Acute Tox. 4 * | H332 | Harmful if inhaled |
| Acute Tox. 4 * | H312 | Harmful in contact with skin |
| Acute Tox. 4 * | H302 | Harmful if swallowed |

Conversion factor: 1 ppm = 6.12 mg/m$^3$; 1 mg/m$^3$ = 1.163 ppm

*Criteria documents used: This summary rests mainly on the documentations of IARC (1995) and DFG (1997). This was further supplemented by data from NTP (2002), WHO-CICAD (2003) and by a recent literature search conducted by SCOEL.*

# 1. Occurrence/use and occupational exposure

The compound is used as a chemical intermediate in the production of other organic chemicals, for instance polysulfone liquid polymers, dichloropropene and hexafluoropropylene, and as a cross-linking agent in the synthesis of polysulfides (IARC 1995, NTP 2002). The manufacturing processes generally occur in closed systems. Occupational exposures are therefore much limited. In principle, such exposures result from inhalation and dermal contact (IARC 1995).

# 2. Health significance

1,2,3-Trichloropropane is mutagenic and causes chromosomal damage *in vitro* after metabolic activation. In long-term animal studies, 1,2,3-trichloropropane was clearly carcinogenic after oral administration to rats and mice.

## 2.1. Toxicokinetics

### 2.1.1. Human data (IARC 1995)

An *in vitro* study of the metabolism of 1,2,3-trichloropropane by human and rat liver microsomes demonstrated that the substance is metabolized to 1,3-dichloroacetone, a direct mutagen. 1,3-Dichloroacetone formation was NADPH-dependent and occurred at a rate of 0.026 ± 0.006 and 0.268 ± 0.029 nmol/min/mg protein in incubations of 1 mM 1,2,3-trichloropropane with human liver microsomes and rat liver microsomes, respectively. If the rats were pretreated with phenobarbital or dexamethasone, the rate of 1,3-dichloroacetone formation was increased by a factor of 24 or 2.5, respectively. However, if the animals were treated with beta-naphthoflavone, the amount of 1,3-dichloroacetone formed was reduced by 50 %. After pretreatment of the rats with the cytochrome P450 inhibitors SKF 525-A or 1-aminobenzotriazole, 85 % and 70 % inhibition of 1,3-dichloroacetone formation was observed. If the incubations were carried out in the presence of N-acetylcysteine, conjugation of the 1,3-dichloroacetone to form 1,3-(2-propanone)bis-S-(N-acetylcysteine) was demonstrated (Weber and Sipes 1992).

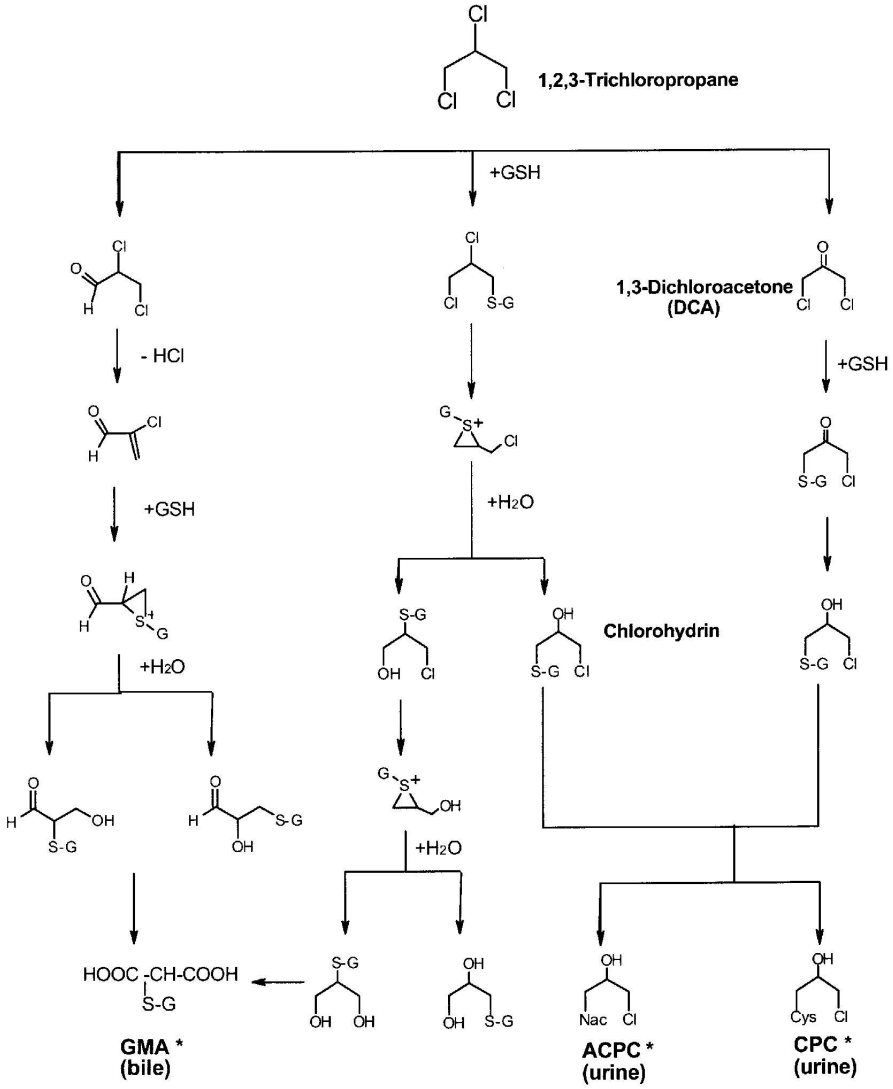
### 2.1.2. Animal data

The main metabolite identified in the urine of F344 rats given an oral dose of radioactively labelled 1,2,3-trichloropropane (30 mg/kg body weight) was N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine. This metabolite accounted for 40 % of the radioactivity found in the urine of male rats after a 6-hour collection period. In the 24-hour urine of male rats, another metabolite was identified, S-(3-chloro-2-hydroxypropyl)-L-cysteine. After intravenous injection of 1,2,3-trichloropropane, 2-(S-glutathionyl)malonic acid was excreted in the bile. The metabolite profile in the urine of female rats was like that in the males but the metabolites were present at lower levels. The metabolite profile in the urine of male mice (female mice were not studied) was different from that in rats: N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine, excreted together with diverse unidentified metabolites, accounted for only 3 % of the radioactivity recovered in the 6-hour urine (Mahmood et al. 1991).

After oral administration of radioactively labelled 1,2,3-trichloropropane (30 mg/kg body weight) to F344 rats and B6C3F$_1$ mice by gavage, most of the administered radioactivity was excreted in the urine. The elimination was rapid; after 24 hours more

than half and after 60 hours more than 90 % of the administered radioactivity had been eliminated via the urine, faeces and exhaled $CO_2$. During the 60-hour collection period, rats (3 male and 3 female) and mice (3 male) excreted 50 % to 57 % and 65 % of the administered radioactivity in the urine and 20 % and 15 %, respectively, in the faeces. In both species about 20 % of the administered radioactivity was exhaled as CO2 and less than 2 % as the unchanged substance. No differences were seen in the excretion patterns of male and female rats. Mice exhaled significantly more $^{14}CO_2$ than rats within the first 24 to 36 hours after administration of the test substance; this indicates that the metabolism of 1,2,3-trichloropropane is more rapid in mice than in rats (Mahmood et al. 1991).

Based on the data of Mahmood et al. (1991), WHO-CICAD (2003) has summarized the metabolism of 1,2,3-trichloroprane as shown in *Figure 1*.




S-G *S*-glutathione
GSH reduced glutathione
* detected *in vivo*

Nac *N*-acetyl-L-cysteine
Cys L-cysteine

*Figure 1:* Metabolic pathways of 1,2,3-trichloropropane, accoring to the compilation of WHO-CICAD (2003). ACPC: N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine; CPC: S-(3-chloro-2-hydroxypropyl)-L-cysteine; GMA: 2-(-glutathionyl)malonic acid

#### 2.1.3 Biological monitoring

There is no published experience on biological monitoring of persons exposed to the compound.

### 2.2. Acute toxicity

#### 2.2.1. Human data

There are only very limited and old published toxicity data in humans. These are on irritation only (see 2.3).

#### 2.2.2. Animal data

The oral $LD_{50}$ of 1,2,3-trichloropropane in rats is reported to be 320 mg/kg bw, whereas its approximate lethal concentration after exposure by inhalation for 4 h is 1000 ppm (Kennedy and Graepel 1991). A similar $LD_{50}$ was observed in rats after dermal (DFG 1997) and oral administration, indicating that it is absorbed by these routes.

### 2.3. Irritation and corrosivity

#### 2.3.1. Human data

The irritant effects of 1,2,3-trichloropropane on human mucous membranes were investigated by exposing 6 male and 6 female test persons by inhalation. Most persons considered a 1,2,3-trichloropropane concentration of 613 mg/m$^3$ (100 ppm) to be irritating for the mucosa of the eyes and throat but not the nose (no other details; Silverman et al. 1946).

#### 2.3.2. Animal data (DFG 1997)

Occlusive application of 0.5 ml 1,2,3-trichloropropane to the intact or scarified dorsal skin of rabbits caused slight irritation. The average primary irritation index on intact skin was 1.63, on scarified skin 2.5 to a maximum of 8.0 (Albert 1982, Bio/dynamics Inc. 1985a). In two other studies after occlusive application for 24 hours, 1,2,3-trichloropropane was described as severely irritating (Clark 1977, McOmie and Barnes 1949).

Non-occlusive application of 2 ml aliquots of 1,2,3-trichloropropane to an area of 100 cm$^2$ of rabbit skin on each of 7 rabbits, 10 times within 15 days, resulted in erythema, scab and fissure formation and painful subdermal bleeding. One animal died with congestion in the lungs (McOmie and Barnes 1949).

Instillation of 0.1 ml 1,2,3-trichloropropane into the conjunctival sac of the rabbit eye caused moderate mucosal irritation. The findings, conjunctival irritation, clouding of the cornea and iris damage, were reversible within 7 days. The maximum total irritation index was 20.0 of 110.0 (Albert 1982, Bio/dynamics Inc. 1985b, Carpenter 1958, Clark 1977).

## 2.4. Sensitisation

In a Magnusson and Kligman maximisation test, 1,2,3-trichloropropane (92 %) was shown to be a "very slight sensitizer" in guinea pigs. After a 2-step induction treatment by intradermal injection of a 0.1 % solution of 1,2,3-trichloropropane in corn oil and one week later dermal occlusive application of 50 % 1,2,3-trichloropropane in corn oil for 48 hours, dermal provocation was carried out after an interval of two weeks by occlusive application of a 25 % solution of 1,2,3-trichloropropane for 24 hours. At the end of the 24-hour provocation time, a weak reaction was seen in one of ten tested males, a positive result was obtained in another male and in one of ten females; a weak reaction was also seen in one of five control males. Weak reactions were still seen in one male and one female after another 24 hours but were no longer visible after 48 hours (Clark 1977).

In contrast, in a study carried out with Guinea pigs according to the Buehler method, no sensitizing effects were seen with 97.5 % 1,2,3-trichloropropane. The induction treatment involved dermal occlusive application of 0.5 ml 1,2,3-trichloropropane to the depilated dorsal skin for 6 hours, three times at 1 week intervals. Provocation was carried out two weeks later, also by occlusive dermal application of 0.5 ml 1,2,3-trichloropropane per animal (Albert 1982).

Another study of the dermal sensitization potential of 1,2,3-trichloropropane according to the Buehler rnethod also found that the substance is not sensitizing. The Guinea pigs (n = 10) were treated 3 times weekly for 3 weeks by dermal occlusive application of 0.3 ml 1,2,3-trichloropropane for 6 hours to the shaved dorsal skin. Provocation was carried out 2 weeks later, also by dermal application of 0.3 ml of the substance (Bio/dynamics Inc. 1985c).

## 2.5. Repeated dose toxicity

### 2.5.1. Human data

No published data are available.

### 2.5.2. Animal data (evaluation of IARC 1995)

Groups of 10 male and female Sprague-Dawley rats were administered 1,2,3-trichloropropane (purity, 99.3%; 0.7% tetrachloropropane) in corn oil by gavage at doses of 0, 0.01, 0.05, 0.20 or 0.80 mmol/kg bw [0, 1.5, 7, 29 or 117 mg/kg bw] daily for 10 days, or 0, 0.01, 0.05, 0.10 or 0.40 mmol/kg bw [0, 1.5, 7, 14 or 60 mg/kg bw] daily for 90 days. The primary histological finding was cardiopathy associated with inflammation. Myocardial necrosis and degeneration occurred in a diffuse pattern, with marked eosinophilia at the highest dose after exposure for 10 days. A mild hepatotoxic response was noted in animals receiving the high dose in each study. Bile-duct hyperplasia was observed after exposure for 90 days at the highest dose (Merrick et al., 1991).

Groups of 20 male and female Fischer 344/N rats and B6C3F1 mice received 1,2,3-trichloropropane (purity, > 99%) in corn oil by gavage at doses of 8, 16, 32, 63, 125 or 250 mg/kg bw an five days per week for eight (interim sacrifice) or 17 weeks; groups of 30 animals of each sex served as controls. Rats receiving the highest dose that died during the first several weeks had severe multifocal, centrilobular hepatocellular necrosis. The necrosis was more extensive in female rats, and the necrosis seen in animals at 125 mg/kg bw was less extensive than that seen at 250 mg/kg bw. Rats that received the

high dose and died had severe nephrotoxicity with diffuse acute tubular necrosis in the outer stripe of the outer medulla. The nephrotoxicity seen at the time of the eight-week interim sacrifice in rats given 125 mg/kg bw was characterized by regenerative hyperplasia with karyomegaly. At the end of the study, chronic renal inflammation was also seen. Rats given 250 mg/kg bw had extensive necrosis of the olfactory and respiratory epithelium in the nose; these lesions were also seen at 125 mg/kg bw later in the study. Mice at the two highest doses had focal hepatocellular necrosis; those that died early while receiving the high dose also had necrosis, regeneration and hyperplasia of the bronchiolar epithelium. Minimal pulmonary changes were noted at the end of the study in the group receiving 125 mg/kg bw. At the time of the eight-week interim evaluation and at the end of the study, a number of mice receiving 250 mg/kg bw had minimal acanthosis and hyperkeratosis of the forestomach (NTP 1993).

Groups of 15 male and female CD rats were exposed by inhalation to 0, 5, 15 or 50 ppm (0, 30, 90 or 302 mg/m$^3$) 1,2,3-trichloropropane (purity, 98.9%) for 6 h per day, on five days per week for 13 weeks. Hepatocellular hypertrophy was observed in male rats at all doses. Dose-related focal peribronchial lymphoid hyperplasia was observed primarily in males and splenic extramedullary haematopoiesis only in females (Johannsen et al., 1988). A follow-up study with lower concentrations under similar conditions by the same authors was referenced by WHO-CICAD (2003). Trichloropropane was aministered by inhalation at concentrations of 0, 0.5 or 1.5 ppm (0, 3.1, 9.2 mg/m$^3$) for 13 weeks. Signs of sensory irritation of mucous membranes (increase of lacrimal discharge) were noted, even at the lowest concentration. However, histopathological examination of the nasal epithelium showed nho treatment-related effects at any concentration.

Groups of 10 male and female Sprague-Dawley rats were administered 1,2,3-trichloropropane (stated purity, 99%), solubilized with 0.5% Emulphor, in their drinking-water at concentrations of 0, 1, 10, 100 or 1000 mg/L for 13 weeks. Animals of each sex receiving the highest concentration showed mild changes, consisting of anisokaryosis, accentuated zonation and occasional fatty vacuolation of the liver; female rats also had biliary hyperplasia. In addition, mild cellular changes were seen in the kidneys and thyroids of animals at the highest dose. The activities of hepatic aminopyrine demethylase and aniline hydroxylase were increased in animals receiving the highest concentration (Villeneuve et al., 1985).

## 2.6. Genotoxicity

For details of the genotoxicity studies, see IARC (1995) and DFG (1997).

### 2.6.1. In vitro (see DFG 1997 for details)

*In vitro,* 1,2,3-trichloropropane was mutagenic in the *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 only with metabolic activation. In just one study in strain TA1535 was 1,2,3-trichloropropane also mutagenic without metabolic activation. In strain TA1538, no evidence of mutagenic properties of 1,2,3-trichloropropane was found, either with or without metabolic activation. The results demonstrate that 1,2,3-trichloropropane is a substance which, after metabolic activation, can cause both base pair substitution and frame shift mutation.

1,2,3-Trichloropropane was not mutagenic in the Ames test with S. *typhimurium* TA100 when reduced glutathione was added to the incubation mixture together with S9 mix. Similarly, addition of the cytochrome P450 inhibitor SKF 525-A reduced the mutagenic effect (no other details, published only as abstracts; Mahmood et al. 1988, 1990).

In the SOS chromotest with *Escherichia coli* strain PQ37, 1,2,3-trichloropropane was not genotoxic in concentrations up to about 1900 µg/ml (solubility limit) either with or without S9 mix (von der Hude *et al.* 1987).

*Saccharomyces cerevisiae* D7 was incubated with 1,2,3-trichloropropane in concentrations between 10 and 5000 µg/ml with and without S9 mix for 1 hour or with S9 mix for 4 hours. After incubation at 37°C with S9 mix for 1 or 4 hours, increased mitotic gene conversion was observed with 1,2,3-trichloropropane concentrations of 100 µg/ml or more or with 10 µg/ml or more, respectively. After incubation at room temperature for 1 hour without S9 mix, an increase in mitotic gene conversion was not observed (Dean and Brooks 1979).

Tested in eukaryotes in the thymidine kinase (TK) test in mouse lymphoma cells, 1,2,3-trichloropropane could be shown to have mutagenic properties only after metabolic activation.

In other *in vitro* studies, chromosomal damage was found in CHO cells (cell line from Chinese hamster ovary); positive results were obtained in an *in vitro* micronucleus test with metabolic activation. Also with metabolic activation, 1,2,3-trichloropropane increased the incidence of sister chromatid exchange (SCE) in V79 and in CHO cells. without metabolic activation there was no increase in SCE. Negative results were obtained in an alkaline elution assay for DNA damage in rat hepatocytes. 1,2,3-Trichloropropane did not induce unscheduled DNA synthesis (UDS) or chromosomal aberrations in rat hepatocytes.

### 2.6.2. In vivo - human data

No published data are available.

### 2.6.3. In vivo – animal data (DFG 1997)

*In vivo,* 1,2,3-trichloropropane was shown to bind to rat hepatocyte DNA. Pre-treatment of the animals with phenobarbital was shown to increase binding; pretreatment with the cytochrome P450 inhibitor SKF 525-A or with the GSH synthesis inhibitor buthionine sulfoximine, on the other hand, reduced the binding (Weber and Sipes 1990a).

A micronucleus test carried out *in vivo* in the mouse (bone marrow cells) yielded negative results. Administered to rats, 1,2,3-trichloropropane did not induce UDS in the hepatocytes. With alkaline elution, DNA damage was demonstrated in rat hepatocytes and kidney cells (DFG 1997).

A dominant lethal test with Sprague-Dawley rats yielded negative results. The 15 male rats were given 1,2,3-trichloropropane doses of 80 mg/kg body weight and day on 5 consecutive days by gavage. The 15 control animals were given just the vehicle (olive oil). At the end of the treatment period, each male was mated with one untreated female every week for 8 weeks. Autopsy of the females was carried out an day 13 or 14 of gestation. There was no evidence of dominant lethal effects. Histopathological examination of the testes of the treated males revealed no changes (Saito-Suzuki *et al.* 1982).

Exposure of rats to a 1,2,3-trichloropropane concentration of 800 mg/m$^3$ for 1 week in animal exposure chambers resulted in disturbance of hepatocyte mitosis: binuclear diploid and tetraploid hepatocytes were significantly reduced in treated animals, mononuclear tetraploid and octaploid cells showed a corresponding increase, and cells with a ploidy of 16n appeared (Belyaeva *et al.* 1974).

## 2.7. Carcinogenicity

### 2.7.1. Human data

There are no studies on carcinogenicity of 1,2,3-trichloropropane in humans.

### 2.7.2. Animal data (evaluation of IARC, 1995)

Groups of 60 male and 60 female B6C3F1 mice, six weeks of age, were administered 1,2,3-trichloropropane (purity > 99%) in corn oil by gavage at doses of 0 (vehicle control), 6, 20 or 60 mg/kg bw and five days per week for 104 weeks. Four to 19 mice per group were removed for histopathological evaluation at 15 months. Survival of treüted mice was significantly lower ($p < 0.001$) than that of vehicle controls; the numbers of survivors at the end of the experiment were: 42 control males and 41 control females and 18 males at the low dose and 13 females at the low dose; none of the animals at- the middle or high doses survived. Histopathological evaluation revealed increased incidences (life-table test or logistic regression analysis) of neoplasms of the forestomach, liver and Harderian gland in males and females and neoplasms of the oral mucosa and uterus in females. The incidence of focal hyperplasia of the forestomach epithelium was increased in treated mice, occurring in 8/52 control males, 29/51 at the low dose, 27/54 at the middle dose and 34/56 at the high dose; and in 10/50 control females, 15/50 at the low dose, 14/51 at the middle dose and 31/55 at the high dose (NTP 1993).

Groups of 60 male and 60 female Fischer 344/N rats, six weeks of age, were administered 1,2,3-trichloropropane (purity > 99%) in corn oil by gavage at doses of 0 (vehicle control), 3, 10 or 30 mg/kg bw an five days per week for up to 104 weeks. Eight to 10 rats per group were removed for histopathological evaluation at 15 months. Survival rates of rats that received 10 or 30 mg/kg were significantly lower ($p < 0.001$) than that of vehicle controls; the numbers of survivors at the end of the experiment were 34 control males, 32 at the low dose and 14 at the middle dose; and 31 control females, 30 at the low dose and 8 at the middle dose; none of the animals at the high dose survived. Histopathological evaluation revealed increased incidences (life-table test or logistic regression analysis) of neoplasms of the oral mucosa and forestomach in males and females, neoplasms of the pancreas, preputial gland and kidney in males, and neoplasms of the clitoral gland and mammary gland in females. The incidence of focal hyperplasia of the forestomach epithelium was increased in treated rats, occurring in 3/50 control males, 28/50 at the low dose, 13/49 at the middle dose and 6/52 at the high dose; and in 1/50 female controls, 25/49 at the low dose, 11/51 at the middle dose and 15/52 at the high dose. The incidence of focal hyperplasia of the renal tubular epithelium was increased in male rats receiving 10 or 30 mg/kg bw, being seen in 0/50 controls, 1/50 at the low dose, 21/49 at the middle dose and 29/52 at the high dose (NTP 1993).

*Metabolite carcinogenicity:* 1,3-Dichloroacetone, a metabolite of 1,2,3-trichloropropane, was tested for initiation in a two-stage mouse skin tumour model. 1,3-Dichloroacetone (purity > 99%) was applied topically in 0.2 ml ethanol to groups of 40 female SENCAR mice [age unspecified] at a dose of 0, 50, 75 or 100 mg/kg bw, three times a week for two weeks. Two weeks after the final application, 1.0 µg of 12-O-tetradecanoylphorbol 13-acetate (TPA) in 0.2 ml acetone was applied three times a week for 20 weeks. The numbers of animals with skin tumours at one year were: 23/199 vehicle controls, 12/25 at the low dose ($p < 0.02$; log rank test), 18/40 at the middle dose ($p < 0.02$) and 12/38 at the high dose ($p < 0.02$). In a second experiment, 1,3-dichloroacetone was given as a single application to groups of 30 female SENCAR mice at a dose of 0, 37.5, 75, 150 or 300 mg/kg bw, and TPA was applied as in the multiple-dose study. After 24 weeks, the numbers of

animals with skin tumours were: 23/199 vehicle controls, 14/30 at 37.5 mg/kg bw ($p < 0.02$), 14/30 at 75 mg/kg bw. ($p < 0.02$), 19/30 at 150 mg/kg bw ($p < 0.02$) and 4/20 at 300 mg/kg bw (IARC 1995).

### 2.7.3. Carcinogenic risk assessment

1,2,3-Trichloropropane had been found in tace amounts in drinking water in the U.S. Therefore, reference doses for non-cancer and cancer values were recently published to be 39 and 10-14 µg/kg per day, respectively. The estimate considered a genotoxic mode of action and a non-linear dose-response relationship (Tardiff and Carson 2010).

## 2.8. Reproductive toxicity

### 2.8.1. Human data

Data on reproductive toxicity in humans are not available.

### 2.8.2. Animal data (DFG 1997)

In a fertility study, groups of 10 male and 20 female Sprague-Dawley rats were exposed to 1,2,3-trichloropropane concentrations of 28.2 ± 1.2 or 92.0 ± 1.2 mg/m$^3$ (4.6 ± 0.2 or 15 ± 0.2 ml/m$^3$; concentrations determined by analysis), 6 hours daily an 5 days per week for 10 weeks before mating and then for a maximum of 40 days during mating. The females were also exposed daily until day 14 of gestation. The control animals were exposed to air in the exposure chamber (air control, 10 males and 10 females) or kept for the whole period in the animal house (untreated control, 10 males and 10 females). During the exposure period, body weight gain in the high concentration group was reduced relative to that in the air control group, sometimes significantly. One animal in the low concentration group and 4 in the high concentration group were killed in a moribund state because of mycoplasma infection. Yellow discoloration of the anogenital area was observed at the end of the exposure period in the female animals exposed to 1,2,3-trichloropropane. The pairing index for the female animals in the 92 mg/m$^3$ group, that is, the proportion of females successfully mated (vaginal plug, sperm detection or pregnancy), was significantly reduced relative to the air control value. However, the pairing index for the untreated control group was also significantly reduced relative to the air control value. The pairing index for the males, that is, the proportion of copulating males, was unusually low (30 % to 60 %) in all the groups. The fertility index for both sexes, litter sizes, and the sex ratio, survival index and body weight gain of the pups were in the range of the air control values. The average number of pups born dead was increased in the two groups exposed to 1,2,3-trichloropropane; this was accounted for by increased mortality in one litter in each concentration group. Histopathological examination of the reproductive organs of the F0 generation revealed no treatment-related changes (Bio/dynamics Inc. 1980, Johannsen et al. 1988).

In a subsequent fertility study, groups of 20 female and 10 male Sprague-Dawley rats were exposed under conditions like those in the above study but to 1,2,3-trichloropropane concentrations of 3.00 ± 0.06 or 9.01 ± 0.18 mg/m$^3$ (0.49 ± 0.01 or 1.47 0.03 ml/m$^3$; concentrations determined by analysis). No treatment-induced effects on pairing or fertility indices were observed, nor on litter and pup parameters. In the histopathological examination, no treatment-related changes in the reproductive organs were found (Johannsen *et al.* 1988).

After intraperitoneal administration of 1,2,3-trichloropropane dosen of 37 mg/kg body weight and day to pregnant Sprague-Dawley rats from day 1 to day 15 of gestation, autopsy an day 21 revealed maternal toxicity in the form of significant changes in organ weights (no other details). There were no signs of embryotoxicity, foetotoxicity or teratogenicity (Hardin et al. 1981).

Further reproduction and fertility studies on 1,2,3-trichloropropane were conducted at NIEHS, Research Triangle Park, NC, and reported by Chapin et al. (1997). The studies used Swiss CD-1 mice and the RACB (Reproductive Assessment by Continous Breeding) protocol. Details of this protocol were published by Chapin et al. (1997a). Data from previous Task 1 studies were used to set exposure concentrations for the Task 2 continuous cohabitation phase at 30, 60, and 120 mg/kg/day by gavage in corn oil.

In Task 2, two, two, one, arid two mice died in the control through high dose groups; three of these deaths were known to have been due to gavage error. There were no differences in body weights between control and treated F-0 mice, though mice in the middle and high dose groups did consume more water than controls by approximately 12 to 14%.

Fertility effects started manifesting at the third litter; by the last litter, the proportion of pairs delivering a litter was (control to high dose) 87, 78, 68, and 42% (the latter being significantly different from controls), respectively. Aggregate data for Task 2 showed at the high dose a 16% decrease in the number of litters per pair, 47% fewer pups per litter, although no change in pup viability or adjusted body weight. Also at the high dose, the days to delivery of the last two litters were increased by 6 and 4 days.
The last litter was reared by the dam until weaning and then begun on 1,2,3-trichloropropane exposure through mating at approximately postnatal day 74. Neither pup weight not viability was adversely affected by 1,2,3-trichloropropane exposure during the nursing period; in fact high dose F-1 pups weighed more than their controls, probably because of smaller litters.

The adverse effects on reproductive indices during Task 2 prompted an attempt to determine the affected sex using the control and high dose animals in the Task 3 crossover mating. Neither group containing a treated partner differed significantly from the controls in their ability to mate or deliver live offspring. Litter size, pup viability, and pup weight were not statistically different from controls, although litters from treated females averaged 5 pups per litter, while control litters and those from treated males averaged 9 to 10 pups per litter.

After crossover litters were evaluated and discarded, the control and high dose F-0 mice were killed and necropsied. While male body weight was not different between the two groups, adjusted liver weight was 20% greater in the treated males. Treated males also had approximately 19% more sperm per milligram *cauda epididymidis* than their controls; reproductive organ weights and other sperm indices did not differ between the groups. For females, body weights were not different, but the liver of treated females weighed approximately 22% more than control, while kidneys weighed approximately 9% less. The oestrous cycle did not differ in length or frequency of the various stages, although ovary weight was reduced in the treated females by approximately 20%. Four of 10 high dose-treated females had microscopic ovarian amyloidosis *versus* 0 of 10 controls. No other microscopic lesions were related to 1,2,3-trichloropropane exposure.

For the F-1 mating trial there were 20 mating pairs at all dose levels except the high dose, which had 9 because of the reduced litter sizes in Task 2. Only 3 of these 9 pairs delivered a litter with any pups. Though control litters averaged 10.8 pups and the high dose litters averaged 7.3 pups, the difference was not statistically significant, probably due to the low

number of litters at the high dose (3 litters). No other end points differed significantly from control for any dose group, including dam weight or days to deliver.
After the delivery of the F-2 litters, the F-1 adults were killed and necropsied. Male body weight was increased by 5 and 11% at the middle and high dose levels, respectively. Adjusted liver weight was increased at these dose levels by 9 and 28%, while adjusted kidney weight was increased at the high dose by 14%. Reproductive organs and sperm indices were unchanged. Female body weight was increased by 9% at both the middle and high dose levels, while adjusted liver weight was increased by 6 and 21%. Female kidney weights were unchanged. Ovary weights showed a monotonic reduction: ovary weight was 15 and 40% lower than controls in the middle arid high dose groups. Interestingly, oestrous cycle length was increased for all dose groups: from control to high dose, cycle length means were 4.66, 5.08, 5.18, and 5.06 days. There were no significant microscopic lesions noted in female organs.

In the interpretation of by the authors, this study found significant reproductive toxicity in Swiss CD-1 mice exposed to 1,2,3-trichloropropane. This was expressed in the first generation as fewer litters and fewer pups per litter, and in the second generation as fewer fertile matings and reduced ovary weight and lengthened oestrous cycles. The F1 ovary weight reduction and cycle increase occurred in the absence of a change in any measure of general toxicity or clinical signs. This was taken by the authors to suggest that 1,2,3-trichloropropane may be a selective female reproductive toxicant (Chapin et al. 1997).

## Recommendation

1,2,3-Trichloropropane is used in the chemical industry as an intermediate in the synthesis of a number of other chemicals. In general, it is handled in closed systems. In consequence, there is almost no published experience of toxicity in humans.

The compound is of only moderate toxicity, but it is converted in the mammalian organism into strongly genotoxic metabolites, such as 1,3-dichloroacetone.

Long-term animal carcinogenicity experiments have been conducted in mice and rats. 1,2,3-Trichloropropane produced tumours of the oral mucosa and of the uterus in female mice and increased the incidences of tumours of die forestomach, liver and Harderian gland in mice of each sex. In rats, increased incidences of tumours were observed in the preputial gland, kidney and pancreas of males, in the clitoral gland and mammary gland of females and in the oral cavity and forestomach of both males and females. Tumours were already induced by the lowest doses tested (oral doses of 3 mg/kg b.w. in rats or 6 mg/kg b.w. in mice). The metabolite, 1,3-dichloroacetone, initiated skin tumour development in mice when applied topically. According to the evaluation of IARC (1995), there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of 1,2,3-trichloropropane. The plausible mode of action of the carcinogenicity of 1,2,3-trichloropropane is genotoxicity of biological reactive metabolic intermediate(s).

*Hence, 1,2,3-trichloropropane is categorised into the SCOEL carcinogen group A as a genotoxic carcinogen to which a threshold cannot be assigned (Bolt and Huici-Montagud 2008). In consequence, it is not possible to derive a health-based OEL. There are no data on biological monitoring. Any occupational contact to the compound should be avoided.*

Data on oral and dermal LD-50 point to a significant potential of skin absorption (see 2.2.2). Therefore, a "skin" notation is assigned.

Methods for biological monitoring of the compound have not been published so far.

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