Annex 1

for evaluation of limit values for 1,2,3-trichloropropane at the workplace

Prepared by the European Chemicals Agency

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Preamble

The Commission, in view of the preparation of the proposals for amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD) and in line with the 2017 Commission Communication '*Safer and Healthier Work for All*' - *Modernisation of the EU Occupational Safety and Health Legislation and Policy*[1], asked the advice of RAC to assess the scientific relevance of occupational exposure limits

Therefore, the Commission made a request on 23 February 2022 to ECHA in accordance with the Service Level Agreement (SLA) (Ares(2022)711149), to evaluate, in accordance with Directive 2004/37/EC, the following substance: 1,2,3 trichloropropane (EC number 202-486-1).

In support of the Commission's request, ECHA has prepared a scientific report concerning occupational limit values at the workplace. This scientific report was made available at: Occupational exposure limits-Consultations on OEL recommendation on **19 October 2022** and interested parties were invited to submit comments by **19 December 2022**.

In the preparatory phase of making this report, a call for evidence was started on **02 May 2022** to invite interested parties to submit comments and evidence by **01 August 2022**.

The Committee for Risk Assessment (RAC) has developed its opinion based on the scientific report submitted by ECHA.

[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes

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List of abbreviations

Abbreviation	Definition
ACPC	*N*-acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine
ATSDR	The Agency for Toxic Substances and Disease Registry (USA)
BGV	Biological guidance value
BLV	Biological Limit Value
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMR	Benchmark response
bw	Body weight
CAD	Chemical Agents Directive 98/24/EC
CAS RN	CAS Registry number, a unique identifier that provides an unambiguous means to distinguish chemical substances or molecular structures when there are many possible systematic, generic, proprietary or otherwise trivial names.
CLP	Regulation EC No 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures (CLP Regulation)
CMD / CMRD	Carcinogens and Mutagens Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. The amendment of the CMD, Directive 2022/431/EU also brought reprotoxic substances within the scope of the directive, changing the original title on the protection of workers from the risks related to exposure to carcinogens or mutagens at work to the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD).
CMR	Carcinogens, Mutagens or substances toxic to Reproduction
CPC	*S*-(3-chloro-2-hydroxypropyl)-L-cysteine
Cys	L-cysteine
DBCP	1,2-dibromo-3-chloropropane
DCA	1,3-dichloroacetone
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
ERR	Exposure-risk relationship
EU	European Union
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act (USA)
GESTIS Substance Database	GEfahrSToffInformationsSystem (German information system for the safe handling of hazardous substances and other chemical substances at work) Substance Database
GC/FID	Gas Chromatography with flame-ionization detection
GC/MS	Gas chromatography–mass spectrometry
GLP	Good Laboratory Practice
GMA	2-(*S*-glutathionyl)malonic acid
GSH	Glutathione
IARC	International Agency for Research on Cancer (World Health Organization)
LOAEC	Lowest observed adverse effect concentration
LOAEL	Lowest observed adverse effect level
LOQ	Limit of quantification

Abbreviation	Definition
MoA	Mode of action
NAc	*N*-acetyl-L-cysteine
NICNAS	Australia National Industrial Chemicals Notification and Assessment Scheme
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OECD TG	OECD Test Guidelines for the testing of chemicals
OEL(s)	Occupational exposure limit(s)
OSHA	Occupational Safety and Health Administration (USA)
PCE	Polychromatic Erythrocytes
PPE	Personal protective equipment
RAC	Risk Assessment Committee (part of ECHA)
REACH	Regulation (EC) No 1907/2006 of the European Union concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
SCOEL	Scientific Committee on Occupational Exposure Limits (former committee of the European Commission)
STEL	Short term exposure limit
1,2,3-TCP	1,2,3-trichloropropane
TWA	Time-Weighted-Average
WHO	World Health Organization

Scope of the task and literature search

ECHA has been tasked by the European Commission to evaluate the exposure to 1,2,3-Trichloropropane (1,2,3-TCP) to assess the option of an airborne occupational exposure limit, other limit values (BLV/BGV) and notations.

This report is based on international assessments such as (ATSDR, 2021, OECD, 2004, SCOEL, 2011, WHO, 2003). A literature search of published papers from the last ten years completed the source of information (date of last literature search: October/2022).[2] Databases used were last accessed: October/2022.

ECHA evaluation and recommendation

1,2,3-Trichloropropane is a non-threshold carcinogen. Consequently, no health-based OEL can be identified and an exposure-risk relationship (ERR) expressing the excess risk for cancer (squamous cell papillomas/carcinomas) in function of air concentration is derived.

The tables below present the outcome of the scientific evaluation to derive limit values for 1,2,3-TCP.

Derived Limit Values

OEL as 8-hour TWA	None
STEL	None
BLV	None
BGV	None

Notations

Notations	Skin

Cancer Exposure-Risk Relationship*

1,2,3-TCP concentration in air (mg/m³)	1,2,3-TCP concentration in air (ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.0004	0.00008	4
0.004	0.0008	40
0.04	0.008	400
0.4	0.08	4000

* Based on total alimentary tract tumours, assuming exposure 8 hours per day and 5 days per week over a 40-year working life period.

RAC notes that, in the future, the European Commission and its relevant stakeholders will aim to set limit values for non-threshold substances between the predetermined “upper risk level” and the “lower risk level”. (ACSH, 2022) opinion agreed that the upper risk level is 4:1 000 (corresponding to 4 predicted cancer cases in 1 000 employees) and the lower

[2] All references are listed at the end of the report.

risk level is 4:100 000, assuming exposure over 8 hours per day, 5 days a week over a 40-year working life period.

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1. Chemical Agent Identification and Physico-Chemical Properties

As explained in the "Handbook of Pollution Prevention and Cleaner Production: Best Practices in the Agrochemical Industry"[3], "*1,2,3-Trichloropropane is a chlorinated hydrocarbon [...]. In its pure form, 1-2-3-TCP is a colorless to yellow liquid with limited solubility in water, a strong chloroform-like odor, moderate volatility, and high flammability.*"

Table 1: Chemical Identification

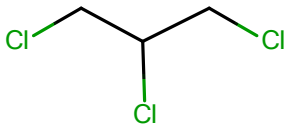
Identifier	
IUPAC Name	1,2,3-trichloropropane
Synonyms	Trichlorohydrin, allyl trichloride
EC/List No	202-486-1
CAS RN	96-18-4
Chemical structure	
Chemical formula	C3H5Cl3
Molecular weight	147.43 g/mol

Table 2: Physico-chemical properties[4]

Endpoint	Value
Appearance	Liquid (at 20°C and 1013 hPa)
Boiling point	157°C (at 1013 hPa)
Density	1.38 g/cm^3 (at 20°C)
Vapour pressure	6.65 hPa (at 32.84°C)
Partition coefficient (log Pow)	2.63 (at 25°C)
Water solubility	1 880 mg/L (at 20°C)
Viscosity	2.23 mPa.s (dynamic) (at 20°C)
Conversion factor	1 ppm = 6.13 mg/m^3 (at 20°C)[5] 1 mg/m^3 = 0.16 ppm (at 20°C)

[3] 5 -1,2,3-Trichloropropane (TCP). In: CHEREMISINOFF, N. P. & ROSENFELD, P. E. (eds.) Handbook of Pollution Prevention and Cleaner Production: Best Practices in the Agrochemical Industry. Oxford: William Andrew Publishing.

[4] Values obtained from registration data published on www.echa.europa.eu

[5] $concentration\left[\frac{mg}{m^3}\right] = 147.43\ \frac{g}{mol} \cdot \frac{1.013 \cdot 10^5 Pa \cdot 1m^3}{8.314 \cdot \frac{Pa \cdot m^3}{mol \cdot K} 293.15K} \cdot 10^{-3} \cdot concentration[ppm]$

2. EU Harmonised Classification and Labelling-CLP (EC) 1272/2008

Table 3: EU classification: Summary of existing classification

Index No	International chemical ID	EC No	CAS RN	Annex VI of CLP hazard class and category	Hazard statement code
602-062-00-X	1,2,3-trichloropropane	202-486-1	96-18-4	Acute Tox. 4 Acute Tox. 4 Acute Tox. 4 Carc. 1B Repr. 1B	H302 H312 H332 H350 H360F

3. Chemical Agent and Scope of Legislation-Regulated uses in the EU

3.1 Directive 98/24/EC and Directive 2004/37/EC

There is currently no binding or indicative occupational exposure limit value for 1,2,3-TCP under CAD or CMRD.

3.2 REACH Registrations

Table 4: REACH Registrations and tonnage

Substance		Tonnage (tonnes/annum)	
Name	EC number	Full registration	Intermediate use
1,2,3-trichloropropane	202-486-1	>1000 (~~45~~ registrants)	Dehydrohalogenation of 1,2,3-TCP as reactant to 2,3-dichloro-propene in closed systems

3.3 Authorised uses under Annex XIV of REACH

1,2,3-TCP is not currently listed in Annex XIV of REACH ("Authorisation List"). 1,2,3-TCP was added to the Candidate List of substances, on 20 June 2011, for possible inclusion in Annex XIV with a reference to carcinogenicity and reproductive toxicity (Article 57(a) and (c)) and pursuant to Article 59(8) of REACH.

3.4 Restricted uses under Annex XVII of REACH

1,2,3-TCP is not currently listed in Annex XVII of REACH.

3.5 Plant Protection Products Regulation (EC) No 1107/2009

There are no plant protection products authorised under Regulation (EC) No 1107/2009[6] which are based on or include 1,2,3-TCP.
1,2,3-TCP is not listed as an active substance in the Annex of Commission Implementing Regulation (EU) No 540/2011[7].

3.6 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

1,2,3-TCP is not listed among the authorised medicines contained in the Article 57 of Regulation (EC) No 726/2004[8]. It is also not subject to maximum residue levels (MRLs)

[6] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1107-20210327
[7] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32011R0540
[8] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726

and is therefore not included in Annex II of Council Regulation (EEC) No 2377/90[9], in accordance with Directive 2004/28/EC.

3.7 Biocidal Products Regulation (EU) 528/2012

There are no biocidal products authorised on the EU/EEA market which are based on or include 1,2,3-TCP. 1,2,3-TCP is not listed as an active substance under Regulation (EC) No 528/2012[10] or Directive 98/8/EC[11].

4. Existing Occupational Exposure Limits

Several EU Member States have established OEL values for 1,2,3-TCP. Some Member States have additionally established short-term limit values (STEL). Table 5 lists these values along with those established in Australia, Canada, China, New Zealand, Norway, Singapore, South Korea, the United Kingdom and the USA. The list should not be considered as exhaustive.

No BLV and BGV have been found.

Table 5: Existing Occupational Exposure Limits (OELs) indicated as 8-h Time-Weighted Average (TWA) for 1,2,3-trichloropropane

Country	TWA (8 h) ppm	TWA (8 h) mg/m³	STEL (15 min) ppm	STEL (15 min) mg/m³	Remarks
EU countries					
Austria	50	300	250	1500	
Belgium	0.005	0.03			Skin notation
Denmark	0.1	0.6	0.2	1.2	Skin notation
Finland	3	18			
Ireland	0.005				
Latvia		2			
Netherlands		0.00108			
Poland		7			
Spain	10	61			Skin notation
Non-EU countries					
Australia	10	60			
Canada-Ontario	0.005				
Canada-Québec	10	60			
China		60			
New Zealand	0.005	0.03			
Norway	10	60			Skin notation
Singapore	10	60			
South Korea	10	60			
United Kingdom	50	306	75	460	
USA-NIOSH [1]	10	60			
USA-OSHA [2]	50	300			

Source: GESTIS-International limit values for chemical agents (Occupational exposure limits, OELs); https://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp (accessed June 2022; searched for "1,2,3-Trichloropropane")

[1] National Institute for Occupational Safety and Health;

[2] OSHA, Occupational Safety and Health Administration

[9] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A01990R2377-20080816

[10] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32012R0528

[11] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31998L0008

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

1,2,3-TCP is a man-made chemical, present in the environment as a result of anthropogenic activity.
Data regarding the concentrations of 1,2,3-TCP in the environment are limited: low levels have been found in a few rivers and bays, drinking water, groundwater, and hazardous waste sites in the United States (ATSDR, 2021). 1,2,3-TCP has been detected in approximately 1% of public water supply and domestic well samples tested by the United States Geological Survey. More specifically, 1,2,3-TCP was detected in 1.2% of public supply well samples collected between 1993 and 2007 by Toccalino et al, and 0.66% of domestic supply well samples collected between 1991 and 2004 by DeSimone et al (as cited in[13]).
1,2,3-TCP was detected at a higher rate in domestic supply well samples associated with agricultural land use studies than in samples associated with studies comparing primary aquifers (3.5% versus 0.2%)[12].

5.2 Production and Use Information

1,2,3-TCP is primarily used in the production of other chemicals.

1,2,3-TCP is a by/co-product, produced in significant quantities, during the manufacturing process of epichlorohydrin, when adding chlorine to allyl chloride (Rossberg et al., 2006). This process consists of three steps:

1. Chlorination of propylene to obtain allyl chloride
2. Reaction of allyl chloride with hypochlorous acid to produce glycerol dichlorohydrins
3. Reaction of the glycerol dichlorohydrin isomers with sodium (or calcium) hydroxide to produce epichlorohydrin.

Hydrochloric acid, sodium (or calcium) chloride and water are produced along with by-products including 1,2-dichloropropane and 1,2,3-TCP. These reactions are carried out in a closed system/ process. 1,2,3-TCP is contained in the organic phase and is further purified by distillation (closed system/process).

The registration data indicate that about 10,000 tonnes/year are manufactured in the EU.

1,2,3-TCP was in the past used as an industrial solvent (for oils, fats, waxes, chlorinated rubber, and resins) and as a degreasing/ extractive agent. Currently, it is used as a monomer in the manufacture of polymers or as an intermediate in the production of 2,3-dichloropropene and other substances (pesticides, polysulphides and hexafluoropropylene). 1,2,3-TCP may remain as an impurity in some of these chemicals.

There are 4 active REACH registrations for the substance, and 3 of them are under REACH Article 18 (transported isolated intermediates used under strictly controlled conditions; indicative of rigorously contained conditions, by technical means during the whole lifecycle). Although the 4th registrant does not operate under the same strictly controlled conditions, the registration indicates that the uses take place in closed systems, so the potential for exposure is limited. A 5th registration became “Inactive” already some years ago (the registrant ceased manufacture/import).
The main activity where exposure is possible is during manual maintenance, but even then, both measured exposure (for inhalation) and modelled exposure (for dermal) are

[12] https://www.enviro.wiki/index.php?title=1,2,3-Trichloropropane

very low due to a low frequency and short duration of the activity, local exhaust ventilation in place and personal protective equipment (PPE) used.

5.3 Occupational exposure

(WHO, 2003) reports that the only data available on inhalation exposure are those relating to 1,2,3-TCP-containing air. Brock & Carroll (1985) (as cited in (WHO, 2003) reported a maximum short-term exposure concentration of 17 mg 1,2,3-TCP/m^3 for maintenance personnel, at a chemical plant in the USA. However, exposure concentrations in other workplaces did not usually exceed 0.61 mg/m^3. It was estimated that workplace exposure (<0.61 mg/m^3 TCP) might lead to a daily intake of up to 277 µg/kg body weight (bw).

Similar studies are not available for the EU, although the registration data indicate measured data for some activities which in a worse-case scenario can be 20 times lower than the 0.61 mg/m^3 level, if the substance can be detected at all. Registration data also presented estimates of dermal exposures (using ECETOC TRA Workers v3) which are very low due to closed systems being mainly used, except during manual maintenance, in which case gloves (PPE) are used.

5.4 Routes of exposure and uptake

5.4.1 Worker exposure

Occupational exposure is by inhalation and dermal exposure during the industrial production and use of 1,2,3-TCP.

There is a lack of information on dermal exposure and intake.

5.4.2 General population

There are no consumer uses of the substance itself.

The most likely routes of exposure of the general population to 1,2,3-TCP are via air and water (WHO, 2003). Human exposure will therefore occur by inhalation of contaminated air or by ingestion of water containing 1,2,3-TCP.

Inhalation:

- Indoor air is more likely to contain higher concentrations of 1,2,3-TCP than outdoor air, due to the greater number of potential sources and lower rates of ventilation.
- 1,2,3-TCP can evaporate from household water and exposure may occur in the air during showering, bathing, or washing dishes. A small part of the population may be exposed this way to very low levels of 1,2,3-TCP.
- People living near facilities that produce or use 1,2,3-TCP could be at greater risk of exposure than the general population. Air near factories which make or use 1,2,3-TCP (and air near hazardous waste sites) may contain low levels of the substance. However, with the manufacturing and use of the substance generally occurring in closed systems, exposure is expected to be limited.

1,2,3-TCP may also be taken up via food. No monitoring data is available that would suggest 1,2,3-TCP exists in drinking water or food products.

6. Monitoring Exposure

6.1 External exposure

We found one official validated method (NIOSH, 2003). However, the limit of quantification indicated in the NIOSH method may not be low enough for the OEL derived later. Thus, also peer review articles have been considered to assess the possibilities of measuring low concentrations of 1,2,3-TCP at the workplace.

The principle of these methods is as follows: air sampling is performed by passing air actively through a sorbent tube or by using diffusive sampling with a sorbent tube. The retained 1,2,3-TCP is then extracted for analysis by either thermal desorption or desorption with CS_2 (depending on the sorbent tube used), followed by analysis via gas chromatography with different detectors. Table 6 shows some of the available methods for the measurement of 1,2,3-TCP in the air in the µg/m^3 (ppb) range (or lower).

Table 6: Methods for the measurement of 1,2,3-TCP in air

Sampling methods/ desorption	Analytical technique	LOQ, flowrate, sampling volume and time	Reference
Coconut shell charcoal (active) CS2 desorption	GC/FID (Gas Chromatography with flame-ionization detection)	3 ppm (18 mg/m^3) Flow rate: 0.2 l/min 60L (5 hours)	(NIOSH, 2003)
Tenax TA tubes (passive) Thermal desorption	GC/MS (Gas chromatography–mass spectrometry)	0.0006 mg/m^3 Passive sampling	(Jia and Fu, 2017)

6.2 Biomonitoring of exposure (internal exposure)

Biomarkers of exposure to 1,2,3-TCP have not been established because no information is available (i) on levels of 1,2,3-TCP or its metabolites in human tissues, fluids, or excreta or (ii) on effects specific for 1,2,3-TCP (ATSDR, 2021).

6.2.1 Background levels

There is no published study on background concentrations in the general population.

6.2.2 Occupational exposure

There is no published experience on biological monitoring of persons exposed to 1,2,3-TCP.

7. Health Effects

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

7.1.1 Human data

There are no human data on toxicokinetic of 1,2,3-TCP.

7.1.2 Animal data

7.1.2.1 Absorption

In Mahmood et al. (1991) F344 male and female rats, and male B6C3F1 mice were administered 30 mg/kg bw (rats) and 30 or 60 mg/kg bw (mice) radiolabelled 1,2,3-TCP by gavage in corn oil. 1,2,3-TCP was rapidly and extensively absorbed (>80%), metabolised and excreted (Mahmood et al., 1991) as reported in (IARC, 1995, WHO, 2003)). DNA adducts have been detected in several tissues in male B6C3F1 mice, following radiolabelled 1,2,3-TCP administration by gavage (see Table 7). The presence of DNA adduct indicates systemic absorption of the substance.

No absorption studies on inhalation or dermal routes of administration were found. It is however noted that systemic absorption is very likely, as 1,2,3-TCP causes acute effects via both routes of administration.

7.1.2.2 Distribution

From the Mahmood et al. (1991) study, six hours after oral administration, the same finding was observed in F344 male and female rats, and male B6C3F1 mice. The highest radioactivity concentration was detected in the forestomach, followed by glandular stomach, intestine, fat, liver and kidney. After 60 hours, the remaining radioactivity was mostly recovered in the liver, kidney and forestomach ((Mahmood et al., 1991) as reported in (IARC, 1995, ATSDR, 2021, WHO, 2003).

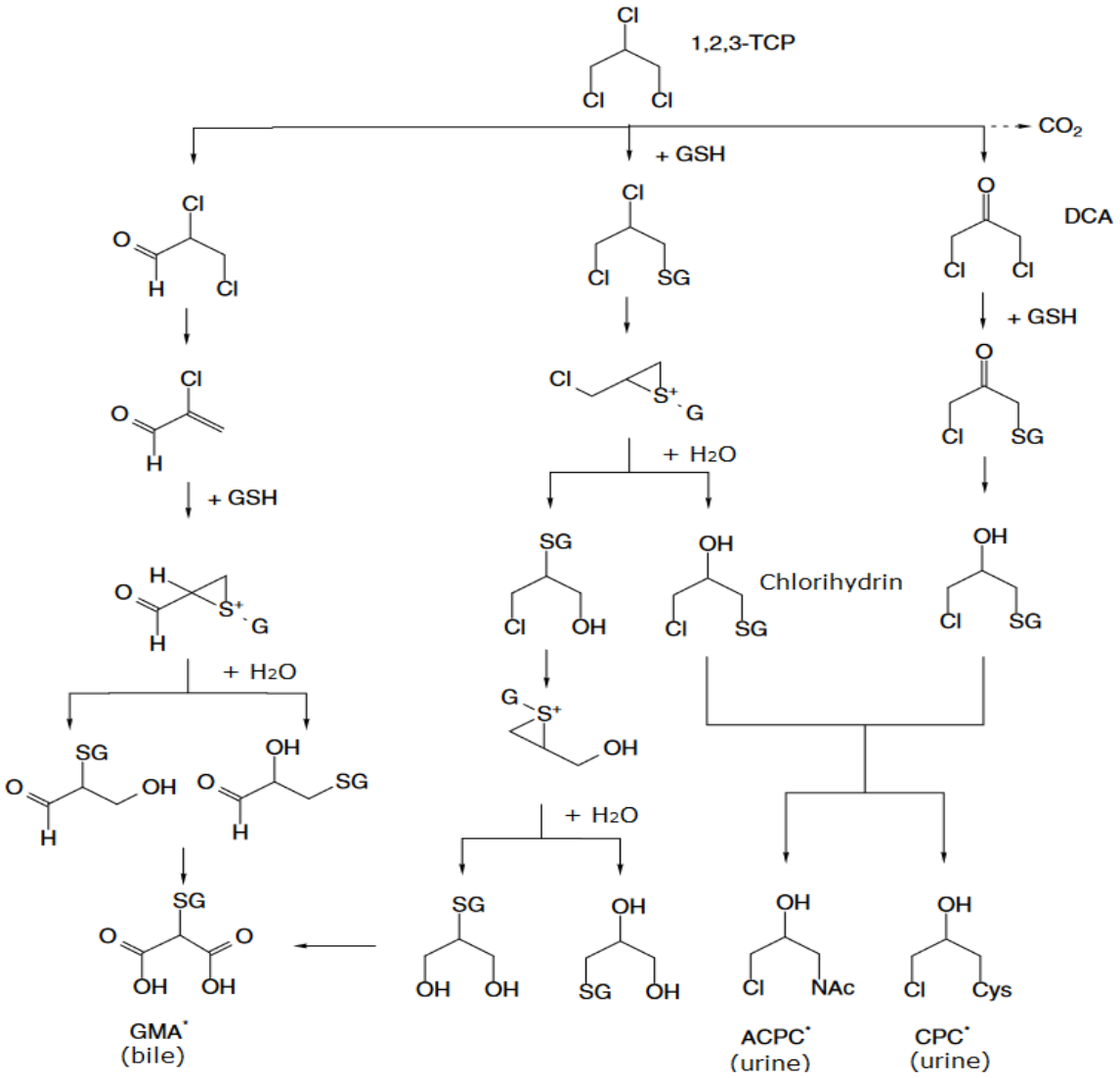
A dose of 3.6 mg/kg bw of radiolabelled 1,2,3-TCP was administered intravenously to male F344/N rats, and was rapidly distributed to several tissues. It mainly accumulated in liver, kidney, small and large intestine, adipose tissue, muscle, and skin. Peak concentrations were achieved within 2 hours after dosing ((Volp et al., 1984) as reported in (DFG, 1993, WHO, 2003, ATSDR, 2021).

7.1.2.3 Metabolism

1,2,3-TCP is metabolised in the liver via two main mechanisms: CYP450-mediated oxidation or glutathione conjugation as first step. The oxidation on a terminal carbon yields a chlorohydrin, which then conjugates with glutathione, with 2-(*S*-glutathionyl) malonic acid (GMA) as the final metabolite detected in the bile.

The oxidation of the central carbon yields 1,3-dichloroacetone which is then conjugated with glutathione and results in the urine metabolites *S*-(3-chloro-2-hydroxypropyl)-L-cysteine (CPC) and *N*-acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine (ACPC).

The direct conjugation with glutathione results to all 3 above-mentioned metabolites, i.e., GMA, ACPC and CPC. Other non-identified metabolites have been detected in the faeces ((Mahmood et al., 1991) as reported in (IARC, 1995, WHO, 2003, ATSDR, 2021). Possible metabolic pathways are presented in Figure 1.



S-G: *S*-glutathione; GSH: reduced glutathione; NAc: *N*-acetyl-L-cysteine; Cys: L-cysteine; *: detected *in vivo*; DCA: 1,3-dichloroacetone; GMA: 2-(*S*-glutathionyl)malonic acid; ACPC: *N*-acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine; CPC: *S*-(3-chloro-2-hydroxypropyl)-L-cysteine

Figure 1: Possible metabolic pathways, adapted from Mahmood et al., 1991, as reported in (WHO, 2003, DFG, 1993)

7.1.2.4 Excretion

In the study by Mahmood et al. (1991) (described above), a similar pattern was observed in rats and mice:

- by 60 hours, in male and female F344 rats, 1,2,3-TCP had been cleared, and 50-57% of the radioactivity of the administered dose was found in the urine, and 20% in both faeces and exhaled air, where less than 2% was unchanged 1,2,3-TCP, the remaining carbon dioxide. ACPC was the major urinary metabolite (~40%) in male rats, while the other metabolite identified was CPC;
- after 60 hours, in male B6C3F1 mice, 65% of the radioactivity of the administered dose was present in the urine, 16% in the faeces, and 20% in exhaled air, almost all of which as carbon dioxide. ACPC in mice accounted for about 3% of the radioactivity while no other metabolites were detected ((Mahmood et al., 1991) as reported in (IARC, 1995, WHO, 2003, ATSDR, 2021)).

In Volp et al. (1984), the excretion was nearly complete (90%) within 2 days. 1,2,3-TCP exhibited biphasic elimination kinetics with a first half-life t½(1) of 0.3–1.8 h and a second t½(2) of 30–45 h, while the radiolabel half-lives were t½(1) of 2.1–5.3 h and t½(2) of 87–182 h. The main route of excretion was in the urine (up to 65% of the administered dose), followed by exhalation for both the unchanged 1,2,3-TCP (~5%) and carbon dioxide (~25%, major metabolite), and through the faeces (~18%) ((Volp et al., 1984) as reported in (ATSDR, 2021, DFG, 1993, WHO, 2003)).

7.1.3 *In vitro* data

In an *in vitro* study, 1 mM radiolabelled 1,2,3-TCP was incubated for 5 minutes with human or rat liver microsomes. In the presence of NADPH, about 1.5 nmol bound radioactive substance/mg protein was detected. In the absence of NADPH or in the presence of reduced glutathione (with or without glutathione-S-transferase) or N-acetylcysteine, no protein-bound radioactivity was observed. In addition, in the presence of NADPH, oxidation of the central carbon led to the formation of 1,3-dichloroacetone (DCA). DCA was identified in both rat and human microsomes, at a rate of 0.27 or 0.03 nmol/min/mg protein, respectively. Oxidation at the terminal carbon yielded 2,3-dichloropropanol as the final metabolite (Weber and Sipes, 1992).

7.1.4 Summary

A limited number of studies have assessed the toxicokinetics of 1,2,3-TCP in exposed animals:

- In rats and mice, about 80% of an oral dose is absorbed through the gastrointestinal tract. No data are available for inhalation and dermal routes. However, based on the adverse effects observed in inhalation and dermal studies, absorption is assumed.
- Once absorbed, 1,2,3-TCP is distributed to several tissues.
- 1,2,3-TCP is rapidly and extensively metabolised, plausibly via CYP450 oxidation and glutathione conjugation.
- 1,2,3-TCP and its metabolites are excreted via urine, faeces and exhaled, mainly as CO_2, within 2 days from a single exposure.

7.2 Acute toxicity

1,2,3-TCP has harmonised classifications for acute effects (Acute Tox. 4) via all routes of exposure (hazard statement codes H302 Harmful if ingested; H312 Harmful in contact with skin; H332 Harmful if inhaled).

7.2.1 Human data

7.2.1.1 Acute oral toxicity

Han (2010) described a case of a 45-year-old farmer who suffered fulminant hepatic failure due to ingestion of 1,2,3-TCP. The farmer had ingested about 10-15 ml of an unknown liquid on a wager. Based on the high blood concentration (7.5 mg/l), it was concluded to be 1,2,3-TCP, although it is not reported if blood measurements had been performed for other substances. A rapid progressive deterioration of liver function occurred within 2 days, which was accompanied by coagulation failure, haemorrhage, elevated blood ammonia and behavioural disturbances, as well as anuria. Because coagulation did not improve with treatment and gastrointestinal haemorrhage continued, family members took the patient back home as there was little hope for recovery. The case is presumed fatal, although this was not explicitly reported. The farmer was reported to have had a past history of untreated chronic hepatitis C and alcohol consumption (not further characterised), for more than 10 years.

Liu et al. (2012) described a case of successful treatment of 1,2,3-TCP poisoning with hemoperfusion and plasma exchange. A 56-year-old female, previously healthy, accidentally swallowed approximately 20 ml of 1,2,3-TCP in a pure form. Shortly after

ingestion, she developed nausea, vomiting, dizziness, and lost her consciousness at about 30 minutes after ingestion. Toxicological examination during hospitalisation showed 9.4 mg/l 1,2,3-TCP in her blood. The patient further developed jaundice, hepatomegaly and hepatic encephalopathy, which were compatible with acute hepatic failure. The peak of liver enzymes was reached on day 4 after ingestion, with the levels decreasing rapidly with the ensuing plasma exchange. The patient regained consciousness on day 12, was discharged from hospital on day 24, but liver enzyme levels were still slightly increased at 2 months and normalised at 6 months.

7.2.1.2 Acute dermal toxicity

No human data are available for acute dermal toxicity. The contribution of dermal exposure remains unknown in the case described by (Mi et al., 2013) reported below.

7.2.1.3 Acute inhalation toxicity

Mi et al. (2013) described a case of a construction worker painting internal walls for 6 days before he developed headache, nausea, vomiting, diplopia and intermittent drowsiness. He worked in confined spaces for up to 8 hours at a time, without any protective equipment. He complained of irritated eyes and throat caused by the strong fumes from the liquid lacquer he used. Brain magnetic resonance imaging (MRI) showed diffuse symmetric white matter lesions in subcortical and periventricular areas and internal capsules compatible with acute toxic leukoencephalopathy. A blood sample from the patient was positive for 1,2,3-TCP (7.6 µg/l) while 1,2,3-TCP was reported to be undetectable in blood samples of the general population. No analyses of the used paints and lacquers or other products were reported, nor were industrial hygiene measurements for 1,2,3-TCP or for other solvents or blood measurements of other compounds . Following intensive treatment, the worker recovered well enough to resume normal life within 6 months.

Silverman et al. (1946) studied the irritation of the mucous membranes after a 15-minute exposure to 1,2,3-TCP in 12 volunteers. The study reported only irritation effects and is described in section 7.4.1. However, no acute general toxicity was reported up to 100 ppm.

7.2.2 Animal data

7.2.2.1 Acute oral toxicity

Acute oral exposure to 1,2,3-TCP in rats caused symptoms including dyspnoea, lethargy, ataxia, ptosis, polyuria, discoloration of the urine, cyanosis, diarrhoea, piloerection, lacrimation, salivation, discharge from the eyes and nose, dilation or contraction of the pupils, clouding of the cornea and liver and kidney damage. The oral LD_{50} values ranged between 150 and 442 mg/kg bw for males and females combined (DFG, 1993).

In a GLP study performed according to FIFRA guideline, Sprague-Dawley rats (n=5/sex/dose) received by gavage a single dose of 100, 180, 320, 560 or 1000 mg/kg bw of 1,2,3-TCP. The LD_{50} values were 205 and 170 mg/kg bw for males and females, respectively (Monsanto, 1985 as reported in (OECD, 2004)).

In a GLP study, Sprague-Dawley rats (n=5/sex/dose) received by gavage a single dose of 0.056, 0.1, 0.18, 0.32, 0.56, 1.0, or 1.8 mL/kg bw 1,2,3-TCP (equivalent to 78.8, 140, 253, 450, 788, 1400 or 2530 mg/kg bw). The LD_{50} values were 0.085 (205) and 0.134 (188) mL/kg bw (mg/kg bw) for males and females, respectively (Shell Development Company, 1980 as reported in (OECD, 2004)).

7.2.2.2 Acute dermal toxicity

After acute dermal exposure to 1,2,3-TCP, rats and rabbits showed intoxication symptoms including dyspnoea, lethargy, ataxia, ptosis, polyuria, discoloration of the urine, cyanosis, diarrhoea, piloerection, lacrimation, salivation, discharge from the eyes and nose, dilation or contraction of the pupils, clouding of the cornea and liver and kidney damage. The

dermal LD_{50} values as reported in several studies were 860 mg/kg bw for rats of both sexes, and 516 mg/kg bw for rabbits of both sexes, and up to 2457 for male rabbits only (DFG, 1993).

In a GLP study performed according to FIFRA guidelines, New Zealand White (NZW) rabbits (n=5/sex/dose) were exposed for 24 hours to 500, 1000 or 2000 mg/kg bw 1,2,3-TCP, occlusively. All animals died at the high dose, one male survived at 1000 mg/kg bw, no deaths were reported on the low dose. Consequently the LD_{50} values were 900, 850 or 880 mg/kg bw for males, females or combined, respectively. Clinical signs in animals exposed to the mid and high dose included decreased activity and food consumption, oral, nasal, and ocular discharge, and staining of the anogenital area. Two out of 5 rabbits in the low dose group displayed hypoactivity, decreased food consumption, and nasal or ocular discharge up to day 7, but returned to normal thereafter. Gross necropsy of animals that died showed primarily post-mortem, autolytic changes. Several rabbits had red fluid in the urinary bladder, and some had red and/or yellow fluid in the abdominal or thoracic cavities (Monsanto, 1985 as reported in (OECD, 2004)).

In a GLP study, NZW rabbits (n=6/sex/dose) were exposed for 24 hours occlusively to 0.18 (M only), 0.32, 0.56, 0.78, 1.00, 1.80, or 3.20 mL/kg bw (equivalent to: 253, 450, 788, 1097, 1406, 2530 or 4500 mg/kg bw) undiluted 1,2,3-TCP on the shaved backs. Clinical signs included activity decrease, ataxia and nasal discharge, few faeces, no urination, haematuria, swollen testes and urethra, iritis, cyanosis, and death with increasing dose. Gross necropsy observations included: discoloured internal organs (kidney, lungs, urinary bladder, liver, intestines), organs distended with blood, mottled organs (kidney, liver), swollen testes, fluid in abdominal cavity and pronounced serosal blood vessels on intestines. Mortality occurred at all doses: all males died at and above 0.56 mL/kg bw, while females from 1.0 mL/kg bw. Therefore, the LD_{50} were 0.277 mL/kg bw (390 mg/kg bw) in males, 0.544 mL/kg bw (765 mg/kg bw) in females or 0.372 mL/kg bw (523 mg/kg bw) in males and females, combined (Shell Development Company, 1980 as reported in (OECD, 2004)).

7.2.2.3 Acute inhalation toxicity

The symptoms of intoxication after acute inhalation of 1,2,3-TCP included prostration, ataxia, sedation and narcosis, dyspnoea, convulsions, lacrimation, salivation, irritation of the mucosa of the eyes and nose, and liver damage. Immediate respiratory depression was a frequent cause of death. Delayed deaths (after 7 to 10 days) were ascribed to liver damage (several studies as reported in (DFG, 1993)). The calculated 4 hours LC_{50} was 3 mg/L (DFG, 1993).

In a GLP study performed according to FIFRA guidelines, Sprague-Dawley rats (n=5/sex/dose) were exposed for 4 h to 4800 mg/m^3 (or 796 ppm) 1,2,3-TCP. No deaths were reported. During exposure animals displayed periocular wetness, clear nasal discharge, hypoactivity, laboured respiration, gasping, rattling sounds in lungs, red/brown perinasal encrustation and ataxia (Monsanto, 1987 as reported in (OECD, 2004)).

F344 rats and B6C3F1 mice (n=6/males/dose) were exposed for 4 hours to 0, 740, 2000, 4100 or 12700 mg/m^3 1,2,3-1,2,3-TCP (equivalent to 0, 123, 332, 680 or 2106 ppm). All rats or mice exposed from 4100 or 12700 mg/m^3, respectively, died during or within a few hours after the exposure. The LC_{50} values were calculated as about 3000 mg/m^3 (or 498 ppm) for both rats and mice. Immediate effects to 4100 mg/m^3 (mice/rats) or 2000 (mice) mg/m^3 included slow, laboured respiration, eye irritation, and inactivity. Prior to death, the animals were inactive, cool to touch (hypothermic), and exhibited basal chromodacryorrhea and perineal wetness (Dow Chemical, 1984 as reported in (OECD, 2004)).

F344 rats were exposed for 1 hour (n=5/sex/dose) to 0, 5000, 10000, 15000 or 20000 mg/m^3 (or 0, 829, 1658, 2488 or 3317 ppm) or for 4 h (n=10/sex/dose) to 0, 200, 3000, or 4000 mg/m^3 (or 0, 332, 498, or 663 ppm) 1,2,3-TCP. In the 1 h exposure group, laboured breathing, prostration, eye tearing, and discharge around eyes and muzzle were

observed immediately, while within the 14 days of the observation period after the exposure, the following symptoms were recorded: weakness, loss of coordination, listlessness, prostration, coldness to touch, anorexia, and changes in breathing patter. A total of 7 males and 15 females died in a dose-response manner. Gross necropsy revealed congestion/thickening of nasal turbinates, discoloration or shape changes of the lung, liver, kidneys, uterine horn, stomach, intestine and lymph node. The 4 h exposure groups initial observations included dyspnoea, lacrimation, languid appearance, and bloody crusts on the nose/mouth. No deaths were reported, while macroscopic changes were limited except for changes in the nasal epithelium in one group (not specified). The study was considered unreliable in the OECD 2004 assessment due to analytical and methodological deficiencies (Shell Development Company, 1982 as reported in (OECD, 2004)).

7.2.3 *In vitro* data

No data available.

7.2.4 Summary

The human data on acute toxicity of 1,2,3-TCP consist of three case reports indicating primarily liver and neurological toxicity after apparently high, but usually not further quantified oral and inhalation exposure. In one case following oral ingestion, the dose was estimated at 20 mL pure 1,2,3-TCP. The contribution of potential other liver or neurological toxicants is not fully excluded in the observed cases.

After administration of 1,2,3-TCP via oral, dermal or inhalation to animals, several adverse effects were reported and the substance is considered as harmful via all three routes of exposure. The oral LD_{50} values ranged between 150 and 442 mg/kg bw for male and female rats combined, while dermal values were 860 mg/kg bw for rats of both sexes, and 516 mg/kg bw for male and female rabbits, and up to 2457 for male rabbits only. After inhalation, the LC_{50} values for rats and mice were about 3000 mg/m^3 (498 ppm); also, after inhalation exposure, laboured respiration, eye irritation and inactivity were the most common observations.

7.3 Specific target organ toxicity / Repeated dose toxicity

7.3.1 Human data

There are no human data on specific target organ toxicity of 1,2,3-TCP.

7.3.2 Animal data

7.3.2.1 Repeated dose oral studies

In a study performed according to OECD TG 408, Sprague-Dawley rats (m, f) were dosed with 1.5, 7.4, 15, or 59 mg/kg bw/day of 1,2,3-TCP in corn oil for 90 days (gavage, 5 d/week), while in the dose range-finding study, animals were dosed for with 1.5, 7.4, 29, or 118 mg/kg bw/d of 1,2,3-TCP for 10 days. A statistically significant decrease in body weight was observed at the high dose in both the range -finding and the main studies, in both sexes. Decreases in absolute organ weights (heart, spleen, thymus and lung, for both sexes) were reported at the high dose in both studies and decreased relative thymus weight in the high dose group of the 10 day study (m, f). In contrast, increases in relative liver and kidneys weights were observed (m, f). Diffuse inflammation-associated necrosis of the myocardium in the 90-day study and in the hight dose group of the 10-day study were noted, with higher prevalence in males and with a dose-dependent increase in severity. Atrophy of the thymus (both sexes, high dose, 10-day study), along with minimal to mild/moderate liver necrosis were observed in the high dose groups in both the 10 day and the 90 day studies. Preneoplastic lesions were reported in the 90 day study: bile duct hyperplasia (m, f, high dose) and a, dose-dependent increase in prevalence of mandibular lymph node hyperplasia (Merrick et al., 1991).

Sprague-Dawley rats (n=10/sex/dose) received 0, 1, 10, 100 and 1000 mg/L 1,2,3-TCP in drinking water, with 0.5% emulphor to increase solubility, for 90 days, (1000 mg/L corresponds to 113 mg/kg bw/d in males and 149 mg/kg bw/d in females). At the end of the dosing period, the body weight gain was lower in the highest dosed animals, due to lower water consumption, while relative organ weights were increased (liver, kidney, and brain). Relative liver and kidney weights were also increased in females at 100 mg/L. At 1000 mg/L changes in liver tissue included accentuated zonation, anisokaryosis, and occasional fatty vacuolation, while biliary hyperplasia was present only in females. Mild changes were observed in kidneys and thyroids in animals of both sexes (Villeneuve et al., 1985 as reported in (OECD, 2004)).

The potential of 1,2,3-TCP was evaluated in 13-week, oral administration NTP studies (GLP) in F344/N rats and B6C3F1 mice (NTP, 1993):

- F344 rats (n=20/sex/dose group; n=30/sex as vehicle controls) were dosed by gavage with 0, 8, 16, 32, 63, 125 or 250 mg/kg bw/d 1,2,3-TCP (>99% purity) in corn oil (5 d/week) for 120 days. After 60 days, half the animals were sacrificed for interim evaluation. At the highest dose, all females and males died within 2 or 5 weeks, respectively. In addition, one male and four females were reported dead at 125 mg/kg bw/day during the study. The mean body weight was lower in the 63 and 125 mg/kg bw dose groups, significantly so at the higher dose. Starting from 16 mg/kg bw/d, mean haematocrit, haemoglobin, and erythrocyte counts were decreased in both sexes. The reported changes in clinical chemistry were significant for liver parameters and indicated hepatocellular damage, with females generally being more sensitive than males. No differences in sperm count and morphology were recorded on 10 animals from the 125 mg/kg bw/d dose group, with respect to control animals. At day 60, statistically significant increases in relative testes weight and a significant decrease in relative epididymis weight was reported for the 125 mg/kg dosed males, while at 120 days the relative testis weight was significantly reduced at the same dose level. Absolute liver weights of all dosed males and relative liver weights of males receiving ≥32 mg/kg bw, and both absolute and relative liver weights of females receiving ≥16 mg/kg bw, significantly increased compared to controls. Absolute and relative kidney weights of males receiving ≥32 mg/kg bw and of females in the 63 and 125 mg/kg bw dose groups were significantly greater compared to controls. In addition, brain and lung relative weights were increased at 125 mg/kg bw/d in both females and males. In females at 125 mg/kg bw/d, focal or multifocal necrosis, necrosis of individual hepatocytes, the presence of sinusoidal pigment and bile duct chronic inflammation and hyperplasia were reported in the liver. In males and females, kidney, tubular regenerative hyperplasia and hyperbasophilia, megalocytosis of diffusely scattered individual tubular epithelial cells, proteinaceous tubular casts and increase in severity of chronic progressive nephropathy at 125 mg/kg bw/d were reported. At the 63 mg/kg bw/d, there was an increased incidence of chronic progressive nephropathy, primarily in males. Nasal turbinate olfactory and respiratory epithelium necrosis, fibrosis and inflammation were observed at the time of death in 14/20 male and 19/20 female rats at the high dose of 250 mg/kg bw/day, and in 3/9 male and 2/11 female rats exposed to 125 mg/kg bw/day. In the latter dose group, foci of mucosal necrosis or necrosis of individual epithelial cells were observed in the nasal turbinates, along with chronic inflammatory changes and attenuation of the epithelial lining, primarily in the dorsal posterior region of the turbinates. Occasionally males presented foci of necrosis of the turbinates. Nasal lesions were observed at the eight-week interim evaluation primarily in females exposed to 125 mg/kg bw/d, and in both sexes at the end of the study ((NTP, 1993) as reported in (NICNAS, 2015, WHO, 2003)).
- B6C3F1 mice (n=20/sex/dosed group; n=30/sex as vehicle controls) were dosed by gavage with 0, 8, 16, 32, 63, 125 or 250 mg/kg bw/d 1,2,3-TCP (>99% purity) in corn oil (5 d/week) for 120 days. After 60 days, half the animals were sacrificed for interim evaluation. At the highest dose level (250 mg/kg bw/d), 6 males and 5 females died within the first week, increasing to a total of 16/20 (males) and 7/20 (females), by

week 4. Half of the surviving high-dose male and female mice were sacrificed at 60 days (interim), thus only 2 males and 7 females were dosed for the whole duration of the assay (120 days). No effects on body weight or haematology were reported. Some effects on sperm count were observed, however, due to the high variability they were not considered treatment related. In addition, no changes in sperm morphology or testis and epididymis histopathology were reported, at the interim sacrifice only, relative and absolute testis and epididymis weight were statistically significantly decreased. After 120 days, statistically significant increase were observed in liver weights (in absolute weights in males receiving ≥125 mg/kg bw/d and relative weights in males receiving 250 mg/kg bw/d, and in absolute and relative weights in females receiving ≥125 mg/kg bw/d), in relative kidney weights in females (receiving 32 and 125 mg/kg bw/d), and in relative and absolute thymus weights in females (receiving 250 mg/kg bw/d). In the liver, necrosis of individual hepatocytes or foci of necrosis, periportal chronic inflammation and nuclear pleomorphism were reported in males at 125 mg/kg bw/d and in females at 250 mg/kg bw/d. In the lungs, regenerative bronchiolar epithelium was present in males at 125 mg/kg bw/d and in females from 32 mg/kg bw/d at the end of the study. Increase in extramedullary haematopoiesis and lymphoid depletion of splenic white pulp were reported in males at 250 mg/kg bw/d and in females from 125 mg/kg bw/d. In the forestomach: acanthosis and/or hyperkeratosis was reported at ≥125 and ≥63 mg/kg bw/d in males and females, respectively. Finally, tubular casts and occasional multiple foci of tubular necrosis in the kidneys and inflammation of the nasal passages and necrosis of serous nasal glands were observed in the high dosed males (NTP, 1993 as reported in (NICNAS, 2015)).

The carcinogenic potential of 1,2,3-TCP was evaluated in 2-year, oral administration NTP studies (similar to OECD TG 451), in F344/N rats and B6C3F1 mice (NTP, 1993).

- F344/N rats (n=60/sex/dose) were dosed by gavage with 0, 3, 10 or 30 mg/kg bw/d 1,2,3-TCP (>99% purity, 5 d/week) in corn oil. A significant decrease in body weight was reported at the high dose level from week 15 and 53 in males and females, respectively. Absolute liver weights were increased in all treated rats; absolute kidney weights were increased in all treated male rats, and in female rats exposed to 10 mg/kg bw/day. The high dose group was terminated due to declining health condition at week 65 or 77 for females and males, respectively; the increase in mortality was attributed to neoplasms (see section 7.7.2). At the mid dose, only 14 males and 8 females survived until the end of the study. Mortality was comparable between the low dose and controls. Moribund animals and animals dying before termination displayed emaciation, lethargy, diarrhoea and dyspnoea. Decreased body weight gain was significant for high dose males, while decreased body weight was significant from week 15 and 53 in males and females, respectively. Absolute liver weights were increased in all treated rats; absolute kidney weights were increased in all treated male rats, and in female rats exposed from 10 mg/kg bw/day. Dose-dependent, non-neoplastic lesions occurred with increased incidence and generally earlier onset, as exposure concentrations increased. In males, lesions significantly increased in all doses in the forestomach (basal and squamous cell hyperplasia) and in the pancreas (hyperplasia, adenoma), and from the mid dose in the kidney (renal tubule hyperplasia and adenoma). In females, non-neoplastic lesions were present at all dose levels and significantly so in the forestomach (basal and squamous cell hyperplasia) and in the pancreas (hyperplasia, adenoma). Similarly, significant lesions emerged from the mid dose in the kidney (renule tubule hyperplasia and adenoma), and in the clitoral gland (adenoma) (NTP, 1993, NTP, 1986) as reported in (WHO, 2003, NICNAS, 2015)).
- B6C3F1 mice (n=60/sex/group), received by gavage 0, 6, 20 or 60 mg/kg bw/d 1,2,3-TCP (>99% purity, 5 d/week) in corn oil. Due to increased mortality, the 20 and 60 mg/kg bw/day groups of mice were terminated at 73 (females) or 79 (males), and 89 weeks (both sexes), respectively. In the low dose group, only 18/60 males and 13/60 females survived until study termination. Neoplasms and moribund condition caused early deaths (see Section 7.7.2). Moribund animals and animals dying before

termination displayed emaciation, lethargy, or tissue masses. Mice body weights were significantly reduced in the mid and high dose, while amongst the low dosed animals the decrease was 8% and 7% for males and females, respectively. Increased relative liver and brain weights in all treated mice, and increased relative kidney weights in high dosed females were reported. Non-neoplastic lesions were evident in all dose groups and were significantly increased in the forestomach (squamous hyperplasia) ((NTP, 1993) as reported in (WHO, 2003, NICNAS, 2015)).

7.3.2.2 Repeated dose dermal studies

No data available.

7.3.2.3 Repeated dose inhalation studies

In two-week repeated dose inhalation toxicity studies (similar to OECD TG 412), F344 rats (5/ sex/ dose) were exposed first to an averaged measured concentration of 0, 13, 40 or 132 ppm (equivalent to 0, 104, 316 or 1030 mg/m^3; target theoretical concentration: 0, 10, 30 or 100 ppm) (6 h/d, 5 d/week), and second to 0, 1, 3 or 10 ppm (equivalent to 0, 6, 18 or 60 mg/m^3 to estimate the NOAEC) (6 h/d, 5 d/week):

- In the first study, a dose-dependent decrease in body weight was recorded in all rats. At 132 ppm, total serum protein and albumin were significantly increased. Absolute and relative liver weights were significantly increased in rats exposed to 132 ppm, and a lower increase was also present in rats exposed to 40 ppm. Decreased amount of abdominal fat was reported in all animals at the mid- and high-dose and in one male and one female at the low dose (13 ppm). Degenerative and inflammatory changes in the olfactory epithelium of nasal turbinates were recorded in all rats in all exposed groups.
- In the second study, , a dose-dependent decrease in body weight was recorded in the mid- and high-dose groups. No changes in the olfactory epithelium were observed at the lowest dose (1 ppm), while effects were recorded at the mid dose (slight decrease in the thickness) and at the high dose (slight degenerative changes and inflammation) for both males and females (Dow Chemical, 1986 as reported in (OECD, 2004)).

In two-week repeated dose inhalation toxicity studies (similar to OECD TG 412), B6C3F1 mice (5, sex, dose) were exposed first to an averaged measured concentration of 0, 13, 40 or 132 ppm (equivalent to 0, 104, 316 or 1030 mg/m^3; target theoretical concentration: 0, 10, 30 or 100 ppm) (6 h/d, 5 d/week), and second to 0, 1, 3 or 10 ppm (equivalent to 0, 6, 18 or 60 mg/m^3 to estimate the NOAEC) (6 h/d, 5 d/week):

- In the first study, No effects on the body weight were reported. The only haematological finding was a slight but statistically significant increase in mean platelet counts at 132 ppm. At the same dose, absolute and relative liver weights were significantly increased. Degenerative and inflammatory changes in the olfactory epithelium of nasal turbinates were recorded in all mice, in all exposed groups.
- In the second study, no effects on the body weight were reported. Changes in the olfactory epithelium were present in the animals exposed to 10 ppm (slight degenerative changes and inflammation) but no changes were observed in the mid and lower dose (3 and 1 ppm)(Dow Chemical, 1986 as reported in (OECD, 2004)).

In a 13-week repeated dose toxicity study (similar to OECD TG 413), CD rats (n=15/sex/dose) were exposed via inhalation (whole body) to 1,2,3-TCP vapour at doses of 0, 28, 92 or 300 mg/m^3 (equivalent to 0, 4.6, 15, 50 ppm; 6 h/d, 5 d/week). Toxic effects were observed at all doses and included upper respiratory tract irritation (red nasal discharge); conjunctival irritation (excessive lacrimation or tears); significantly reduced (7–9%) body weight in female rats (mid and high dose); significantly increased (13–21%) absolute and relative liver weights in all dosed males; significant increases in absolute (10%, high dose) and relative (8–20%, mid and high dose) liver weights in females; significantly increased (13–14%, mid and high dose) relative lung weights in females; and

significantly increased (10%) relative kidney weights in high dosed males. Changes in organ weights were associated with histopathological lesions, including liver cell hypertrophy and lung inflammation (peribronchial lymphoid hyperplasia). Dose-related focal peribronchial lymphoid hyperplasia was found primarily in males, whereas splenic extramedullary haematopoiesis was observed only in treated females (Bio/dynamics Inc., 1979; Johannsen et al., 1988 as reported in (WHO, 2003)).

As adverse effects were observed at all doses, a follow-up study (similar to OECD TG 413) was performed with lower concentrations. CD rats (n=15/sex/dose) were exposed via inhalation (whole body) to 1,2,3-TCP vapour at doses of 0, 3.1 or 9.2 mg/m^3 (equivalent to 0, 0.5, 1.5 ppm; 6 h/d, 5 d/week, for 13 weeks). Signs of mucous membrane irritation (increased lacrimation or tears) were noted in all dose groups. However, no treatment-related findings were reported after histopathological examination of the nasal epithelium. The only systemic effects were changes of haematological parameters and increases in lung and ovary weights without any corresponding microscopic findings (Bio/dynamics Inc., 1979; Johannsen et al., 1988 as reported in (WHO, 2003); EPA, 2009 as reported in (NICNAS, 2015).

In a GLP study (performed similarly to OECD TG 412), Sprague-Dawley rats (n=15/sex/dose) were dosed with 0, 5, 15 or 50 ppm (0, 28, 92 or 300 mg/m^3) 1,2,3-TCP via inhalation for 13 weeks (6 h/d, 5 d/week). Absolute and relative liver weights were increased in both males (all dosed groups) and females (mid and high dose). A significant increase in the liver/brain weight ratio was noted in all dosed males and in high dosed females. Histopathology releveled mild centrilobular to midzonal hepatocellular hypertrophy, mild to marked peribronchial lymphoid hyperplasia, and mild to marked extramedullary haematopoiesis in the spleen. Increased leukocyte (m, f) and serum glutamic pyruvic transaminase (f) in the mid and high dose (Rusch et al., 1979 as reported in (OECD, 2004)).

In a GLP study, performed similarly to OECD TG 413, Sprague-Dawley rats (n=10/sex/dose) were dosed with 0, 0.5 or 1.5 ppm (0, 3.1 or 9.2 mg/m^3) 1,2,3-TCP via inhalation for 13 weeks (6 h/d, 5 d/week). All treated animals showed conjunctival irritation (excessive lacrimation or tears). Changes in haematology (increased erythrocyte count and haemoglobin in dosed males) were observed at week 7 but not at 13 weeks, and changes in clinical chemistry (decreased bilirubin and lactic dehydrogenase in dosed males) were not considered of toxicological relevance. In treated males, increased lung weight (significant at the high dose) was observed in animals with decreased body weight; in treated females the only reported effect was an increase in ovarian weight (significant at the high dose) (Terrill et al., 1983 as reported in (OECD, 2004)).

7.3.3 *In vitro* data

No data available.

7.3.4 Summary

There are no human data on specific target organ toxicity of 1,2,3-TCP.

Several studies were conducted in rats and mice via the oral or inhalation route. In all studies, the liver was identified as a target organ (mild centrilobular to midzonal hypertrophy, necrosis, inflammation and hyperplasia of the bile duct). In oral studies, effects in the forestomach (mainly basal and squamous cell hyperplasia) and in the pancreas (hyperplasia, adenoma) were reported. Kidneys were also affected by exposure to 1,2,3-TCP displaying tubular regenerative hyperplasia, hyperbasophilia, megalocytosis, chronic progressive nephropathy. In one oral study, effects on the respiratory tract were reported and included nasal turbinate olfactory and respiratory epithelium inflammation, fibrosis, or necrosis from the nasal cavity to the lungs. These effects, as well as those on the liver and kidneys, were also reported consistently in the inhalation studies. In those , effects on the eyes (conjunctival irritation) were attributed to eye irritant properties of

1,2,3-TCP. Effects on the spleen and thymus were observed in some studies. Diffuse inflammation-associated necrosis in the heart was reported in an oral study.

7.4 Irritancy and corrosivity

7.4.1 Human data

(Silverman et al., 1946) exposed 12 volunteers to 1,2,3-TCP for 15 minutes. The concentrations that irritated the "majority" of the subjects were 100 ppm for eyes and throat and >100 ppm for nose. The highest concentration which the majority of subjects considered tolerable for an 8-hour exposure was 50 ppm.

7.4.2 Animal data

7.4.2.1 Skin irritation

In a GLP study performed according to FIFRA guidelines and similar to OECD TG 404, 0.5 mL 1,2,3-TCP was applied undiluted on the intact shaved back of NZW rabbits (5 males, 1 female) for 4 h under semi-occlusive and for 24 h under occlusive dressings. One animal died on day 5. The maximum erythema score was 2 and it reversed in all animals by day 10 for both 4 or 24 h exposures. The oedema scores were 1, reversible within 3 days or 7 days for 4 h or 24 h exposures, respectively (maximum possible value 8) (Bio/dynamics Inc., 1985, as reported in (OECD, 2004) and (SCOEL, 2011).

1,2,3-TCP was applied undiluted (0.5 mL) to the abraded and intact shaved back of 12 NZW rabbits (3, sex, group) occlusively, for 24h. In non-abraded skin, the erythema was reversible within 2 days, while the erythema in abraded skin and the oedema were reversible in all groups, within 3 days. The severity of reaction was higher in abraded skin; the overall primary irritation index was 1.63 (maximum possible value 8.0) (Stillmeadow, 1980 as reported in (OECD, 2004), or Albert, 1982 in other reviews e.g. (WHO, 2003)).

1,2,3-TCP was applied undiluted (0.5 mL) on intact and abraded skin of rabbits (3 males, 11 females) for 24 h, occlusively. Irritation was scored with the Draize test and the values ranged between 1.6 and 3.0 (maximum 4), consequently 1,2,3-TCP was deemed severely irritating (Clark, 1977, as reported in (WHO, 2003)).

1,2,3-TCP applied occlusively for 24 h to rabbit was considered as severely irritating. No other information is available (McOmie and Barnes, 1949 as reported in (DFG, 1993) and (SCOEL, 2011)).

1,2,3-TCP (2 mL) applied non-occlusively to 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 as reported in (SCOEL, 2011)).

7.4.2.2 Eye irritation

In a GLP study performed according to FIFRA guidelines (similar to OECD TG 405), 0.1 mL 1,2,3-TCP was applied undiluted in the eye of NZW rabbits (n=3/sex). Corneal opacity and ulceration and iritis were present in 3/6 rabbits, reversible by day 7. Maximum score for opacity was 2 in one rabbit, while 1/6 had a score of 1 and 1/6 was positive; the observed opacities were reversible within 7 days. Minimal ulceration (score 1 or above) was reported in 3/6 rabbits. Iritis scores in 3/6 rabbits reached a maximum score of 1, reversible within 72 hours, while conjunctivitis was reported in all animals and was reversible within 7 days. Redness, chemosis and discharges were observed in all rabbits, with scores ranging between 1 and 3. Based on these observations, 1,2,3-TCP was considered moderately irritating to the rabbit eyes (Bio/Dynamics, 1985 as reported in (OECD, 2004)).

In another eye irritation test (similar to Draize test), 0.1 mL 1,2,3-TCP was applied undiluted to the eyes of 6 NZW rabbits (n=3/sex) in the unwashed group and 3 NZW males in the washed group (eyes were washed after 30 seconds of exposure with tap water). The primary irritation scores were 20/110 and 16.3/110 in unwashed and washed eyes, respectively. Superficial corneal ulcerations were detected in 4/6 unwashed eyes by 1 hour

and in 5/6 by 6 hours; it was also observed in 2/3 washed eyes at 24 hours, all reversed within 72 hours. Iritis was observed in 5/6 unwashed (reversible within 72 hours) and 1/3 washed (reversible within 24 hours). Some conjunctival irritation remained in both groups for 7 days (1/6 and 1/3, respectively). As a result, 1,2,3-TCP was considered moderately irritating (Shell Development Company, 1980 as reported in (OECD, 2004), or Albert, 1982 in (WHO, 2003)).

In a 13-week repeated dose toxicity study (similar to OECD TG 413), CD rats (n=15/sex/dose) were exposed via inhalation (whole body) to 1,2,3-TCP vapour at doses of 0, 28, 92 or 300 mg/m^3 (equivalent to 0, 4.5, 14, 48 ppm; 6 h/d, 5 d/week). Toxic effects were observed at all doses and included upper respiratory tract irritation (red nasal discharge) and conjunctival irritation (excessive lacrimation or tears). (Bio/dynamics Inc., 1979; Johannsen et al., 1988 as reported in (WHO, 2003)).

As adverse effects were observed at all doses, a follow-up study (similar to OECD TG 413) was performed with lower concentrations. CD rats (n=15/sex/dose) were exposed via inhalation (whole body) to 1,2,3-TCP vapour at doses of 0, 3.1 or 9.2 mg/m^3 (equivalent to 0, 0.5, 1.5 ppm; 6 h/d, 5 d/week, for 13 weeks). Signs of mucous membrane irritation (increased lacrimation or tears) were noted in all dose groups. The lowest observed adverse effect concentration (LOAEC) for irritation was thus 3.1 mg/m^3 (0.5 ppm) (Bio/dynamics Inc., 1979; Johannsen et al., 1988 as reported in (WHO, 2003); EPA, 2009 as reported in (NICNAS, 2015).

7.4.3 *In vitro* data

No data available.

7.4.4 Summary

The human data on irritancy or corrosivity of 1,2,3-TCP (old human study with a 15-minute exposure of 12 volunteers) indicated irritation of throat and eyes at concentrations around 100 ppm.

In rabbit studies, 1,2,3-TCP (undiluted) exerted inconclusive results in skin irritation studies, while it was considered moderately irritating to the eyes. Eye irritation was also observed in CD rats after 13-week exposure.

7.5 Sensitisation

7.5.1 Human data

7.5.1.1 Respiratory sensitisation

There are no human data on respiratory sensitisation of 1,2,3-TCP.

7.5.1.2 Skin sensitisation

There are no human data on skin sensitisation of 1,2,3-TCP.

7.5.2 Animal data

7.5.2.1 Respiratory sensitisation

No data available.

7.5.2.2 Skin sensitisation

In a guinea pig maximisation test, animals were treated with 1,2,3-TCP (92% purity) 0.1% in corn oil via intradermal injection twice, then with 50% in corn oil for the topical induction (48 h application) and 25% for the topical challenge (2 weeks after the topical induction). A weak reaction was seen in 1/10 males, and a positive reaction in 2/20 (1 male, 1 female) but were all reversible within 48h; a weak reaction was also seen in 1/5 control males. As a result, 1,2,3-TCP was considered a "very slight sensitizer" in guinea pigs (Clark, 1977 as reported in (WHO, 2003) and (SCOEL, 2011)).

In a Buehler test (similar to OECD TG 406), Dunkin-Hartley guinea pigs (n=5/sex) were topically treated with vehicle and a positive control substance, and with undiluted 1,2,3-TCP (97.5% purity, 0.5 mL, occlusive) for 6 h on days 2, 9 and 16. The skin was challenged on day 30, with one topical application (0.5 mL, occlusive) and was evaluated using Draize criteria 24 and 48 hours after the challenge. No effects indicative of skin sensitisation were reported (WHO, 2003, ECHA, SCOEL, 2011).

In a GLP-compliant study conducted similarly to the Buehler method, Hartley-Albino guinea pigs (n=5/sex/group) were exposed to vehicle and a positive control substance, and 1,2,3-TCP neat (2 groups; one for sensitisation and a second for irritation). Groups 1 to 3 were treated on days 2, 9 and 16 with 0.5 mL of testing material for 6 hours, and all animals were challenged on day 30. Two females died in group 3 (treatment with 1,2,3-TCP) which was considered dose-related. 1,2,3-TCP did not produce skin sensitisation (Shell Development Company, 1980 as reported in (OECD, 2004)).

Ten Hartley-Albino guinea pigs were dosed with 0.3 mL of 1,2,3-TCP occlusively for 6 h, 3 times a week for 3 weeks. Challenge was performed with 0.3 mL after 2 weeks. 1,2,3-TCP was considered non-sensitiser (Bio/dynamics Inc., 1985c as reported in (SCOEL, 2011) and (WHO, 2003)).

7.5.3 *In vitro* data

No data available.

7.5.4 Summary

There are no human data on respiratory or skin sensitisation of 1,2,3-TCP.

In two studies conducted with a protocol similar to the Buehler method on guinea pigs, 1,2,3-TCP was considered to be ‘non-sensitiser’ for skin, while in a guinea pig maximisation test it was concluded to be ‘very slight sensitizer’. No information is available for respiratory sensitisation.

7.6 Genotoxicity

7.6.1 Human data

There are no human data on genotoxicity of 1,2,3-TCP.

7.6.2 Animal data (*in vivo*)

A number of studies have evaluated the *in vivo*, genotoxic potential of 1,2,3-TCP (summarised and tabulated in Table 7). In *Drosophila melanogaster*, exposure to 1,2,3-TCP by inhalation for 48 h, at the LC_{50} dose, yielded positive results in the somatic and recombination test (SMART), significantly increasing the number of total wing spots and the frequency of large wing spots induced by a series of genotoxic effects including somatic mutation, chromosomal rearrangements or nondisjunction) (Chroust et al., 2007). 1,2,3-TCP did not induce dominant lethal mutations when administered orally to rats, neither did it increase the incidence of micronucleated polychromatic erythrocytes over controls in mice (Table 7). Although 1,2,3-TCP did not display any clastogenic/aneugenic activity in mouse bone marrow cells following i.p. administration, DNA covalent binding and dose-dependent DNA damage in the form of DNA strand breaks detected by alkaline elution, were observed in rodents treated by the i.p. route. Additionally, the major DNA adduct S-[1-(hydroxymethyl)-2-(N^7-guanyl)-ethyl]glutathione has been isolated and characterised by physicochemical methods. 1,2,3-TCP was one of three, out of a total of 20 possible carcinogens evaluated by genomic analysis, significantly increasing the mutational frequencies in chemically-induced tumours.
1,2,3-TCP-related tumours of the liver and forestomach presented as high mutational burden tumours. Forestomach tumours harboured >2-10 fold the number of mutations, compared to the other tumour genomes analysed. Three unique TCP-exposure-related (exogenous) mutational signatures were identified; 1 common in liver and forestomach

and 2 present only in forestomach samples. These signatures exhibited strong transcriptional bias and when aligned with human signatures of known aetiologies, revealed a significant association between the animal data and the induction of human cancers including liver tumours and astrocytomas (low-grade gliomas), cholangiocarcinoma and liver hepatocellular carcinomas ((Riva et al., 2020);see also section 8.1).

Table 7: *In vivo* genotoxicity studies

Assay / Species, strain, sex, (No / group)	Lowest effective / highest (ineffective) * dose	Findings	Remarks	References
Dominant lethal studies/SD rats (M; n=15)	(80 mg/kg)	negative for induction of dominant lethal/dominant lethal mutation index or testicular lesions	Males treated by gastric incubation for 5 successive days	(Saito-Suzuki et al., 1982)
In vivo mouse bone marrow micronucleus test/CD-1 mice (M+F; n=5/sex)	(200 mg/kg)	negative no increase in incidence of micronucleated PCEs over vehicle controls despite clinical signs of acute toxicity no significant toxicity on bone marrow cells.	One i.p. administration of two doses (up to 70% of the LD_{50} value, sampling: 24h and 48h, part of a ten halogenated aliphatic hydrocarbons survey;	Crebelli et al., 1999)
Alkaline elution assay/F344/N male rat hepatocytes	30 mg/kg/ 300 mg/kg	**positive** dose-dependent increase in DNA strand breaks (peaking within 1 h, declining but detectable up to 48 h) negative no DNA or DNA-protein crosslinks detected	i.p. administration	(Weber and Sipes, 1991)
Alkaline elution assay/Wistar rats (M; n=5/dose)	≥375 mmol/kg/ 3000 mmol/kg	**positive** for dose-dependent renal DNA damage; markedly less potent than other halogenated propanes tested concurrently; low nephrotoxic potential	Single i.p doses; animals sacrificed 60 min after administration	(Lag et al., 1991)
DNA covalent interaction with rat hepatic macromolecules (DNA, RNA, protein), liquid scintillation counting/F344 rats (M)	30 mg/kg	**positive** covalent binding to hepatic protein, DNA and RNA, persisting for 72 h, cumulative after repeated dosing, CYP450 inhibition increased DNA/protein binding, GSH depletion increased protein binding (+324%) and decreased DNA binding (-56%)	[^{14}C]-TCP, i.p., binding assessed 4 h post-injection; repeated dosing: 2-3 doses, 24 h apart	(Weber and Sipes, 1990)
DNA adduct formation, isolation (HPLC),	6 or 60 mg/kg (mice); 3 or 30 mg/kg	**positive** major adduct identified (in small yields): S-[1-(hydroxymethyl)-2-(N^7-	[^{14}C]-TCP gavage administration (same method as the NTP	(La et al., 1995)

Assay / Species, strain, sex, (No / group)	Lowest effective / highest (ineffective) * dose	Findings	Remarks	References
detection/ Characterisation (radioactivity; MS)/B6C3F1 mice (M), Fischer-344 rats (M) (n=15)	(rats) 300 mg/kg (i.p, rats, for high yield adduct formation)	guanyl)-ethyl]glutathione; wide distribution among target/non-target organs; no specific relationship between adduct formation and tumorigenesis; highest yield of DNA adducts: rats: forestomach, glandular stomach, kidney, liver, pancreas, and tongue; mice: forestomach, glandular stomach, kidney, and liver	carcinogenicity study), organs excised 6 h later, i.p. administration in rats for subsequent scaled-up investigation for better adduct characterisation	
DNA adduct formation, isolation (HPLC), quantification (radioactivity)/ B6C3F1 mice (M) (n=15)	0 and 6 mg/kg (lowest dose used in the NTP study)	**positive** gavage administration resulted in 1.4-2.4 fold greater yields of the major DNA adduct previously identified as N7-guanyl adduct by (La et al., 1995); adduct concentration: Liver>kidney> forestomach> glandular stomach; Adduct formation significantly greater (2-fold) in liver/kidney when administered by gavage vs drinking water.	[^{14}C]-TCP was administered for 5 days by gavage or in drinking water, for 1 day; DNA adducts in two target (forestomach and liver) and two non-target (glandular stomach and kidney) were hydrolysed from DNA, isolated by HPLC and radioactivity quantified by scintillation counting.	(La et al., 1996)
DNA mutational signature profiling (liver tumours, forestomach squamous cell carcinomas)/B6 C3F$_1$/N mice (as in the NTP study)		**positive** Significantly increased mutation number in liver and forestomach tumours; Three unique TCP-exposure-related "exogenous" mutational signatures identified with strong transcriptional bias	B6C3F$_1$/N mice from the 2 year carcinogenicity, gavage NTP study (NTP TR384); as a comparator, untreated (spontaneous) tumours (originating in the lung or liver) were also analysed; matched normal control tissues included	(Riva et al., 2020)

*concentrations in brackets refer to highest ineffective doses
Note: Positive outcomes are always presented in bold

7.6.3 *In vitro* data

1,2,3-TCP mutagenicity has been assessed in various *Salmonella typhimurium* strains and the results are summarised in Table 8. 1,2,3-TCP consistently displayed mutagenic activity

in strains TA100 and TA1535, but only following metabolic activation. Other tester strains (e.g. TA98, TA1538, TA1537) were largely negative, regardless of S9 activation. Additionally, 1,2,3-TCP was not genotoxic in *Escherichia coli*, failing to induce SOS repair.

Table 8: Summary of bacterial genotoxicity studies

Assay / Species, strain	Lowest effective / highest (ineffective)* dose	Findings	Remarks	References
Bacterial reverse mutation assay/ *S. typhimurium* TA100	+S9 TA100 0.1 µmol/plate/1 µmol/plate -S9 (1 µmol/plate)	**positive** up to 1120 revertant colonies (+S9) negative; little or no direct mutagenic activity; 34 revertants at 1 mmol/plate		(Stolzenberg and Hine, 1980)
Bacterial reverse mutation assay/ *S. typhimurium* TA100	+S9: TA98, TA100, TA1535: 0.02-1.0 mg/plate/ 1.0 mg/plate -S9	**positive** negative		Kier 1982, as cited in (DFG, 1993)
Bacterial reverse mutation assay/ *S. typhimurium* TA1535 and TA100	+S9 TA100, TA1535: 1 µg/plate/ >100 µg/plate	**positive** responses (number of revertants induced) in TA100>TA1535; hamster S9>rat S9	Preincubation procedure; two species S9	(Haworth et al., 1983)
Bacterial reverse mutation assay/ *S. typhimurium* TA1535, TA100, TA98, TA1538, and TA1537	+S9: TA100, TA1535 5 µg/plate/100 µg/plate -S9: TA100, TA1535 (100 µg/plate) +/-S9: TA98, TA1538, TA1537 (100 µg/plate)	**positive** (strong mutagenic effect); 4.4-fold increase (TA100) and 6.5-fold increase (TA1535), over solvent controls negative negative		(Ratpan and Plaumann, 1988)
Bacterial reverse mutation assay/ *S. typhimurium* TA97, TA98, TA100, TA1535 and TA1537	-S9: (333 µg/plate) or (667 µg/plate) +S9: TA100: 3 µg/plate/333 µg/plate or 10 µg/plate/667 µg/plate TA1535: 1 µg/plate/333 µg/plate or 10	negative in TA100, TA1535, TA1537, TA97, TA98 **positive** up to 13-fold increase in the number of revertants/plate (hamster S9) and 4-fold (rat S9) or up to 36.3-fold increase (hamster S9) at 333 mg/plate. **positive** up to 56-fold (hamster S9) or 23-fold increase (rat S9) in the		(NTP, 1993)

Assay / Species, strain	Lowest effective / highest (ineffective)* dose	Findings	Remarks	References
	µg/plate/1000 µg/plate	number of revertants/plate or up to 321-fold increase (rat S9) at 333.		
	TA1537: (333 µg/plate)	negative (tested in one laboratory only).		
	TA98: 3-33 µg/plate/333 µg/plate or 33-100 µg/plate/ 1000 µg/plate	**positive** in one laboratory (up to 3.7-fold increase in number of revertants (hamster S9) but negative with rat S9 or **positive** (in the other laboratory) up to 5-fold (hamster S9; 333 mg/plate) or 2.4-fold (rat S9; 667 mg/plate) increase in number of revertants/plate		
	TA97: 10 µg/plate/1000 µg/plate	**positive** (tested in one laboratory only) up to 13-fold (hamster S9) or 4.4-fold (rat S9) increase in number of revertants/plate (at 333-667 mg/plate).		
Bacterial reverse mutation assay/ *S. typhimurium* TA100	+S9: 0.1 µmol/plate/ (0.1 µmol/plate)	Weakly **positive**; least mutagenic among the trihalogenated propane analogues (<1000 revertants at the highest dose tested)	Dose range used: 0.01-1.0 µmol/plate	(Lag et al., 1994)
Bacterial reverse mutation assay/*S. typhimurium* TA100, TA98	-/+ S9: TA98	negative		(Kubo et al., 2002)
	-S9: TA100	negative		
	+S9: TA100	**positive** mutagenicity strength 2.2 net rev./nmol under TA100+S9		
SOS chromotest/*E. coli* PQ37		negative	Substances were tested up to the limit of solubility or up to 100 mM.	(von der Hude et al., 1988)

*concentrations in brackets refer to highest ineffective doses
Note: Positive outcomes are always presented in bold

In mammalian cells, 1,2,3-TCP yielded largely positive results in a number of *in vitro* genotoxicity studies (Table 9). It exhibited mutagenic activity at the thymidine kinase (*tk*) locus in mouse lymphoma cells upon metabolic activation, while in cytogenetic tests in CHO cells, 1,2,3-TCP induced both sister chromatic exchanges and chromosomal aberrations; both endpoints requiring S9 activation. Conflicting results were reported for

the induction of micronuclei in human lymphocytes, and DNA strand breaks, as detected by alkaline elution and the comet assay. 1,2,3-TCP did not induce unscheduled DNA synthesis in rat hepatocytes.

Table 9: *In vitro* genotoxicity studies

Assay / Species, strain or cell line	Lowest effective / highest (ineffective)* dose	Findings	Remarks	References
In vitro mammalian cell gene mutation test using the Thymidine kinase gene/L5178Y mouse lymphoma	+S9: 0.01 µg/ml/0.06 µg/ml -S9 (0.06 ug/ml)	**positive** (significant responses p≤0.05) in inducing trifluorothymidine resistance at all doses tested in the presence of metabolic activation; average mutant fraction (frequency) up to 440/10^6 cells treated, at the top dose (0.06 ug/ml). negative	Assay initially performed without S9 and in the absence of a positive response repeated with induced S9.	(NTP, 1993)
SCE/V79 cells	+S9: 0.3 mM/1.0 mM -S9	**positive** up to 3.3-fold increase (significant, p<0.005) in SCE induction, compared to solvent controls negative	V79 cells exposed for 28 hr (-S9) or for 3 hr (+S9)	(von der Hude et al., 1987)
SCE/CHO cells	+S9: 14.170 µg/ml /59.510 µg/ml -S9	**Weakly positive / positive** significant increases (p<0.001) up to 88.8% (at 49.6 mg/ml) in SCEs/chromosome of chemical-exposed cultures relative to culture exposed to solvent. negative	CHO cells were incubated with 1,2,3-TCP for 25 h (-S9) or 2-3 h (+S9); 2 trials	(NTP, 1993)
Chromosomal aberrations/ CHO cells	+ S9 59.5 µg/ml/ 79.2 µg/ml -S9	**positive** in one trial (significant responses p=0.018) at extended incubation time and harvest at 20 h, up to 26% cells with Abs (at 59.5 mg/ml) vs 8% of solvent treated cells negative at harvest time of 10.8 h negative	3 trials (2 +S9, 1 -S9); marked cytotoxicity was noted in all trials	(NTP, 1993)
Alkaline elution/Wistar rats hepato-cytes	(100 mM)	negative no increases in normalised area above the curve, compared to control.	1 h exposure for alkaline elution; no marked cytotoxicity: 2 h in suspension culture: >80% viable at 2.5 mM; 20 h in monolayer	(Holme et al., 1991)

Assay / Species, strain or cell line	Lowest effective / highest (ineffective)* dose	Findings	Remarks	References
			cultures: >90% viable at 1 mM)	
Alkaline Comet assay/human lymphocytes	-/+ S9: 2 mM/4 mM	**positive** significant ($p < 0.0001$) increase in DNA damage (tail length and tail moment); significant dose-response in tail moment only the absence of S9	3 h treatments -/+ S9, 100 cells scored per experimental point; > 60% cells identified as dead (+S9; at 2 mM)	(Tafazoli and Kirsch-Volders, 1996, Tafazoli et al., 1998)
In vitro micronucleus assay/human lymphocytes	+S9:(8 mM) -S9: (2 mM)	negative no increase in frequency of micronucleated binucleated lymphocytes	Two donors, -/+ S9, (+S9; 3 h exposure); no marked decline in division indices	(Tafazoli and Kirsch-Volders, 1996)
In vitro micronucleus assay (+kinetochore labelling+FISH)/human lymphoblastoid AHH-1 cells and genetically engineered cells expres-sing metabo-lising enzymes: MCL-5 and h2EI lymphocytes	-S9: AHH-1: 0.01 mM/5 mM; MCL-5: 1 mM/5 mM; H2E1: 0.01 mM/5 mM	**positive** 8-fold induction of micronuclei between 0 and 5 mM in the AHH-1 and h2EI cell lines. The majority of micronuclei stained negatively with the kinetochore antibody (K+ve<K-ve); reduced but significant induction of micronuclei induced in MCL-5 cells (4-fold) in which K+ve>K-ve micronuclei were produced.	Metabolically competent cell lines used: human lymphoblastoid cell line AHH-1, with native cytochrome CYP1A1 activity (parental); MCL-5 cells stably expressing cDNAs encoding human CYP1A2, 2A6, 3A4, 2E1 and microsomal epoxide hydrolase, and h2EI cells containing a cDNA for CYP2E1; treatments:18 h for AHH-1, 24 h for MCL-5 and h2EI	(Doherty et al., 1996)
DNA repair synthesis/F344 rats' hepatocytes	(10^{-3} % (M)	Negative		(Williams et al., 1989)

*concentrations in brackets refer to highest ineffective doses;
[a] depending on the laboratory where the test was performed; [b] toxicity was observed in certain cases, at doses ≥666 mg/plate, limiting the highest dose tested
Note: Positive outcomes are always presented in bold

Other halogenated propanes have generally been found to be positive in assays which indicate mutagenicity (Lag et al., 1994; Ratpan and Plaumann, 1988, as cited in (EPA, 2017). *In vitro* genotoxicity studies in bacterial and mammalian cells of 1,2,3-TCP metabolites (e.g. 1,3-dichloro-2-propanol, 1,3-dichloroacetone) have been reviewed by (IARC, 1995).

7.6.4 Summary

There are no human data on genotoxicity of 1,2,3-TCP.

In a limited number of studies in rodents, 1,2,3-TCP did not induce dominant lethal mutations in exposed rats, nor did it increase the frequency of micronucleated polychromatic erythrocytes in mice. Its covalent interaction with DNA and the induction of DNA strand breaks however were both documented, while the major DNA adduct was isolated, characterised and quantified in relevant studies. *In vitro*, 1,2,3-TCP exhibited mutagenic activity in the *Salmonella typhimurium* tester strains TA100 and TA1535, in all of the assays conducted, and this activity was dependent upon S9 activation. In mammalian cells, 1,2,3-TCP displayed mutagenic activity on the *tk* locus in mouse lymphoma cells and yielded largely positive results in cytogenetic test including the induction of SCE and chromosomal aberrations in CHO cells; Again these findings were dependent on metabolic activation.

7.7 Carcinogenicity

1,2,3-TCP may cause cancer and has a harmonised classification under CLP as Carc 1B.

IARC (1995) concluded that 1,2,3-TCP is "*probably carcinogenic to humans" (Croup 2A)*. This conclusion was based on "*inadequate evidence* in humans" and "*sufficient evidence"* in experimental animals for the carcinogenicity of 1,2,3-TCP.

In their evaluation, IARC (1995) noted that 1,2,3-TCP has been tested for carcinogenicity by oral administration in mice and in rats. This exposure resulted in tumours of the oral mucosa and of the uterus in female mice and increased the incidences of tumours of the 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. The reactive and mutagenic metabolite, 1,3-dichloroacetone, initiated skin tumour development in mice when applied topically and was formed by hepatic metabolism in rat and human microsomes *in vitro*. Also the metabolic products of 1,2,3-TCP bound covalently to rat hepatic protein and DNA.

In making the overall evaluation, IARC took into account the following evidence:

1. 1,2,3-TCP causes tumours at multiple sites and at high incidence in mice and rats;
2. The metabolism of 1,2,3-TCP is qualitatively similar in human and rodent microsomes;
3. 1,2,3-TCP is mutagenic to bacteria and to cultured mammalian cells and binds to the DNA of animals treated *in vivo*.

SCOEL (2011) concluded that there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of 1,2,3-TCP. The plausible mode of action of the carcinogenicity of 1,2,3-TCP is genotoxicity of its biological reactive metabolic intermediates. 1,2,3-TCP was categorised into the SCOEL carcinogen group A (genotoxic carcinogen), genotoxic to which a threshold cannot be assigned.

7.7.1 Human data

(IARC, 1995) did not identify any human data regarding carcinogenicity of 1,2,3-TCP.

More recently ATSDR (2021) did not identify any data regarding carcinogenicity in humans after exposure to 1,2,3-TCP.

No human carcinogenicity data were identified since ATSDR (2021).

7.7.2 Animal data

The carcinogenic potential of 1,2,3-TCP was first evaluated in a 2-year oral administration study in male and female F344/N rats and B6C3F1 mice (n=60/sex/dose), conducted by the NTP (NTP, 1993).

In F344/N rats, exposed to 3, 10 or 30 mg/kg 1,2,3-TCP, survival of males and females at10 or 30 mg/kg was significantly lower than that of the controls with early deaths and early terminations due to the development of chemical-related neoplasms (Table 10). Final mean body weights were reduced compared to those of controls, by a maximum of 5% in the high dose male and female groups. Statistically significant or biologically noteworthy neoplasms or non-neoplastic lesions of the oral mucosa, forestomach, pancreas, kidney, preputial gland, clitoral gland, mammary gland, Zymbal's gland, intestine, skin, and liver occurred in the exposed F344/N rats (summarised and presented in Table 10).

Significant increases in the incidences of exophytic papillary or nodular masses in the oral mucosa, the pharynx and tongue were observed in male and female rats, exposed to 10 and 30 mg/kg 1,2,3-TCP, compared to concurrent controls. Squamous cell papilloma or carcinoma occurred in 37% of males and 54% of females in the 10 mg/kg group, increasing to 77% of males and 62% of females in the high dose group, unambiguously rendering these findings “chemical-related”. The squamous cell carcinomas of the oral cavity exhibited invasion of the underlying tissues and in a few instances metastasised to distant organs.

Squamous cell papillomas or carcinomas similar to those of the oral mucosa were also observed in the forestomach of the majority of exposed rats at necropsy. The incidences of the forestomach neoplasms (combined) were significantly higher across all dosed groups, in either sex, compared to controls. A reduction in the incidences observed in the high dose groups compared to the 10 mg/kg groups, more prominent in female rats, was attributed to the lower survival and the competing risks from other tumour types. Focal hyperplasia of the stratified squamous epithelium, regarded as a continuum with the above-mentioned papillomas/ carcinomas was induced in the forestomach of exposed rats.

Significant, dose-related increases of up to 73% in pancreatic acinar adenomas occurred in all treated male rats, reflecting a significant induction of hyperplasia in the pancreas. However, the occurrence of adenocarcinoma was isolated and did not exceed 4% in males (two occurrences in the 10 mg/kg group and one in the 30 mg/kg group). In female rats, lower compared to males but significant increase in the incidence of hyperplasia of the pancreas in all dosed groups did not coincide with a corresponding induction of adenomas. There were only two occurrences in the 10 mg/kg group.

In the kidney, focal hyperplasia of the renal tubule epithelium occurred at significantly increased incidences in male rats, in the 10 and 30 mg/kg groups accompanied by a concomitant significant increase in the incidence of renal tubule adenomas. Despite a significant, albeit less marked compared to males, increase in the incidence of hyperplasia in the 10 and 30 mg/kg groups of exposed females, only one renal tubule neoplasm occurred at 30 mg/kg. Nephropathy was evident in almost all control and treated male animals, with the severity increasing in the latter. Female animals were also affected, but to a lesser degree.

A significant increase in preputial gland adenomas or carcinomas (combined) occurred in the 30 mg/kg males while dosed females exhibited a similar positive trend for clitoral gland neoplasms, with significant increases in the 10 and 30 mg/kg groups. Focal hyperplasia of the preputial or clitoral gland was observed in several dosed males and females.

Dose-related increases in the incidence of mammary gland adenocarcinomas occurred in all treatment groups of female rats, reaching significance in the 10 and 30 mg/kg groups.

Zymbal’s gland carcinomas occurred in one 3 mg/kg and three 30 mg/kg females and in three 30 mg/kg males, with no occurrences in the concurrent controls. These tumours are fast growing and highly invasive. Despite their incidences in the high dose groups being low and close to the highest incidence in the NTP historical controls, taking into account

the shortened life-span of the 1,2,3-TCP exposed groups by competing malignancies, this effect was considered to be substance-related.

Adenomatous polyps or adenocarcinomas of the intestine occurred in two males and one female receiving 10 mg/kg and three males and two females in the 30 mg/kg groups. No occurrence was reported in the controls. Although non-significant and small in number, it was suggested that the increased incidence of these neoplasms "*may have been chemical related*", in view of their rarity in F344/N rats and the reduced survival and shortened life span of the 30 mg/kg groups. In contrast, non-significant, dose-related increases in the incidence of squamous cell papillomas (alone or combined with carcinomas) of the skin and of hepatocellular adenomas or carcinomas (combined) evident in male rats, were not considered to be chemical related.

Table 10: Carcinogenicity studies in animals

Species, strain, sex (no/group)	Route, dose levels, duration of exposure	Results/remarks	Reference
F344/N rats (n=60/sex/dose)	Oral administration of 1,2,3-TCP (>99% pure) in corn oil by gavage, 0, 3, 10 or 30 mg/kg bw, 5 d/wk for up to 104 wk	Study compliant with FDA GLP; 10 M and 10 F rats/dose were subjected to 15-month interim evaluations, which revealed chemical-related neoplasms of the forestomach, oral mucosa (tongue and pharynx), pancreas (M), kidney, mammary gland (F), preputial gland, and clitoral gland primarily in the 10 or 30 mg/kg groups. Non-neoplastic lesions included focal hyperplasia of the stratified squamous epithelium in the forestomach and of the renal tubule epithelium. Survival of M/F rats receiving 10 or 30 mg/kg was significantly lower than that of controls. Due to high mortality, surviving 30 mg/kg rats were evaluated at 77 (M) or 67 (F) weeks. Mean body weights of M/F rats receiving 3 or 10 mg/kg were similar to controls throughout the studies; Final mean body weights of the surviving 30 mg/kg M and F were 5% lower than those of controls (wk 77 and wk 58, respectively). **Oral mucosa/pharynx and tongue; squamous cell papilloma or squamous cell carcinoma** (in the 0, 3, 10 and 30 mg/kg dose groups): M: 1/50 (2%)[a], 4/50 (8%), 18/49 (37%)* and 40/52 (77%)* F: 1/50 (2%), 6/49 (12%), 28/52 (54%)*, and 32/52 (62%)* **Forestomach neoplasms; squamous cell papilloma or squamous cell carcinoma** (in the 0, 3, 10 and 30 mg/kg dose groups):	(NTP, 1993)

Species, strain, sex (no/group)	Route, dose levels, duration of exposure	Results/remarks	Reference
		M: 0/50 (0%)[a], 33/50 (66%)*, 42/49 (86%)* and 43/52 (83%)* F: 0/50 (0%), 16/49 (33%)*, 37/51 (73%)* and 19/52 (37%)*	
		Pancreatic acinar lesions; adenoma (in the 0, 3, 10 and 30 mg/kg dose groups):	
		M: 5/50 (10%)[a], 21/50 (42%)*, 36/49 (73%)* and 29/52 (56%)* F: 0/50 (0%), 0/49 (0%), 2/52 (4%) and 0/52 (0%)	
		Kidney; adenoma (in the 0, 3, 10 and 30 mg/kg dose groups):	
		M: 0/50 (0%)[a], 2/50 (4%), 20/49 (41%)* and 21/52 (40%)*	
		Preputial Gland and clitoral gland neoplasms; adenoma or carcinoma (in the 0, 3, 10 and 30 mg/kg dose groups):	
		M: 5/49 (10%)[a], 6/47 (13%), 8/49 (16%) and 16/50 (32%)** F: 5/46 (11%), 10/46 (22%), 17/50 (34%)* and 15/51 (29%)***	
		Mammary gland; adenocarcinoma (in the 0, 3, 10 and 30 mg/kg dose groups):	
		F: 1/50 (2%)[a], 6/49 (12%), 12/52 (23%)* and 21/52 (40%)*	
		Zymbal's gland carcinomas (in the 0, 3, 10 and 30 mg/kg dose groups):	
		M: 0.50 (0%)[a], 0/50 (0%)[-], 0/49 (0%)[-] and 3/52 (6%) F: 0/50 (0%), 1/49 (2%), 0/52 (0%)[-] and 3/52 (6%)**	
		Intestine neoplasms (adenomatous polyps or adenocarcinomas)	
		potentially "chemical related", occurred in 2 M and 1 F in the 10 mg/kg group and 3 M and 2 F in the 30 mg/kg dose group	
B6C3F1 mice (n=60/sex/dose)	Oral administration of 1,2,3-TCP	Study compliant with FDA GLP; 10 M and 10 F mice/dose group were	(NTP, 1993)

Species, strain, sex (no/group)	Route, dose levels, duration of exposure	Results/remarks	Reference
	(>99% pure) in corn oil by gavage; 0, 6, 20 or 60 mg/kg bw, 5 d/wk for up to 104 wk	subjected to 15-month interim evaluations, which revealed chemical-related, non-neoplastic lesions or neoplasms of the forestomach (focal hyperplasia, squamous cell papillomas/carcinomas) and liver (eosinophilic foci, hepatocellular adenomas/carcinomas), primarily in the 20 and 60 mg/kg groups. Significantly lower survival of all dosed groups of M and F. Due to high mortality, surviving 20 mg/kg mice (M and F) were evaluated at 89 weeks, and surviving 60 mg/kg mice were evaluated at 79 (M) or 73 (F) weeks. Significantly decreased final mean body weights in the 20 mg/kg and 60 mg/kg groups in M (-13% and -16%, respectively) and in the 60 mg/kg in F (-18%), compared to controls. **Oral mucosa/pharynx and tongue; squamous cell papilloma or squamous cell carcinoma** (in the 0, 6, 20 and 60 mg/kg dose groups): M: 0/52 (0%)[a, b], 0/51 (0%), 0/54 (0%) and 2/56 (4%) F: 1/50 (2%), 0/50 (0%), 2/51 (4%) and 5/55 (9%)** **Forestomach neoplasms; squamous cell papilloma or squamous cell carcinoma** (in the 0, 6, 20 and 60 mg/kg dose groups): M: 3/52 (6%)[a], 50/51 (98%)*, 53/54 (98%)* and 55/56 (98%)* F: 0/50 (0%), 48/50 (96%)*, 50/51 (98%)* and 54/55 (98%)* **Liver neoplasms; hepatocellular adenoma or carcinoma (combined)** (in the 0, 6, 20 and 60 mg/kg dose groups): M: 13/52 (25%)[a], 24/51 (47%), 24/54 (44%)** and 31/56 (55%)* F: 7/50 (14%), 11/50 (22%), 8/51 (16%) and 31/55 (56%)* **Harderian gland; adenoma** (in the 0, 6,	

Species, strain, sex (no/group)	Route, dose levels, duration of exposure	Results/remarks	Reference
		20 and 60 mg/kg dose groups): M: 1/52 (2%)[a], 2/51 (4%), 10/54 (19%)** and 11/56 (20%)** F: 2/50 (4%), 6/50 (12%), 7/51 (14%) and 10/55 (18%)*** **Uterine neoplasms** (in the 0, 6, 20 and 60 mg/kg dose female groups); Stromal polyp F: 0/50 (0%)[a], 2/50 (4%), 1/51 (2%) and 6/54 (11%)** Endometrium adenoma or adenocarcinoma F: 0/50 (0%)[a], 5/50 (10%)***, 3/51 (6%)***, and 9/54 (17%)*	

[a]: Number of neoplasms-bearing animals/number of animals necropsied at the end of the studies or number of lesion-bearing animals/number of animals with the lesion-relevant anatomic site (e.g. pancreas/liver/preputial/clitoral glands) examined microscopically at the end of studies, [b]: in males only squamous cell papilloma was reported; *p<0.001, ** p≤0.007, *** p≤0.05 by logistic regression, fisher exact test or life table test; - not applicable; no neoplasms in animal group

In B6C3F1 mice, exposed to 6, 20, or 60 mg/kg 1,2,3-TCP, survival of all exposed males and females was significantly lower than that of the controls with early deaths and early terminations due to the development of chemical-related neoplasms (see Table 10). Final mean body weights were reduced compared to those of controls, by up to 16% and 18% in the high dose male and female groups, respectively.

Statistically significant or biologically noteworthy neoplasms or non-neoplastic lesions of the oral mucosa, forestomach, liver, harderian gland, uterus, and large intestine occurred in mice receiving 1,2,3-TCP (summarised and presented in Table 10).

Compared to rats, fewer neoplasms of the oral mucosa occurred in dosed mice. Squamous cell papillomas occurred in one control, two 60 mg/kg males and one 20 mg/kg female mouse. Squamous cell carcinomas were only observed in females, in one 20 mg/kg and five 60 mg/kg dosed mice. These lesions rarely occur spontaneously in mice with no reported incidence in either sex, in the NTP historical controls. As a result, the induction of squamous cell carcinomas in females was clearly attributed to the administration of 1,2,3-TCP, while the finding of the papillomas in males was deemed uncertain.

Exophytic papillary or nodular masses, comprising squamous cell papillomas or carcinomas, similar to those observed in rats, were also reported in the forestomach of nearly all dosed male and female mice at necropsy, at significantly increased incidences across all dosed groups, compared to controls and markedly exceeding the historical control data. As a result, this finding was unambiguously deemed substance-related. A dose-dependent increase in focal hyperplasia, regarded as part of a morphological continuum with the above-mentioned squamous cell papillomas/carcinomas was noted in all dosed male mice and in the high dose group in females.

In the liver, the combined incidence of hepatocellular adenoma or carcinoma, dominated by adenomas, was significantly greater in the 20 and 60 mg/kg males and in the 60 mg/kg females, compared to controls, providing clear evidence of 1,2,3-TCP carcinogenicity in mice of either sex. The incidence of hepatocellular carcinoma, however, was significantly

increased only in 6 mg/kg males. Eosinophilic foci believed to be precursors of hepatocellular adenoma, occurred more frequently in 20 mg/kg and 60 mg/kg male mice and in all dosed groups of female mice, than in controls.

Harderian adenomas were observed at significantly increased rates in the 20 and 60 mg/kg dose groups in males and in the 60 mg/kg group in females. Although the incidences of these neoplasms in concurrent controls was higher than that of historical controls, the 20 and 60 mg/kg groups in males and the 60 mg/kg in females, exceeded the upper boundary of the historical control range, despite the lower survival and shortened life span of these groups, rendering this finding chemical-related.

Similarly, the occurrence of stromal polyps of the uterus – relatively uncommon spontaneous neoplasms - were deemed chemical-related, because of a significant increase observed in the high dose female group.

The incidences of uterine endometrial adenomas or adenocarcinomas (combined), dominated by the latter, were increased in all dosed females and were considered to be related to the administration of 1,2,3-TCP, since the incidences in each group exceeded the range in historical controls and were significantly greater than the concurrent controls.

Finally, two occurrences of squamous cell carcinoma in the large intestine were noted in two females (one exposed to 20 and the other to 60 mg/kg 1,2,3-TCP).

Additionally, (NTP, 1982) showed that halogenated propanes including 1,2-dibromo-3-chloropropane (DBCP) and 1,2-dibromoethane are carcinogenic in inhalation studies in F344/N rats and B6C3F1 mice (as cited in (EPA, 2017). DBCP also forms the same major DNA adduct, S-[1-(hydroxymethyl)-2-(N7-guanyl)ethyl]-glutathione, as 1,2,3-TCP (Humphreys et al., 1991).

7.7.3 Summary

There are no human data on carcinogenic effects of 1,2,3-TCP.

The carcinogenic potential of 1,2,3-TCP was evaluated in 2-year, oral NTP studies in F344/N rats and B6C3F1 mice (1993). Increases in the incidence of neoplastic lesions were observed at all doses tested (≥ 3 mg/kg bw in rats and ≥ 6 mg/kg bw in mice).

Collectively, "*clear evidence of carcinogenic activity*" of 1,2,3-TCP in F344/N rats of either sex was provided by significantly increased incidences of:

- squamous cell papillomas and carcinomas of the forestomach (≥ 3 mg/kg bw)
- squamous cell papillomas and carcinomas of the oral mucosa (≥ 10 mg/kg bw)
- carcinomas of the Zymbal's gland (significant at 30 mg/kg in F)

"*Clear evidence of carcinogenic activity*" was also provided

a. in males by significantly increased incidences of:

- adenomas of the pancreas (≥ 3 mg/kg bw) and kidney (≥ 10 mg/kg bw)
- adenomas or carcinomas of the preputial gland (30 mg/kg)

b. in females by increased incidences of:

- mammary gland adenocarcinomas (≥ 10 mg/kg bw)
- adenomas or carcinomas of the clitoral gland (≥ 10 mg/kg bw)

Finally, adenomatous polyps and adenocarcinomas of the intestine in males and females may have been related to chemical administration.

In B6C3F1 mice, "*clear evidence of carcinogenic activity"* of 1,2,3-TCP, in either sex was provided by significantly increased incidences of:

- squamous cell papillomas and carcinomas of the forestomach (≥6 mg/kg bw)
- hepatocellular adenomas or carcinomas of the liver (M: ≥20 mg/kg bw; F: 60 mg/kg bw)

- Harderian gland adenomas (M: ≥20 mg/kg bw; F: 60 mg/kg bw)

"*Clear evidence of carcinogenic activity*" was additionally provided in female mice only, by significantly increased incidences of:

- squamous cell carcinomas of the oral mucosa (60 mg/kg bw)
- uterine adenomas/adenocarcinomas (≥6 mg/kg bw)
- stromal polyps (60 mg/kg bw)

Squamous cell papillomas of the mucosa in the oral cavity of male mice may have been related to substance exposure.

7.8 Reproductive toxicity

7.8.1 Human data

There are no human data regarding fertility effects of 1,2,3-TCP.

Brender et al. (2014) examined the relation between maternal residential proximity to industrial air releases of chlorinated solvents and birth defects in offspring of 60,613 case-mothers and 244,927 control-mothers. Maternal residential exposures to solvent emissions were estimated with a model that took into account residential distances to industrial sources and annual amounts of chemicals released. The exposure was characterised as an exposure risk index. Odds ratios were calculated for associations between residential proximity to emissions of 14 chlorinated solvents and 12 selected birth defects, including neural tube, oral cleft, limb deficiency, and congenital heart defects. Risk estimates were adjusted for year of delivery and maternal age, education, race/ethnicity, and public health region of residence. The modelled exposure risk values were categorized either dichotomously into two groups (exposure risk values for a given solvent equalling zero or greater than zero) or to four or seven levels. The lowest level of exposure risk value served as the reference group for all analyses. In addition to the dichotomous analyses by exposure, further analyses of odds ratios associated with varying intensities of exposure risk values were performed to test for significance of linear trends. For 1,2,3-TCP, an increased risk was observed for neural tube defects (OR 1.5, 95% CI 1.1 - 2.1) and spina bifida (OR 1.8, 95% CI 1.2 - 2.6), but not for anencephaly (OR 1.2, 95% CI 0.6 - 2.4). No statistically significant increase in risk was observed for oral cleft defect, cleft palate alone, cleft lip with or without cleft palate, conotruncal heart defects, obstructive heart defects, septal heart defects, any type of limb deficiency, longitudinal limb deficiency or transverse limb deficiency. When testing the linear trend across four exposure index categories, significant trends by 1,2,3-TCP categories were found for spina bifida ($p < 0.0001$) and septal heart defects ($p = 0.033$), but not for cleft palate ($p = 0.083$). It is noted that testing 14 solvents and 12 birth defects results in multiple testing and the statistical significance tests were not corrected for that. There were also several statistically significant associations observed for the other chlorinated solvents examined. The risk estimates for 1,2,3-TCP were not controlled for potential confounding by exposure to the other chlorinated solvents or by life-style factors.

7.8.2 Animal data

In a GLP study (Gulati et al., 1990 as reported in (OECD, 2004)), conducted according to OECD TG 416, Swiss CD-1 mice received 1,2,3-TCP by gavage in corn oil in the "Reproductive Assessment by Continuous Breeding (RACB)" protocol in which four tasks are performed:

1. Task 1: 14 day dose setting (n=8/sex/dose; 0, 12.5, 25, 50, 100 or 200 mg/kg bw/d);
2. Task 2: 18 weeks distributed as 1 week pre-mating, 14 weeks cohabitation and 3 weeks thereafter (40 breeding pair in the control and 20 in the dosed groups; 0, 30, 60 or 120 mg/kg bw/d);

3. Task 3: 24 weeks (cross-over mating trial: 3 groups of 20 pairs each (control males x control females; control males x high-dose females; and control females x high-dose males), dosed with 0 or 120 mg/kg bw/d), performed only if decreased fertility was observed in Task 2 to determine which of the two sex, if not both, were affected;
4. Task 4 was the second generation from Task 2 pups: 30 weeks (20 breeding pairs in control, low and mid dose groups; 10 breeding pairs in high dose group, dosed with 0, 30, 60 or 120 mg/kg bw/d).

The findings were as follows:

1. Task 1: one male mouse died at 200 mg/kg bw/d.
2. In Task 2: fertility was reduced at the mid and high dose with increase in duration of exposure: there were no effects on the first 2 litters. However a reduction of fertility was visible and was dose- and litter-dependent. In the 3rd litter the proportion of pairs delivering a litter were 87, 78, 68, and 42% (statistically significant), for control, low, mid and high dose, respectively. Cumulative data showed that the effects were more evident on the high dose (120 mg/kg bw/d) and those included: a decrease in the number of litters per pair (16%), a decrease in the number of live pups/litter (47%) although pups viability was not affected, an increase in the live pup weight and cumulative days to delivery for the 4th and 5th litters, by 4 and 6 days. Dam weights were not different from control during gestations.
3. In Task 3: body weights were lower on the high dosed animals for both sexes, but significant in females only on week 24. The mating index was not different, although the fertility index was slightly lower. In particular, treated females mated to control males produced fewer live pups (5 on average); no effect on fertility was found with treated males mated to control females (9 to 10 as in control). These data suggest an impairment of female fertility (WHO, 2003). The number of live pups/litter was reduced, but not the pup viability. There were fewer males/litter and adjusted live pup weights for males were reduced compared to control. After Task 3, the F0 animals were necropsied. Relative liver weights were increased in exposed males and females (20 and 22%, respectively). Furthermore, relative kidney and ovary weights were decreased in exposed females (9 and 20%, respectively). There were no effects on sperm parameters or on the length of the oestrous cycle. Four out of 10 treated females had microscopic ovarian amyloidosis versus 0 of 10 control females.
4. In Task 4: the last litter from Task 2 (F1) were retained and weighed on postnatal days 0, 4, 7, 14 and 21. Live pup weights were significantly increased at the high dose in both sexes, probably due to smaller litter size. However, the proportion of pups born alive and postnatal survival were not different from control. The smaller litter size of the high dose group resulted in only 9 breeding pairs compared to 20 in the other groups and control. The mating index, pregnancy index and fertility index were all reduced at the high dose, with only 3 out of 9 pairs delivering litters with any pups. There were no statistically significant effects on the number of liver pups/litter (control 10.8 vs high dose 7.3), the proportion of pups born alive, the sex ratio or the average live pup weight. Body weights of F1 animals were increased in the mid and high dose groups (5, 11% in males and 9, 9% in females, respectively), while water consumption was increased only in the high dosed animals. At necropsy, increased relative liver weights (9, 28%, mid, high dose, respectively), and relative kidney weights (14%, high dose) were observed in males. There were no effects on any of the sperm parameters measured. In females, there were increased relative liver (6 and 21%, mid and high dose, respectively) and decreased ovary weights (15 and 40%, mid and high dose, respectively). Oestrous cycle length was increased at all dose levels and were 4.66, 5.08, 5.18, and 5.06 days, from control to high dose. At the high dose (120 mg/kg

bw/d), only few signs of systemic toxicity were observed, thus the authors concluded that 1,2,3-TCP is a reproductive toxicant in Swiss CD-1 mice.

The main findings were: in the first generation fewer litters and fewer pups per litter, and in the second generation fewer fertile matings and reduced ovary weights and lengthened oestrous cycles. The F1 ovary weight reduction and cycle increase occurred in the absence of any change in any indications/signs of general toxicity or clinical signs. In particular, the findings in F0 and F1 females and the lower female than male fertility as observed from the cross-mating (Task 3), led the authors to suggest that 1,2,3-TCP could be a selective female reproductive toxicant (Gulati et al., 1990 as reported in (OECD, 2004)).

In a GLP compliant, 1-generation study, CD rats (n=12 (m) and n=22 (f)/dose) were exposed via inhalation to 5 or 15 ppm 1,2,3-TCP (6 h/d, 5d/week), from 10 days pre-mating until gestation day (GD) 14. Significantly lower body weights were reported for high dose males and females during the pre-mating period and continued during gestation and lactation in females. Poor mating performance was observed for all rats; after four 10-day mating periods, the mating performance was 20, 85, 80 and 50% in the two controls, low and high dose groups, respectively. This resulted in the following combined pregnancy rates[13]: 25, 71, 75 and 90% in the two controls, low and high dose groups, respectively. This poor mating rate was attributed to the low mating index of the males involved, rather than the females. Gestation length and litter survival on PND21 were not affected, neither were the number of live pups compared to the total number of pups in the low dose. At the high dose, the number of live pups was significantly reduced. No effects were reported on the pups, while in high dosed females, alteration of the organs weight was as follows: significantly higher spleen, spleen/body weight, spleen/brain weight, ovary/body weight and ovary/brain ratios, and significantly lower kidney weight, kidney/body weight and kidney/brain weight ratios (Schroeder and Rinehart, 1980 as reported in (OECD, 2004) and considered non-reliable[14]).

Male Sprague-Dawley rats (n=15/dose) were treated with 80 mg/kg bw/d 1,2,3-TCP in corn oil for 5 days, by gastric intubation in a dominant lethal study. No impairment of mating performance and no meaningful changes in the indices measured, such as numbers of implants, live embryos, and dead implants were noted (Saito-Suzuki et al., 1982, as reported in (WHO, 2003)).

In a GLP study, F344 rats (n=20/sex/dose; n=30/sex as vehicle controls) received by gavage with 0, 8, 16, 32, 63, 125 or 250 mg/kg bw/d 1,2,3-TCP in corn oil (5 d/week, 120 d). No differences in sperm count and morphology were recorded in 10 animals from the 125 mg/kg bw/d dose, with respect to control animals. At 60 days, statistically significant increases in relative testes weight and a significant decrease in relative epididymis weights were observed in 125 mg/kg bw/d males while at 120 days the testis relative weight was significantly reduced at the same dose. (NTP, 1993 as reported in (NICNAS, 2015); Ulland et al., 1983 as reported in (OECD, 2004)).

In a GLP study, B6C3F1 mice (n=20/sex/dosed group; n=30/sex, vehicle controls) received by gavage with 0, 8, 16, 32, 63, 125 or 250 mg/kg bw/d 1,2,3-TCP in corn oil (5 d/week, 120 d). Some effects on sperm count were observed However due to the high variability, they were not considered treatment-related. In addition, no changes in sperm morphology or testis and epididymis histopathology were reported. At interim sacrifice only, relative and absolute testis and epididymis weights were significantly decreased (Ulland et al., 1983 as reported in (OECD, 2004)).

[13] Pregnancy rate was calculated equal to (number of pregnant females/ number of sperm positive females)x100

[14] “Significant methodological deficiencies. Test protocol did not adequately examine the fertility and reproductive parameters, and reproductive success was significantly lower than acceptable standards” OECD 2004. OECD SIDS, 1,2,3-Trichloropropane. OECD.

In a teratogenic study, Sprague-Dawley rats (n=10-15 females/dose) received 0 or 37 mg/kg bw/d 1,2,3-TCP in corn oil, intraperitoneally, between GD1 and CD15. No treatment-related effects were observed in uterus, ovaries or foetuses, however the authors concluded that due to the route of exposure and the small group size the results must be considered preliminary (Hardin et al., 1981 as reported in (OECD, 2004)).

7.8.3 Summary

There are no human data on fertility following exposure to 1,2,3-TCP. The data on developmental effects relate to one study analysing the effects from estimated environmental release which indicate an association between exposure to 1,2,3-TCP and risk of some birth defects. However, the effect of life-style factors and environmental exposure to other chlorinated solvents, as well as of multiple testing were not adjusted for, and no quantitative estimates of airborne exposure concentrations were provided.

In the animal studies, 1,2,3-TCP showed "*clear evidence*" of impaired female fertility at 120 mg/kg bw/d in Swiss CD-1 mice on the RACB study (Gulati et al., 1990 in (OECD, 2004)). A marginal decrease of mating rate was reported in an inhalation study in CD rats, however the study is considered non-reliable (OECD, 2004). Changes in male organs (testes and epididymis weights) were reported in repeated dose studies (120 days) in rats but not in mice (Ulland et al., 1983 in (OECD, 2004)). No teratogenic effects were reported on the multigeneration study (Gulati et al., 1990 in (OECD, 2004)) or in the screening teratogenic study (Hardin et al., 1981 in (OECD, 2004)).

8. Other considerations

8.1 Mode of action (MoA) considerations

Although animal studies provide evidence of the multiple-site carcinogenicity of 1,2,3-TCP, very little information is available on the mechanisms of action for carcinogenicity. In the 2-year NTP carcinogenicity study, the highest incidence of neoplasms and most marked dose-response effect for both rodent species was in the forestomach. A 97% and 90% incidence of tumours of the forestomach was evident in male and female mice, respectively at the lowest dose tested.

The mutagenic activity of 1,2,3-TCP has been demonstrated in bacterial and mammalian cell systems, typically in the presence of an S9 fraction, while DNA damage has been detected in several different rat and mouse tissues. 1,2,3-TCP is therefore concluded to be carcinogenic by a mutagenic mode of action.

Liver and forestomach (squamous cell carcinoma) samples from the 1,2,3-TCP exposed mice in the 2-year gavage NTP study were recently analysed for the number and frequency of somatic SNVs and mutational signatures (Riva et al., 2020). This was part of a more extended study of tumour genome sequencing from mice chronically exposed to known/suspected carcinogenic chemicals resulting in clear/some evidence of tumorigenicity in the NTP bioassay. 1,2,3-TCP-induced liver and forestomach tumours presented as high mutational burden tumours, displaying a significantly increased number of mutations, ranging from >2 to up to 10-fold increase compared to the comparator chemical-related and spontaneous tumours. Out of the only four mouse mutational signatures identified to exclusively occur in chemical-exposed animals and therefore deemed "exogenous", three were associated specifically to TCP-exposure with two present only in forestomach tumours. These TCP-specific signatures aligned with high similarity with known signatures from the human categories of somatic mutations in cancer (COSMIC) catalogue, where an aetiology for each signature has been proposed. This analysis revealed that one TCP-related mouse signature corresponded to a previously identified and experimentally validated as a unique signature to human cholangiocarcinoma arising from occupational exposure to haloalkanes (Mimaki et al.,

2016). Significant associations also occurred with two human signatures for liver tumours and pilocytic astrocytomas (low-grade gliomas). The third signature corresponded mainly to human liver hepatocellular carcinomas – albeit occurring only in 2% of cases. Further analysis revealed that the TCP-signatures exhibited a strong transcriptional strand bias, consistent with their exogenous nature and the repair of DNA adducts by transcription-coupled nucleotide excision repair. Finally, forestomach tumours displayed increased numbers of dinucleotide substitutions and indels over liver, kidney and lung tumours from other chemicals and spontaneous tumours (Riva et al., 2020).

These mouse data provide experimental evidence linking mouse exposure to 1,2,3-TCP and the generation of signatures causally connected to specific human tumours, providing a mechanistic basis on how 1,2,3-TCP can shape the mutational landscape of human cancers. Notably, the mouse signature corresponding to human cholangiocarcinoma was tissue-specific and found only in forestomach but not in liver tumours from TCP-treated animals.

8.2 Lack of specific scientific information

No specific information gaps were identified.

8.3 Groups at Extra Risk

No specific groups at extra risk were identified.

9. Evaluation and recommendations

9.1 Cancer risk assessment

9.1.1 Published approaches for cancer risk assessment

SCOEL (2011) noted that 1,2,3-TCP is mutagenic and causes chromosomal damage *in vitro* after metabolic activation. In long-term animal studies, 1,2,3-TCP was clearly carcinogenic after oral administration to rats and mice. This exposure resulted in tumours of the oral mucosa and of the uterus in female mice and increased the incidences of tumours of the forestomach, liver and Harderian gland in mice of either 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/bw in rats or 6 mg/kg/bw in mice). In addition, the metabolite, 1,3-dichloroacetone, initiated skin tumour development in mice when applied topically. In agreement with IARC (IARC, 1995), SCOEL concluded that there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of 1,2,3-TCP. The plausible mode of action of the carcinogenicity of 1,2,3-TCP was considered to be the genotoxic activity of its biological reactive metabolic intermediates. No cancer risk calculations were conducted.

DFG (1993) noted that 1,2,3-TCP is mutagenic and causes chromosomal damage *in vitro* but only after metabolic activation. *In vivo* the substance has been shown to cause DNA damage in the liver and kidneys of rats but does not induce dominant lethal mutations. DFG (1993) concluded that "*The studies available to date demonstrate that 1,2,3-trichloropropane has marked genotoxic potential both in vitro after metabolic activation and in vivo; oral administration of the substance to both rats and mice in a 2-year study resulted in numerous neoplastic changes*". No cancer risk calculations were conducted.

ATSDR (2021) considered cancer as one of the most sensitive effects related to 1,2,3-TCP exposure. The most sensitive target tissue appeared to be the forestomach, in particular squamous cell papillomas and carcinomas in the forestomach (observed at the lowest

doses tested). Other targets included the oral mucosa, liver, and kidneys. No cancer risk calculations were conducted.

US EPA (2009) performed a toxicological review and cancer assessment of 1,2,3-TCP. They concluded that "*1,2,3-trichloropropane is "likely to be carcinogenic to humans," based on a statistically significant and dose-related increase in the formation of multiple tumors in both sexes of two species from an NTP (1993) chronic oral bioassay".* Dose-related, statistically significant increasing trends in tumours were observed at the following sites: squamous cell carcinomas or papillomas of the alimentary system (male and female rats and mice), Zymbal's gland carcinomas (male and female rats), pancreatic acinar cell adenomas or adenocarcinomas, preputial gland adenomas or carcinomas, and kidney tubular cell adenomas (male rats), clitoral gland adenomas or carcinomas, and mammary gland adenocarcinomas (female rats), hepatocellular adenomas or carcinomas, and harderian gland adenomas (male and female mice), uterine adenomas or adenocarcinomas (female mice).

To account for the uncertainty associated with forestomach tumours, EPA performed quantitative carcinogenicity dose-response analyses for the total alimentary system tumours (combined incidence of squamous papillomas or squamous cell carcinomas of the pharynx/palate, tongue, or forestomach) and for oral cavity tumours only (squamous papillomas or squamous cell carcinomas of the pharynx/palate or tongue), in rats and mice. US EPA recommended the upper bound estimate on human extra cancer risk from continuous lifetime oral exposure to 1,2,3-trichloropropane (oral slope of 30 per mg/kg-day). The oral slope they presented is based on incidences of tumours in the alimentary system (including oral cavity and forestomach tumours), liver, harderian gland and uterus of female mice because female mice were the most sensitive to tumour induction following exposure to 1,2,3-TCP.

9.1.2 Cancer risk assessment

1,2,3-TCP has a harmonised classification as Carc. 1B, based on animal data. No threshold for the effects can be identified and the substance is concluded to be carcinogenic by a mutagenic mode of action. Based on positive mutagenicity findings in the presence of metabolic activation it is assumed that the genotoxicity of its reactive metabolic intermediates is important for the carcinogenicity of 1,2,3-TCP. No human cancer data was found and therefore an exposure-risk relationship (ERR) was derived from animal data.

The 2-year oral rat and mice study (NTP 1993) showed increases in the incidence of neoplastic lesions at all (including low) doses tested (≥ 3 mg/kg bw in rats and ≥ 6 mg/kg bw in mice) at multiple locations and was identified as the key study. No carcinogenicity study conducted by inhalation was available. Similar to US EPA (2009) (Section 9.1.1), cancer in the total alimentary tract category was chosen as the most sensitive endpoint.

However the dose-response correlations reported were not very clear or suitable for benchmark dose modelling. Therefore, T25 was used to identify the point-of-departure for total alimentary tract findings[15].

T25 can be defined as "the chronic dose rate which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life-time of that species" (Sanner et al., 2001).

15 https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

9.1.2.1 Cancer risk calculations on male rat data

T25 was calculated as:

$$T25 = C \times \frac{\text{reference incidence}}{(\text{incidence at C} - \text{control incidence})} \times \frac{(1 - \text{control group incidence})}{1}$$

with C being the lowest observed adverse effect level (LOAEL) of 3 mg/kg bw/day for total alimentary tract tumours, 36/60 incidence at C, 1/59 control incidence, and 0.25 being the reference incidence.

$$T25 = 3 \text{ mg/kg} \times \frac{0.25}{(39/60 - 1/59)} \times \frac{(1 - 1/59)}{1} = 1.16 \text{ mg/kg}$$

The additional cancer risk was calculated as follows:

1) Conversion of the oral rat dose to the corresponding air concentration using the standard breathing volume for the rat (0.38 m^3/kg bw):

- T25(inhalation): 1.16 mg/kg bw/d / 0.38 m^3/kg bw= 1.74 mg/m^3

2) Correction for exposure duration (considering 40 years of work), bioavailability (oral 80% (see section 7.1.2.), inhalation 80% absorption) and inhalation volume (rats in rest vs worker light activity)

- T25(worker): 1.74 mg/m^3 *x* (75/40 years) *x* (52/48 weeks) *x* 0.8 *x* (6.7/10 m^3) = 1.9 mg/m^3.

3) Additional lifetime cancer risks calculated as follows according to a linearised approach (high to low dose extrapolation)

- The exposure concentration representing a $1x10^{-5}$ risk would be: 1.9 mg/m^3 / 25 000 ≈ 0.00008 mg/m^3 (0.00001 ppm)

9.1.2.2 Cancer risk calculations on female rat data

T25 of 2.07 mg/kg bw/day was calculated as above (Section 9.1.2.1) using the following parameters: C being the of LOAEL of 3 mg/kg bw/day (total alimentary tract tumours), incidence at C (22/59), control incidence (1/60).

1) Conversion of the oral rat dose to the corresponding air concentration using the standard breathing volume for the rat (0.38 m^3/kg bw):

- T25(inhalation): 2.07 mg/kg bw/d / 0.38 m^3/kg bw= 5.4 mg/m^3

2) Correction for exposure duration (considering 40 years of work), bioavailability (oral 80% (see section 7.1.2.), inhalation 100% absorption) and inhalation volume (rats in rest vs worker light activity)

- T25(worker): 5.4 mg/m^3 *x* (75/40 years) *x* (52/48 weeks) *x* 0.8 *x* (6.7/10 m^3) = 5.9 mg/m^3.

3) Additional lifetime cancer risks calculated as follows according to a linearised approach (high to low dose extrapolation)

- The exposure concentration representing a $1x10^{-5}$ risk would be: 5.9 mg/m^3 / 25 000 ≈ 0.0002 mg/m^3 (0.00003 ppm)

9.1.2.3 Cancer risk calculations on male mice data

T25 of 1.55 mg/kg bw/day was calculated as above (Section 9.1.2.1) using the following parameters: C being the LOAEL of 6 mg/kg bw/day (total alimentary tract tumours), incidence at C (57/59), control incidence (3/59).

1) Conversion of the oral mice dose to the corresponding worker air concentration (allometric scaling mouse factor 7, inhalation volume worker light activity 10 m^3):

T25(inhalation): 1.55 mg/kg bw/d *x* 70 kg bw / 10m^3 / 7 = 1.55 mg/m^3

2) Correction for exposure duration (considering 40 years of work) and bioavailability (oral 80% (see section 7.1.2.) inhalation 100% absorption)

- T25(worker): 1.55 mg/m^3 *x* (75/40 years) *x* (52/48 weeks) *x* 0.8 = 2.5 mg/m^3.

3) Additional lifetime cancer risks calculated as follows according to a linearised approach (high to low dose extrapolation)

- The exposure concentration representing a 1x10^{-5} risk would be: 2.5 mg/m^3 / 25 000 ≈ 0.0001 mg/m^3 (0.00002 ppm)

9.1.2.4 Cancer risk calculations on female mice data

T25 of 1.67 mg/kg bw/day was calculated as above (Section 9.1.2.1) using the following parameters: C being the LOAEL of 6 mg/kg bw/day (total alimentary tract tumours), incidence at C (54/60), control incidence (0/59).

1) Conversion of the oral mice dose to the corresponding worker air concentration (allometric scaling mouse factor 7, inhalation volume worker light activity 10 m^3):

T25(inhalation): 1.67 mg/kg bw/d *x* 70 kg bw / 10m^3 / 7 = 1.67 mg/m^3

2) Correction for exposure duration (considering 40 years of work) and bioavailability (oral 80% (see section 7.1.2.), inhalation 100% absorption) using default values

- T25(worker): 1.67 mg/m^3 *x* (75/40 years) *x* (52/48 weeks) *x* 0.8 = 2.7 mg/m^3.

3) Additional lifetime cancer risks calculated as follows according to a linearised approach (high to low dose extrapolation)

- The exposure concentration representing a 1x10^{-5} risk would be: 2.7 mg/m^3 / 25 000 ≈ 0.0001 mg/m^3 (0.00002 ppm)

9.1.2.5 ERR for total alimentary findings

For the purpose of deriving an ERR, we calculated the mean of all 4 exposure concentrations (as presented in sections 9.1.2.1.-9.1.2.4. and summarised in Table 11) representing a 1x10^{-5} additional lifetime cancer risk in male/female rats and mice.

Table 11: Exposure concentrations representing a 1x10^{-5} additional lifetime cancer risk (total alimentary tract tumours, NTP, 1993)

	1,2,3-TCP concentration in air (mg/m^3)	1,2,3-TCP concentration in air (ppm)
Male rats	0.00008	0.00001
Female rats	0.0002	0.00003
Male mice	0.0001	0.00002
Female mice	0.0001	0.00002

The result was 0.0001 mg/m^3 (equivalent to 0.00002 ppm). Assuming linearity, excess life-time cancer risks were calculated and are presented in Table 12.

Table 12: Cancer exposure-risk relationship (total alimentary tract tumours) after working life exposure to a given 8-hour air concentration for five working days a week over a 40-year working life period.

1,2,3-TCP concentration (mg/m^3)	1,2,3-TCP concentration in air (ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.0004	0.00008	4
0.004	0.0008	40
0.04	0.008	400
0.4	0.08	4000

9.2 Derived Occupational Exposure Limit (OEL) Values

1,2,3-TCP has been shown to cause carcinogenicity in experimental animals and it is assumed to be related to a non-threshold MoA. For that reason, it is not possible to derive a health-based OEL, and exposure-risk relationships (ERR) were calculated from animal data (see section 9.1.2). No human carcinogenicity data were found.

9.2.1 Published approaches to establishing OELs

No published approaches to establishing OELs for 1,2,3-TCP were found.

SCOEL (2011) concluded that there is inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of 1,2,3-TCP. The plausible mode of action of the carcinogenicity of 1,2,3-TCP was identified as genotoxicity of its biological reactive metabolic intermediates. SCOEL did not to derive a health-based OEL value because 1,2,3-TCP was categorised into the SCOEL Group A (genotoxic carcinogen for which a threshold cannot be supported).

9.2.2 Occupational Exposure Limits (OELs) - 8h TWA

9.2.2.1 Derivation of 8h TWA for non-cancer effects

If 8 h TWA levels for non-cancer effects were to be derived from data on threshold effects, the bile duct hyperplasia findings (which can be considered as early signs for carcinogenicity), observed at doses of 3-30 mg/kg bw/day in rats after 15 months of exposure (NTP, 1993) could be used as the starting point. Other studies, including studies on reproductive toxicity, had higher NOAEC/LOAEC values.

Employing the BMD approach using EFSA Open Analytics software (quantal response, without/with model averaging, extra-risk: BMD10%, 95%CI) on the bile duct hyperplasia findings yielded a BMDL of 1.14 mg/kg. It should be noted that this estimation was based on small number of cases in male rats.

Next, the calculations would include the following steps:

1) Conversion of the oral rat dose to the corresponding air concentration using the standard breathing volume for the rat (0.38 m^3/kg) and correction for inhalation volume (rats in rest vs worker light activity) using default values [17] :

1.14 mg/kg bw/d / 0.38 m^3/kg bw) *x* (6.7 mg/m^3 / 10 mg/m^3) = 2.0 mg/m^3 [16]

2) Application of assessment factors: a factor 2.5 to cover interspecies differences, and a factor of 5 for worker intraspecies differences. As the exposure time of the study was 15 months, no assessment factor is applied for the study duration. Application of these factors would lead to:

8h TWA: 2 mg/m^3 / 2.5 *x* 5 ≈ 0.16 mg/m^3 (corresponding to 0.03 ppm).

This would correspond to an excess life cancer risk of about 230 cases per 100 000 exposed workers. As a consequence, a BOEL based on cancer risk will also protect from non-cancer effects, provided that the value will not exceed 0.16 mg/m^3.

The only validated method for 1,2,3-TCP has a LOQ of about 18 mg/m^3 (3 ppm) which is presumably far higher than the future OEL However, data from literature indicate that it should be possible to measure 1,2,3-TCP in lower concentrations by developing new analytical methods or optimising the available ones. Thus, no analytical problems are foreseen

9.2.3 Short Term Exposure Limits (STELs)

The available data does not indicate a need to propose a STEL.

9.2.4 Biological Limit Value (BLV)

There is no information available on biomonitoring of 1,2,3-TCP exposure and no limit value is proposed.

9.2.5 Biological Guidance Value (BGV)

There is no information available on biomonitoring of 1,2,3-TCP exposure and no limit value is proposed.

9.3 Notations

1,2,3-TCP causes acute toxicity via the dermal route, indicating significant systemic uptake after skin exposure. A ‘skin’ notation is therefore proposed.

There are no human data on respiratory or skin sensitisation of 1,2,3-TCP. In two studies conducted with a protocol similar to the Buehler method on guinea pigs, 1,2,3-TCP was considered to be ‘non-sensitiser’ for skin, while in a guinea pig maximisation test it was concluded to be "very slight sensitizer". No information is available for respiratory sensitisation. Altogether, no notation for ‘Sensitisation’ is proposed.

16 https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258?t=1353935239897

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