Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for

1,2,3-Trichloropropane

ECHA/RAC/OEL-O-0000007251-82-01/F

16 March 2023

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR 1,2,3-Trichloropropane

Commission request

The Commission asked the advice of RAC to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances, in support of the preparation of 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)[1].

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission RAC is requested to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for 1,2,3-Trichloropropane with a deadline of 22 February 2024.

Chemical name(s): 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**.

RAC developed its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion, the scientific report was further developed as an Annex to ensure alignment.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Andrea Hartwig.**

The opinion was adopted by **consensus** on **16 March 2023**.

RAC Opinion of the assessment of the scientific relevance of OELs for 1,2,3-Trichloropropane (1,2,3-TCP)

RECOMMENDATION

The opinion of RAC on the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for 1,2,3-Trichloropropane (1,2,3-TCP; EC number 202-486-1) is set out in the tables below and in the following summary of the evaluation, supported by Annex 1.

1,2,3-TCP is considered to be a non-threshold carcinogen.

Consequently, no health-based occupational exposure limit (OEL) nor a short-term exposure limit (STEL) can be identified. Instead, RAC derived an exposure-risk-relationsship (ERR) expressing the excess cancer risk (squamous cell papillomas/carcinomas of the oral cavity) as a function of the air concentration of 1,2,3-TCP.

SUMMARY TABLE

The tables present the outcome of the RAC evaluation to derive limit values, notations and exposure-risk-relationsships 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 relationships (ERR)*

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, Aassuming exposure 8 hours per day and 5 days per week over a 40-year working life period.

RAC notes that the European Commission and its interlocutors aim to set limit values for non-threshold carcinogens between predetermined upper and lower risk levels. ACSH (2022) agreed in its opinion that the upper risk level is 4:1 000 (corresponding to 4 predicted cancer cases in 1 000 employees), that the lower risk level is 4:100 000, assuming exposure over 8 hours per day, 5 days a week over a 40-year working lifetime and concluded that "*The OEL cannot be set above the risk level of 4:1 000*".

Since 1,2,3-TCP is considered to be a non-threshold carcinogen, it is not possible to derive a safe level for a biological limit value (BLV). Also, no correlations between biomonitoring and air levels can be derived for this substance, and no biological guidance value (BGV) can be stated.

According to LD_{50} data, marked systemic uptake via the skin needs to be considered, and a 'skin' notation is proposed.

RAC OPINION

Background

This evaluation is based on Annex 1, prepared by ECHA, which takes previous reviews into account, such as ATSDR (2021), OECD (2004), SCOEL (2011), WHO (2003) and DFG (19930.

A literature search of published papers from the last ten years completed the source of information (date of last literature search: October/2022). Databases used were last accessed: October/2022.

Key conclusions of the evaluation

- 1,2,3-TCP has a harmonised classification as Carc. 1B and Repr. 1B.
- 1,2,3-TCP is a man-made chemical that is present in the environment as a result of anthropogenic activity. 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.
- Occupational exposure occurs by inhalation and dermal exposure in industrial production and use of 1,2,3-TCP. However, there is a lack of quantitative information on dermal exposure and uptake. In general, workplace exposure appears to be limited due to handling under strictly controlled conditions. The main activity where exposure is possible is during manual maintenance, but even then, both measured exposure (for inhalation) and modelled exposure (for dermal uptake) are very low due to a low frequency or duration of the activity, local exhaust ventilation in place and use of personal protective equipment (PPE).
- Registration data indicate a worst case scenario of air concentrations around 0.03 mg/m^3 (0.005 ppm), if the substance can be detected at all. According to literature, a published air monitoring method exerts a LOQ of 0.0001 ppm (see section 6.1 of Annex 1 for further details).
- There are no human data on toxicokinetics of 1,2,3-TCP. In rats and mice, more than 80% of an oral dose were absorbed through the gastrointestinal tract, metabolized and excreted. Even though no quantitative data are available for inhalation or dermal routes, absorption is assumed, based on the adverse effects observed in inhalation or dermal studies. Once absorbed, 1,2,3-TCP is distributed to several tissues. 1,2,3-TCP is rapidly and extensively metabolised, via CYP450 oxidation and glutathione conjugation. 1,2,3-TCP and its metabolites are excreted via urine, faeces and exhaled breath, the latter mainly as CO_2, within 2 days from a single exposure. 1,2,3-TCP is of only moderate general toxicity, but it is converted in the mammalian organism into strongly genotoxic metabolites, such as 1,3-dichloroacetone.
- Regarding acute toxicity, a few case reports in humans indicated primarily liver and neurological toxicity after apparently high, but usually not further quantified, oral or inhalation exposure. In experimental animals, oral LD_{50} values ranged between 150 and 442 mg/kg bw in rats, while dermal values were found between 516 mg/kg bw for male and female rabbits, and up to 2457 mg/kg bw for male rabbits only. After inhalation, the LC_{50} values for rats and mice were about 3000 mg/m^3 (corresponding to 500 ppm).

- The most relevant health impact upon chronic exposure to 1,2,3-TCP is carcinogenicity. There are no data available indicating carcinogenicity of 1,2,3-TCP in humans. With regard to experimental animals, 1,2,3-TCP causes tumours at multiple sites and at high incidence in mice and rats. Since the metabolism of 1,2,3-TCP is qualitatively similar in human and rodent microsomes, it is considered to be also carcinogenic to humans.
- 1,2,3-TCP is mutagenic to bacteria and to cultured mammalian cells in the presence of metabolic activation. Furthermore, it binds to DNA of animals treated *in vivo*. Also, as one of few chemicals, 1,2,3-TCP causes specific signature mutations in different tumour locations in mice, indicative for direct mutagenicity. Therefore, it is considered to be genotoxic with a non-threshold mode of action.
- Concerning chronic toxicity apart from carcinogenicity, the liver was identified as a target organ. Bile duct hyperplasia appeared to be most sensitive, observed in rats after 15 months oral exposure at all concentrations applied (3-30 mg/kg bw/day).
- There are no human data on fertility following exposure to 1,2,3-TCP. 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. A marginal decrease of mating rate was reported in one inhalation study in CD rats; however the study is considered non-reliable. Changes in male organs (testes and epididymis weights) were reported in repeated dose studies (120 days) in rats but not in mice. No teratogenic effects were reported on the multigeneration study or in the screening teratogenic study. Altogether, dose levels causing fertility effects were clearly higher than the doses leading to bile duct hyperplasia.
- Biomarkers of exposure to 1,2,3-TCP have not been established due to the lack of specific data on levels of 1,2,3-TCP or its metabolites in human tissues, fluids, or excreta. Consequently, there are no published data on internal background levels nor on biomonitoring at workplaces.
- Data on dermal LD_{50} point to a significant potential of skin absorption. Therefore, a “skin” notation is proposed.
- There are no human data on respiratory or skin sensitisation of 1,2,3-TCP. In guinea pigs, very slight skin sensitisation occurred in one study, but not in two others. No information is available for respiratory sensitisation. Altogether, no notation is proposed for either skin or respiratory sensitisation.

Carcinogenicity and Mode of action considerations (see section(s) 7.7 and 7.9 of Annex 1 for full discussion)

Epidemiological evidence

There are no human data regarding the carcinogenicity of 1,2,3-TCP.

Animal carcinogenicity studies

The carcinogenic potential of 1,2,3-TCP was evaluated in 2-year, oral administration NTP studies in F344/N rats and B6C3F1 mice (NTP, 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) at multiple locations.

The highest incidence of neoplasms and most marked dose-response effect for both rodent species was evident in the forestomach, with 97% and 90% incidence of tumours in male and female mice, respectively, at the lowest dose tested.

In rats, additional tumour locations were squamous cell papillomas and carcinomas of the oral mucosa as well as carcinomas of the Zymbal’s gland. Also, increased incidences of adenomas of the pancreas and kidney as well as adenomas or carcinomas of the preputial gland were observed in males, and adenomas or carcinomas of the clitoral gland as well as adenocarcinomas of the mammary gland in females.

In mice, also hepatocellular adenomas and carcinomas of the liver as well as Harderian gland adenomas were observed. In female mice, squamous cell carcinomas of the oral mucosa, uterine adenomas/adenocarcinoma and stromal polyps were also found. Finally, the metabolite 1,3-dichloroacetone initiated skin tumour development in mice when applied topically.

Mode of action

1,2,3-TCP is mutagenic in bacteria and in cultured mammalian cells in the presence of metabolic activation. Furthermore, it binds to DNA of animals treated *in vivo*. 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 and displayed a significantly increased number of mutations, ranging from >2 to up to 10-fold increase compared to other chemical-related and spontaneous tumours in the collection. 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 1,2,3-TCP-exposure with two present only in forestomach tumours. These 1,2,3-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 1,2,3-TCP-related mouse signature found in forestomach tumours corresponded to a previously identified and experimentally validated unique signature of cholangiocarcinoma arising from occupational exposure to haloalkanes, very prominent in case of 1,2-dichloropropane. Significant associations also occurred with the other two corresponding human signatures to liver tumours and pilocytic astrocytomas (low-grade gliomas). Further analysis revealed that the 1,2,3-TCP signatures exhibited a strong transcriptional strand bias, consistent with their exogenous (as opposed to endogenous) nature and the repair of DNA adducts by transcription-coupled nucleotide excision repair. Altogether, these mouse data provide experimental evidence for the genotoxic mode of action, linking mouse exposure to 1,2,3-TCP and the generation of defined signature mutations with high similarity with known signatures from the human categories of somatic mutations in cancer (COSMIC).

Therefore, 1,2,3-TCP is considered to be genotoxic with a non-threshold mode of action.

Cancer exposure-risk assessment (see section 9 of Annex 1 for full discussion)

1,2,3-TCP has a harmonised classification as Carc. 1B, based on animal data. No threshold for carcinogenicity 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. One of them, namely dichloroacetone, has been identified as a tumour initiator.

No human cancer data was found and therefore an exposure-risk relationship (ERR) was derived from animal data.

The 2-year oral rat and mouse studies (NTP, 1993) were identified as the key studies, showing carcinogenic effects at low dose levels in various target organs. No carcinogenicity study conducted by inhalation was available.

One critical part of our assessment concerned the inclusion of forestomach tumours in risk assessment, as their relevance for humans has been discussed in different scientific settings. The key question concerned the mode of action for tumour induction. If the forestomach tumours would be only due to local interactions and thus irritation of the

gastric mucosa, they could be considered as less relevant, due to shorter retention times in humans. However, the mutagenic mode of action of 1,2,3-TCP is due to specific mutational signatures, also in forestomach tumours (see scientific documentation above and in Annex 1), which is considered relevant also for humans. Futhermore, tumors developed also in comparable tissues, such as the oral cavity. Therefore, in agreement with the approach taken by US EPA (2009), RAC included the forestomach tumours also in the quantitative risk calculations, finally based on total alimentary tract tumors.

Calculation of additional lifetime cancer risks of 1 x 10^{-5} for both mice and rats and sexes, including the conversion of the oral rat dose to the corresponding T25 inhalation values, the correction for exposure duration, for the oral and inhalation absorption, as well as for the inhalation volume, and assuming a linear extrapolation, revealed very similar values for male and female rats and mice.

For example, cancer risk calculations on male rat data (38/60 additional tumours at 3 mg/kg bw/d) include the following steps:

1) The dose-response correlations reported were not suitable for benchmark dose modelling. Therefore, T25 was used to identify the point-of-departure for total alimentary tract.

The 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 LOAEL of 3 mg/kg bw/day total alimentary tract tumours as identified above and 0.25 being the reference incidence.

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

2) 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 / 8 h):

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

3) Correction for exposure duration (considering 40 years of work), bioavailability (oral 80% (see section 7.1.2. of Annex 1), inhalation 100% 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.

4) 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)

Respective calculations were conducted for both species and sexes (as presented in sections 9.1.2.1.-9.1.2.4. of Annex 1).

Exposure concentrations representing a 1x10-5 additional lifetime cancer risk (total alimentary tract tumours, NTP, 1993), assuming linearity:

Species/ sex	1,2,3-TCP concentration in air (mg/m³)	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

For the purpose of deriving an ERR, the mean of the exposure concentrations representing a $1x10^{-5}$ additional lifetime cancer risk in male/female rats and mice (as presented in sections 9.1.2.1.-9.1.2.4. of Annex 1) was calculated as 0.0001 mg/m³ (equivalent to 0.00002 ppm).

Uncertainties

There are no human data concerning the carcinogenicity of 1,2,3-TCP. Therefore, the ERR is derived from animal studies. However, the clear evidence for carcinogenicity in multiple organs in both rats and mice at the lowest concentration as well as defined signature mutations in mice support the relevance also for human exposure. There is no uncertainty on the non-threshold genotoxic mode of action.

Concerning the risk numbers, total alimentary tract tumours including forestomach tumors have been considered relevant also for human exposure, since 1,2,3-TCP is genotoxic and comparable squamous epithelial tissue in the oral cavity was also effected. This leads to very similar cancer risk calculations for mice and rats of both sexes, and the mean value across species and sexes has been chosen for ERR calculation.

Chronic toxicity

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

Several studies have been 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). Bile duct hyperplasia appeared to be most sensitive and was observed at all concentrations applied, i.e. 3-30 mg/kg bw/day in rats after 15 months of exposure (NTP, 1993). 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. The latter revealed also eye irritant properties (conjunctival irritation). Effects on the spleen and thymus were observed in some studies. Diffuse inflammation-associated necrosis in the heart was reported in an oral study.

Cancer risk values can be compared to an **8 h TWA on non-cancer effects,** which would protect from chronic toxicity other than carcinogenicity. bile duct hyperplasia (which can be considered as early signs for carcinogenicity),induced by 1,2,3-TCP and observed at doses of 3-30 mg/kg bw/day in rats after 15 months of exposure (NTP, 1993), could be used as the point of departure. Other studies had higher NOAEC/LOAEC values.

Employing the benchmark dose (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 bw/day.

Next, the derivation of an 8h TWA would comprise 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 bw / 8 h) and correction for inhalation volume (rats in rest vs worker light activity) using default values:

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

2) Application of assessment factors of 2.5 to cover interspecies differences and 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 an **8h TWA based on chronic toxicity**:

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, the BOEL based on cancer risk will also protect from non-cancer effects, provided that the value will not exceed 0.16 mg/m^3.

Reproductive toxicity

Regarding reproductive toxicity, according to the harmonised classification, 1,2,3-TCP is classified as Repr. 1B.

There are no human data on fertility following exposure to 1,2,3-TCP.

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

As the dose level causing fertility effects is clearly higher than the one causing bile duct hyperplasia (see above), no 8h TWA is derived for reproductive toxicity.

Derived limit values (see section 9 of Annex 1 for full discussion)

1,2,3-TCP is considered to be an non-threshold carcinogen. Consequently, **no health-based occupational exposure limit (OEL) nor a STEL can be identified.** Instead, an exposure-risk-relationship has been established, as described above and presented in the table below.

Cancer exposure-risk relationship (total alimentary tract tumours)*

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

* Assuming exposure 8 hours per day and 5 days per week over a 40-year working life period.

Analytical feasibility

According to literature, a published air monitoring method exerts a LOQ of 0.0001 ppm, thus covering most of the ERR (see section 6.1 of Annex 1). It is anticipated that methods also covering concentrations in the lower end of the ERR can be validated.

Short Term Exposure Limit (STEL)

No STEL is proposed.

(Bio) monitoring of exposure (see section 6 of Annex 1 for full discussion)

Biomarkers of exposure specific for 1,2,3-TCP or its metabolites have not been established since no respective information for human tissues, fluids, or excreta are available (ATSDR, 2021).

There is also no information available on biomonitoring of 1,2,3-TCP exposure.

Biological limit value (BLV) (see sections 6, 7 and 9 of Annex 1 for full discussion)

Since 1,2,3-TCP is considered as a non-threshold carcinogen, it is not possible to derive a health-based BLV. Also, no correlations between biomonitoring and air levels can be derived, due to the lack of suitable biomarkers.

Biological guidance value (BGV)

No BGV is proposed, due to the lack of suitable biomarkers.

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.

Groups at extra risk

No specific groups at extra risk were identified.

ANNEXES:

Annex 1 gives the scientific background for the opinion.