Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for 2-chloro-1,3-butadiene (chloroprene)

ECHA/RAC/OEL-0000007364-73-01/F

14 September 2023

Telakkakatu 6, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

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

In accordance with the Service Level Agreement (SLA) (Ares (2022)711149), the Committee for Risk Assessment (RAC) adopted by **consensus** on **14 September 2023** an opinion on the evaluation of the occupational exposure limits (OELs) for:

Chemical name: 2-Chloro-1,3-butadiene (Chloroprene)

EC number: 204-818-0

Rapporteur, appointed by RAC: Andrea Hartwig (rapporteur),

Co-Rapporteur, appointed by RAC: Ruth Moeller (co-rapporteur)

Administrative information on the opinion

The Commission asked on 23 February 2022 the advice of RAC to assess the scientific relevance of occupational exposure limits for 2-Chloro-1,3-butadiene (Chloroprene, EC number 204-818-0), 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), 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].

ECHA has prepared a scientific report concerning occupational limit values for 2-Chloro-1,3-butadiene (Chloroprene) at the workplace. This scientific report was made available at: Occupational exposure limits-Consultations on OEL recommendation on **26 January 2023** and interested parties were invited to submit comments by **28 March 2023**.

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.

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

RAC Opinion of the assessment of the scientific relevance of OELs for 2-Chloro-1,3-butadiene (Chloroprene)

RECOMMENDATION

The opinion of RAC on the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for 2-Chloro-1,3-butadiene (Chloroprene, EC number 204-818-0) is set out in the tables below and in the following summary of the evaluation, supported by Annex 1.

Chloroprene is considered to be a non-threshold carcinogen. Consequently, no health-based occupational exposure limit (OEL) nor a STEL can be identified. Instead, RAC derived an exposure-risk relationship (ERR) expressing the excess cancer risk in function of the air concentration of chloroprene.

SUMMARY TABLE

The tables present the outcome of the RAC evaluation to derive limit values, notations and exposure-risk relationships for chloroprene.

Derived Limit Values

OEL as 8-hour TWA:	Not proposed
STEL:	Not proposed*
BLV:	Not proposed
BGV:	Not proposed

* Please see text in the STEL section

Notations

Notations:	Skin

Cancer exposure-risk relationships (ERR)*

2-Chloro-1,3-butadiene concentration in air (ppm)	2-Chloro-1,3-butadiene concentration in air (mg/m³)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.014	0.052	4
0.14	0.52	40
1.4	5.2	400
14	52	4000

* Assuming exposure of 8 hours per day and 5 days per week over a 40-year working life period. 1 ppm = 3.68 mg/m³ (at 20°C) (see Annex 1 Table 2, section 1)

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

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

Since chloroprene is considered a non-threshold carcinogen, it is not possible to derive a safe level for a BLV. Also, no correlations between internal and external exposure levels are available. No BGV can be stated due to the non-specificity of potential biomarkers and lack of data for almost all European countries.

RAC OPINION

Background

This opinion concerns 2-Chloro-1,3-butadiene (Chloroprene) (see section 1 of Annex 1).

This report takes into account previous international assessments such as DFG (2001), EPA (1985 and 2010), IARC (1999) and AGS (2019). This has been complemented by a literature search of published papers from the last ten years. In addition, comments submitted during the open consultation may also be reflected in the report and were replied to in Annex 2.

Key conclusions of the evaluation

- Chloroprene has, among other classifications, a **harmonised classification as Carcinogen category 1B,** Acute Tox 4 and STOT SE3.
- Chloroprene is **used mainly in the polymerization of polychloroprene**. Exposure levels have dropped considerably during the last years.
- Worker **exposure occurs by inhalation and dermal contact**, and chloroprene is absorbed well by all routes.
- Even though **no quantitative data on absorption** are available, based on the lipophilic nature of chloroprene and modelling data for skin uptake, a **potential also for high dermal absorption must be assumed**.
- A physiologically based toxicokinetic (PBPK) model and detailed *in vitro* investigations identified the **lung and liver as the main organs where metabolism takes place;** Chloroprene is mainly metabolised to two reactive epoxides. Especially their detoxification is markedly slower in mice than in other species.
- Chloroprene has a harmonised classification as Acute Tox 4 via inhalation. **Acute toxicity** via inhalation appears to be restricted to high exposure levels.
- The **most relevant health effect after chronic exposure** to chloroprene is **carcinogenicity:**
  - There is **no consistent evidence for carcinogenicity of chloroprene in humans.**
  - Chloroprene was **clearly carcinogenic in both mice and rats**, leading to tumours at multiple sites. The carcinogenic potency was higher in mice as compared to rats.
  - A **primarily genotoxic mechanism of action must be assumed**, with pronounced species- and strain-specific differences.
  - Therefore, **chloroprene** is considered to be a **non-threshold carcinogen.**
- As no human data on carcinogenicity are suitable for quantitative risk assessment, **the exposure-risk relationship (ERR)** is derived from animal carcinogenicity studies. **Even though mice are most sensitive, rat data were considered for the derivation of an ERR**, namely oral cavity tumours in the Fischer rat. This is **based on the higher similarity of rat and human chloroprene metabolism as opposed to mice.**
- Concerning **non-cancer chronic toxicity**, the most sensitive endpoints for non-cancer chronic toxicity are **olfactory epithelium hyperplasia and necrosis.** The latter (observed in the 2-year NTP inhalation study) would result in a 8h-TWA for non-cancer effects of 0.6 mg/m^3 (equivalent to 0.16 ppm) and would correspond to a residual cancer risk of about 4:10 000. **As a consequence, a BOEL based on cancer risk will also protect from non-cancer effects, provided that the value will not exceed 0.6 mg/m^3 (0.16 ppm).**

- A 15-min **STEL** would be needed to protect from local irritation. However, the excursion factor depends on the actual BOEL finally decided.

  When setting a respective STEL, it should be ensured that the 8h-TWA for non-cancer effects, i.e. 0.16 ppm, will not be exceeded.

- Chloroprene is **not classified as reproductive toxicant under CLP**. Available human data are limited and come with significant methodological deficiencies. No effects on sexual function and fertility or developmental toxicity were identified in animal studies.
- Since chloroprene is considered a non-threshold carcinogen, it is **not possible to derive a health-based BLV**.
- **No BGV** is proposed, due to missing information of respective background levels in Europe and the lack of specific exposure biomarkers.
- **No correlations between biomonitoring and air levels** can be derived. However, monitoring of the not chloroprene-specific chloroprene biomarkers DHBMA and MHBMA may be considered in the absence of butadiene exposure.
- A **skin notation** is proposed, based on the chemical properties and modelling data for dermal uptake.
- There are **no reliable data available relating to possible sensitizing effects** induced by chloroprene.

Exposure, absorption and distribution

Chloroprene is used mainly in the polymerization of polychloroprene, and the chloroprene monomer is produced as an intermediate on site. **Worker exposure** is mainly linked to the final **chloroprene manufacturing step and chloroprene polymerization**. Occupational exposure **has reduced largely** as a result of engineering and work-practice improvements applied in polymer plants over the years. Worker exposure occurs by **inhalation and dermal contact**, and chloroprene is absorbed well by all routes. Skin absorption may make a significant contribution to systemic exposure (DFG, 2021a). As butadiene has replaced acetylene as feedstock in the polymerization in most countries since the 1960s, co-exposure of workers to butadiene needs to be considered.

No quantitative data on chloroprene absorption via the **oral, inhalation or dermal route** were found. However, based on the lipophilic nature of chloroprene and modelling data for skin uptake, a **potential also for high dermal absorption must be assumed**.

A physiologically based toxicokinetic (PBPK) model identified the **lung and liver as the main organs where metabolism takes place**, supported by detailed *in vitro* investigations. Chloroprene is mainly metabolised to the reactive epoxide (1-chloroethenyl)oxirane (CEO), and to a lesser extent to 2-chloro-2-ethenyloxirane. Pronounced species differences have been identified, indicating that **especially the detoxification of the critical metabolites is markedly slower in mice than in other species**.

Acute and chronic toxicity

Regarding **acute toxicity**, there is one case report describing the death of a worker found in an empty vessel used for chloroprene. No estimates of air concentration of chloroprene in the vessel were available, but the authors assumed that a significant amount of chloroprene was not only inhaled but also absorbed through the skin because the man wore a respiratory mask. Chloroprene has been reported to induce mortality in rats after acute oral and inhalation exposure, and a LC_{50}-value of 2280 ppm (8227 mg/m^3) was derived from acute (4-hour) exposure data in male rats. Chloroprene has a harmonised classification as Acute Tox 4 via inhalation.

The most relevant adverse health effect upon chronic exposure towards chloroprene is carcinogenicity.

Nonetheless, other adverse health effects have been described as well. Concerning **non-cancer chronic toxicity**, hair loss, irritation of mucous membranes and neurological effects have been observed in humans after long-term heavy exposure to chloroprene. However, the type of contact as well as the duration and level of exposure were not characterised and adjustment for the effect of potential confounders is lacking in those studies. Animal effects include local nasal effects in chloroprene inhalation studies. At higher doses, anaemia, liver and kidney effects were reported. The most sensitive endpoints for non-cancer chronic toxicity are **olfactory epithelium hyperplasia findings** observed in the 13-week inhalation NTP study in rats (1998), with a LOAEC of 32 ppm and a NOAEC of 12 ppm, and **necrosis of the olfactory epithelium** at 12.8 ppm (47 mg/m^3 LOAEC; no NOAEC identified) as seen in male rats of the 2-year inhalation NTP study (1998). These observations are taken as a starting point for calculating a 8h-TWA for non-cancer effects (see below).

Carcinogenicity and Mode of action considerations (see sections 7.6, 7.7 and 8.1 of Annex 1 for full discussion)

Epidemiological evidence

Altogether, nine studies on eight cohorts are available. Even though earlier epidemiological studies suggested some evidence of an association between chloroprene exposure and liver cancer risk, this was not supported by more recent larger cohort studies. The earlier studies were based on small number of cases and exerted methodological limitations, such as cohort selection and reference population (the latter exerting partly pronounced healthy worker effects), as well as the lack of consideration of potential confounders such as liver cirrhosis and smoking. More recently, larger cohort studies with more detailed exposure information and considering longer exposure times did not provide consistent evidence of increased liver or lung cancer risk, nor for increased overall cancer risk. All study authors of the recent studies as well as IARC (1999), EPA (2010), DFG (2001) and AGS (2019) concluded that there is no consistent evidence for carcinogenicity in humans. RAC agrees with this conclusion.

Animal carcinogenicity studies

In contrast to the limited evidence in humans, there is consistent evidence for chloroprene carcinogenicity in rats and mice, leading to tumours in multiple organs in two-year inhalation studies conducted by NTP (1998):

- In B6C3F$_1$ mice, chloroprene was clearly carcinogenic: when exposed to up to 80 ppm, significant increases were observed for lung tumours (alveolar/bronchiolar adenoma and carcinoma) in both sexes, starting at the lowest concentration of 12.8 ppm, hemangiosarcoma in the circulatory system (males ≥12.8 ppm; females 32 ppm), Harderian gland adenoma or carcinoma (males ≥32 ppm; females 80 ppm), as well as non-significant increases in forestomach tumours. An additional tumour location in male mice was the kidney, while female mice exerted additionally tumours in the mammary gland, liver, skin, mesentery and Zymbal's gland.
- In rats, "clear evidence" of carcinogenic activity of chloroprene was based on the increased incidences of neoplasms of the oral cavity (squamous cell papilloma or carcinoma), significantly elevated in both male and female rats at ≥32 ppm and 80 ppm, respectively. Further exposure-related effects comprised neoplasms of lung in male rats, of the mammary gland in female rats and of the thyroid gland and kidney in both sexes. Male rats generally had a higher incidence of kidney neoplasms than females becoming significant at all doses in males upon extended histopathologic evaluations. Slight numerical increases of urinary bladder neoplasms in male and female rats and lung neoplasms in female rats may have also been related to chloroprene exposure.

Tumour incidences and multisite distribution were generally greater among mice compared to rats. Furthermore, in mice, neoplastic lesions at multiple sites such as circulatory-system hemangioma/hemangiosarcoma in males, skin sarcoma in females, and lung adenoma and/or carcinoma in both sexes, were significantly increased at all exposure concentrations (≥12.8 ppm). Statistically significant increases were observed at ≥32 ppm in rats, except for renal tubule adenomas/carcinomas, which were significant at ≥12.8 ppm in males.

The higher carcinogenic potency of chloroprene in mice compared to rats could be explained by the observed differences in metabolism, i.e. higher rate of chloroprene oxidation and slower rate of epoxide detoxification in mouse over rat microsomes (see below).

Mode of action

Regarding the mode of action, a primarily genotoxic mechanism must be assumed, even though there are clearly species- and strain-specific dependencies.

Human data on genotoxicity are limited to studies with important methodological deficiencies. Regarding *in vitro* mutagenicity studies, chloroprene itself has produced overall conflicting results in *Salmonella typhimurium* tester strains, showing no mutagenic activity in the relevant NTP-conducted studies. The purity, stability and solvent of the chloroprene solution appear to be relevant to the outcome, as well as dimerization during storage.

Chloroprene's major metabolite, the epoxide CEO, is mutagenic in *S. typhimurium* and alkylates DNA in a sequence-specific manner. *In vivo*, dominant lethal mutations in mice and rats have been reported, with conflicting findings in *Drosophila melanogaster*. Negative results were yielded in all *in vivo* cytogenetic tests performed by the NTP, however tumours induced at the same dose levels harboured a higher frequency of *ras*-mutations, compared to the spontaneous neoplasms in control animals.

The metabolism of chloroprene has been extensively studied *in vitro* using liver and lung microsomes from different species, including pooled human microsome fractions of five to fifteen individuals. The equilibrium between the formation and detoxification of the critical metabolites (CEO and a minor epoxide, 2-chloro-2-ethenyloxirane, both occurring as R- and S enantiomers) appears to be critical and also explains the observed species differences in organ toxicity and carcinogenicity. Thus, in the studies by Himmelstein et al. (Himmelstein et al., 2004a, Himmelstein et al., 2004b, Himmelstein et al., 2001a) and Cottrell et al. (2001), much more (1-chloroethenyl)oxirane was formed by lung microsomes from B6C3F$_1$ mice than by microsomes from rats, hamsters or humans (B6C3F$_1$ mice >Fischer 344 rats > Wistar rats, hamsters, humans).
Furthermore in the same experiments it was shown that the detoxification of CEO by epoxide hydrolases is far slower in liver microsomes of B6C3F$_1$ mice when compared to microsomes of rats, and particularly slower when compared to microsomes derived from hamsters or humans. Especially, an accumulation of the R enantiomer of CEO was observed in microsomes from mice, indicating its resistance towards the epoxide hydrolase.

Cancer risk assessment (see section 9.1.2 of Annex 1 for full discussion)

A non-threshold mode of action is assumed for chloroprene. Based on epidemiological evidence including most recent updates and follow-up studies, there is no consistent increase in cancer risk in humans. Therefore, data from experimental animals are taken to establish an ERR. Reliable quantitative data as described above are available from mice and rats (NTP, 1998).

While both rats and mice carried tumours at multiple locations, pronounced quantitative differences were observed. Thus, the BMD10 values derived from lung tumours in mice were about 10 times lower when compared to the most sensitive tumour location in rats, i.e. tumours of the oral cavity (BMD10= 2.5 ppm as compared to 34.5 ppm, see AGS, 2019). Even though usually the most sensitive species is selected for quantitative cancer risk assessment, in this special case of chloroprene, detailed investigations on the pronounced species differences point towards the better suitability of rat vs. mice data for the human cancer risk assessment. As stated above, the critical metabolite of chloroprene is the epoxide CEO, more precisely the balance between its formation and detoxification. Detailed *in vitro* studies with microsomes derived from rats, mice, hamsters and humans revealed that in mice the most relevant metabolite accumulates in the liver and lung at far higher levels when compared to rats and humans, predominantly due to the resistance of the R enantiomer of CEO towards mouse epoxide hydrolase. Therefore mice are considered not to be quantitatively representative for humans, and, as a consequence, carcinogenicity data from the more conservative (NTP, 1998) of the two rat studies available in different strains (Fischer and Wistar) are selected as point of departure (PoD) (and not the lung tumours observed in mice).

The BMD10 (34.5 ppm) calculated for the oral cavity tumours from the 2-year study in the Fischer rat (NTP, 1998) is selected as the PoD for deriving the ERR. This BMD10 was calculated by AGS (2019). Even though no details were provided on the modelling and software used, this value was confirmed by independent calculations by scientists of the German MAK commission, deriving also a BMDL10 value (25.5 ppm). The BMD10 of 34.5 ppm also agrees well with the T10 calculated by RAC for the Fischer rat (36 ppm).

The following standard correction for PoD from a 2-year rat inhalation assay to occupational exposure was performed to reflect differences in exposure circumstances:

> BMD10 (corrected) = BMD10 (animal) * (75/40 years) * (52/48 weeks) * (6/8 h) * (6.7/10 m^3) = 34.5 ppm * 1.0207 = 35.2 ppm.

Applying the corrected BMD10 and a linear extrapolation, the ERR below was calculated.

Cancer exposure-risk relationship*

2-Chloro-1,3-butadiene concentration in air (ppm)	2-Chloro-1,3-butadiene concentration in air (mg/m^3)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.014	0.052	4
0.14	0.52	40
1.4	5.2	400
14	52	4000

* Assuming exposure of 8 hours per day and 5 days per week over a 40-year working life period. 1 ppm = 3.68 mg/m^3 (at 20°C) (see Annex 1 Table 2, section 1)

Uncertainties

Due to the lack of quantitative human data, uncertainties result from the selection of animal data for the derivation of ERR. Especially, because not the most sensitive species has been chosen (mice), but rather the tumours formed in the oral cavity of rats in the 2-year NTP study.

However, this selection was done based on very detailed investigations on metabolism in lung and liver microsomes, indicating that mice accumulate the critical metabolite, i.e. the epoxide CEO, due to the low activity of the detoxifying epoxide hydrolase. Since not the most sensitive species was selected, RAC also assessed whether the rat carcinogenicity data may underestimate human cancer risk. Based on the epidemiological data available

for chloroprene and based on the general population background cancer incidences, RAC is confident that the rat data do not underestimate human cancer risks.

One further aspect of the rat study which needs to be considered is the potential impact of early mortality on cancer risk assessment, since in principle early death may prevent tumour development and thus may underestimate tumour incidences. Nevertheless, in the case of chloroprene, mean survival of the rats was > 600 days, suggesting sufficient time for tumour development, and all animals were necropsied and considered in the statistical analysis. Therefore, RAC assumes no significant bias on the tumour rate calculation due to early death and no survival-adjusted BMD is deemed required.

Chronic toxicity

There are no quantitative human data on longer-term chloroprene exposure and non-cancer chronic disease.

Upon inhalation (13 weeks, NTP, 1998), hyperplasia of the alveolar and olfactory epithelium was observed in rats and mice; in mice, additionally hyperplasia of the forestomach and renal tubulus were evident.

Olfactory epithelium hyperplasia findings

If an OEL was derived from data on threshold effects, the **olfactory epithelium hyperplasia** findings observed after inhalation exposure (6 h /day, 5 days/week) as the most sensitive endpoint could be used as the PoD. Effects were seen at 32 ppm (LOAEC= 120 mg/m^3) and the NOAEC was 12 ppm (44 mg/m^3). Other studies had higher NOAEC/LOAEC values.

A 8h **TWA for non-cancer effects** could be calculated as follows. Correction of the PoD to correspond to worker exposure conditions:

44 mg/m^3 * 6h/8h * 6.7 m^3/10 m^3= 22.11 mg/m^3.

Assessment factors proposed to be applied include a factor of 2 for extrapolation for the duration from sub-chronic to chronic, 2.5 to cover interspecies differences, and 5 for worker intraspecies differences. Application of these factors would lead to:

8h TWA= 22.11 mg/m^3 / 2*2.5*5 ≈ 0.9 mg/m^3 (equivalent to 0.24 ppm).

Necrosis of the olfactory epithelium

Alternatively, a 8h TWA for threshold effects can be derived for **necrosis of the olfactory epithelium** at 12.8 ppm (LOAEC= 47 mg/m^3; no NOAEC identified) as seen in male rats in the 2-year inhalation study by NTP (1998).

Correction of the PoD to correspond to worker exposure conditions:

47 mg/m^3 * 6h/8h * 6.7 m^3/10 m^3= 23.6 mg/m^3.

Assessment factors proposed to be applied include a factor of 3 for the conversion from LOAEC to NOAEC, 2.5 to cover interspecies differences, and 5 for worker intraspecies differences. Application of these factors would lead to:

8h-TWA= 23.6 mg/m^3 / 3*2.5*5 ≈ **0.6 mg/m^3** (equivalent to **0.16 ppm**).

Also, BMD/BMDL calculations performed by US EPA would derive the same value. As explained, a non-threshold MoA is assumed for the carcinogenic effects and thus the TWA calculations for non-cancer effects described above should be seen as comparative calculations.

It is noted that according to the derived cancer ERR, the lowest 8h TWA (0.16 ppm) would correspond to a residual cancer risk of about 4:10 000. **As a consequence, a BOEL**

based on cancer risk will also protect from non-cancer effects, provided that the value will not exceed 0.6 mg/m³ (0.16 ppm).

Reproductive toxicity

Chloroprene is not classified as reprotoxic under Annnex VI of the CLP Regulation. Available human data are limited and affected by significant methodological deficiencies. No effects on sexual function and fertility or developmental toxicity were identified in animal studies.

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

OEL – 8h TWA

Chloroprene is considered to be a non-threshold carcinogen. Consequently, **no health-based occupational exposure limit (OEL) can be identified.** Instead, an ERR has been established, as described above.

Short Term Exposure Limit (STEL)

While no STEL would be required to protect from carcinogenicity, chloroprene is also classified as STOT SE3, based on local irritation (necrosis of the olfactory epithelium). Therefore, a 15-min STEL would be needed to protect from local irritation. It is not possible to derive a specific 15-minute value based on the available (animal) data. Derivation of a STEL based on a BOEL is also not possible, as the BOEL is not yet established.
When setting a respective STEL, it should be ensured that the 8h-TWA for non-cancer effects, i.e. 0.16 ppm as presented above, will not be exceeded.

Air monitoring of exposure: Analytical feasibility

Chloroprene in air can be analysed by validated standard analytical methods for workplace exposure. The measurement is based on sampling through a sorbent tube, extraction and gas chromatography analysis. The LoQs are in the µg/m³ or ppb range:

- The method according to **DFG (2013)** based on charcoal absorbant and N,N-Dimethylacetamide desorption with FID detection allows an **LoQ of 300 µg/m³ or 82 ppb** (0.5 l/min, 30 l, 1h).
- The method according to **OSHA (1998)** was developed as a more sensitive method than NIOSH (1994) and is based on Chromosorb 106 sampling tubes, toluene desorption with ECD detection allowing a **LoQ of 80 µg/m³ or 22 ppb** (0.05 l/min, 6l, 2 hours).

Thus, in principle the methods would allow the measurement of air concentrations related to cancer risks of about $4*10^{-5}$ (DFG) or $1*10^{-5}$ (OSHA). Nevertheless, the analytical sensitivity should be around 10% of the actual OEL. Therefore, only air concentrations associated with cancer risks in the range of $4*10^{-4}$ to $1*10^{-4}$ can at present be reliably quantified. This would not cover the entire ERR, and it would be desirable to further optimize the method(s), also depending on the final BOEL.

In addition to the specific air monitoring methods described above, which have been validated for workplace exposure to chloroprene, one additional method might be suitable to measure lower air concentrations of chloroprene. This is the **US EPA Compendium Method TO-15A (2019, update of Method TO-15 (1999))** with a specific adsorbent pre-concentration step for VOC analysis of low ambient air concentrations. However, this method is not specific for chloroprene and has not been validated for workplace exposure.

While no LoD is provided for chloroprene in the EPA compendium, some example LoDs for other VOC are provided, these are typically between **1 ppt**[2] and **4 ppt**.

Biomonitoring of exposure (see section 6.2 of Annex 1 for full discussion)

Available parameters discussed for biomonitoring of exposure to chloroprene are different mercapturic acids, i.e. 3,4-Dihydroxybutyl mercapturic acid (DHBMA), 2-Hydroxy-3-butenyl mercapturic acid (MHBMA), 4-Hydroxy-3-oxobutyl mercapturic acid (HOBMA) and the chlorinated 3-Chloro-2-hydroxy-3-butenyl mercapturic acid (Cl-MA-III).

The non-chlorinated mercapturic acids are also metabolites of 1,3-butadiene and therefore not specific biomarkers of chloroprene. DHBMA and MHBMA are established biomarkers of exposure of 1,3-butadiene (DFG, 2021b). DHBMA is the main metabolite and may thus be a sensitive indicator for occupational sites without 1,3-butadiene use and exposure. For non-smokers, the median concentrations were reported in the range 100-300 µg/l creatinine, while in smokers, levels were usually slightly increased with median values 150-400 µg/g creatinine (data mainly from USA and Germany).
The only European general population 95th percentiles available were reported from German studies with 760 µg/l urine (Schettgen et al., 2009) and 329 µg DHBMA/g creatinine (Eckert et al., 2011). Based on the latter, DGF (2021a) derived a BAR for the non-occupationally exposed reference population of 400 µg DHBMA/g creatinine applicable to non-smokers.

Detection of the specific metabolite Cl-MA-III in workers indicates exposure to chloroprene, but no Cl-MA-III reference value was established so far due to lack of data. Limited available data indicate elevated levels in chloroprene workers while no metabolite was measured in control subjects.

No human studies are available that enable the derivation of a correlation between external and internal exposure to chloroprene.

Biological limit value (BLV)

Since chloroprene is considered a non-threshold carcinogen, it is **not possible to derive a health-based BLV**. Also, no human data enabling correlations between external and internal levels are available at present.

Biological guidance value (BGV)

No BGV can be stated. The background level of DHBMA in human urine is well described only with data from one EU Member State (Germany). Also, due to the non-specificity of this parameter, a BGV for this metabolite is not proposed. In the case of Cl-MA-III not enough human data is available for the derivation of a BGV.

Notations

There are no quantitative data on dermal absorption of chloroprene.

However, one human fatality case report seems to support the potential significant dermal absorption. Given that chloroprene is highly lipophilic, it seems likely to be readily absorbed via the dermal route. Furthermore, a structure-activity based estimate of dermal permeability constant indicates very high dermal permeability of chloroprene. Therefore, a **skin notation** is proposed for chloroprene.

[2] ppt= part per trillion

There are no data indicating skin or respiratory sensitisation effects after chloroprene exposure. Thus **no notation is proposed for skin sensitisation or respiratory sensitisation.**

Groups at extra risk

As the toxicity of chloroprene is related to the formation of reactive metabolites, it is noted that for example CYP2E1 or epoxide hydrolase polymorphisms may influence the individual risks of workers exposed to chloroprene.

No further groups at extra risk were identified.

ANNEXES

Annex 1 - The ECHA scientific report gives the detailed scientific grounds for the opinion.

Annex 2 - The RCOM reflects the comments received on the ECHA scientific report, and the responses provided by ECHA and RAC (excluding confidential information).