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1,2-Dichloropropane – Evaluation of study results in biological material

Assessment Values in Biological Material – Translation of the German version from 2021

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated 1,2-dichloropropane [78-87-5]. As 1,2-dichloropropane has been removed from Category 3 B for carcinogenic substances and is now classified as carcinogenic to humans (Category 1), evaluation of a biological tolerance value (BAT value) is not possible. In addition, studies concerning human metabolism of 1,2-dichloropropane are missing. In animal studies, S-(2-hydroxypropyl)-mercapturic acid (2-HPMA) is described as a main metabolite of 1,2-dichloropropane. The background value of 2-HPMA in human urine is sufficiently well known as this mercapturic acid is also a metabolite of several other hazardous substances (e. g. propylene oxide). However, due to the lack of human studies and due to the non-specificity of the parameter, a biological reference value (BAR) for 1,2-dichloropropane could not be derived.

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BAR (2020)	**not established**
MAK value	–
Peak limitation	–
Absorption through the skin (2020)	H
Sensitization	–
Carcinogenicity (2020)	Category 1
Prenatal toxicity	–
Germ cell mutagenicity	–
CAS number	78-87-5
Density at 20 °C	1.16 g/cm³ (IFA 2021)
log K_{OW}	2.02 (IFA 2021)
Solubility at 20 °C	2700 mg/l water (IFA 2021)
1 ml/m³ (ppm) ≙ 4.688 mg/m³	1 mg/m³ ≙ 0.213 ml/m³ (ppm)

1,2-Dichloropropane was formerly used as a solvent and now occurs mainly as a by-product or intermediate in the chemical synthesis of other organic compounds, such as propylene, tetrachloromethane, and tetrachloroethene. After the ban of 1,1,1-trichloroethane, 1,2-dichloropropane was used to clean printing presses in Japan (IARC 2017).

1 Metabolism and Toxicokinetics

1.1 Uptake and distribution

At the workplace, 1,2-dichloropropane is absorbed by inhalation and dermal contact but oral absorption after ingestion has also been confirmed in humans (Greim 1998; IARC 2017). Data from animal experiments indicate almost complete absorption of 1,2-dichloropropane, regardless of the route of uptake (IARC 2017).

1.2 Metabolism and excretion

After administration of radiolabelled 1,2-dichloropropane, excretion in animal studies, regardless of the route of administration (oral or by inhalation), was mainly via the urine (37–65%) or exhaled air (18–40%), with much of the exhaled radioactivity present as the unchanged parent compound (Timchalk et al. 1991). Other animal studies also confirmed excretion via the urine and exhaled air, with more than 50% of the radioactive labelling being recovered in the urine (IARC 2017). In general, elimination in animal studies was comparatively rapid with a half-life in blood of 3.1 to 5.0 hours (Greim 1998). After oral and inhalation exposure to 1,2-dichloropropane, a large part of the dose was excreted in the urine within 24 hours (Timchalk et al. 1991).

In analogy to many other halogenated alkanes, metabolism of 1,2-dichloropropane takes place via oxidative dehalogenation catalysed by cytochrome P450 enzymes and conjugation with glutathione by glutathione S-transferases, although the order of these metabolism steps may vary (Bartels and Timchalk 1990; IARC 2017; Timchalk et al. 1991). A postulated metabolism scheme can be found in Hartwig and MAK Commission (2021).

The two main urinary metabolites identified in experiments in rats after oral or inhalation exposure to 1,2-dichloropropane were the mercapturic acids S-(2-hydroxypropyl)mercapturic acid (2-HPMA, N-acetyl-S-(2-hydroxypropyl)-L-cysteine) and S-(2-oxopropyl)mercapturic acid (N-acetyl-S-(2-oxopropyl)-L-cysteine), although a chemical equilibrium exists between both forms and they may thus be interconverted. As another metabolite, but to a much lesser extent, the mercapturic acid S-(1-carboxyethyl)mercapturic acid (N-acetyl-S-(1-carboxyethyl)-L-cysteine) has been detected in rat urine (Greim 1998; Timchalk et al. 1991). 2-HPMA is described in several independent animal studies as the main urinary metabolite of 1,2-dichloropropane in rats with a proportion of 10% to 30% (among others Jones and Gibson 1980; Timchalk et al. 1991). Data from human studies are not available.

2 Critical Toxicity

Carcinogenicity is considered the critical toxicity following occupational exposure to 1,2-dichloropropane, with increased incidences of bile duct tumours observed in humans (Hartwig and MAK Commission 2021; IARC 2017).

In addition, irritation occurred after inhalation exposure. Liver and kidney toxicity have been described in humans after oral or dermal absorption of 1,2-dichloropropane (Hartwig and MAK Commission 2021; IARC 2017; Pozzi et al. 1985).

Data on toxicology and especially on the carcinogenicity of 1,2-dichloropropane are summarised and discussed in detail in the respective MAK documentations (Greim 1998; Hartwig and MAK Commission 2021) and in an IARC monograph (IARC 2017).

3 Exposure and Effects

3.1 Relationship between external and internal exposure

Two studies in humans have shown that external air exposure to 1,2-dichloropropane is in correlation to the urinary levels of 1,2-dichloropropane (Ghittori et al. 1987; Kawai et al. 2015). In the urine of unexposed individuals, 1,2-dichloropropane could not be detected using an analytical method with a detection limit of 10 µg/l (Kawai et al. 2015). Metabolites of 1,2-dichloropropane were not yet determined in human urine of exposed individuals.

3.2 Relationship between internal exposure and effects

No appropriate studies in humans are available for 1,2-dichloropropane.

4 Selection of the Indicators

Up to now, available parameters for a biomonitoring of 1,2-dichloropropane are the 2-HPMA in urine or urinary 1,2-dichloropropane. For other metabolites in urine, no relevant human data on internal exposure are currently available.

2-HPMA is a non-specific parameter for 1,2-dichloropropane exposure, since 2-HPMA is also a metabolite of several other compounds such as 1,2-epoxypropane (propylene oxide), propylene, and other halogenated propanes (Barnsley 1966; IARC 1994).

5 Analytical Methods

Various analytical methods are available for the determination of the mercapturic acid 2-HPMA in urine (Eckert et al. 2010; Pluym et al. 2015; Schettgen et al. 2008), including a method tested by the Commission using LC-MS/MS analysis after external solid-phase extraction of the analyte from the urine matrix. The detection limit of the method is 1.0 µg 2-HPMA/l urine (Schettgen et al. 2013).

Kawai et al. (2015) determined 1,2-dichloropropane in urine using GC-FID analysis (gas chromatography flame ionisation detector) with a detection limit of 10 µg 1,2-dichloropropane/l urine as part of a human study. However, the method used was only sparsely described in the publication.

Ghittori et al. (1987) investigated the relationship between the external concentration of various solvents (including 1,2-dichloropropane) in the workplace air and the excretion levels of these solvents in urine and found a linear relationship between the parameters. The determination of 1,2-dichloropropane in urine was performed after headspace enrichment by gas chromatographic separation and mass-spectrometric detection. The description of the procedure, however, is very brief. Information on the detection limit or other reliability criteria is not available.

6 Background Exposure

The background concentration of 2-HPMA in urine of humans has been investigated in three studies so far. Based on the studies by Schettgen et al. (2008) and Eckert et al. (2011), a biological reference value (BAR) of 25 µg 2-HPMA/g creatinine was derived for 1,2-epoxypropane (Bader et al. 2016). In another study with 25 non-smokers and 25 smokers, a median level of 3.2 µg 2-HPMA/g creatinine was determined in the urine of the non-smokers (range: 0.93 to 17.8 µg/g creatinine) (Pluym et al. 2015). The results of this study are thus in the lower range of the other two studies (Eckert et al. 2011; Schettgen et al. 2008) and confirm the current BAR for 1,2-epoxypropane. Furthermore, the study of Pluym et al. (2015) confirmed, that smokers show significantly higher levels of 2-HPMA in urine (median 19.0 µg/l, range: 6.9 to 37.3 µg/l), as already observed in the studies by Schettgen et al. (2008) and Eckert et al. (2011).

Background concentrations of 1,2-dichloropropane in the urine of non-occupationally exposed subjects have not yet been described. Kawai et al. (2015) examined urine samples of five non-occupationally exposed men and could not detect 1,2-dichloropropane. However, the detection limit of the method used was quite high at 10 µg 1,2-dichloropropane/l urine.

7 Evaluation

As 1,2-dichloropropane is now classified as carcinogenic to humans (Category 1), the evaluation of a biological tolerance value (BAT value) is not possible.

For the derivation of a BAR, 2-HPMA in urine can be considered as a parameter. To date, however, no human studies are available that prove beyond doubt that 1,2-dichloropropane is metabolised to 2-HPMA in humans. All data available to date on the metabolism of 1,2-dichloropropane are based exclusively on animal studies. In two human studies with occupational exposure to 1,2-dichloropropane, only 1,2-dichloropropane was determined in urine. Therefore, the derivation of a BAR based on the urinary excretion of 2-HPMA is not possible at this time. If it can be shown in the future that 1,2-dichloropropane is metabolised to 2-HPMA, the corresponding BAR of 1,2-epoxypropane (propylene oxide) can be used for evaluation. No reliable human data are currently available on the urinary excretion of unchanged 1,2-dichloropropane in non-occupationally exposed persons. The published analytical methods are only sparsely described, have comparatively high detection limits or use analytical techniques that no longer correspond to the current state of the art. Given these uncertainties,

a BAR for 1,2-dichloropropane could not be established.

Notes

Competing interests

The established rules and measures of the commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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