The MAK Collection for Occupational Health and Safety

1-Chloro-2,3-epoxypropane (Epichlorohydrin)

Assessment Values in Biological Material – Translation of the German version from 2017

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1-Chloro-2,3-epoxypropane (Epichlorohydrin)

BAT Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated EKA (exposure equivalents for carcinogenic substances) for epichlorohydrin (CAS-No 106-89-8) in 2017. Available publications are described in detail.
In rodents, epichlorohydrin induces malignant lymphomas, hyperplasias, forestomach papillomas and carcinomas, subcutaneous fibromas and lung and pituitary tumours. Epichlorohydrin was classified in category 2 for carcinogenic substances. The substance can easily pass through the skin, so biological monitoring is indicated for a valid individual risk assessment.
In several biomonitoring studies the mercapturic acids derivatives N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine (CHPMA) and N-acetyl-S-(2,3-dihydroxypropyl)-L-cysteine (DHPMA) in urine as well as the hemoglobin adducts N-(3-chloro-2-hydroxypropyl)valine and N-(2,3-dihydroxypropyl)valine are suggested as biomarkers after epichlorohydrin exposure. Validated analytical procedures for their quantification are available. Data of a correlation of epichlorohydrin in the air and the CHPMA-excretion in urine were considered for the evaluation of exposure equivalents for carcinogenic substances. Sampling time is at the end of exposure or end of shift and after long term exposure at the end of the shift after several shifts.

Keywords

epichlorohydrin; 1-chloro-2,3-epoxypropane; 2-(chloromethyl)oxirane; gamma-chloropropylene oxide; (D,L)-alpha-epichlorohydrin; BAT value; EKA (exposure equivalents for carcinogenic substances); occupational exposure; biological tolerance value; toxicity

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1-Chloro-2,3-epoxypropane (Epichlorohydrin)

EKA (2016)

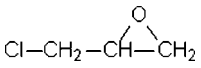
The following correlations between external and internal exposure are obtained:

Air		Urine
1-Chloro-2,3-epoxypropane		S-(3-chloro-2-hydroxy-propyl)-mercapturic acid
[ml/m³]	[mg/m³]	[mg/g creatinine]
0.06	0.23	0.80
0.13	0.5	1.75
0.26	1	3.5
*0.6**	*2.3**	*8**
*2**	*8**	*28**

* equivalents for the exposure-risk relationship for carcinogenic substances according to TRGS 910 ("Risk-related concept of measures for activities involving carcinogenic hazardous substances")

Sampling time: end of exposure or end of shift; for long-term exposure: at the end of shift after several shifts

MAK value	**–**
Absorption through the skin (1961)	H
Sensitization (2003)	Sh
Carcinogenicity (1979)	Category 2
Prenatal toxicity	–
Germ cell mutagenicity (2003)	Category 3B

Synonyms	1-Chloro-2,3-epoxypropane 2-(Chloromethyl)oxirane γ-Chloropropylene oxide (D,L)-α-epichlorohydrin
Chemical name	1-Chloro-2,3-epoxypropane
CAS	106-89-8
Molecular formula	C_3H_5ClO
Structural formula	
Molecular weight	92.53 g/mol
Melting point	–48 °C
Boiling point	116 °C
Density at 20 °C	1.183 g/cm^3
Vapour pressure at 20 °C	17 hPa
Log P_{OW}	0.45

1-Chloro-2,3-epoxypropane (epichlorohydrin) is an important component in the production of epoxide resins, which are used either as material or as wet-strengthening agents in the production of cellulose products, such as tea bag paper and paper towels (BfR 2015; NTP 2014). Furthermore, epichlorohydrin is a constituent of other synthetic polymers such as epoxide rubber or polyamide epichlorohydrin polymers. In addition, the substance is used as solvent for resins, rubbers, cellulose, paints and lacquers (NTP 2014).

Parts of the Chapters "Metabolism and Toxikokinetics" and "Critical Toxicity" have been taken from the MAK documentation of epichlorohydrin (Greim 2003, translated).

1 Metabolism and Toxikokinetics

1.1 Absorption, distribution and elimination

After both inhalation and oral administration, more than 90% of epichlorohydrin was rapidly absorbed and distributed in the organism of rats within 2–4 hours (CMA 1979; Gingell et al. 1985; Weigel et al. 1978). The highest systemic tissue concentrations were reached in the kidneys, intestine, liver, lacrimal glands, pancreas and spleen after administration of radioactively labelled epichlorohydrin. The highest level of radioactivity was found in the stomach after oral administration and in the nasal mucosa after inhalation. Lower radioactivity was detected in the blood, lungs, brain and sex organs (Weigel et al. 1978).

At different dose levels and with various types of administration of ^{14}C-labelled epichlorohydrin, 90% of the activity was excreted within 72 hours, i.e. 46–54% in the urine, 25–40% via the lungs and maximally 4% via the faeces (CMA 1979; Gingell et al. 1985). After oral administration 46.3% of the dose is recovered in the urine of rats within the first 12 hours and further 2.3% of the dose within the following 12 hours (Gingell et al. 1985).

1.2 Metabolism

After initial reaction with glutathione, epichlorohydrin is metabolized at one of the two reactive centres (see Figure 1), leading to the formation of excretable metabolites that were detected in the urine. These were the mercapturic acid derivatives N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine (CHPMA), S-(2,3-dihydroxypropyl)-L-cysteine and N-acetyl-S-(2,3-dihydroxypropyl)-L-cysteine (DHPMA). In addition, 3-chloro-1,2-propanediol was excreted in urine too, which is formed from hydrolysis of epichlorohydrin. CHPMA (36% of the dose) and 3-chloro-1,2-propanediol (4%) are considered to be the main metabolites (Gingell et al. 1985). According to Fakhouri and Jones (1979), 3-chloro-1,2-propanediol in vivo leads to the formation of β-chlorolactic acid, which in turn yields oxalic acid. The latter metabolite was however not detected in other studies. The studies showed two-phase elimination kinetics of the metabolites in urine, with an elimination half-life of 2.16 hours during the first 12 hours after exposure and thereafter an elimination half-life of 17.02 hours (Gingell et al. 1985).

Epichlorohydrin forms the haemoglobin adducts N-(2,3-dihydroxypropyl)-valine (DHPV) (Hindsø L and in et al. 1996) and N-(3-chloro-2-hydroxypropyl)-valine (CHPV) (Bader et al. 2009). The coupling product DHPV was detected in rats after intraperitoneal administration of 40 mmol/kg body weight (Hindsø Landin et al. 1999). An increased amount of it was found in smokers (Hindsø Landin et al. 1996). CHPV could be demonstrated in human blood after accidental exposure to epichlorohydrin (Wollin et al. 2014). Incubation of epichlorohydrin in the presence of human cells of the lung and bronchial parenchyma led to a decrease in mutagenicity (see below) which is assumed to have been caused by rapid inactivation, perhaps by thiol formation (De Flora et al. 1984; Petruzzelli et al. 1989).

2 Critical Toxicity

After chronic and subchronic administration in rodent studies epichlorohydrin causes damage to the lungs, liver, kidneys, adrenals and the CNS and leads to a decrease in haemoglobin levels and lymphocyte count in peripheral blood. In rodents, epichlorohydrin induces malignant lymphomas, hyperplasias, papillomas and carcinomas in the forestomach, subcutaneous fibromas and lung and pituitary tumours. It has been shown to be an initiator in the two-stage experiment and directly binds to target organ DNA, which explains the tumorigenicity. It is corrosive to the skin, eyes and the mucous membranes of the respiratory tract. Local irritation is due to high reactivity with nucleophiles. Lethal doses lead to paralysis of the respiratory

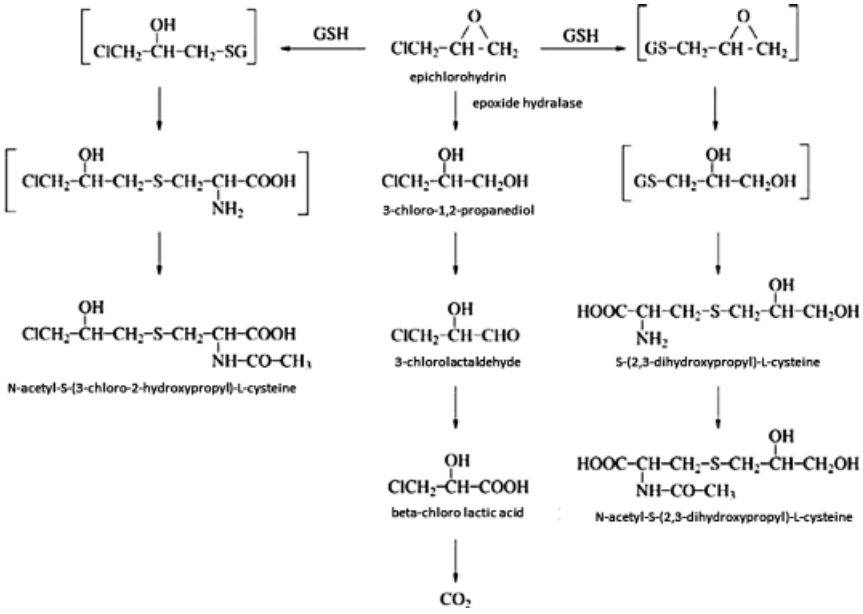


Figure 1 Metabolism of epichlorohydrin in the rat (-SG = glutathione conjugate) (Greim 2003, translated, modified according to Gingell et al. 1985)

centre. Reduced fertility of male rodents might be related to a reducation of sperm ATP levels. The metabolite 3-chlorolactaldehyde inhibits enzymes of the glycolysis (particularly glyceraldehyde-3-phosphatedehydrogenase). Proteins necessary for the interaction between sperms and ovum are also diminished after administration of epichlorohydrin. Epichlorohydrin is a local carcinogen in rodents. In exposed workers, DNA adducts, sister chromatid exchanges and chromosomal damage were found in lymphocytes. With regard to the carcinogenicity of the substance in humans only a few reliable studies with a small number of cases are available (Greim 2003, translated).

3 Exposure and Effects

There are two studies available with biological monitoring of persons with occupational exposure to epichlorohydrin.

In the Netherlands, epichlorohydrin exposure was investigated in 19 workers employed in a chemical plant in which epichlorohydrin was used for the production of glycidyl ethers (De Rooij et al. 1997). The epichlorohydrin concentration in the air was determined over the entire workshift for each person using passive sampling measurements and GC-FID analysis (gas chromatography with flame

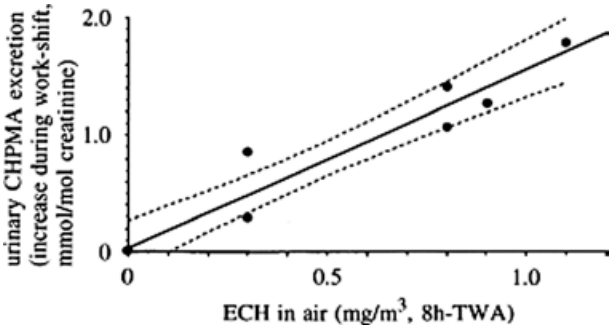


Figure 2 Correlation between urinary CHPMA excretion and exposure to epichlorohydrin in air (mean value over the entire shift) (De Rooij et al. 1997). Reprinted from Environmental Toxicology and Pharmacology, Volume 3, De Roij BM, Boogaard PJ, Commandeur JN, Vermeulen NP, 3-Chloro-2-hydroxypropylmercapturic acid and a-chlorohydrin as biomarkers of occupational exposure to epichlorohydrin, pages 175–185, Copyright 1997, with permission of Elsevier.

ionization detector). In addition, urine samples were obtained from the workers before the shift, after the shift and before the beginning of the next shift, and the levels of CHPMA, DHPMA and 3-chloro-1,2-propanediol analyzed. For the determination of the metabolites in urine various GC-MS methods (gas chromatography coupled to mass spectrometry) were used. In some participants, biomonitoring was carried out on several days of exposure. However, not all of the 40 biomonitoring investigations were accompanied by air measurements. In total, 23 air analyses were carried out. The obtained shift mean values were in the range of < 0.03–1.1 mg epichlorohydrin/m^3. CHPMA could be detected in 63% of the post-shift urine samples. The CHPMA concentrations were in the range of < 0.05 to 5.35 mmol/mol creatinine (corresponding to < 0.11–12.1 mg/g creatinine). In the pre-shift urine and in the urine samples obtained before the next shift CHPMA was detectable in only 30% of the samples. A peak value of 3.51 mmol/mol creatinine (7.9 mg/g creatinine) was found. As possible cause for the in some cases pronounced pre-shift exposure levels of the workers the authors postulated dermal exposure to epichlorohydrin, which could explain a delayed uptake of the substance. The comparison of the CHPMA concentrations in the post-shift urine with the shift mean values of the individual epichlorohydrin exposure revealed a clear linear relationship between biomarker and epichlorohydrin concentration in the air (see Figure 2). In a correlation the increase in the CHPMA excretion levels during the day in seven individual cases was compared with the individual shift mean value. In six cases the CHPMA levels in the pre-shift urine were < 0.05 mmol/mol creatinine and in one case 0.12 mmol/mol creatinine. It can be seen from the figure that an exposure to 1 mg/m^3 air (shift mean value) results in a CHPMA exretion of 1.55 mmol/mol creatinine (corresponding to 3.50 mg/g creatinine). In the publication of the study, reference was made to the fact that some exposed persons had said they carried out their activites under respiratory protection. However, a differentiated evaluation of the associations between CHPMA

excretion and air exposure revealed no difference between workers who reported to have worn respiratory protection and those who had not. From this result the authors concluded that the respiratory protection used was not effective. DHPMA and 3-chloro-1,2-propanediol could not be quantified in the urine samples since, with the method used, the detection limits for these metabolites are 1 mg/l (DHPMA) and 0.4 mg/l (3-chloro-1,2-propanediol).

In the second study with epichlorohydrin-exposed persons the haemoglobin adduct N-(2,3-dihydroxypropyl)-valine (DHPV) was used as biomarker for biomonitoring (Hindsø Landin et al. 1997). This parameter was determined in blood samples of 14 persons occupationally exposed to epichlorohydrin, 14 non-exposed office workers of the same plant and 10 external control persons without epichlorohydrin exposure. Workplace air exposure of the persons occupationally exposed to epichlorohydrin was in the range of 0.4–0.86 mg/m^3 (0.11–0.23 ml/m^3). The DHPV concentrations in the blood of non-smokers were 2.1 ± 1.1 pmol/g globin (mean value ± standard deviation) in the external control collective, 6.8 ± 3.2 pmol/g globin in the internal control collective and 7.3 ± 2.7 pmol/g globin in the exposed persons. In the case of smokers, the DHPV concentrations were 9.5 ± 2.2 pmol/g globin (mean value ± standard deviation) in the external control persons, 13.1 ± 2.7 pmol/g globin in the internal control persons and 21.1 ± 17.1 pmol/g globin in persons exposed to epichlorohydrin. The difference between the DHPV exposure in the blood of exposed persons and that of the internal control persons was not statistically significant. Furthermore, this study, as already did a previous pilot study (Hindsø Landin et al. 1996), confirmed a significant impact of smoking behaviour on the DHPV concentrations in blood.

4 Selection of the Indicators

Systemic epichlorohydrin exposure of humans can be detected, on the one hand, by determination of the mercapturic acids of epichlorohydrin excreted in urine and, on the other hand, by the determination of the haemoglobin adducts of epichlorohydrin. In animals, both S-(3-chloro-2-hydroxypropyl) mercapturic acid (CHPMA) and S-(2,3-dihydroxypropyl) mercapturic acid (DHPMA) are formed and are excreted in urine. Both compounds can therefore be used as possible biomarkers of an exposure to epichlorohydrin.

The chlorine-containing mercapturic acid CHPMA better reflects the original structure of epichlorohydrin and is thus the more specific parameter compared with the dihydroxylated mercapturic acid DHPMA. In addition, a considerable background exposure to DHPMA was demonstrated in a collective of the general population, so that this biomarker is obviously also formed physiologically. The range of variation of the values is low and a relation to creatinine excretion exists (Eckert et al. 2011). No background excretion was found for CHPMA (Eckert et al. 2012).

Basically the same should be expected for the haemoglobin adducts, however there are fewer data available. Here as well, relevant excretion levels are found for N-(2,3-dihydroxypropyl)-valine (DHPV) in persons not occupationally exposed to epichlorohydrin (Hindsø Landin et al. 1996). The chlorinated adduct N-(3-chloro-2-hydroxypropyl)-valine (CHPV) can be detected specifically only

after exposure to epichlorohydrin. After a chemical accident elevated CHPV levels were measured in some cases even after some weeks, whereas DHPV could not be detected (Wollin et al. 2014).

5 Analytical Methods

Several published analytical methods are available both for the mercapturic acids and for the haemoglobin adducts of epichlorohydrin.

For the determination of the mercapturic acids CHPMA and DHPMA procedures using GC-MS (De Rooij et al. 1997) and LC-MS/MS (liquid chromatography with tandem mass spectrometry) (Eckert et al. 2010, 2012) have been published.

For the two haemoglobin adducts CHPV and DHPV there are procedures based on modified Edman degradation using GC-MS/MS (Bader et al. 2009) and GC-MS (Müller et al. 2013, translated). The quantification limits in each case are at 25 pmol/g globin.

The procedures for the determination of the S-(3-chloro-2-hydroxypropyl) mercapturic acid (CHPMA) (Eckert et al. 2015, translated) and the adducts N-(3-chloro-2-hydroxypropyl)-valine (CHPV) (Bader et al. 2012, translated) and N-(2,3-dihydroxypropyl)-valine (DHPV) (Müller et al. 2013, translated) have been included in the MAK Collection for Occupational Health and Safety.

6 Background Exposure

The epichlorohydrin-specific chlorinated metabolites CHPMA and CHPV have to date not been detected in the urine or blood of persons without occupational exposure to epichlorohydrin. The detection limit for CHPMA in the most sensitive procedure was 2.7 µg/l (Eckert et al. 2012). The less specific metabolites exhibited a wide range of variation, and were influenced to a varying degree by smoking behaviour. For the non-chlorinated metabolite DHPMA a background excretion could be detected in all urine samples (54 non-smokers and 40 smokers, range 114–369 µg/g creatinine) (Eckert et al. 2011). For non-smokers a median of 206 µg/g creatinine and a 95th percentile of 279 µg/g creatinine were determined; for smokers a median value of 217 µg/g creatinine and a 95th percentile of 294 µg/g creatinine.

In a study by Hindsø Landin et al. (1997) the DHPV concentration in the blood of non-smokers in the Swedish collective was 2.1 ± 1.1 pmol/g globin (mean value ± standard deviation) and in the German collective 6.8 ± 3.2 pmol/g globin. For smokers the DHPV concentrations were 9.5 ± 2.2 pmol/g globin in the Swedish collective and 13.1 ± 2.7 pmol/g globin in the German collective.

7 Evaluation

Because epichlorohydrin is clearly carcinogenic in the animal experiment, no BAT value (biological tolerance value) can be evaluated. The derivation of EKA (exposure equivalents for carcinogenic substances) is possible for the parameter S-(3-chloro-2-hydroxypropyl) mercapturic acid in urine. In the occupational-medical study by De Rooij et al. (1997) a significant linear relationship between epichlorohydrin exposure in the air and this biomonitoring parameter was determined. The study reports about in some cases high pre-shift CHPMA excretion levels which are attributed to delayed absorption of the substance through the skin. Accordingly, an accumulation of this parameter over several consecutive shifts with epichlorohydrin exposure cannot be excluded

According to the correlation from the study by De Rooij et al. (1997) the following EKA are obtained:

Air		**Urine**
1-Chloro-2,3-epoxypropane		**S-(3-chloro-2-hydroxypropyl)-mercapturic acid**
[ml/m³]	**[mg/m³]**	**[mg/g creatinine]**
0.06	0.23	0.80
0.13	0.5	1.75
0.26	1	3.5
*0.06**	*2.3**	*8**
*2**	*8**	*28**

* equivalents for the exposure-risk relationship for carcinogenic substances according to TRGS 910 ("Risk-related concept of measures for activities involving carcinogenic hazardous substances")

Sampling time is at the end of exposure or end of shift and in the case of long term exposure at the end of shift after several shifts.

8 Interpretation of Data

The EKA relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l (WHO 1996). As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended.

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