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Glycidol – Evaluation of a BAR

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

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Keywords

glycidol; biological reference value; BAR; N-(2,3-dihydroxypropyl)valine; S-(2,3-dihydroxypropyl)mercapturic acid

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated glycidol (2,3-epoxy-1-propanol) [556-52-5] and has derived a biological reference value (BAR) at the workplace for its adduct at the N-terminal valine of the haemoglobin protein complex (N-(2,3-dihydroxypropyl)valine, DHPV).

Glycidol is an alkylating agent, which generated DNA adducts in an in vitro assay. Moreover, DHPV was found in rats and humans after consumption of glycidol-generating fatty acid glycidyl esters. Studies in populations without occupational exposure to glycidol demonstrated significantly higher DHPV levels in smokers compared to non-smokers. Based on the 95th percentile of DHPV levels in individuals without occupational exposure to glycidol, a BAR of 15 pmol DHPV/g globin was evaluated for non-smokers. Sampling has to be performed after exposure for at least 3 months.

Additionally, S-(2,3-dihydroxypropyl)mercapturic acid (DHPMA), a secondary product of the glutathione conjugation with glycidol, was determined in the urine of the general population. However, no studies were performed which could demonstrate the increase of DHPMA levels by glycidol exposure. No data were available which depict a quantitative relation between the biomarkers of exposure and the external exposure to glycidol or the carcinogenic risk. Despite the existing background levels of DHPMA, no BAR was evaluated for this parameter due to the missing data for the association between urinary DHPMA levels and glycidol exposure.

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BAR (2020)	**15 pmol N-(2,3-dihydroxypropyl)valine/g globin** Sampling time: after exposure for at least 3 months
MAK value	–
Absorption through the skin (2000)	H
Sensitization	–
Carcinogenicity (2014)	Category 2
Prenatal toxicity	–
Germ cell mutagenicity (2014)	Category 3 A
Synonyms	Glycerine glycide Glycide Glycide alcohol Oxirane-2-methanol
Chemical name	2,3-Epoxy-1-propanol
CAS number	556-52-5
Formula	$C_3H_6O_2$
Molar mass	74.08 g/mol
Melting point	−45 °C (IFA 2021)
Boiling point at 1013 hPa	163 °C (decomposition) (IFA 2021)
Density at 20 °C	1.12 g/cm^3 (IFA 2021)
Vapour pressure at 25 °C	1.2 hPa (IFA 2021)
log K_{OW}	−0.95 (IFA 2021)

Glycidol occurs in two stereoisomeric forms and, as a bifunctional alkylating agent, is a key substance for the synthesis of numerous glycidol and glycerol derivatives. The derivatives are used for the production of surface-active compounds, plastic additives, paints, photochemicals, pharmaceuticals and biocides. Glycidol is used as a stabiliser in the production of vinyl polymers. It is also used as an additive for oils and synthetic hydraulic fluids, and as a solvent for certain epoxy resins (Hartwig 2015). It is also present in small amounts in tobacco smoke (Schumacher et al. 1977).

1 Metabolism and Toxicokinetics

1.1 Absorption, distribution and elimination

Male Fischer 344 rats were given 37.5 or 75 mg glycidol/kg body weight orally (po) or intravenously (iv). Approximately 87% to 92% of the dose was absorbed from the gastrointestinal tract of the rat. Seventy-two hours after exposure to ^{14}C-labelled glycidol, most of the administered dose was excreted in the urine (37.5 mg/kg: 39.9 ± 1.9% (po) and 43.3 ± 2.5% (iv), respectively; 75 mg/kg: 41.8 ± 2.3% (po) and 48.0 ± 8.3% (iv), respectively). The second major route of excretion was via CO_2 exhalation. Excretion via the faeces, on the other hand, played a minor role (Nomeir et al. 1995).

In a toxicokinetic study in three male SD rats and three male monkeys (cynomolgus, macaque species), the bioavailability of glycidol after oral administration of 75 mg/kg body weight (equivalent to approx. 1 mmol/kg body weight) was 68.8% in rats and 34.3% in monkeys. In rats, the maximum blood concentration and AUC (area under the curve)

were 3.9- and 2.0-times as high as in monkeys after administration of 75 mg glycidol/kg body weight. The half-life of glycidol in plasma was 0.367 hours after intravenous administration in the rats and 0.409 hours in the monkeys, as well as 1.28 hours after oral administration in the rats and 1.48 hours in the monkeys. In the same study, both species were also treated orally with 341 mg glycidyl linoleate (equivalent to approximately 1 mmol/kg body weight). Again, glycidol was determined in plasma and the resulting glycidol plasma levels showed very similar kinetics as after oral glycidol exposure. After administration of 341 mg glycidyl linoleate/kg body weight, the maximum concentration in the blood and the AUC corresponded to 77% and 128%, respectively, of those after glycidol administration in the rat experiment. In the monkey experiment the maximum concentration in the blood and the AUC corresponded to 17% and 56%, respectively, of those after glycidol administration. Therefore, the bioavailability of glycidol from glycidyl linoleate is lower in monkeys (Wakabayashi et al. 2012).

In another toxicokinetic study, rats were treated orally with 0, 4.92, 12, 30 or 75 mg glycidol/kg body weight and the concentration of the haemoglobin adduct N-(2,3-dihydroxypropyl)valine (DHPV) was determined 24 hours after administration (Honda et al. 2014). A dose-dependent increase in the DHPV level was found. Further blood samples from animals treated with 12 mg glycidol/kg body weight were obtained over a period of 40 days and analysed for DHPV levels. A linear decrease was observed, which was in good agreement with the 61-day erythrocyte life span. In addition, in the blood of rats and humans, a second-order kinetics was found for the formation reaction of DHPV with a rate constant of 6.7 ± 1.1 and 5.6 ± 1.3 pmol/g globin/(μM × h), respectively (Honda et al. 2014).

In 16 male Wistar rats, after oral administration of 50 mg glycidol/kg body weight (equivalent to 0.67 mmol/kg body weight), 2.30 ± 0.71 mg S-(2,3-dihydroxypropyl)mercapturic acid (DHPMA) were excreted in the first eight hours, 3.40 ± 0.54 mg DHPMA in the following 16 hours and 0.34 ± 0.06 mg DHPMA in the following 24 hours, corresponding to 5.4 ± 1.6%, 7.8 ± 1.3% and 0.8 ± 0.1 % of the dose, respectively (Appel et al. 2013).

In a human study, eleven test persons consumed 36 g of palm fat daily over a period of four weeks, which contained 8.7 mg glycidol/kg in the form of glycidyl fatty acid esters. To determine the kinetics of the glycidol-haemoglobin adduct DHPV, two blood samples were obtained in the week before exposure one blood sample at the end of each week of exposure and one at the end of every third week within a 15-week follow-up period. The DHPV level increased constantly during the four weeks of oral exposure. After the exposure phase, the DHPV concentration decreased again following zero-order elimination kinetics with a half-life of 104 days (Abraham et al. 2019).

1.2 Metabolism

The degradation pathways of glycidol in rats are described in Greim (2003). After intraperitoneal injection of glycidol, S-(2,3-dihydroxypropyl)glutathione, S-(2,3-dihydroxypropyl)cysteine and β-chlorolactic acid were isolated as major metabolites in the urine (NTP 1990). Male rats were given 100 mg glycidol/kg body weight orally 48, 54 and 72 hours after intraperitoneal injection of radiolabelled isotonic sodium chloride solution ($Na^{36}Cl$). Up to 80 hours after the start of the experiment, the only radiolabelled metabolite found in the urine was β-chlorolactic acid (Jones and O'Brien 1980). The identified urinary metabolites correspond to those found after treatment with 3-chloro-1,2-propanediol (α-chlorohydrin, monochloropropanediol). A conversion of glycidol to 3-chloro-1,2-propanediol by direct reaction with hydrochloric acid in the stomach can therefore be assumed. The transformation of 3-chloro-1,2-propanediol into a glutathione derivative (S-(2,3-dihydroxyproyl)glutathione) with the participation of a glutathione transferase is likely to be in competition with the oxidation to β-chlorolactic acid with the successive participation of an alcohol and an aldehyde dehydrogenase (ACGIH 1996).

By cleavage of glutamic acid and glycine and subsequent acetylation, S-(2,3-dihydroxyproyl)glutathione is converted into the corresponding mercapturic acid (DHPMA), which is excreted in the urine. The conversion of glycidol to glycerol by rat liver and lung microsomes has also been demonstrated. This hydrolysis is catalysed by epoxide hydrolases (Patel et al. 1980).

Glycidol is very reactive due to its epoxide structure and is a direct alkylating agent. In an in vitro model, the reaction of glycidol with purified DNA to the DNA adducts 3-(2,3-dihydroxypropyl)-dUrd and 3-(2,3-dihydroxypropyl)-dThd

was demonstrated (Segal et al. 1990). The corresponding adduct at the *N*-terminal valine of the globin groups of the haemoglobin complex (DHPV) was demonstrated both in animal experiments (male Wistar rat) and in experiments in test persons after oral administration of glycidyl fatty acid ester (Abraham et al. 2019; Appel et al. 2013).

2 Critical Toxicity

After acute inhalation exposure, glycidol caused pneumonia and emphysema in rats and mice. Glycidol is irritating to the skin and mucous membranes and shows neurotoxic effects in animal experiments. It was mutagenic in numerous short-term tests with prokaryotes and eukaryotes in vitro and has genotoxic properties in vivo. When administered by gavage, glycidol proved to be clearly carcinogenic in rats and mice (Greim 2003).

3 Exposure and Effects

No studies are available that establish a quantitative association between glycidol biomonitoring parameters and health effects or between glycidol biomonitoring parameters and glycidol inhalation exposure.

4 Selection of the Indicators

The detection of systemic glycidol exposure in humans can be performed on the one hand by determining the mercapturic acids of glycidol excreted in the urine and on the other hand by determining the haemoglobin adducts of glycidol. However, both parameters are formed following exposure to epichlorohydrin (Göen et al. 2018).

The animal studies on metabolism indicate that DHPMA is formed as a secondary product of the direct reaction of glycidol with glutathione and excreted in the urine, and thus can be used as a possible parameter of glycidol exposure. Studies on a collective of the German general population have shown that DHPMA has a clearly measurable background excretion that has only a small range of variation and is very closely associated with creatinine excretion (Eckert et al. 2011).

As a further parameter DHPV is available. For this parameter, several studies found DHPV levels in persons without occupational exposure to glycidol or epichlorohydrin (see Section 6). In contrast to DHPMA, DHPV concentrations showed a clear difference between smokers and non-smokers, indicating that for this parameter exogenous sources are of greater importance than a possible physiological formation (Hindsø Landin et al. 1997). In addition, elevated blood levels of DHPV were observed in one study after consumption of food containing glycidyl fatty acid esters (Abraham et al. 2019). To date, there are no studies on occupational exposure to glycidol using this parameter, only studies using it in workers with occupational exposure to epichlorohydrin (Hindsø Landin et al. 1997) and in emergency workers following an accidental spill of epichlorohydrin (Wollin et al. 2014). In the first study, DHPV could be determined in the chemical workers (regular exposure in the range from 0.11 to 0.23 ml/m³ epichlorohydrin) in the range from 3.32 to 58.22 pmol/g globin. However, the in-plant controls showed comparably high DHPV levels (range 3.01–40.3 pmol/g) (Hindsø Landin et al. 1997). In the study on the epichlorohydrin accident (Wollin et al. 2014), DHPV was not detectable in the emergency workers – presumably due to the high detection limit (see Section 5).

5 Analytical Methods

Published analytical methods are available for both the mercapturic acid and the haemoglobin adducts of glycidol.

De Rooij et al. (1997) used a method with GC-MS technique for the determination of DHPMA in urine. In the procedure, the urine was lyophylised, subsequently methylated (reaction with methanol and HCl) and silylated (reaction with N,O-bis(trimethylsilyl)trifluoroacetamide) and finally the derivatives were separated and detected by GC-MS.

For DHPMA, the authors reported analytical interferences that allowed a determination of this parameter only at a concentration of 1 mg/l and above. A much more specific and sensitive determination of DHPMA is possible with the coupling of high-performance liquid chromatography and tandem mass spectrometry (LC-MS/MS). Eckert and colleagues presented an analytical procedure with which DHPMA can be reliably quantified in urine (Eckert et al. 2010). In this procedure, this mercapturic acid is enriched together with other hydroxyalkyl mercapturic acids from the urine matrix by solid phase extraction and separated using hydrophilic interaction liquid chromatography (HILIC). With this method, a detection limit of 5.5 µg/l urine was achieved for DHPMA.

For DHPV, a method based on modified Edman degradation and the GC-MS analysis technique exists (Müller et al. 2013). This method has a limit of quantification of 25 pmol/g globin and is thus not suitable for the reliable detection of background exposure or slightly elevated exposures. The limit of quantification can be lowered by using tandem mass spectrometry. However, Hindsø Landin et al. (1996) were able to achieve a detection limit of 2 pmol/g globin with a similar method using GC tandem MS technology. Hielscher et al. (2017) developed an analytical procedure for the determination of DHPV based on Edman degradation and the UPLC-MS/MS technique (ultra-performance liquid chromatography-tandem mass spectrometry).

6 Background Exposure

DHPMA formed from glycidol was detected in all urine samples in a German population study (54 non-smokers and 40 smokers). The DHPMA concentrations were in the range of 114 to 369 µg/g creatinine. For non-smokers, a median of 206 µg DHPMA/g creatinine and a 95th percentile of 279 µg DHPMA/g creatinine were determined; for smokers, a median of 217 µg DHPMA/g creatinine and a 95th percentile of 294 µg DHPMA/g creatinine (Eckert et al. 2011).

Hindsø Landin et al. (1997) reported a statistically significant difference in DHPV concentrations between smokers and non-smokers in an occupational health study of workers exposed to epichlorohydrin and control subjects without occupational exposure to epichlorohydrin from Germany and Sweden. The DHPV concentration in the blood of the non-smokers was 2.1 ± 1.1 pmol/g globin (mean ± standard deviation) in the Swedish collective and 6.8 ± 3.2 pmol/g globin in the German collective. Among smokers, DHPV concentrations were 9.5 ± 2.2 pmol/g globin in the Swedish collective and 13.1 ± 12.4 pmol/g globin in the German collective.

Honda et al. (2011), who analysed the formation of DHPV following ingestion of glycidyl fatty acid ester, explored the effect of diet with different levels of glycidyl fatty acid ester. The working group found significantly lower levels of DHPV in a small non-smoking group of people (n = 6) with increased glycidyl fatty acid ester intake via canteen food than in non-smokers of the same company (n = 5) with non-increased glycidyl fatty acid ester intake (3.8 ± 2.0 pmol/g globin vs. 7.6 ± 3.1 pmol/g globin). In a follow-up study (Honda et al. 2012), the authors found no difference between DHPV levels in the blood of 14 non-smoking individuals with increased glycidyl fatty acid ester intakes and 42 non-smoking individuals with lower glycidyl fatty acid ester diets (6.9 pmol/g globin (95% CI (confidence interval) 4.9–9.0) vs. 7.3 pmol/g globin (95% CI 6.1–8.5)). The DHPV level in the group without increased glycidyl fatty acid ester exposure was in the range between 1.4 and 16.0 pmol/g globin and had a 95th percentile of 15.0 pmol/g globin.

To assess glycidol exposure from regular dietary intake of glycidyl fatty acid esters, blood samples from 50 children aged about 12 years (35 boys, 15 girls) and 6 each of male adult smokers and non-smokers were analysed for DHPV levels in Sweden. In the children, DHPV levels were 7.3 ± 2.5 pmol/g globin (mean ± standard deviation), with no significant difference found between the sexes. In the adult collective, DHPV levels in the blood of smokers were significantly elevated at 23.4 ± 4.6 pmol/g globin (range: 18.1–31.4 pmol/g) compared with levels in the blood of non-smokers (10.3 ± 2.7 pmol/g globin, range: 6.3–14.0 pmol/g globin) (Aasa et al. 2019).

Further data on DHPV background exposure are available from studies by the Federal Institute for Risk Assessment (BfR) (Abraham et al. 2019; Hielscher et al. 2017). As part of the development of a new method for the determination of DHPV in human globin, two blood samples each were obtained from 12 adult non-smokers (6 women and 6 men) at intervals of 7 to 15 days and analysed for DHPV content using the new method (Hielscher et al. 2017). DHPV levels

in the range of 2.2 to 4.9 pmol/g globin were found with low intraindividual variability. In a subsequent study, the baseline DHPV levels in 11 subjects before ingestion of palm fat contaminated with particularly high levels of glycidyl fatty acid esters were in the range of 3.21 to 5.09 pmol/g globin (Abraham et al. 2019). However, this working group used the hydantoin product formed after cleavage from the globin chain for calibration in its analytical procedure, so that the influence of the protein structure on the cleavage reaction is not included. It is unclear whether the results of this study are comparable to those of the studies with the established calibration (see Section 5).

7 Evaluation

Due to the classification of glycidol as a proven carcinogen in animal experiments, a biological tolerance value (BAT value) cannot be derived. A derivation of exposure equivalents for carcinogenic substances (EKA) is also not possible due to the lack of data.

The derivation of a biological reference value (BAR) for the parameter DHPMA is waived because there are currently no human studies available that unequivocally identify DHPMA as a human glycidol metabolite.

On the other hand, the formation of the glycidol-haemoglobin adduct DHPV has been documented in humans after exposure to glycidol-forming fatty acid glycidyl esters (Abraham et al. 2019). For the derivation of a BAR based on DHPV levels, the Japanese study (Honda et al. 2012) contains the largest sample of non-smoking adults, and the range of results (1.4–16 pmol DHPV/g globin) agrees well with the results for non-smokers in a recent Swedish study (6.3–14 pmol DHPV/g globin; Aasa et al. 2019). In the study by Honda et al. (2012), the 95th percentile in the non-smoking collective was 15.0 pmol DHPV/g globin. Therefore,

a BAR for non-smokers of 15 pmol N-(2,3-dihydroxypropyl)valine/g globin

is established. Sampling should be carried out after at least 3 months of exposure, as the haemoglobin adduct is an indicator of subchronic exposure.

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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