The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Ethylene oxide – Addendum: Derivation of BAR

Assessment Values in Biological Material – Translation of the German version from 2022

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Keywords

ethylene oxide; biological reference value; BAR

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the Deutsche Forschungsgemeinschaft has evaluated biological reference values (BAR) for two metabolites of ethylene oxide [75-21-8]. Considering the available studies on the mercapturic acid of ethylene oxide in urine, *S*-(2-hydroxyethyl)mercapturic acid (HEMA), a BAR of 5 µg HEMA/g creatinine for background exposure to ethylene oxide was established. Sampling time after short-term exposures is at the end of exposure or at the end of the working shift. For long-term-exposures, a BAR of 60 pmol/g globin was established for the haemoglobin adduct of ethylene oxide, *N*-(2-hydroxyethyl)valine (HEV). Sampling time is after at least 3 months of exposure.

Citation Note:
Eckert E, Bader M, Drexler H, Hartwig A, MAK Commission. Ethylene oxide – Addendum: Derivation of BAR. Assessment Values in Biological Material – Translation of the German version from 2022. MAK Collect Occup Health Saf. 2022 Mar;7(1):Doc018. https://doi.org/10.34865/bb7521e7_1ad

Manuscript completed:
12 Apr 2021

Publication date:
31 Mar 2022

BAR (2021)

5 µg HEMA/g creatinine
Sampling time: end of exposure or end of shift; for long-term exposures: at the end of the shift after several previous shifts

60 pmol HEV/g globin
Sampling time: after at least 3 months of exposure

EKA (1999)

Correlations between external and internal exposure:

Air Ethylene oxide		Blood/erythrocytes HEV
[ml/m³]	[mg/m³]	[µg/l blood]
0.5	0.92	45
1	1.83	90
2	3.66	180

Sampling time: after at least 3 months of exposure

MAK value	–
Peak limitation	–
Absorption through the skin (1984)	H
Sensitization	–
Carcinogenicity (1984)	Category 2
Prenatal toxicity	–
Germ cell mutagenicity (2002)	Category 2

Re-evaluation

Ethylene oxide was evaluated in 1987 (Bolt 1989; Norpoth and Bolt 1995) and 1999 (translated in Bolt 2010). Detailed information on the metabolism and toxicokinetics of ethylene oxide can be found in the MAK documentation of 2019 and an IARC documentation of 2012 (Hartwig and MAK Commission 2019; IARC 2012). Due to the classification of ethylene oxide as a Category 2 carcinogen, no Biological Tolerance Value (BAT value) can be derived. Therefore, in 1999, exposure equivalents for carcinogenic substances (EKA) were established for the relation between the concentration of ethylene oxide in air and the biomarker *N*-(2-hydroxyethyl)valine (HEV) in blood (Bolt 2010). Since the last evaluation, substantial work has appeared that now makes it possible to establish Biological Reference Values (BAR) for biomarkers of ethylene oxide.

In principle, both HEV in blood and *S*-(2-hydroxyethyl)mercapturic acid (HEMA) in urine are suitable for the biomonitoring of ethylene oxide.

BAR for *N*-(2-hydroxyethyl)valine (HEV) in blood

Information on the parameter HEV and analytical methods were already published (Bolt 2010).

Background exposure

Several studies are available on the concentration of the haemoglobin adduct HEV in the blood of persons without occupational exposure to ethylene oxide. These are compiled in Table 1. In general, there is a significant difference between HEV concentrations in samples from non-smokers and smokers; the values of smokers are higher. Various studies indicate that the increase in HEV concentration in the blood of smokers depends directly on the number of cigarettes consumed daily (Bader et al. 1995; Bono et al. 1999). Therefore, only the results for non-smokers are used to derive a BAR for HEV.

The published median or mean values for HEV in samples from non-smokers are in the range between 9.1 and 57 pmol/g globin (see Table 1). It is striking that the studies can, in principle, be assigned to two groups: some studies (Bono et al. 1999; Boogaard et al. 1999; CDC 2020; Fennell et al. 2000; Filser et al. 1992; Schettgen et al. 2016; von Stedingk et al. 2011) showed lower medians of below 30 pmol/g globin, while other studies (Bader et al. 1995; Bailey et al. 1988; Mayer et al. 1991; Wu et al. 2004; Yong et al. 2001) reported median or mean HEV levels in the haemoglobin of non-smokers between 40 and 60 pmol/g globin. These differences cannot be explained by regional factors. Possible reasons are the selection of subjects (inclusion of passive smokers, objective assessment of smoking status) as well as the choice of the analytical method.

Tab. 1 HEV in the blood of persons not occupationally exposed to ethylene oxide

Collective	Persons	HEV [pmol/g globin]			References
		Median	95th Percentile	Range	
Germany					Bader et al. 1995
Non-smokers	37	47	63	19–64	
Smokers	32	144	318	31–327	
UK					Bailey et al. 1988
Non-smokers	23	56	80[a)]	22–106	
Smokers	26	167	370[a)]	38–501	
Italy					Bono et al. 1999
Non-smokers	74	9.1	~35[b)]		
Smokers	44	45.4	~70[b)]		
Netherlands					Boogaard et al. 1999
Non-smokers	23	19		6–49	
USA					CDC 2020
2013/2014					
Non-smokers ≥20 years	1266	28	59		
Smokers > 18 years	416	219	653		
2015/2016					
Non-smokers ≥20 years	1267	25	64		
Smokers > 18 years	377	220	652		
USA					Fennell et al. 2000
Non-smokers	13	12.9			
Germany					Filser et al. 1992
Non-smokers	5	19.5		16–25.5	
USA					Mayer et al. 1991
Non-smokers	16	45 (MV)			
Smokers	4	150 (MV)			
Germany					Schettgen et al. 2016
Non-smokers	104	17.8	35.6	7.7–64.6	
Denmark					von Stedingk et al. 2011
Non-smokers	55	22		6.4–64	
Smokers	6	410		210–560	

Tab. 1 *(continued)*

Collective	Persons	HEV [pmol/g globin]			References
		Median	95th Percentile	Range	
Taiwan					Wu et al. 2004
Non-smokers	78	57 (MV)			
Smokers	70	204 (MV)			
USA					Yong et al. 2001
Non-smokers	5	50 (MV)			

[a] Calculation from reported individual data
[b] estimated from figure
MV: mean value

Evaluation of a BAR for HEV

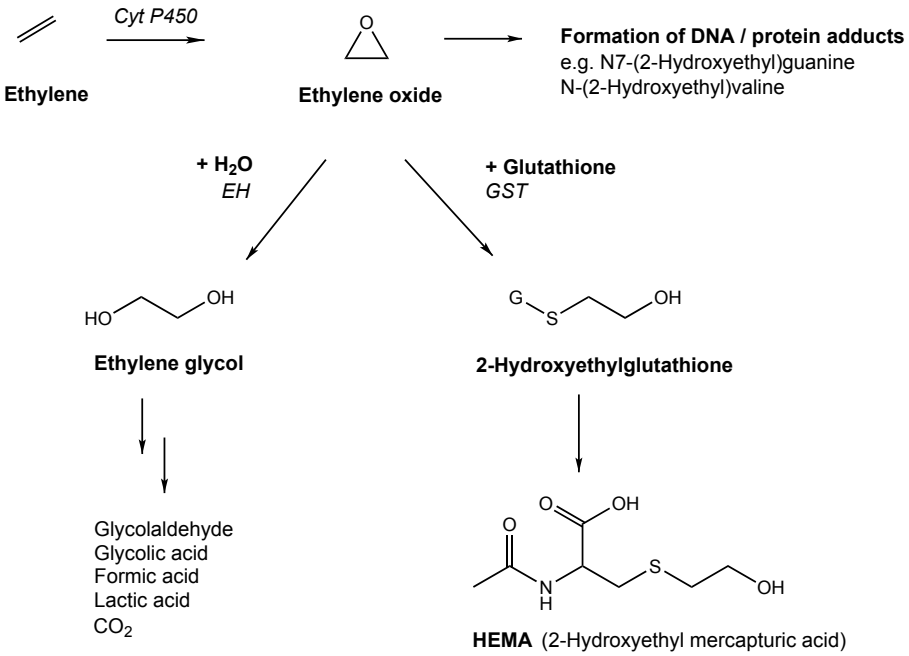
Taking into account the very elaborate and demanding analytics for the determination of haemoglobin adducts, the studies listed in Table 1 nevertheless give a well consistent picture of the background concentrations of HEV in non-smokers. The largest study in terms of sample size is the NHANES study of the US Centers for Disease Control and Prevention (CDC 2020), in which HEV levels were determined in samples from 1266 (2013/2014) or rather 1267 (2015/2016) non-smokers (≥ 20 years old); the 95th percentile was 59 or rather 64 pmol/g globin. Based on other studies in which a 95th percentile was given or could be read from the paper, a 95th percentile of 53 pmol HEV/g globin can be derived on average. Considering all these data, a

BAR of 60 pmol HEV/g globin

is established for non-smokers. Smokers can show higher concentrations by a factor of 5 to 10. HEV represents a long-term parameter whose concentration in blood builds up over a period of several months (due to the lifespan of the erythrocytes of about 120 days). Sampling should therefore be carried out after at least three months of exposure.

BAR for *S*-(2-hydroxyethyl)mercapturic acid (HEMA) in urine

In recent years, more and more studies have been published dealing with the determination of HEMA as an exposure biomarker for ethylene oxide. Unlike the long-term biomarker HEV, HEMA represents a classical short-term biomarker for ethylene oxide with an estimated half-life of < 5 hours (Haufroid et al. 2007), which, due to the short elimination half-life, well reflects the current exposure situation. In addition, there are advantages with regard to non-invasive sampling and significantly less complex analytics. Figure 1 shows the metabolism of ethylene oxide. To form HEMA, ethylene oxide is conjugated with the endogenous tripeptide glutathione (GSH) by the polymorphic enzyme glutathione-*S*-transferase (GST). After cleavage of the glycine and glutamyl residues and subsequent *N*-acetylation, the urinary metabolite HEMA is formed from the conjugate. For ethylene oxide as a substrate of GSTT1 (Hallier et al. 1993; Haufroid et al. 2007; Müller et al. 1998; Yong et al. 2001), there are a number of studies on the influence of the activity of this enzyme on the formation of HEMA. About 20% of Whites have the GSTT1-null genotype (Garte et al. 2001) and belong to the so-called "slow" conjugators (Hallier et al. 1993; Hayes and Strange 2000). The influence of the GSTT1 genotype on the excretion of HEMA was investigated by Haufroid et al. (2007) in 80 hospital workers occupationally exposed to ethylene oxide. Given the detectable but minor influence of genetic disposition, they concluded that the level of exposure is the most important determinant of the level of mercapturic acid excretion. Nevertheless, the polymorphism of certain enzymes is obviously one of several causes for the sometimes quite high individual variations in the concentrations of mercapturic acid in urine.



EH: epoxide hydrolase; GST: glutathione S-transferase; Cyt P450: cytochrome P450; G: glutathione

Fig. 1 Metabolism of ethylene and ethylene oxide according to IARC (2012)

Analytical methods

An analytical method tested by the Commission is already available for the determination of HEMA in urine (translated in Schettgen et al. 2013). This method is based on the external enrichment of the mercapturic acids in urine via solid-phase extraction and subsequent determination by means of high-performance liquid chromatography and tandem mass spectrometric detection (LC-MS/MS). Most other published methods are also based on LC-MS/MS analysis, whereby an enrichment procedure is usually carried out either in the form of an external solid-phase extraction or by means of column switching (online SPE) (Eckert et al. 2010; Frigerio et al. 2019; Pluym et al. 2015; Schettgen et al. 2008). Many published methods are multi-methods that detect other mercapturic acids in urine in addition to HEMA.

The detection limit of the tested method by Schettgen et al. (2013) is 0.5 µg HEMA/l urine, which means that HEMA can also be reliably detected in most non-smoker urines. External quality assurance of this parameter is possible through participation in the quality assessment scheme for occupational and environmental toxicological analyses (G-EQUAS) of the German Society for Occupational and Environmental Medicine.

Exposure and effects

There are currently no studies establishing a relationship between external exposure to ethylene oxide exposure and HEMA concentration in urine.

Background exposure

There are several studies that have investigated the concentrations of HEMA in urine samples from persons without occupational exposure to ethylene oxide ("background exposure"). An overview of the published studies is given in Table 2. As a rule, the HEMA concentrations are given in relation to the creatinine concentration, since it could be shown for other mercapturic acids as well, that an adjustment to urinary creatinine reduces the variability of the results. Analogous to the haemoglobin adduct HEV, smokers show higher HEMA concentrations in the urine compared

with non-smokers. The derivation of a BAR is based only on the results for non-smokers. The median HEMA concentration in the published studies was in the range of 0.3 and 1.7 µg/g creatinine; the study results generally showed high agreement. Only the study by Hou et al. (2012) stands out due to comparatively low HEMA concentrations for smokers and non-smokers, which were about a factor of three below the results of the other studies. The observed geographical differences could at least partly be explained by the fact that the incidence of GSTT1 deletions is higher in the East Asian region than in other regions (Bolt and Thier 2006).

Tab. 2 Background concentrations of HEMA in the urine of persons not occupationally exposed to ethylene oxide

Collective	Persons	HEMA [µg/g creatinine]			References
		Median	95th Percentile	Range	
USA					Alwis et al. 2012
Non-smokers	1203	0.7 MV 0.66 ± 1.16 µg/l			
Smokers	347	1.9 MV 1.90 ± 3.7 µg/l			
USA (NHANES)					Calafat et al. 1999
Non-smokers	214	1.1	6.0		
Smokers	152	2.9	16.5		
USA					Ding et al. 2009
Non-smokers	59	0.8		< 0.03–1.1	
Smokers	61	3.1		< 0.03–16.0	
Germany					Eckert et al. 2011
Non-smokers	54	1.6	4.7	0.6–8.1	
Smokers	40	4.9	23.9	1.11–67.7	
Italy					Frigerio et al. 2020
Non-smokers	39	1.3	4.1		
Smokers	21	3.2	26.7		
China					Hou et al. 2012
Non-smokers	58	0.25[a)]	2.0[a)]	< 0.08–2.8[a)]	
Smokers	246	0.81[a)]	8.1[a)]	0.02–23.3[a)]	
Germany					Pluym et al. 2015
Non-smokers	25	1.1	~ 4–5	0.11–38.3	
Smokers	25	2.3		1.1–6.2	
Germany					Schettgen et al. 2008
Non-smokers	14	1.7		0.7–4.2	
Smokers	14	4.0		1.3–6.0	

[a)] calculated from nmol/24-h urine with molar mass of 207.25 g/mol, 1.2 g creatinine/l urine and 1.5 l urine/day
LOQ: limit of quantification; MV: mean value

Evaluation of a BAR for HEMA

In the studies that give a 95th percentile for the concentrations of HEMA in urine, this lies in the range between 2.0 and 6.0 µg/g creatinine for samples from non-smokers. In the two studies from Germany in which a 95th percentile was calculated or can be read off from study data, this was for non-smokers 4.7 µg HEMA/g creatinine (Eckert et al. 2011) and ~ 4–5 µg HEMA/g creatinine (Pluym et al. 2015).

From this, a

BAR of 5 µg HEMA/g creatinine

is derived for non-smokers. Smokers can show higher concentrations in urine by a factor of 3 to 5. HEMA is a short-term biomarker and has a half-life of a few hours. Sampling should therefore be done immediately after the end of exposure or at the end of shift.

Interpretation

When interpreting the results, personal influencing factors, especially smoking habits and passive smoke exposure have to be taken into account, as exposure to tobacco smoke leads to higher HEMA concentrations in urine. The BAR for HEMA refers to normally concentrated urine in which the creatinine concentration should be in the range of 0.3–3.0 g/l (translated in Bader et al. 2016). As a rule, for urine samples with creatinine concentrations outside the above limits, it is recommended to repeat the measurement at normal hydration.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

References

Alwis KU, Blount BC, Britt AS, Patel D, Ashley DL (2012) Simultaneous analysis of 28 urinary VOC metabolites using ultra high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UPLC-ESI/MSMS). Anal Chim Acta 750: 152–160. https://doi.org/10.1016/j.aca.2012.04.009

Bader M, Lewalter J, Angerer J (1995) Analysis of N-alkylated amino acids in human hemoglobin: evidence for elevated N-methylvaline levels in smokers. Int Arch Occup Environ Health 67(4): 237–242. https://doi.org/10.1007/BF00409405

Bader M, Ochsmann E, Drexler H, Hartwig A, MAK Commission (2016) Addendum to creatinine as reference parameter for the concentration of substances in urine. BAT Value Documentation, 2010. MAK Collect Occup Health Saf 1(1): 266–268. https://doi.org/10.1002/3527600418.bbgeneral05e1715

Bailey E, Brooks AG, Dollery CT, Farmer PB, Passingham BJ, Sleightholm MA, Yates DW (1988) Hydroxyethylvaline adduct formation in haemoglobin as a biological monitor of cigarette smoke intake. Arch Toxicol 62(4): 247–253. https://doi.org/10.1007/BF00332482

Bolt HM (1989) Ethylenoxid. In: Lehnert G, Henschler D, editors. Biologische Arbeitsstoff-Toleranz-Werte (BAT-Werte) und Expositionsäquivalente für krebserzeugende Arbeitsstoffe (EKA). 4th issue. Weinheim: VCH. Also available from https://doi.org/10.1002/3527600418.bb7521d0004

Bolt H (2010) Addendum to ethylene oxide. BAT Value Documentation, 2001. In: Drexler H, Greim H, Hartwig A, editors. The MAK-Collection for Occupational Health and Safety. Part II: BAT Value Documentations. Volume 5. Weinheim: Wiley-VCH. p. 169–173. Also available from https://doi.org/10.1002/3527600418.bb7521e0005

Bolt HM, Thier R (2006) Relevance of the deletion polymorphisms of the glutathione S-transferases GSTT1 and GSTM1 in pharmacology and toxicology. Curr Drug Metab 7(6): 613–628. https://doi.org/10.2174/138920006778017786

Bono R, Vincenti M, Meineri V, Pignata C, Saglia U, Giachino O, Scursatone E (1999) Formation of N-(2-hydroxyethyl)valine due to exposure to ethylene oxide via tobacco smoke: a risk factor for onset of cancer. Environ Res 81(1): 62–71. https://doi.org/10.1006/enrs.1998.3937

Boogaard PJ, Rocchi PS, van Sittert NJ (1999) Biomonitoring of exposure to ethylene oxide and propylene oxide by determination of hemoglobin adducts: correlations between airborne exposure and adduct levels. Int Arch Occup Environ Health 72(3): 142–150. https://doi.org/10.1007/s004200050353

Calafat AM, Barr DB, Pirkle JL, Ashley DL (1999) Reference range concentrations of N-acetyl-S-(2-hydroxyethyl)-L-cysteine, a common metabolite of several volatile organic compounds, in the urine of adults in the United States. J Expo Anal Environ Epidemiol 9(4): 336–342. https://doi.org/10.1038/sj.jea.7500032

CDC (Centers for Disease Control and Prevention) (2020) National report on human exposure to environmental chemicals. Ethylene oxide hemoglobin adduct concentrations among non-smokers – National Health and Nutrition Examination Survey, 2013–2016. Atlanta, GA: CDC. https://www.cdc.gov/exposurereport/ethylene_oxide_hemoglobin.html, accessed 08 Nov 2021

Ding YS, Blount BC, Valentin-Blasini L, Applewhite HS, Xia Y, Watson CH, Ashley DL (2009) Simultaneous determination of six mercapturic acid metabolites of volatile organic compounds in human urine. Chem Res Toxicol 22(6): 1018–1025. https://doi.org/10.1021/tx800468w

Eckert E, Drexler H, Göen T (2010) Determination of six hydroxyalkyl mercapturic acids in human urine using hydrophilic interaction liquid chromatography with tandem mass spectrometry (HILIC-ESI-MS/MS). J Chromatogr B Analyt Technol Biomed Life Sci 878(27): 2506–2514. https://doi.org/10.1016/j.jchromb.2009.09.003

Eckert E, Schmid K, Schaller B, Hiddemann-Koca K, Drexler H, Göen T (2011) Mercapturic acids as metabolites of alkylating substances in urine samples of German inhabitants. Int J Hyg Environ Health 214(3): 196–204. https://doi.org/10.1016/j.ijheh.2011.03.001

Fennell TR, MacNeela JP, Morris RW, Watson M, Thompson CL, Bell DA (2000) Hemoglobin adducts from acrylonitrile and ethylene oxide in cigarette smokers: effects of glutathione S-transferase T1-null and M1-null genotypes. Cancer Epidemiol Biomarkers Prev 9(7): 705–712

Filser JG, Denk B, Törnqvist M, Kessler W, Ehrenberg L (1992) Pharmacokinetics of ethylene in man: body burden with ethylene oxide and hydroxyethylation of hemoglobin due to endogenous and environmental ethylene. Arch Toxicol 66(3): 157–163. https://doi.org/10.1007/BF01974008

Frigerio G, Mercadante R, Polledri E, Missineo P, Campo L, Fustinoni S (2019) An LC-MS/MS method to profile urinary mercapturic acids, metabolites of electrophilic intermediates of occupational and environmental toxicants. J Chromatogr B Analyt Technol Biomed Life Sci 1117: 66–76. https://doi.org/10.1016/j.jchromb.2019.04.015

Frigerio G, Mercadante R, Campo L, Polledri E, Boniardi L, Olgiati L, Missineo P, Fustinoni S (2020) Urinary biomonitoring of subjects with different smoking habits. Part I: profiling mercapturic acids. Toxicol Lett 327: 48–57. https://doi.org/10.1016/j.toxlet.2020.03.010

Garte S, Gaspari L, Alexandrie A-K, Ambrosone C, Autrup H, Autrup JL, Baranova H, Bathum L, Benhamou S, Boffetta P, Bouchardy C, Breskvar K, Brockmoller J, Cascorbi I, Clapper ML, Coutelle C, Daly A, Dell'Omo M, Dolzan V, Dresler CM, Fryer A, Haugen A, Hein DW, Hildesheim A, Hirvonen A, Hsieh L-L, Ingelman-Sundberg M, Kalina I, Kang D, Kihara M, Kiyohara C, Kremers P, Lazarus P, Le Marchand L, Lechner MC, van Lieshout EMM, London S, Manni JJ, Maugard CM, Morita S, Nazar-Stewart V, Noda K, Oda Y, Parl FF, Pastorelli R, Persson I, Peters WHM, Rannug A, Rebbeck T, Risch A, Roelandt L, Romkes M, Ryberg D, Salagovic J, Schoket B, Seidegard J, Shields PG, Sim E, Sinnet D, Strange RC, Stücker I, Sugimura H, To-Figueras J, Vineis P, Yu MC, Taioli E (2001) Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev 10(12): 1239–1248

Hallier E, Langhof T, Dannappel D, Leutbecher M, Schröder K, Goergens HW, Müller A, Bolt HM (1993) Polymorphism of glutathione conjugation of methyl bromide, ethylene oxide and dichloromethane in human blood: influence on the induction of sister chromatid exchanges (SCE) in lymphocytes. Arch Toxicol 67(3): 173–178. https://doi.org/10.1007/BF01973304

Hartwig A, MAK Commission (2019) Ethylenoxid. MAK Value Documentation in German language. MAK Collect Occup Health Saf 4(3): 1392–1424. https://doi.org/10.1002/3527600418.mb7521d0067

Haufroid V, Merz B, Hofmann A, Tschopp A, Lison D, Hotz P (2007) Exposure to ethylene oxide in hospitals: biological monitoring and influence of glutathione S-transferase and epoxide hydrolase polymorphisms. Cancer Epidemiol Biomarkers Prev 16(4): 796–802. https://doi.org/10.1158/1055-9965.EPI-06-0915

Hayes JD, Strange RC (2000) Glutathione S-transferase polymorphisms and their biological consequences. Pharmacology 61(3): 154–166. https://doi.org/10.1159/000028396

Hou H, Xiong W, Gao N, Zhang X, Tang G, Hu Q (2012) A column-switching liquid chromatography-tandem mass spectrometry method for quantitation of 2-cyanoethylmercapturic acid and 2-hydroxyethylmercapturic acid in Chinese smokers. Anal Biochem 430(1): 75–82. https://doi.org/10.1016/j.ab.2012.07.026

IARC (International Agency for Research on Cancer) (2012) Chemical agents and related occupations. Ethylene oxide. In: A review of human carcinogens. IARC monographs on the evaluation of carcinogenic risks on cancer. Volume 100F. Lyon: IARC Press. p. 379–400. https://publications.iarc.fr/_publications/media/download/5295/3ca0442b8e4c2efd2d1abe0ab9146f94c3a2b9a5.pdf

Mayer J, Warburton D, Jeffrey AM, Pero R, Walles S, Andrews L, Toor M, Latriano L, Wazneh L, Tang D (1991) Biologic markers in ethylene oxide-exposed workers and controls. Mutat Res 248(1): 163–176. https://doi.org/10.1016/0027-5107(91)90098-9

Müller M, Krämer A, Angerer J, Hallier E (1998) Ethylene oxide-protein adduct formation in humans: influence of glutathione-S-transferase polymorphisms. Int Arch Occup Environ Health 71(7): 499–502. https://doi.org/10.1007/s004200050312

Norpoth K, Bolt HM (1995) Ethylene oxide. BAT Value Documentation, 1995. In: Lehnert G, Greim H, editors. Biological Exposure Values for Occupational Toxicants and Carcinogens. Volume 2. Weinheim: VCH. p. 146–151. Also available from https://doi.org/10.1002/3527600418.bb7521e0002

Pluym N, Gilch G, Scherer G, Scherer M (2015) Analysis of 18 urinary mercapturic acids by two high-throughput multiplex-LC-MS/MS methods. Anal Bioanal Chem 407(18): 5463–5476. https://doi.org/10.1007/s00216-015-8719-x

Schettgen T, Musiol A, Kraus T (2008) Simultaneous determination of mercapturic acids derived from ethylene oxide (HEMA), propylene oxide (2-HPMA), acrolein (3-HPMA), acrylamide (AAMA) and N,N-dimethylformamide (AMCC) in human urine using liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom 22(17): 2629–2638. https://doi.org/10.1002/rcm.3659

Schettgen T, Scherer G, Sterz K (2013) Mercapturic acids (N-acetyl-S-2-carbamoylethyl-L-cysteine, N-acetyl-S-2-hydroxyethyl-L-cysteine, N-acetyl-S-3-hydroxypropyl-L-cysteine, N-acetyl-S-2-hydroxypropyl-L-cysteine, N-acetyl-S-(N-methylcarbamoyl)-L-cysteine) in urine. Biomonitoring Method, 2012. In: Göen T, Hartwig A, editors. The MAK-Collection for Occupational Health and Safety. Part IV: Biomonitoring Methods. Volume 13. Weinheim: Wiley-VCH. p. 123–162. Also available from https://doi.org/10.1002/3527600418.bi0mercapace0013

Schettgen T, Müller J, Ferstl C, Angerer J, Weiß T, Leng G, Göen T, Hartwig A, MAK Commission (2016) Haemoglobin adducts of ethylene oxide (N-(2-hydroxyethyl)valine), propylene oxide (N-(2-hydroxypropyl)valine), acrylonitrile (N-(2-cyanoethyl)valine), acrylamide (N-(2-car-

bonamide ethyl)valine) and glycidamide (N-(2-hydroxy-2-carbonamide ethyl)valine). Biomonitoring Method, 2016. MAK Collect Occup Health Saf 1(1): 473–506. https://doi.org/10.1002/3527600418.bi7521e2115

von Stedingk H, Vikström AC, Rydberg P, Pedersen M, Nielsen JKS, Segerbäck D, Knudsen LE, Törnqvist M (2011) Analysis of hemoglobin adducts from acrylamide, glycidamide, and ethylene oxide in paired mother/cord blood samples from Denmark. Chem Res Toxicol 24(11): 1957–1965. https://doi.org/10.1021/tx200284u

Wu K-Y, Chiang S-Y, Huang T-H, Tseng Y-S, Chen Y-L, Kuo H-W, Hsieh C-L (2004) Formation of N-(2-hydroxyethyl)valine in human hemoglobin – effect of lifestyle factors. Mutat Res 559(1–2): 73–82. https://doi.org/10.1016/j.mrgentox.2003.12.011

Yong LC, Schulte PA, Wiencke JK, Boeniger MF, Connally LB, Walker JT, Whelan EA, Ward EM (2001) Hemoglobin adducts and sister chromatid exchanges in hospital workers exposed to ethylene oxide: effects of glutathione S-transferase T1 and M1 genotypes. Cancer Epidemiol Biomarkers Prev 10(5): 539–550