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Ethylene oxide – Addendum: re-evaluation of the EKA

Assessment Values in Biological Material – Translation of the German version from 2024

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Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarised and re-evaluated the data for the exposure equivalents for carcinogenic substances (EKA) of ethylene oxide [75-21-8]. Relevant studies were identified from a literature search. Based on the available studies on the correlation between external and internal exposure of ethylene oxide in the air and of its haemoglobin adduct N-(2-hydroxyethyl)valine (HEV), the EKA were confirmed and extended to a lower exposure range using linear extrapolation. Additionally, the adduct concentrations were converted into the internationally common unit [pmol/g globin]. Sampling time is after at least 3 months of exposure.

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EKA (2023)

Ethylene oxide air [ml/m³]	N-(2-Hydroxyethyl)valine blood [pmol/g globin]
0.1	*400*
0.5	2000
1	*4000*
2	8000

Sampling time: after at least 3 months of exposure

BAR (2022)

5 µg S-(2-Hydroxyethyl)mercapturic acid/g creatinine
Sampling time: at the end of exposure or end of shift
60 pmol N-(2-Hydroxyethyl)valine/g globin
Sampling time: after at least 3 months of exposure

MAK value	–
Absorption through the skin (1984)	H
Carcinogenicity (1984)	Category 2
Germ cell mutagenicity (2002)	Category 2

Re-evaluation

Ethylene oxide was already evaluated several times (translated in Bolt 2010; Eckert et al. 2022; Norpoth and Bolt 1995). Due to the classification of ethylene oxide in Carcinogen Category 2, no biological tolerance value (BAT value) can be derived. In 1999 exposure equivalents for carcinogenic substances (EKA) were established with the parameter N-(2-hydroxyethyl)valine (HEV) in blood using the unit [µg/l] (Bolt 2010). These EKA need to be revised, as the EKA of 1999 were based mainly on unpublished data and the Commission meanwhile specifies the concentration of haemoglobin adducts in blood in the unit [pmol/g globin] to avoid conversion from the original literature. In addition, the equivalence value for the acceptable concentration of 0.1 ml ethylene oxide/m³ (AGS 2023) should also be included in the EKA.

Biological reference values (BAR) for ethylene oxide were already derived in the last evaluation in 2022. For the background exposure of the general population not exposed to ethylene oxide, a BAR of 60 pmol HEV/g globin was derived for non-smokers. HEV concentrations in smokers were observed to be 5 to 10 times as high (Eckert et al. 2022).

Re-evaluation of the EKA

Since the last establishment of the EKA, studies have been published dealing with the relationship between external and internal exposure to ethylene oxide and HEV. In addition, reviews on the risk assessment of ethylene oxide have been published (Kirman et al. 2021; Rietjens et al. 2022). Figure 1 shows a representation of the data situation based on published studies including the EKA of 1999. In addition, a physiology-based pharmacokinetic (PBPK) modelling by Filser and Klein (2018) was included, which is based largely on the calculations of Csanády et al. (2000).

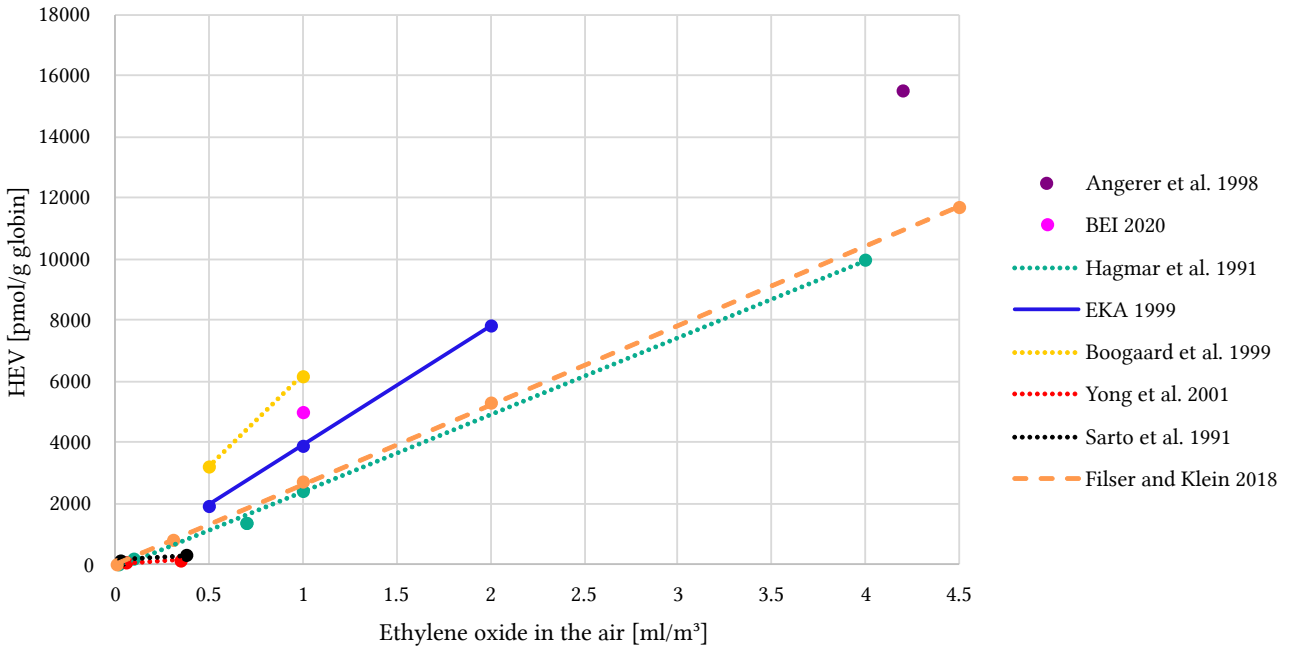

Fig. 1 Correlations between ethylene oxide in air and HEV in blood in the respective concentration range measured in each of the studies as well as the EKA of 1999 and the Biological Exposure Index (BEI, ACGIH 2020)

Figure 1 shows that in two studies (Sarto et al. 1991; Yong et al. 2001) the external exposure to ethylene oxide was in a very low range (< 0.5 ml/m³) (with only two measuring points in each case) and these revealed significantly lower HEV values compared with those in the other studies. In addition, it is unclear whether the measured concentrations in the air and the exposure of the persons examined are representative of continuous exposure (40 hours/week), as these were workplaces in the field of medical gas sterilisation. For this reason, and because the EKA are intended to cover a wider range, the two studies are not taken into account.

A significantly larger concentration range of 0.02 to 4 ml/m³ ethylene oxide is covered in the study by Hagmar et al. (1991), in which 4 to 16 employees occupationally exposed to ethylene oxide (production and initial sterilisation of disposable medical cutlery) were examined in each group. One shortcoming of this study, however, was that the external exposure to ethylene oxide was not measured directly, but only estimated or determined indirectly.

In a very well described study, Boogaard et al. (1999) investigated the internal exposure of workers from the petrochemical industry using specific haemoglobin adducts after exposure to ethylene oxide and propylene oxide, determined by personal air monitoring. In comparison with the study by Hagmar et al. (1991), HEV values were significantly higher combined with a steeper regression function.

The relationship between ethylene oxide and HEV derived by Filser and Klein (2018) essentially runs parallel to that from the study by Hagmar et al. (1991).

The EKA from 1999, which were derived on the basis of unpublished data, lie roughly between these two relationships, whereby the good agreement with a data point from Angerer et al. (1998) was also used as support. In the study by Angerer et al. (1998), three employees (production and initial sterilisation of disposable medical cutlery) were exposed to an average ethylene oxide concentration of 4.2 ± 1.3 ml/m³ and had an HEV level of 15.49 ± 7.68 nmol/g globin.

As the EKA from 1999 represent a good average of the studies published to date, the derivation is additionally supported by the study of Angerer et al. (1998) and more recent studies are not available, the EKA from 1999 are retained. Rietjens et al. (2022) also state that the available studies on the relationship between external exposure to ethylene oxide and internal HEV concentration indicate a range between 2.5 and 7 nmol HEV/g globin per 1 ml/m³ ethylene oxide exposure under workplace conditions (40 hours/week). With an HEV level of 4 nmol/g globin per 1 ml ethylene oxide/m³, the

EKA derived here are in the middle of this range. By means of linear extrapolation, the acceptable concentration level of 0.1 ml ethylene oxide/m^3 specified in TRGS 910 (AGS 2023) is further added to the EKA.

The level of the adduct HEV is commonly given in the unit [pmol/g globin] in international publications. Previously, the concentration of the EKA was given in the unit [µg/l]. A conversion of the two units is possible assuming an average globin concentration of 150 g/l (Bunn 1997). Furthermore, it is assumed that the contribution of the four haem groups to the total molecular weight of haemoglobin of 64 kDa can be neglected.

The following formula is used for conversion:

HEV [pmol/g] = HEV [µg/l blood] / (molecular weight HEV [µg/pmol] × globin concentration in blood [g/l])

molecular weight HEV: 160.2 g/mol = 160.2 × 10^{-6} µg/pmol; globin concentration in blood: 150 g/l

This results in the following EKA for ethylene oxide:

Air Ethylene oxide [ml/m^3]	[mg/m^3]	Erythrocyte fraction of whole blood HEV [µg/l blood]	[pmol/g globin]
0.1	*0.18*	*10*	*400*
0.5	0.92	48	2000
1	*1.83*	*96*	*4000*
2	3.66	192	8000

HEV is a long-term parameter whose concentration in the blood accumulates over a period of several months (according to the lifespan of erythrocytes of around 120 days). Samples should therefore be taken after at least three months of exposure.

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.

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