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Ethylene oxide

MAK Value Documentation, supplement – Translation of the German version from 2019

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Keywords

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated ethylene oxide [75-21-8] considering all toxicological end points. Ethylene oxide is an alkylating agent that is mutagenic and carcinogenic in animals. A number of epidemiological studies have indicated a carcinogenic potential, but others showed no excess cancer risk upon exposure to ethylene oxide. Re-evaluation has shown that a maximum concentration at the workplace (MAK value) cannot be derived. Accordingly, ethylene oxide remains classified in Carcinogen Category 2. Nevertheless, the Commission has derived an excess risk of lymphoid tumours for both men and women. Forty-year exposure to 0.1 ml/m^3 ethylene oxide at the workplace thus results in a risk of 1.4 or 4 per 100 000. Ethylene oxide is a mutagen in vitro and in vivo and a known germ cell mutagen. Accordingly, it remains classified in Germ Cell Mutagen Category 2. Ethylene oxide can be taken up via the skin in toxicologically relevant amounts. Therefore, the designation "H" is retained. The published reports do not indicate a relevant potential for sensitization of skin and airways in humans.

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

EKA (1999)	**ethylene oxide (air)**	**hydroxyethylvaline (whole blood)**
	0.5 ml/m³	**45 µg/l**
	1 ml/m³	**90 µg/l**
	2 ml/m³	**180 µg/l**

1 ml/m (ppm) ≙ 1.83 mg/m³ **1 mg/m³ ≙ 0.55 ml/m³ (ppm)**

Documentation for the carcinogenicity of ethylene oxide was published in 1984 (Henschler 1993), followed by supplements for its allergenic effects in 1996 (Greim 1999) and germ cell mutagenicity in 2002 (Greim 2002, available in German only); since then, findings from new studies have made a re-evaluation necessary. The EU established a binding occupational exposure limit value for ethylene oxide that is valid as of 2020 (European Parliament and European Council 2017).

1 Toxic Effects and Mode of Action

See the 1984 documentation (Henschler 1993) for the carcinogenicity of ethylene oxide.

2 Mechanism of Action

Ethylene oxide was found to be carcinogenic in animal studies, and there is evidence that tumours of the haematopoietic/lymphatic system develop in humans after exposure to ethylene oxide.

Ethylene oxide induced brain tumours, mononuclear leukaemia and peritoneal mesotheliomas in rats and adenomas and carcinomas of the lungs in mice.

Ethylene oxide is an endogenous substance that may form during the metabolism of ethylene. Ethylene is produced in the body by the intestinal microflora, lipid peroxidation and the endogenous metabolism (Swenberg et al. 2008).

The directly alkylating effect of ethylene oxide initiates the mechanism of tumour development. Ethylene oxide reacts with the DNA. *N*7-(2-hydroxyethyl)guanine (*N*7-HEG) accounts for 95% of the adducts that are formed; *N*3-(2-hydroxyethyl)deoxyadenosine, *N*3-(2-hydroxyethyl)deoxyuridine and *O*6-(2-hydroxyethyl)deoxyguanosine are formed in addition, but in considerably smaller amounts (no other details). The half-lives of these three adducts are much shorter than that of *N*7-HEG. Although *N*7-HEG is not a promutagen, it may induce a non-basic site by depurination and thereby lead to mutagenicity if it is present during DNA replication. All the information available for genotoxicity shows that ethylene oxide is a weak mutagen (Bolt 2012; Bolt et al. 1997; Swenberg et al. 2011; Walker et al. 1990, 1992; Wu et al. 1999).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Ethylene oxide may form from endogenous ethylene in the organisms of humans and animals (Filser et al. 1992). Inhaled ethylene oxide is readily absorbed by the lungs and distributed in the body with the blood stream. Alveolar retention in humans was determined to be 75% to 80% (Brugnone et al. 1985, 1986). The half-life of ethylene oxide was estimated to be about 42 to 48 minutes in human blood (Fennell and Brown 2001; Filser et al. 1992). Non-linear elimination of ethylene oxide and the depletion of glutathione (GSH) was observed in rats and mice after a single exposure to ethylene oxide concentrations above 100 ml/m^3 (Brown et al. 1996).

The kinetics of inhaled ethylene oxide in humans, rats and mice were investigated with physiologically based pharmacokinetic models (PBPK models) using published analytical data. Overall, the toxicokinetics of ethylene oxide is similar in animals and humans; thus, the ethylene oxide concentrations in the blood of rats, mice and humans in the steady state were about the same after exposure to the same external ethylene oxide concentration (Fennell and Brown 2001). The PBPK model of Csanády et al. (2000) took into account that in humans about 80%, and in rats 50% to 60% of inhaled ethylene oxide penetrates the alveoli and is absorbed systemically. The tissue-to-blood partition coefficients suggest that ethylene oxide is distributed almost uniformly in the organs and tissues of the body. Ethylene oxide is eliminated mainly in the form of metabolites. According to the PBPK models, 92% of systemically available ethylene oxide is metabolized and only 8% is exhaled unchanged. Elimination half-lives of 0.7 to 1.0 hours were calculated for humans by modelling. Modelling yielded values of 19 minutes and 9 minutes, respectively, for rats and mice, while in the literature, values between 10 and 17 minutes for rats (Brown et al. 1996; Osterman-Golkar et al. 1983) and between 3 and 9 minutes for mice (Brown et al. 1996; Ehrenberg et al. 1974) were reported.

The modelled levels of haemoglobin (Hb) and DNA adducts of ethylene oxide in humans agreed with the values determined. Assuming exposure to ethylene oxide at a concentration of 1 ml/m^3 under workplace conditions (8 hours/day; 5 days/week), the average adduct levels calculated for *N*-(2-hydroxyethyl)valine in the steady state were 4.6 nmol/g globin based on the data of Boogaard et al. (1999) and 2.4 nmol/g globin based on the model of Csanády et al. However, the simulated and determined adduct levels in rats and mice differed substantially (Csanády et al. 2000).

Ethylene oxide forms only this adduct with haemoglobin; it is chemically stable and can be easily quantified by means of GC-MS (gas chromatography mass spectrometry). Therefore, the determination of *N*-(2-hydroxyethyl)valine is routinely used for the biomonitoring of ethylene oxide. This adduct can be regarded as a surrogate for DNA adducts and is a measure of the body burden. Unlike DNA adducts, haemoglobin adducts are not repaired, and their elimination is a process obeying zero order kinetics that depends only on the half-life of the erythrocytes of 126 days. The mean background concentration is 0.02 nmol/g globin. *N*-(2-Hydroxyethyl)valine levels ranging from 0.005 to 0.050 nmol/g globin were determined in 23 non-smokers without exposure. Higher levels were determined in smokers. Toxicokinetic calculations yielded values of 6.4 to 6.8 nmol/g globin for *N*-(2-hydroxyethyl)valine after exposure to an ethylene oxide concentration of 1 ml/m^3 for 8 hours a day (Boogaard 2002; Boogaard et al. 1999). However, this calculation assumed exposure for 7 days a week. A level of 4.6 nmol/g globin was calculated by Csanády et al. (2000) for exposure on 5 days a week. This value is in good agreement with the EKA (Exposure Equivalents for Carcinogenic Substances) correlation (3.9 nmol/g globin).

According to a PBPK model, the adduct level of *N*-(2-hydroxyethyl)valine is 3.5 nmol/g Hb in mice and 4.2 nmol/g Hb in rats after 6-hour exposure to an ethylene oxide concentration of 3 ml/m^3 on 5 days a week for 4 weeks. In humans, Hb adduct levels of *N*-(2-hydroxyethyl)valine are predicted to be about 7 nmol/g Hb and 2.5 nmol/g Hb in the steady state after 8-hour exposure to concentrations of 3 ml/m^3 and 1 ml/m^3, respectively, on 5 days a week. At 3 ml/m^3, the DNA adduct concentration of *N*7-HEG is 1 nmol/g DNA in mice, 1.9 nmol/g DNA in rats and about 1.5 nmol/g DNA in humans (according to a figure and linear extrapolation) (Filser and Klein 2018). Therefore, the adduct levels are similar in the three species after the same external exposure.

In vitro studies of the dermal absorption of aqueous ethylene oxide were carried out by Kreuzer (1992) in human and rat skin. In human skin, in vitro fluxes of 8.17, 32.8 and 57.5 nmol/cm^2 and hour (0.36, 1.44 and 2.53 µg/cm^2 and hour) were determined at concentrations of 0.35, 1.06 and 3.32 µmol/ml (15, 47 and 146 mg/l). Ethylene oxide causes severe irritation; the non-irritant concentration for the skin is not known. Concentrations greater than 0.1% caused irritation of the rabbit eye (IFA 2017). Therefore, the non-irritant concentration is assumed to be 0.1% for the skin. For a 0.1% ethylene oxide solution (1 g/l), a mean flux of 15.6 µg/cm^2 and hour can be extrapolated from the findings of Kreuzer (1992). Based on standard conditions (exposed skin area of 2000 cm^2 and exposure for 1 hour), this flux corresponds to the transdermal absorption of about 31 mg ethylene oxide.

Background concentration of the DNA adducts

Background concentrations of *N*7-HEG of between 0.068 and 5.8 pmol/mg DNA were determined in the leukocytes and lymphocytes of volunteers (Bolt et al. 1997 (5 volunteers; no information about smoking habits): 2.1–5.8 pmol/mg DNA; Wu et al. 1999 (23 volunteers; no information about smoking habits): 0.9–7.4 pmol/µmol guanine, corresponding to 0.60–4.9 pmol/mg DNA; Zhao et al. 1998 (8 non-smokers): 2.1–8.1 adducts/10^8 nucleotides, corresponding to 0.068–0.26 pmol/mg DNA; Zhao and Hemminki 2002 (34 non-smokers): 7–106 adducts/10^8 nucleotides, corresponding to 0.23–3.4 pmol/mg DNA; Zhao et al. 1999 (1 non-smoker): 3.7 adducts/10^8 nucleotides, corresponding to 0.12 pmol/mg DNA). These values are between 143 and 11 800 or between 33 and 2760 times as high as those resulting from endogenous ethylene. Therefore, this adduct seems to originate mainly from a source that has yet to be identified.

The lowest background adduct levels determined for *N*7-HEG in rat tissues were 2.6/10^8 nucleotides (0.08 pmol/mg DNA; van Sittert et al. 2000), 1.1 to 3.5/10^8 nucleotides (0.036–0.11 pmol/mg DNA; Marsden et al. 2007) and 0.16 pmol/mg DNA (Wu et al. 1999) and thus in a range similar to that of the lowest values determined in humans. However, as a level of 0.004 pmol/mg DNA was calculated for endogenous ethylene oxide, it is not the main source of adducts also in rats (Csanády et al. 2000).

3.2 Metabolism

In humans, ethylene oxide is metabolized by epoxide hydrolase and glutathione *S*-transferase (Li et al. 2011). In addition, ethylene oxide is spontaneously hydrolysed and conjugated with GSH (Filser and Klein 2018). Ethylene oxide is metabolized to ethylene glycol, oxalate, formate and carbon dioxide. The detoxification of ethylene oxide by glutathione leads to the excretion of the metabolites *N*-acetyl-*S*-(2-hydroxyethyl)-*L*-cysteine, *S*-(2-hydroxyethyl)-*L*-cysteine and thiodiacetic acid with the urine.

The genotoxicity of ethylene oxide was found to vary considerably from individual to individual (Fennell and Brown 2001; Fuchs et al. 1994; Müller et al. 1998; Pemble et al. 1994). The main cause of this is assumed to be the polymorphism of glutathione *S*-transferase GSTT1 (Schröder et al. 1996). It has been demonstrated that GSTT1-positive persons ("conjugators") detoxify ethylene oxide more rapidly by glutathione-dependent metabolism than GSTT1-negative persons ("non-conjugators"). Accordingly, the genotoxicity of ethylene oxide is less severe in "conjugators" than in "non-conjugators" (Hallier et al. 1993; Schröder et al. 1995). In addition, this enzyme polymorphism influences the formation of haemoglobin adducts (Fennell and Brown 2001; Thier et al. 1999; Thier and Bolt 2000). Microsomal epoxide hydrolase is likewise polymorphic in humans. However, this does not result in any great differences in the enzyme activity on the substrate ethylene oxide (Li et al. 2011). The difference in the body burden of ethylene oxide (measured as haemoglobin adducts) resulting from the differences in GSTT1 activity is about two-fold (Fennell et al. 2000). According to Li et al. (2011), the body burden of ethylene oxide differs between conjugators and non-conjugators by at most a factor of 4.

4 Effects in Humans

4.1 Single exposures

No new data are available.

4.2 Repeated exposure

No new data are available.

4.3 Local effects on skin and mucous membranes

Ethylene oxide solutions or vapours may cause marked irritation of the skin, eyes and mucous membranes of the respiratory tract.

The irritant effects that are observed about 1 to 5 hours after exposure to a 1% aqueous ethylene oxide solution may also lead to blistering and vesiculation on the skin (Sexton and Henson 1949; see also Henschler 1993). Likewise, exposure to ethylene oxide vapour for 5 to 20 minutes caused a syndrome with blistering described as protracted chemical burns. The latency period until the development of the clinical symptoms was up to 48 hours (Ippen and Mathies 1970). In addition, severe irritation may be caused by materials and clothing sterilized with ethylene oxide that were not properly aerated (Biro et al. 1974; Fisher 1973, 1988; Hanifin 1971; LaDage 1970; Lerman et al. 1995; Royce and Moore 1955). Two nurses and 2 other hospital employees who, among other things, were sterilizing linen in a canister containing ethylene oxide developed generalized itching following the accidental release of ethylene oxide. In 2 of them, eczematous reactions were observed mainly on the trunk and the upper extremities; the authors assessed these reactions as irritation. Patch tests were not carried out (Romaguera and Vilaplana 1998).

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

In patch tests with 1% ethylene oxide in water, sensitization was not observed in 30 workers in the chemicals industry who may have been exposed to ethylene oxide over a period averaging 10.4 years or in 41 workers who had accidentally been exposed, in some cases to large amounts, although some of them had severe skin lesions (Thiess 1963).

A nurse presented herself at a clinic with eczematous lesions on her forearms that she had had for 12 months since wearing surgical gowns sterilized with ethylene oxide. Patch testing with a piece of gown sterilized with ethylene oxide resulted in a vesicular reaction after 72 hours, while a patch test with gamma-sterilized material yielded negative results (Caroli et al. 2005). A nurse developed eczema on both forearms 1 month after she had started to work on a catheter ward and began wearing gowns sterilized with ethylene oxide. In the patch test with a sample of the gown, a 2+ reaction was observed after 48 and 96 hours. A patch test was carried out with 1% epichlorohydrin in ethanol because of its structural similarity with ethylene oxide; this induced a 1+ reaction after 48 and 96 hours. However, ethylene oxide was not tested (Kerre and Goossens 2009).

In 20 employees of a surgical department, eczematous reactions were observed in those areas of the skin that had been in contact with the wrist bands of surgical gowns sterilized with ethylene oxide. Patch tests with the gowns were not carried out, but 8 of the employees were tested with 0.1% and 1% epichlorohydrin in petrolatum. After 72 hours, the higher concentration induced a 1+ reaction in 3 employees (later assessed as irritation in two cases), whereas a questionable or irritant reaction was found in 4 of the tested persons. The lower concentration caused a 1+ reaction in only one of the tested persons after 72 hours. On the assumption that the test result was evidence of a cross reaction between ethylene oxide and epichlorohydrin, the authors considered this reaction to indicate sensitization to ethylene oxide among these employees. Irritant reactions to 1% epichlorohydrin were observed also in 4 control persons, and

active sensitization was probably induced in 1 of the controls (Breuer et al. 2010). Therefore, it is highly questionable whether testing with epichlorohydrin is suitable in this case.

A face mask that had been sterilized with ethylene oxide, but probably insufficiently aerated, caused erythematous, scaly and exudative skin reactions in a hospitalized female patient after 6 hours. Patch tests with samples of fabric that had been sterilized with ethylene oxide and aerated for 8 and 24 hours caused 3+ reactions, whereas a patch test with a sample aerated for 48 hours yielded negative results. A group of 25 control persons did not react to any of the samples (Romaguera and Grimalt 1980). Another patient developed a vesicular, erythematous reaction on her face 2 days after wearing an oxygen mask. The reaction persisted for another 8 days after the mask was no longer worn. Patch tests with samples of fabric that had been sterilized with ethylene oxide and aerated for 24, 48 or 72 hours caused 2+ to 3+ reactions after 96 hours. Reactions to these samples were not observed in 12 control persons (Alomar et al. 1981). A patient developed a bullous irritant reaction during surgery immediately after contact with a mat sterilized with ethylene oxide. Two months later, the same patient developed what was presumably an allergic reaction after undergoing another surgical procedure, but after a delay of 2 days. After 48 and 72 hours, patch testing yielded 2+ and 3+ reactions to samples sterilized with ethylene oxide and aerated for only 0.5 and 3.5 hours, respectively, but no reaction to a sample aerated for 24 hours. A group of 12 control persons did not react to the samples (Boonk and van Ketel 1981).

The skin reactions that developed in a nurse following a skin biopsy were found to be caused by suture material sterilized with ethylene oxide. Also in an exposure test, the patient reacted to suture material pre-treated with ethylene oxide. After 2 days, an erythematous plaque developed around the site of the stitch, which subsequently reached a diameter of 6 cm. Testing with material sterilized with gamma radiation did not lead to a reaction (Dagregorio and Guillet 2004).

An erythematous and oedematous skin reaction was observed in 1 of 12 volunteers 3 weeks after a patch test with a PVC sample containing ethylene oxide in a concentration of 1545 mg/kg; the reaction persisted for 2 weeks. Another test with a 2 mm-thick PVC film that contained an ethylene oxide concentration of 100 mg/kg caused a mild reaction that flared up again after 3 weeks (Shupack et al. 1981).

In an earlier study, 8 workers who developed skin reactions after having contact with ethylene oxide were repeatedly exposed to undiluted ethylene oxide and varying concentrations of aqueous solutions of ethylene oxide for a period lasting between 20 seconds and 95 minutes. In 3 of the workers, sensitization developed 5 to 9 days after the last exposure at the sites originally exposed irrespective of whether skin reactions had previously been observed at these sites (Sexton and Henson 1949, 1950).

4.4.2 Sensitizing effects on the airways

There are several reports available of reactions of the airways after occupational exposure to ethylene oxide. In most cases, these involved exposure to or the use of gowns sterilized with ethylene oxide:

A surgeon with dermatitis on his hands caused by sterile powdered latex gloves developed occupational dyspnoea 6 months after exposure (forced expiratory volume in 1 second (FEV1): 3.6 l; expected value: 4.5 l). Symptoms were not observed with powdered or non-powdered latex gloves sterilized with gamma radiation. Radio-allergosorbent tests (RASTs) for Aspergillus (4.5 U/ml) and ethylene oxide (2.6 U/ml) yielded positive results (Verraes and Michel 1995).

A radiology assistant reported occupational urticarial reactions on her hands and face, rhinoconjunctivitis and asthma over the preceding 9 months. A skin test, a provocation test with fabric sterilized with ethylene oxide and a RAST yielded positive results (no other details) (Déchamp et al. 1990).

A casuistic report described occupational allergic rhinoconjunctivitis in a midwife caused by the use of gloves sterilized with ethylene oxide. The diagnosis was based on positive results in a cutaneous test with the glove material sterilized with ethylene oxide and an immediate reaction (rhinitis, attacks of sneezing and itching in the nose) in a provocation test with gloves sterilized with ethylene oxide. However, changes in the respiratory function parameters were not observed. Ethylene oxide-specific IgE was not detected. There was no evidence of a concurrent latex allergy (Wendling et al. 1994).

In other cases in which the symptoms were attributed to rubber products sterilized with ethylene oxide, for example gloves, there was additional evidence of latex sensitization. Therefore, the symptoms may (additionally) have been induced by latex proteins, which are regarded as potent allergens.

A nurse in a dialysis unit complained of occupational airway reactions after handling artificial kidneys sterilized with ethylene oxide and wearing latex gloves. The RAST yielded IgE specific for ethylene oxide and latex (no other details). In an open exposure test (opening of a dialyzer sterilized with ethylene oxide), the FEV1 was decreased by 6%, the specific airway resistance was increased by 64% and there was an increase in non-specific airway reactivity (tested against carbachol). More pronounced reactions were observed after exposure to latex gloves for 20 minutes (FEV1: −40%, specific airway resistance: +100%) (Dugue et al. 1991).

A nurse developed urticarial reactions on her hands and conjunctivitis after contact with surgical gloves; these symptoms were followed later by rhinitis and asthma (although she had avoided wearing gloves sterilized with ethylene oxide as far as possible). A prick test with latex sterilized with ethylene oxide yielded positive results, whereas a prick test with latex sterilized with gamma radiation yielded negative results. Prick tests carried out 3 years later with latex and vinyl material sterilized with ethylene oxide and with non-sterilized latex material yielded positive results, whereas a prick test for formaldehyde yielded negative results. The RAST demonstrated IgE specific for latex (RAST class 2: 1.32 PRU/ml), ethylene oxide (RAST 2+; no other details) and formaldehyde (RAST class 1) (Jacson et al. 1991).

A nurse with asthmatoid dyspnoea following sensitization to trypsin developed urticarial reactions and rhinorrhoea after she had contact with gloves. Prick tests with latex and fabric sterilized with ethylene oxide yielded positive results, and a RAST (no other details) yielded positive results for ethylene oxide, whereas a RAST for latex yielded negative results (Meurice et al. 1990).

In 3 nurses, latex gloves sterilized with ethylene oxide caused urticaria and rhinitis/asthma. According to the authors, the diagnostic findings (skin test, RAST, provocation test and RAST inhibition) indicated sensitization to latex and ethylene oxide (no other details) (Balland et al. 1990).

A publication reported a case of a nurse with occupational sensitization to ethylene oxide, but did not provide any other details (Olivieri et al. 1988).

Occupational obstructive airway reactions following accidental exposure to ethylene oxide that leaked from a tank were attributed to non-immunological, chemical-irritant mechanisms (Deschamps et al. 1992).

4.4.3 Sensitizing effects in exposed patients

Probable sensitization to ethylene oxide was frequently reported in dialysis patients or patients who had contact with products sterilized with ethylene oxide during surgery or anaesthesia.

Various authors independently concluded that immediate-type allergies to ethylene oxide are by far the primary aetiopathogenetic causes of these reactions. The RAST provided evidence of IgE specific for ethylene oxide–human serum albumin (HSA) conjugates. The following describes examples of the findings that have not been included in the evaluation of the sensitizing effects of ethylene oxide because the studies used routes of administration which are not relevant for workplace conditions.

A study in 83 dialysis patients, 16 staff members of the dialysis unit and 44 healthy control persons found IgE specific for ethylene oxide–HSA conjugates in 35 dialysis patients, but only in 2 control persons and 2 staff members. Allergic complications during dialysis were more common in dialysis patients with specific IgE antibodies than in patients without these antibodies. In the sensitized patients who underwent dialysis with material that had not been sterilized with ethylene oxide for 8 weeks, the specific IgE antibodies decreased markedly or were no longer detected and the clinical symptoms improved strikingly. Re-exposure to materials sterilized with ethylene oxide resulted in the re-appearance of the clinical symptoms (Bommer et al. 1985).

Avoiding exposure led to a clear improvement in symptoms in 3 dialysis patients with a marked increase in IgE values specific for ethylene oxide–HSA conjugates, whereas there was hardly any improvement in the (less pronounced) symptoms in patients with lower RAST values (Röckel et al. 1989).

Other studies found IgE specific for ethylene oxide–HSA conjugates in 6 of 7 dialysis patients with symptoms, 1 of 6 dialysis patients without symptoms and in none of 3 control persons (Grammer et al. 1985), 16 of 24 dialysis patients who had experienced anaphylactic reactions and 3 of 41 dialysis patients who had not (Grammer and Patterson 1987), and in 11 of 20 dialysis patients with symptoms, 3 of 50 dialysis patients without symptoms and in none of 30 control persons (Purello D'Ambrosio et al. 1997).

Among 140 unselected dialysis patients, the values for IgE specific for ethylene oxide–HSA conjugates were clearly increased in 9 test persons (RAST > 2.0) and questionably increased in 4 test persons (RAST 1.5–2.0). Patients with high RAST values (> 5.0) almost always had clinical symptoms whereas in patients with RAST values between 1.0 and about 3.0 usually no symptoms were observed (Rumpf et al. 1985 a, b).

A study of 138 unselected dialysis patients found 18 cases of IgE specific for ethylene oxide–HSA conjugates (among these 3 of 8 patients with anaphylactic symptoms and 15 of 130 patients without symptoms) (Kessler et al. 1990).

Between May 2004 and June 2009, 201 patients with suspected allergic reactions (during surgery or anaesthesia) underwent allergological examinations at Copenhagen University Hospital. IgE specific for ethylene oxide–HSA conjugates was detected in 3 of the patients (> 0.35 kU/l; ImmunoCAP). However, previous exposure to ethylene oxide was reported only for 2 of the 3 patients (Opstrup et al. 2010).

A female dialysis patient went into anaphylactic shock 3 times after treatment with dialyzers that had been sterilized with ethylene oxide. Immediately after surgical stabilization of the cervical spine with cement sterilized with ethylene oxide, the patient developed Quincke's oedema with massive swelling of the larynx, pharynx and tongue. The RAST yielded a marked increase in the level of IgE specific for ethylene oxide–HSA conjugates (RAST 10.6) (Rumpf et al. 1986).

The specificity of the RAST findings was confirmed by RAST inhibition tests performed on several dialysis patients (Dolovich and Bell 1978; Grammer et al. 1985; Wass et al. 1988). In addition, the findings obtained from skin tests performed on 5 patients with ethylene oxide–HSA conjugates correlated well with the evidence of specific IgE antibodies determined in the enzyme-linked immunosorbent assay (Grammer et al. 1991); likewise, a test for passive cutaneous anaphylaxis carried out with ethylene oxide–HSA conjugates in primates yielded positive results (Grammer et al. 1985).

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

The results of studies of genotoxicity are described in detail in the documentations of IARC (1994, 2008), in Dellarco et al. (1990) and in the 2002 supplement (Greim 2002).

In a recent study in 64 hospital workers, *N*7-HEG levels in the DNA of granulocytes were determined quantitatively by means of GC-EC-MS (gas chromatography electron capture mass spectrometry). The ethylene oxide concentrations were determined over a period of 2 to 4 days and the cumulative exposure was calculated for every exposed person for a period of 4 months. The GSTT1 genotype was determined for every participant in the study and the persons were categorized as either "null" (homozygous) or "positive". In addition, the statistical analysis took smoking habits and potential confounders such as age, ethnicity, sex, education and the duration of employment into account. Of the 64 hospital workers, 6 (9%) were assigned to the control group, 38 (59%) to the low exposure group (< 32 ml/m^3 × hour) and 20 (31%) to the high exposure group (> 32 ml/m^3 × hour). The mean cumulative exposure for the low and high exposure groups was 12.3 ml/m^3 × hour and 234.7 ml/m^3 × hour, respectively. The GSTT1 "null" genotype had a prevalence of 19% (n = 12) in the overall group of workers, 18% (n = 7) in the low exposure group and 26% (n = 5) in the high exposure group. *N*7-HEG adduct levels did not differ between the genotype groups "null" and "positive". Interindividual variability

was considerable and ranged from 1.6 to 241.3 adducts/10^7 nucleotides. Arithmetic means of 3.8 ± 17.9, 16.3 ± 10.9 and 20.3 ± 11.6 adducts/10^7 nucleotides were determined for the workers assigned to the group with no exposure (0 ml/m^3), low exposure (0.03 ± 0.05 ml/m^3; 8-hour mean) and high exposure (0.36 ± 0.31 ml/m^3; 8-hour mean), respectively, after adjustment for the number of cigarettes smoked per day and other potential confounders. The observed increase in *N*7-HEG adducts that was dependent on the exposure concentration was not statistically significant. Although earlier studies (Yong et al. 2001) had shown that exposure to ethylene oxide increased *N*-(2-hydroxyethyl)valine adducts in the erythrocytes of exposed workers, this study did not establish a correlation between *N*-(2-hydroxyethyl)valine and *N*7-HEG adducts. The authors emphasized the shortcomings of their study, such as the group size, the small number of persons in the control group (5 non-smokers and 1 smoker) and the large individual variability in *N*7-HEG adducts. According to the authors, exposure to 0.36 ml/m^3 (8-hour mean) did not cause a significant increase in *N*7-HEG adducts compared with the endogenous background levels, but further studies are needed to verify these results (Yong et al. 2007).

4.7 Carcinogenicity

4.7.1 Case–control studies

The results of a multicentre case–control study were published in 2010. A total of 2347 lymphoma cases and 2463 control persons from 6 European countries were evaluated based on the WHO classification of lymphomas (2001). Exposure was recorded retrospectively in questionnaires and classified by occupational physicians in a 4-point scale with regard to frequency and intensity; in addition, the duration of exposure was taken into account. The odds ratios were 1.3 (95% CI: 0.7–2.1) for persons who were exposed at some time during their employment and 4.3 (95% CI: 1.4–13) for workers with a high/medium exposure duration. Based on a TLV (the occupational exposure limit in the United States) of 1 ml/m^3, exposure levels lower than 50% of this value were defined as low exposure, 51% to 150% as medium exposure and above 150% as high exposure (Kiran et al. 2010).

4.7.2 Cohort studies

4.7.2.1 NIOSH cohort

A cohort study included 18 235 workers exposed to ethylene oxide at 14 plants. The workers sterilized medical instruments. The study included only workers with exposure to ethylene oxide for at least 3 months. The proportion of men in the cohort was 55%. For the period from 1976 to 1985, the average exposure for sterilizer operators was calculated to be 4.3 ml/m^3 (7.7 mg/m^3) based on the analysis of 627 personal samples, and the average exposure at other workplaces was 2.0 ml/m^3 (3.6 mg/m^3) based on 1888 personal samples. It is assumed that exposure levels were much higher in the period before 1978. There is no evidence of exposure to other carcinogens. The observed/expected deaths were: 36/33.8 (standardized mortality ratio (SMR): 1.06; 95% CI: 0.8–1.5) for all lymphatic and haematopoietic types of cancer; 6/11.6 (SMR: 0.52; 95% CI: 0.2–1.1) for cancer of the brain and nervous system; 11/11.6 (SMR: 0.95; 95% CI: 0.5–1.7) for stomach cancer; 16/16.9 (SMR: 0.95; 95% CI: 0.5–1.5) for pancreatic cancer; 8/7.7 (SMR: 1.0; 95% CI: 0.4–2.1) for oesophageal cancer and 13/7.2 (SMR: 1.8; 95% CI: 0.96–3.1) for cancer of the kidneys. However, a significant increase in the SMR for all haematopoietic types of cancer (SMR: 1.6) and for lymphosarcomas/reticulosarcomas (SMR: 2.6) was observed in men. The increase in the SMRs that were observed for Hodgkin's disease (SMR: 2.0), non-Hodgkin's lymphomas (SMR: 2.2) and renal carcinomas (SMR: 2.1) were not statistically significant (Steenland et al. 1991).

In an additional internal analysis of the same cohort, but with workers from only 13 plants, a relationship was found between the cumulative exposure (but not peak exposure, average exposure or exposure duration) and malignant neoplasms of the haematopoietic system such as chronic lymphatic leukaemia/non-Hodgkin's lymphomas. However, this was observed only in men, but not in women (Stayner et al. 1993).

Another internal analysis of the same cohort established a weak trend towards an increased incidence of breast cancer mortality in women with the increase in cumulative ethylene oxide exposure and after a lag time of 15 years. The

standardized incidence ratio (SIR) in the top quintile of cumulative exposure was 1.27 (0.94–1.69) after a lag time of 15 years. A positive trend of the SIR with increasing exposure was observed (Steenland et al. 2003). The US EPA (2016) calculated a statistically significant increase in breast cancer mortality in the highest exposure quartile after a lag time of 20 years (SMR = 2.07; 95% CI: 1.10–3.54; 13 observed cases).

An updated analysis of the same cohort no longer provided evidence of an increase in cancer mortality. Only individual internal analyses revealed a relationship between cumulative exposure and lymphoid tumours after a lag time of 15 years. However, this was found only in men, but not in women. Lymphoid tumours included non-Hodgkin's lymphomas, multiple myelomas and lymphatic leukaemia. A statistical evaluation of the dose–response relationships yielded an average SMR for non-Hodgkin's lymphomas of 2.4 (95% CI: 1.02–4.67) for men at an exposure of 13 500 ml/m^3 × days and above. The average cumulative exposure was 26.9 ml/m^3 × years (Steenland et al. 2004).

4.7.2.2 Union Carbide Corporation (UCC) cohort

A follow-up study of a mortality study of workers in ethylene oxide production failed to establish a significant association between exposure to ethylene oxide and all types of cancer combined (SMR: 86; 95% CI: 71–104); the assessment included pancreatic, brain and stomach cancer, leukaemia and non-Hodgkin's lymphomas (Teta et al. 1993).

Another study updated the Union Carbide Corporation cohort of male workers at ethylene oxide production plants. All 2063 workers were employed in the plants between 1940 and 1988 and were observed for mortality until 2003. There was no evidence of an additional cancer risk arising from ethylene oxide exposure. The SMR for all types of cancer was 94.6 (95% CI: 84.1–105.9). Twelve different types of cancer were taken into account. Likewise, no increased mortality was observed for lymphoid tumours: 11 workers died from leukaemia (11.8 expected) and 12 from non-Hodgkin's lymphomas (11.5 expected). The average cumulative exposure to ethylene oxide was 67 ml/m^3 × years (Swaen et al. 2009).

4.7.2.3 Other cohorts

A mortality study in a British cohort of 2876 persons exposed to ethylene oxide failed to establish a significant association with any type of tumour. There were 565 observed deaths compared with 607.7 expected cases. Of the deaths, 188 (184.2 expected) were from all types of cancer, 10 (11.6 expected) from stomach cancer, 11 (13.2 expected) from breast cancer, 7 (4.8 expected) from non-Hodgkin's lymphomas and 5 (4.6 expected) from leukaemia. According to the authors, a risk of cancer is assumed, but it is relatively low (Coggon et al. 2004).

Mortality from cancer and the cancer incidence (SIR) were investigated in a Swedish cohort with a total of 2171 male and female workers. The median cumulative exposure was 0.13 ml/m^3 × year. The SIR for all types of cancer was 0.94 (95% CI: 0.82–1.08). A total of 203 cases of cancer were observed compared with 216 expected. There were 18 cases (14.4 expected) of lympho-haematopoietic cancer (SIR: 1.25; 95% CI: 0.74–1.98), 9 cases (6.25 expected) of non-Hodgkin's lymphomas (SIR: 1.44; 95% CI: 0.66–2.73), 1 case of a Hodgkin's lymphoma (1.31 expected) and 2 multiple myelomas (2.08 expected). The SIR was not significantly increased for cancer of the oesophagus, rectum, cervix, urinary bladder or brain. Similar results were obtained for a lag time of 15 years, but a significant increase in the SIR was found for rectal cancer (1.94; 95% CI: 1.0–3.4). An internal analysis found an increase in the incidence rate ratio (IRR) for mammary carcinomas in women with cumulative exposure to ethylene oxide at levels ranging from 0.14 to 0.21 ml/m^3 × year (IRR: 2.8; 95% CI: 1.2–6.3) or at a level of ≥ 22 ml/m^3 × year (IRR: 3.6; 95% CI: 1.6–7.9). The authors emphasized the lack of data available for reproductive history, BMI or lifestyle; these are important factors in the development of mammary carcinomas (Mikoczy et al. 2011). The relatively small cohort of only about 2000 workers and the low overall exposure levels have to be taken into account in the evaluation of the study. According to the authors, this study suggests that the risk of developing cancer after exposure to ethylene oxide is low or limited.

4.7.2.4 Meta-analyses

A meta-analysis of 10 cohorts investigated cancer mortality among a total of 33 000 workers; there were 876 observed deaths compared with 928 expected deaths. No association was found between exposure to ethylene oxide and pancreatic, brain or stomach tumours. The meta-SMR, standardized for age, sex and year, was 1.08 for leukaemia and 1.34 for non-Hodgkin's lymphomas, but was not statistically significant. However, these SMRs differed across the individual studies, and different diagnostic methods were used. Therefore, the authors regarded the associations found between the incidence of leukaemia and non-Hodgkin's lymphomas and exposure to ethylene oxide as inconsistent (Teta et al. 1999).

A pooled analysis of the NIOSH and Union Carbide cohorts evaluated the mortality data for 19 000 workers who were exposed to ethylene oxide. Cumulative exposure–response relationships were not statistically significant for tumours of the lympho-haematopoietic system, non-Hodgkin's lymphomas, multiple myelomas, leukaemia, brain tumours, mammary tumours, pancreatic tumours or stomach tumours. The cumulative mortality risk for tumours of the central nervous system was significantly reduced in men (Valdez-Flores et al. 2010). Although this analysis did not reveal a definite target organ for cancer, a later study by the same authors (Valdez-Flores et al. 2011) considered the mortality caused by lymphoid tumours to be suitable for estimating the cancer risk (see Section 5.8).

4.7.2.5 Summary

Most epidemiological studies suggested a possible increase in the risk for lympho-haematopoietic cancer and breast cancer, but the overall evidence is not sufficient to draw conclusions with regard to causality. In addition, the studies did not provide evidence of consistent dose–response relationships, and the magnitude of the relative risks are not high (US EPA 2016).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

There are no new data available.

5.2 Subacute, subchronic and chronic toxicity

Inhalation

A 2-year inhalation study in rats reported significant decreases in body weight gains at ethylene oxide concentrations of 60.4 mg/m^3 and above and a decrease in survival time at 92 mg/m^3 and above. At concentrations of 92 mg/m^3 and above, ethylene oxide increased the levels of aspartate aminotransferase in the serum, reduced absolute kidney and adrenal weights, and increased the incidence of inflammatory lesions in the lungs, nose, trachea and internal ear. In addition, ethylene oxide caused proliferative and degenerative lesions in the adrenal glands, an increase in splenic extramedullary haematopoiesis and multifocal mineralization of the eyes. At concentrations of 183 mg/m^3 and above, skeletal atrophy was found in the exposed rats (Lynch et al. 1984; WHO and IPCS 2003).

In an inhalation study in mice exposed to concentrations up to 183 mg/m^3 for 2 years, no exposure-related effects were observed (WHO and IPCS 2003).

Neurotoxic effects and effects on the eyes (lens opacity) were found when monkeys were exposed by inhalation to a concentration of 92 mg/m^3 (Lynch et al. 1992; WHO and IPCS 2003).

5.3 Local effects on skin and mucous membranes

There are no new data available.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

Guinea pigs were not sensitized by the topical and intradermal application of 0.5 ml ethylene oxide carried out 3 times a week over a period of 3 weeks (no other details) (ECB 2000).

5.4.2 Sensitizing effects on the airways

No findings are available for sensitizing effects on the airways.

In mice and rats, parenteral administration of the protein conjugates of ethylene oxide induced the formation of specific IgE antibodies. Transfer tests (test for passive cutaneous anaphylaxis) provided evidence of the specificity of IgE antibodies in vivo (Chapman et al. 1986).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no new studies available.

A 1-generation study in rats was described in the 1984 documentation (Henschler 1993). When male and female rats were exposed to ethylene oxide concentrations of 10, 33 or 100 ml/m^3 for a period of 12 weeks (6 hours/day; 5 days/week) before mating and the females were subsequently exposed up to day 19 of gestation and during lactation, pre-implantation and post-implantation losses were observed only in the group exposed to 100 ml/m^3. The survival of the pups was not affected.

5.5.2 Developmental toxicity

In an unpublished study from 1982, groups of 30 New Zealand White rabbits were exposed whole-body to ethylene oxide concentrations of 0 or 150 ml/m^3 for 7 hours a day from days 1 to 19 or from days 7 to 19 of gestation. The offspring were examined on day 30. The exposure did not affect the body weights of the dams. Significant effects on foetal weights, body length, the sex ratio or placental weights were not observed. The examination of visceral and skeletal changes revealed supernumerary ribs in most foetuses (no other details) (ECHA 2018).

A developmental toxicity study in rats was described in the 1984 documentation (Henschler 1993). The exposure of pregnant rats to concentrations of 10, 33 or 100 ml/m^3 from days 6 to 15 of gestation (6 hours/day) did not induce any teratogenic effects.

5.6 Genotoxicity

5.6.1 In vitro

Ethylene oxide is mutagenic and clastogenic at all phylogenetic levels (IARC 2008, see also Greim 2002). Ethylene oxide was found to be a weak genotoxic agent when compared with other genotoxic chemicals, such as methyl methanesulfonate and ethyl methanesulfonate (Tompkins et al. 2009).

The treatment of pSP189 plasmid with ethylene oxide concentrations of 10 to 2000 µM caused significant 2-hydroxyethylation at the *N*7 position of guanine. When plasmids containing up to 290 *N*7-HEG adducts/10^6 nucleotides (this

value far exceeds the values detected in human DNA) were replicated in human Ad293 cells, they failed to increase the mutation frequency. According to the authors, the findings suggest that DNA adducts have to be induced up to a certain level before mutations develop (Tompkins et al. 2009).

5.6.2 In vivo

Male Fischer rats (number not reported) were exposed by inhalation to an ethylene oxide concentration of 100 ml/m^3 on 1, 3 or 20 days, for 6 hours a day, on 5 days a week. The animals exposed for 3 or 20 days were sacrificed 2 hours after the end of exposure while the animals exposed for 1 day were sacrificed after 6, 24 or 72 hours. Tissues from the brain, spleen and liver were analysed. Ethylene oxide induced dose-dependent increases in *N*7-HEG in the brain, spleen and liver and in *N*-(2-hydroxyethyl)valine in the blood. 3-Methyladenine-DNA glycosylase was decreased 3-fold to 7-fold in the brain and spleen of rats exposed to ethylene oxide for 1 day. The activities of 8-oxoguanine-DNA glycosylase, alkaline phosphatase, endonuclease, polymerase β and alkylguanine methyltransferase were increased by 20% to 100% in the rats exposed for 20 days (Rusyn et al. 2005).

Groups of 32 male Lewis rats were exposed to ethylene oxide concentrations of 0, 50, 100 or 200 ml/m^3 for 6 hours a day, on 5 days a week, for 4 weeks. The *N*7-HEG levels in the liver were analysed 5, 21, 35 and 49 days after the end of exposure. The *N*-(2-hydroxyethyl)valine levels in the blood and HPRT mutations, sister chromatid exchanges, chromosomal aberrations and translocations in splenic lymphocytes were determined. *N*7-HEG and *N*-(2-hydroxyethyl)-valine values immediately after exposure were extrapolated from the values measured 5 days after the end of exposure. Thus, the mean concentrations of *N*7-HEG were 2.6 (control), 310, 558 and 1202 adducts/10^8 nucleotides. After 49 days, the *N*7-HEG values were the same as the control values. The mean concentrations of *N*-(2-hydroxyethyl)-valine adducts were 0.045, 61.7, 114 and 247 nmol/g globin. Linear relationships were established between the levels of *N*7-HEG, determined on day 1 after the end of exposure, and HPRT mutants, determined on day 21/22 and day 49/50 after the end of exposure, and sister chromatid exchange, determined 5 days after the end of exposure. The increase in HPRT mutants was statistically significant only in the animals of the high exposure group on day 21/22 after the end of exposure. The increase in micronuclei, chromosomal breaks or translocations was not statistically significant (van Sittert et al. 2000).

An ethylene oxide concentration of 50 ml/m^3 was the lowest concentration that caused an increase in HPRT mutants in mice after inhalation for 4 weeks (Swenberg et al. 2008). This confirms that ethylene oxide is only a weak mutagen.

Background levels of 1.1 to 3.5 adducts/10^8 nucleotides were determined for *N*7-HEG in the liver tissue of male Fischer 344 rats by means of LC-MS/MS with a limit of detection for *N*7-HEG of 0.1 fmol. Groups of 3 animals were given intraperitoneal injections of either single doses of 0, 0.01, 0.1, 0.5 and 1.0 mg/kg body weight or doses of 0, 0.1 and 1 mg/kg body weight on 3 consecutive days. DNA adduct levels were determined in the liver, heart and colon of the animals given a single dose and in the liver, heart, colon, lungs, kidneys, spleen and stomach of the animals treated on 3 consecutive days. The highest level of DNA adducts were found in the liver. After a single intraperitoneal ethylene oxide dose of 0.01 mg/kg body weight, the increase in DNA adducts in rat liver was negligible. A marked increase was observed only at the dose of 0.1 mg/kg body weight (equivalent to 0.11 ml/m^3). At higher doses, a dose-dependent increase in DNA adducts was induced in all organs. DNA damage did not accumulate in this dose range (Marsden et al. 2007).

Male B6C3F1 mice were exposed by inhalation to ethylene oxide concentrations of 0, 25, 50, 100 or 200 ml/m^3 for up to 48 weeks. The animals were sacrificed after 6, 12, 24 and 48 weeks and reciprocal translocations were determined in the lymphocytes and germ cells. After exposure for 6 weeks, no significant increase in the number of reciprocal translocations in lymphocytes was observed. There was a dose-dependent increase in the number of reciprocal translocations in lymphocytes after exposure to concentrations of 25 ml/m^3 and above for 12, 24 and 48 weeks. A statistically significant, but not dose-dependent increase in reciprocal translocations was found in the germ cells of all concentration groups only after exposure for 48 weeks (Donner et al. 2010).

Both endogenous and exogenous *N*7-HEG adducts were determined in vivo by means of liquid chromatography-tandem mass spectrometry and high-performance liquid chromatography/accelerator mass spectrometry. Groups of 5 rats were given daily intraperitoneal injections of ^{14}C-ethylene oxide of 0, 0.1, 0.01, 0.005, 0.001, 0.0005 or 0.0001 mg/kg

body weight on 3 consecutive days. The animals were sacrificed 4 hours after the last treatment. A linear increase in the concentrations of the radioactive adducts was observed in the splenic, liver and stomach DNA of the animals (0.002 to 4 adducts/10^8 nucleotides). Likewise, the concentration of non-radioactive endogenous *N*7-HEG adducts was increased in the liver and spleen of the animals in the 2 high dose groups. According to the authors, this suggests that ethylene oxide induces the formation of ethylene and thus indirectly promotes *N*7-HEG adduct production. 1-Aminocyclopropane-1-carboxylic acid is known to be the direct precursor of ethylene in plants. Its conversion to ethylene is inhibited by radical scavengers. Therefore, the authors concluded that the increase in the conversion of 1-aminocyclopropane-1-carboxylic acid to ethylene was caused by oxidative stress. In addition, 1-aminocyclopropane-1-carboxylic acid was detected in rat livers and human HCA cells. The authors demonstrated that hydrogen peroxide increased the levels of *N*7-HEG adducts in HCA intestinal cells and reported that ethylene oxide induced lipid peroxidation in the liver of rats by glutathione depletion. The following mechanism has been proposed for the increase in endogenous *N*7-HEG adducts caused by ethylene oxide: ethylene oxide induces lipid peroxidation by glutathione depletion and thus oxidative stress; this leads to an increase in the conversion of aminocyclopropane-1-carboxylic acid to ethylene, which is subsequently metabolized to ethylene oxide. However, at all dose levels, the concentrations of the radioactive exogenous adducts were much lower than those of the endogenous adducts (Marsden et al. 2009).

5.7 Carcinogenicity

5.7.1 Short-term studies

There are no new data available.

5.7.2 Long-term studies

After inhalation exposure to ethylene oxide concentrations of 50 to 200 ml/m^3 (92–366 mg/m^3), brain tumours, mononuclear leukaemia, peritoneal mesotheliomas in the testes, and subcutaneous fibrosarcomas were induced in rats, while adenomas and carcinomas of the lungs, malignant lymphomas, Harderian gland tumours, uterine adenocarcinomas, and mammary gland carcinomas were observed in mice (see Henschler 1993; IARC 2008).

In A/J mice, inhalation exposure to ethylene oxide concentrations of 0, 70 or 200 ml/m^3 for 6 hours a day, on 5 days a week, for several months induced a dose-dependent increase in pulmonary adenomas (Adkins et al. 1986; IARC 2008).

Groups of 50 male and 50 female B6C3F1 mice were exposed to ethylene oxide concentrations of 0, 50 or 100 ml/m^3 for 6 hours a day, on 5 days a week, for 102 weeks. In male animals, the prevalence of alveolar/bronchiolar carcinomas was 5/50, 10/50 and 16/50, respectively, and the prevalence of the sum of adenomas and carcinomas was 11/50, 19/50 and 26/50, respectively. In female animals, the prevalence of alveolar/bronchiolar carcinomas was 0/49, 1/48 and 7/49, respectively, and the prevalence of the sum of adenomas and carcinomas was 2/49, 5/48 and 22/49, respectively (NTP 1987). In a re-evaluation, uterine adenocarcinomas were found in female mice (0/49, 2/47 and 5/49 (10%), respectively). One of the adenocarcinomas metastasized to the peritoneum, lungs and lymph nodes. The historical control value for these adenocarcinomas was 4/236 (1.7%) (Picut et al. 2003).

5.8 Risk assessment

There are 4 cohort studies and 1 case–control study; tumours of the haematopoietic system or lymphomas were the main findings (Section 4.7). Comprehensive dose–response analyses were carried out for risk evaluation. Exposure data from two cohort studies, the NIOSH cohort (Steenland et al. 2004) and the Union Carbide Corporation (UCC) cohort (Swaen et al. 2009), were used for these analyses.

Steenland et al. (2004) analysed the relationship between mortality from tumours of the haematopoietic system and cumulative exposure. The analysis was performed based on untransformed data and using a log-transformation both without and with consideration of lag times of 5, 10, 15 and 20 years. Possible exposure in the years leading up to death or after the end of the follow-up period was not taken into account. Depending on the level of exposure, 4 groups

were formed and a categorical analysis was carried out. A statistically significant result ($p = 0.02$) was obtained only in men, using log-transformation with a lag time of 15 years.

The US EPA (2006) analysed the data of the NIOSH cohort of Steenland et al. (2004) by means of a linear regression model using categorical cumulative exposure with a lag time of 15 years. The high exposure group was not included in the regression to obtain a better fit for the low exposure concentrations of environmental relevance. The risk levels calculated using continuous (log-transformed) cumulative exposure data varied considerably (see Table 1).

Tab. 1 Estimated mortality risk from all lympho-haematopoietic tumours in men at various concentrations of (lifetime) exposure (US EPA 2006)

Exposure (ml/m^3)	Continuous log-transformed cumulative exposure model[a)]	Continuous cumulative exposure model	Categorical cumulative exposure model[b)]	
		additional risk		upper 95% confidence limit
0.0001	4.70×10^{-3}	6.22×10^{-7}	4.22×10^{-5}	9.25×10^{-5}
0.001	1.24×10^{-2}	6.22×10^{-6}	4.22×10^{-4}	9.25×10^{-4}
0.01	2.25×10^{-2}	6.23×10^{-5}	4.21×10^{-3}	9.19×10^{-3}
0.1	3.55×10^{-2}	6.32×10^{-4}	–	–
1	5.22×10^{-2}	7.28×10^{-3}	–	–
10	7.36×10^{-2}	3.34×10^{-1}	–	–

[a)] with a lag time of 15 years
[b)] from linear regression of the categorical results

In another analysis of this cohort, the risk (maximum likelihood) of developing lymphoid tumours (mortality) after 35 years of occupational exposure to 0.1 ml/m^3 ranged from 0.9×10^{-2} to 1.2×10^{-2} for men and women depending on the model used. The risk of developing breast tumours ranged from 0.3×10^{-2} to 2.5×10^{-2} (US EPA 2016).

A significant increase in the tumour risk was not determined in a meta-analysis of 10 studies with 876 deaths from cancer, compared with 928 expected cases. By applying non-linear models using only the data from the NIOSH study, an additional risk of lymphoid tumours of 2.8×10^{-4} to 8.1×10^{-4} depending on the lag time and latency period was calculated for a lifetime occupational exposure of 45 years and an exposure concentration of 1 ml/m^3. No additional risk was determined if only the data from the UCC study were taken into account (Teta et al. 1999). In this way, the authors demonstrated the inconsistencies between the two studies of NIOSH and UCC.

Another study derived a unit risk value of 4.5×10^{-8} $(\mu g/m^3)^{-1}$ for the risk of developing leukaemia after exposure to ethylene oxide (Kirman et al. 2004).

In another study, a quantitative estimate of the cancer risk for lymphoid tumours was carried out. The data of the NIOSH study (Steenland et al. 2004) and the UCC study (Swaen et al. 2009) were analysed although the latter study had not found any evidence of a positive cumulative exposure–response relationship. However, in the NIOSH cohort, a significant increase in mortality from lymphoid tumours was found for men in the quintile with the highest exposure compared with that with the lowest exposure. Cumulative exposure was used without transformation and without a lag time. An additional risk of dying from lymphoid tumours (non-Hodgkin's lymphomas, multiple myelomas and lymphocytic leukaemia) of 4 to 10 000 (0.0004) was calculated for men and women after exposure at a concentration of 2.77 ml/m^3 over a period of 40 years (as from 20 years of age) (Valdez-Flores et al. 2011, see Table 2). The authors regarded this risk as the worst case because, although there was a slight increase in mortality, the observed exposure–response relationship was not statistically significant. At 2.82, the odds ratio for bone tumours was significantly increased in the NIOSH cohort. However, a dose–response relationship was not found. If bone tumours are included, a cancer risk of 12 per 100 000 (0.00012) is derived for an exposure concentration of 0.25 ml/m^3 (Arand and Marowsky 2016).

To sum up, the dose–response relationships for the induction of tumours by ethylene oxide determined in epidemiological studies were not statistically significant. The level of risk calculated greatly depends on the chosen model.

However, in rats and mice, ethylene oxide significantly increased the incidences of tumours at exposure concentrations of 50 ml/m^3 and above.

An inhalation study carried out in rats with ethylene oxide for 4 weeks reported a doubling in the number of Hprt mutants only at the highest exposure concentration of 200 ml/m^3. However, no increase in micronuclei, chromosomal aberrations or translocations was observed in the splenic lymphocytes of the animals (van Sittert et al. 2000). In mice exposed to ethylene oxide by inhalation for 4 weeks, the lowest concentration at which an increase in Hprt mutants was observed was 50 ml/m^3 (Swenberg et al. 2008).

After long-term inhalation exposure to concentrations up to 100 ml/m^3, a linear dose–response relationship was found for the formation of DNA adducts in the spleen, brain, liver and lungs of the exposed animals. This indicates that both metabolic detoxification and DNA repair were not yet saturated at this exposure concentration (Marsden et al. 2007).

A study in rats did not report a significant increase in *N*7-HEG in the liver, heart, colon, lungs, kidneys, spleen and stomach of the animals after intraperitoneal injection of 0.01 mg/kg body weight. The authors calculated that 0.05 mg/kg body weight is equivalent to occupational exposure in humans of 1 ml/m^3 (Marsden et al. 2009).

DNA adducts are a measure of exposure. However, in this case, they cannot be used for the evaluation of risk because the type of adduct formed in the various organs differs, as does their quantity. Ethylene oxide forms at least 5 adducts with DNA, most importantly *N*7-HEG, but only 1 adduct with haemoglobin. The *N*7-HEG adduct has a half-life of 2 days, while that of *N*-(2-hydroxyethyl)valine is 126 days. The DNA adducts are repaired, but not the haemoglobin adduct. Particularly in humans, the background concentrations of *N*7-HEG vary greatly, and the ethylene oxide that is formed by endogenous ethylene is not the main source of adducts (Csanády et al. 2000). However, the haemoglobin adduct concentration correlates very well with the exposure concentration of ethylene oxide at the workplace. In addition, haemoglobin adducts are easier to determine in practice than DNA adducts.

N-(2-hydroxyethyl)valine levels of 6.2 to 6.8 nmol/g globin were calculated for exposure to an ethylene oxide concentration of 1 ml/m^3 for 8 hours, whereas the mean background concentration was 0.02 nmol/g globin (Boogaard 2002).

5.8.1 Summary

Several end points can be used for risk derivation:

a) Epidemiological studies

The epidemiological studies yielded weak evidence that tumours of the haematopoietic/lymphatic system were induced after exposure to ethylene oxide concentrations higher than 4 ml/m^3. However, no statistically significant dose–response relationships were derived from these studies and the calculated risk greatly depends on the chosen model and the assumptions made (Section 5.7.2).

The analysis of the most important cohort studies of Valdez-Flores et al. (2011) with the end point of mortality caused by lymphoid tumours yielded the following concentrations at the workplace using defined risk levels (Table 2) and the corresponding haemoglobin adducts as determined based on the EKA correlation (1 ml/m^3 corresponds to 3.9 nmol *N*-(2-hydroxyethyl)valine/g globin:

Tab. 2 Workplace concentrations, haemoglobin adducts and additional risks of mortality caused by lymphoid tumours for women and men after occupational exposure for 40 years

Additional risk	Corresponding workplace concentration (ml/m^3)	Corresponding Hb adducts with EKA correlation (nmol HOEtVal/g globin)
4×10^{-3}	21.35	83.3
1×10^{-3}	6.58	25.7
4×10^{-4}	2.77	10.8
1×10^{-4}	0.712	2.8
4×10^{-5}	0.286	1.1
1×10^{-5}	0.072	0.28

HOEtVal: *N*-(2-hydroxyethyl)valine

An estimated risk of 1.4 : 100 000 at an ethylene oxide concentration of 0.1 ml/m^3 (Hb adducts: 0.39 nmol *N*-(2-hydroxyethyl)valine/g globin) and a corresponding risk of 1.4 : 1 000 000 at a concentration of 0.01 ml/m^3 (Hb adducts: 0.039 nmol *N*-(2-hydroxyethyl)valine/g globin) are calculated by linear interpolation from the relationships in Table 2.

If bone tumours are included, the risk is about 3 times as high (Arand and Marowsky 2016).

At an ethylene oxide concentration of 0.25 ml/m^3, the corresponding risk is 4 : 100 000 or 12 : 100 000 (including bone tumours).

b) Carcinogenicity studies in animals

In an evaluation of the US EPA (2016), unit risks were calculated from the sum of the tumours observed in the ethylene oxide carcinogenicity studies in mice and rats. The highest unit risk of 4.6×10^{-5} $(\mu g/m^3)^{-1}$ was derived from the data for female mice. The other unit risks were about half as high. The highest unit risk corresponds to an additional risk at the workplace of 0.011 for 1 ml/m^3, that is 1.1%, at an occupational exposure level of 40 ml/m^3-years. Tumour localizations in B6C3F1 mice included lung tumours and malignant lymphomas, for which this strain of mice has a high spontaneous incidence. In F344 rats, localizations were mononuclear leukaemia and peritoneal mesotheliomas of the testes. These types of tumours are specific to the F344 rat strain. The tumour localizations in rats do not coincide with those in mice. It cannot be explained at present why this species difference exists. Therefore, even if the tumours in rats and mice are assessed together, it is difficult to evaluate the extrapolation of these types of tumours to humans and calculate a risk for humans.

The study of Swaen et al. (2009) did not report an increase in tumour mortality in 2063 men who were exposed to 67 ml/m^3-years on average. A total of 315 deaths from tumours were expected; 298 deaths were observed.

According to the risk estimate of the US EPA (2016) and assuming a linearity between tumour mortality and cumulative exposure (1.1% × 67 ml/m^3-years/40 ml/m^3-years = 1.84%), 38 (2063 × 1.8%) additional tumour cases would have been expected. On the basis of the data for the general population, 154 deaths from tumours of the respiratory system and brain and lympho-haematopoietic tumours, the primary target organs in animal studies, would have been expected among exposed persons. However, 139 deaths were observed. This suggests a healthy worker effect. If the risk estimate were correct, 139 plus 38, or about 177 cases would have been observed in spite of the healthy worker effect. This number of expected cases is 15% higher than the 154 cases calculated from the general population data. This risk would probably have been detected.

Therefore, the risks calculated from animal studies are much higher than those calculated from epidemiological studies. The animal studies cannot be used to derive risk levels for human exposure to ethylene oxide because of the uncertainties described.

c) Comparison with the unavoidable risk from endogenous ethylene/ethylene oxide

A cancer risk of about 1:10 000 was estimated for the unavoidable background level of ethylene/ethylene oxide (Greim 1998). However, according to Arand and Marowsky (2016), a comparison of the cancer risks determined by the study of Valdez-Flores et al. (2011) and the values for the background adducts of *N*-(2-hydroxyethyl)valine demonstrated that the (unavoidable) risk posed by endogenously formed ethylene oxide was greatly overestimated.

d) Haemoglobin adducts

N-(2-Hydroxyethyl)valine, a haemoglobin adduct, is a good indicator of ethylene oxide exposure, and can easily be determined in the blood. The average background level of *N*-(2-hydroxyethyl)valine is 0.02 nmol/g globin. The 95th percentile is 0.035 and the range 0.0077 to 0.065 nmol/g globin (Schettgen et al. 2016). At an exposure concentration of 0.01 ml/m^3, the haemoglobin adduct concentration would be approximately in the range of the 95th percentile of the background concentration of the haemoglobin adduct if the EKA correlation is used as a basis. At an exposure concentration of 0.05 ml/m^3, the *N*-(2-hydroxyethyl)valine concentration would be about 10 times as high as the mean background concentration. A high formation of haemoglobin adducts is expected to lead to a decrease in haemoglobin function. For comparison, when the BAT value was established, the inactivation of haemoglobin by 5% was deemed tolerable. To reach this level of inactivation, the haemoglobin adduct concentration would have to be 50 000 times as high as that found at an exposure concentration at the workplace of 0.01 ml/m^3 (Arand and Marowsky 2016).

e) DNA adducts

DNA adducts are a measure of exposure, but they are not suitable for a risk evaluation, particularly if adduct formation differs from organ to organ, both in the type of adduct formed and in the quantity of each adduct. Ethylene oxide forms at least 5 adducts with the DNA, most importantly *N*7-HEG. *N*7-HEG has a half-life of 2 days. DNA adducts are difficult to determine. The background concentrations of *N*7-HEG vary greatly, and the ethylene oxide that is formed by endogenous ethylene is not the main source of adducts (Csanády et al. 2000). Therefore, DNA adducts are less suitable for evaluating the risk posed by ethylene oxide.

It was calculated that exposure to 0.36 ml/m^3 (8-hour mean) does not cause a significant increase in DNA adducts in the leukocytes of exposed persons.

After the intraperitoneal injection of an ethylene oxide dose of 0.01 mg/kg body weight (corresponding to 0.01 ml/m^3), a negligible increase in DNA adducts was found in the rat liver.

After taking all data into account, exposure to an ethylene oxide concentration of 0.1 ml/m^3

- is not expected to increase DNA adduct levels in the leukocytes of exposed persons,
- is expected to induce haemoglobin adducts at a level 20 times as high as the background concentration, and
- is expected to lead to an exposure-related increase in the cancer risk of 1.4 or 4 per 100 000.

6 Manifesto (MAK value/classification)

Carcinogenicity. Since 1984, ethylene oxide has been classified in Carcinogen Category 2. This classification is based on findings of exposure-related tumours in rats and mice. After inhalation, ethylene oxide concentrations of 50 to 200 ml/m^3 (92–366 mg/m^3) caused brain tumours, mononuclear leukaemia, peritoneal mesotheliomas of the testes, and subcutaneous fibrosarcomas in rats and adenomas and carcinomas of the lungs, malignant lymphomas, Harderian gland tumours, uterine adenocarcinomas, and mammary carcinomas in mice.

A number of epidemiological studies provided evidence of a relationship between the cumulative exposure to ethylene oxide and an increase in lymphoid tumours of the haematopoietic system (non-Hodgkin's lymphomas, multiple

myelomas and chronic lymphocytic leukaemia) and revealed a trend towards an increase in breast cancer mortality in women. However, there are studies that did not yield evidence of an increase in cancer mortality for workers after exposure to ethylene oxide.

The carcinogenicity of ethylene oxide is based on its reactivity as a directly alkylating agent, which reacts, for example, with the DNA. Ethylene oxide was weakly genotoxic both in studies in vitro and in studies in vivo. In addition, it induced a dose-dependent increase in haemoglobin adducts in humans and animals.

As ethylene oxide is carcinogenic and genotoxic and genotoxicity is assumed to be the main effect, the substance would be a candidate for Carcinogen Category 5. However, the risk calculated on the basis of the epidemiological studies greatly depends on the chosen model (see Section 5.8). For example, after exposure to an ethylene oxide concentration of 0.1 ml/m^3, men and women have an additional risk of dying from lymphoid tumours of 1.4 or 4 per 100 000 if bone tumours are additionally regarded as exposure-related. As the additional cancer risk varies over several powers of ten depending on the model, it is not possible at present to derive a MAK value at which a very low contribution to the cancer risk is expected. Therefore, ethylene oxide remains classified in Carcinogen Category 2.

Germ cell mutagenicity. See also the 2002 supplement (Greim 2002).

Ethylene oxide is mutagenic and clastogenic at all phylogenetic levels. All the information available for genotoxicity demonstrates that ethylene oxide is a weak mutagen. Ethylene oxide induced an increase in sister chromatid exchange, chromosomal aberrations and micronuclei in the lymphocytes of exposed workers. In addition, the substance caused heritable translocations in the germ cells of animals. Therefore, ethylene oxide remains classified in Category 2 for germ cell mutagens.

Absorption through the skin. After exposure to 0.1 ml/m^3 (EU binding occupational exposure limit value), about 1.6 mg is absorbed by inhalation assuming pulmonary absorption of 80% over a period of 8 hours. A dermal absorption of 31 mg is calculated from in vitro data for a non-irritant solution of ethylene oxide under standard conditions. The dermal route of exposure may thus significantly contribute to the total body burden and the designation of ethylene oxide with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts) has been retained.

Sensitization. Only a few cases of occupational eczematous skin reactions to ethylene oxide have been observed. These findings cannot be used to determine whether ethylene oxide causes contact sensitization because severe irritation appears to be by far the main effect. Therefore, ethylene oxide has not been designated with "Sh" (for substances which cause sensitization of the skin). In addition, immediate-type reactions have frequently been reported, but with a few exceptions these were observed in dialysis patients without occupational exposure. The case reports of occupationally exposed persons were not described in detail and in most cases the complaints may have been caused by a latex allergy. Thus, should ethylene oxide induce sensitizing effects on the airways of occupationally exposed persons, these effects are not sufficiently supported by the data. Therefore, ethylene oxide has not been designated with "Sa" (for substances which cause sensitization of the airways).

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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