1,2-Epoxypropane

[75-56-9]	
Supplement 2013	
MAK value (2012)	**2 ml/m³ (ppm) ≙ 4.8 mg/m³**
Peak limitation (2012)	**Category I, excursion factor 2**
Absorption through the skin	**–**
Sensitization (2012)	**Sh**
Carcinogenicity (2012)	**Category 4**
Prenatal toxicity (2012)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
BAR value (2011)	**10 pmol *N*-(2-hydroxypropyl) valine/g globin**
	25 µg 2-hydroxypropyl mercapturic acid/g creatinine
EKA (2012)[1)]	**see DFG** (2013)

Since the documentation of 1984 (documentation "1,2-Propylene oxide" 1993) and the supplement of 2003 on absorption through the skin (supplement "1,2-Propylene oxide" 2013), studies of the metabolism, genotoxicity and carcinogenicity of the substance have been carried out. These refindings make a reassessment necessary.

1 Toxic Effects and Mode of Action

See documentation "1,2-Propylene oxide" 1993.

After long-term exposure to 1,2-epoxypropane, changes were observed in the nasal epithelia of rats at and above the lowest concentration tested of 30 ml/m³. The

1) A term established by the BAT (Biologischer Arbeitsstoff-Toleranz-Wert = Biological Tolerance Value) working group: EKA = Exposure Equivalent for Carcinogenic Substances

The MAK-Collection Part I, MAK Value Documentations 2015
DFG, Deutsche Forschungsgemeinschaft

BMDL05 for this effect was 11 ml/m^3. Cell proliferation in the nasal epithelium of rats occurred at concentrations of 100 ml/m^3 and above, depletion of glutathione (GSH) at and above the lowest concentration tested of 5 ml/m^3.

Case reports confirm that 1,2-epoxypropane has a skin-sensitizing potential.

2 Mechanism of Action

1,2-Epoxypropane is a weakly electrophilic substance that can directly alkylate macromolecules; it has the potential to alkylate proteins, nucleobases and DNA.

The reaction of 1,2-epoxypropane with DNA results mainly in the formation of the alkylation product N7-(2-hydroxypropyl)guanine (N7-HPG). The sequence of reactivity of the different deoxynucleosides is: deoxyguanosine > deoxyadenosine > deoxycytidine > deoxythymidine. In addition, N3-(2-hydroxypropyl)deoxyuridine was found to be present as an alkylation product of 1,2-epoxypropane (BUA 1992). On the contrary N7-HPG, which is not premutagenic, the DNA adducts N1-(2-hydroxypropyl)adenine and N6-(2-hydroxypropyl)adenine, formed in small amounts (2%), are premutagenic. DNA alkylation is considered to be the cause of the direct mutagenic effects of 1,2-epoxypropane. The DNA-purine adducts at the N7 and N3 positions can be efficiently repaired (Albertini and Sweeney 2007).

1,2-Epoxypropane results in nasal tumours in rats and mice. After inhalation exposure to 1,2-epoxypropane, increased cell proliferation in the nasal epithelial cells of rats was observed at concentrations of 100 ml/m^3 and above; this was accompanied by the depletion of non-protein-bound thiols (mainly glutathione) (ACGIH 2001; Khan et al. 2009; Sweeney et al. 2009). It is not the loss of the detoxification capacity as a result of GSH depletion that is crucial here, but the GSH depletion per se, that represents a cytotoxic stimulus which indirectly leads to regenerative cell proliferation.

With the depletion of the glutathione, degenerative and inflammatory effects occur in the nasal mucosa. Below concentrations at which neither local inflammatory processes nor cell degeneration occur, and at which glutathione is not depleted and cell proliferation does not take place, the DNA-reactive effects and consequently the tumour incidences did not increase (Khan et al. 2009; Lee et al. 2005; Sweeney et al. 2009). From the concentration–effect relationships for DNA adducts, GSH depletion and nasal tumours (Figure 1), it is clear that the amount of DNA adducts is linear down to the lowest concentration tested, but tumours are not induced until concentrations at which there is marked GSH depletion and increased cell proliferation (lowest observed adverse effect concentration (LOAEC) 100 ml/m^3).

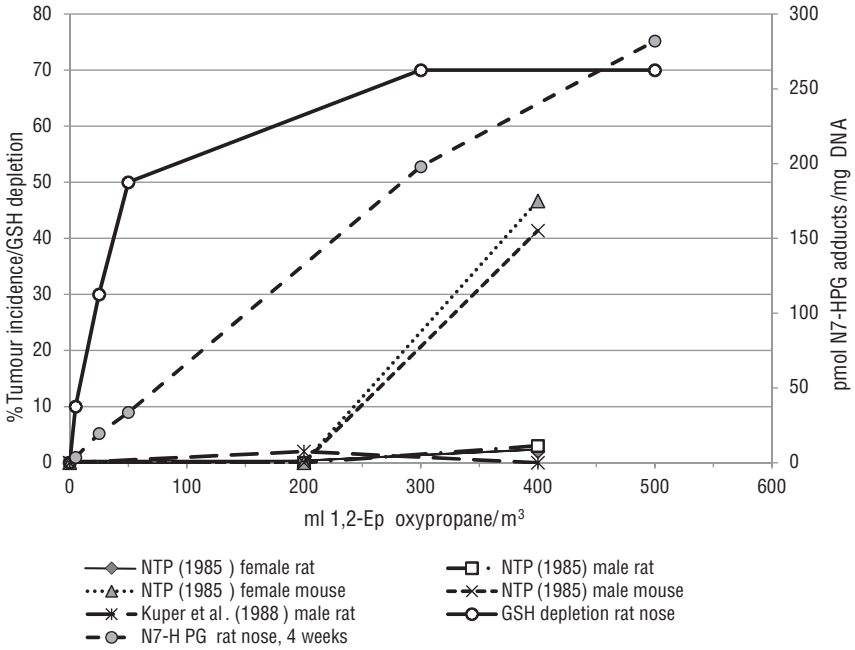

Figure 1 Concentration–effect relationships for nasal tumours (%) in rats and mice, GSH depletion (%) and DNA adducts in the nasal epithelium of rats

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Q1 See documentation "1,2-Propylene oxide" 1993.

In the following, only new data for inhalation and dermal absorption are described. Oral absorption plays no role.

In a study with male Fischer 344 rats exposed to 1,2-epoxypropane concentrations of 14 ml/m³ for 60 minutes, the concentration of 1,2-epoxypropane in blood increased during the first 10 minutes until a plateau of 3 ng/g blood was reached (Maples and Dahl 1993).

Physiologically-based pharmacokinetic models have been developed for extrapolating values for humans from the results for experimental animals. These revealed that the exposure of the nasal epithelia to 1,2-epoxypropane in rats and humans at equal external concentrations is the same, if the detoxifying metabolism in the human nasal epithelia is neglected. With many substances, exposure of the nose is determined not only by local, but also by systemic exposure. In the case of

1,2-epoxypropane, the respiratory activity is also decisive for the burden of the substance (Csanády and Filser 2007; Filser et al. 2008).

There are no data available for the dermal absorption of 1,2-epoxypropane in humans or experimental animals. Nor are in vitro data available. The extent of possible dermal absorption from the gaseous phase can be estimated using model calculations. According to the Dalton's and Henry's laws, after exposure to 2 ml/m^3 a 1,2-epoxypropane concentration of 613 µg/l is to be expected in the sweat. Model calculations for skin penetration yielded fluxes of 0.51, 1.31 and 3.26 ng/cm^2 and hour, respectively, with an aqueous solution at this concentration on the surface of the skin (Fiserova-Bergerova et al. 1990; Guy and Potts 1993; Wilschut et al. 1995). Assuming an exposure of the total body surface (17 000 cm^2) is for 8 hours to 1,2-epoxypropane concentrations in the air of 2 ml/m^3, amounts of 70, 178 and 443 µg would be absorbed through the skin, depending on the respective model.

3.2 Metabolism

1,2-Epoxypropane is metabolized in two ways: by glutathione transferase (GST) via spontaneous or enzymatic conjugation with glutathione, and via spontaneous or enzymatic hydrolysis to form 1,2-propanediol, which is further converted to lactic acid and pyruvate (BUA 1992; IARC 1994). In vitro, 1,2-epoxypropane was metabolized by epoxide hydrolase (EH) obtained from the liver microsomes of male rats after pretreatment with phenobarbital. The turnover rate for 1,2-epoxypropane was lower than that for other epoxides (Guengerich and Mason 1980).

The half-life for the spontaneous hydrolysis of 1,2-epoxypropane at 37°C at a pH of 7.4 was 15.8 hours, that for the spontaneous reaction with GSH 2.5 hours. The kinetics of the metabolism of 1,2-epoxypropane catalyzed by GST and EH was investigated in the cytosol and in microsomes of the liver and lungs of B6C3F1 mice, F344 rats and humans, and in the olfactory and respiratory epithelium of F344 rats. In all tissues, GST and EH activity was demonstrated, GST activity however only in the cytosolic fractions. EH activity was found in microsomes. Only in human liver was cytosolic activity also observed, representing 1% to 3% of the corresponding GST activity. For GST, the Vmax to Km ratio in the liver and lungs was between 12 (human liver) and 106 (mouse lung) µl/min and mg protein. The corresponding values for EH were in the range from 4.4 (mouse liver) to 46 (human lung). The lowest Vmax value for EH of 7.1 nmol/min and mg protein was found in the mouse lung, the highest in the human liver. The Km values for EH-mediated hydrolysis were in the range from 0.83 (human lung) to 3.7 nmol/l (mouse liver). In the liver and lungs, the highest Vmax/Km ratios were obtained for EH in human tissue and for GST in mouse tissue. GST activities were higher in the lungs than in the liver of mice and humans, and were alike in rats. In rat nasal mucosa, GST and EH activities were much higher than in rat liver (Faller et al. 2001).

In a study with male Fischer 344 rats, GSH depletion was determined. The rats were exposed either once to 1,2-epoxypropane concentrations between 0 and 750 ml/m^3 for 6 hours, or to 0, 5, 25, 50, 300 or 500 ml/m^3 either for 6 hours a day for 3 days, or on 5 days a week for 4 weeks. At the end of the exposure, the concentrations of 1,2-epoxypropane in the blood and of non-protein-bound sulfhydryl (NPSH) in tissues were determined. After exposure for one day, the concentration of NPSH was lowest. The depletion in the nasal mucosa was higher than in the liver and the lungs. The concentration of NPSH in the nasal mucosa of the animals in the 50 ml/m^3 group was 43% and of the animals in the 300 ml/m^3 group 16% of the control values. After exposure for 3 and 20 days, the depletion of NPSH was less pronounced. The concentrations in the nasal mucosa after exposure to 5, 25, 50, 300 and 500 ml/m^3 were 90%, 70%, 50%, 30% and 30% of the control value, respectively. The degree of depletion was the same after 3-day and 4-week exposure (Lee et al. 2005).

Male Fischer 344 rats were exposed to 1,2-epoxypropane concentrations of 0, 50, 100, 200 or 300 ml/m^3 for 6 hours a day for 3 days. At the end of the exposure period, the GSH concentration and cell proliferation in the nasal respiratory epithelium were determined. These two parameters were determined also in animals given intraperitoneal injections of diethylmaleate in doses of 500 or 650 mg/kg body weight and day or buthionine sulfoximine in doses of 500 mg/kg body weight and day for 3 days. Both of these chemicals cause GSH depletion. Exposure to 1,2-epoxypropane concentrations of 50 ml/m^3 and treatment with diethylmaleate doses of 500 mg/kg body weight resulted in NPSH levels of about 50% and 80% of the levels in untreated controls, respectively; cell proliferation was unaffected. In animals exposed to 1,2-epoxypropane concentrations of 100 ml/m^3 and above or treated with buthionine sulfoximine or diethylmaleate doses of 650 mg/kg body weight, the NPSH level was depleted to one third of the level of the control animals; the cell proliferation in these animals was increased 2.0 to 3.7-fold. However, this cell proliferation was not observed at the site of tumour formation, but in the nasal septum. Cell proliferation was, however, significantly increased at the site of tumour formation (nasal concha) after exposure to 1,2-epoxypropane concentrations of 200 ml/m^3 (Khan et al. 2009).

4 Effects in Humans

4.1 Single exposures

See documentation “1,2-Propylene oxide” 1993.

4.2 Repeated exposure

Biological monitoring

1,2-Epoxypropane is capable of forming adducts with proteins such as haemoglobin. The number of *N*-terminal valine adducts in the haemoglobin of mice is linearly dependent on the dose. The efficiency of alkylation in mice is only half of that found in rats and dogs (IARC 1994). The chemical reactivity of 1,2-epoxypropane is four times lower than that of ethylene oxide (Pauwels and Veulemans 1998). There is evidence of the enantioselective reactivity of the two optical isomers (Peter et al. 1991); all studies were, however, carried out with the racemate of 1,2-epoxypropane. As with ethylene oxide, 1,2-epoxypropane is a substrate of hGSTT1-1 in humans (Thier et al. 1999). The adducts of 1,2-epoxypropane on the imidazole ring of histidine (HOPrHis) and on the *N*-terminal valine (HOPrVal) of haemoglobin are indicators for the internal dose and are thus used in biomonitoring. Corresponding biomonitoring procedures have proved suitable in practice (Boogaard 2002; Törnqvist et al. 1986).

In a study carried out in a starch alkylation factory, the level of HOPrVal in control persons was found to be 20 pmol/g haemoglobin while in those exposed to 1,2-epoxypropane concentrations of 0.33 to 11.4 ml/m^3 it was 3500 pmol/g haemoglobin. A correlation was found between the adduct level and the concentrations of 1,2-epoxypropane in the breathing zone (Högstedt et al. 1990).

It has been estimated that exposure to 1,2-epoxypropane concentrations of 1 ml/m^3 for 40 hours a week during a working life results in an increase in HOPrVal levels of up to 500 pmol/g haemoglobin (Kautiainen and Törnqvist 1991; van Sittert and van Vliet 1994;).

In addition, it has been reported that the detection limit for HOPrVal is close to 0.1 pmol/g globin. After repeated exposure to 1,2-epoxypropane concentrations of 2 ml/m^3, the HOPrVal level in the steady state was 2.56 ± 0.34 nmol/g globin (Boogaard 2002; Boogaard et al. 1999;). This is consistent with values obtained from animal studies (Albertini and Sweeney 2007; Osterman-Golkar et al. 2003).

In a small field study, the HOPrVal level was determined in persons exposed to 1,2-epoxypropane concentrations of between 0.9 and 6.9 ml/m^3 (mean concentration 2.69 ± 1.52 ml/m^3) for a period of 1 to 1.5 hours. The values were in the range from 0.13 to 4.91 nmol/g globin. The range of the control values was 0.005 to 0.008 nmol/g globin (Czene et al. 2002).

4.3 Local effects on skin and mucous membranes

See documentation “1,2-Propylene oxide” 1993.

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

A 52-year-old female worker employed in a histopathology laboratory, who had been using 1,2-epoxypropane in the preparation of tissue slides in a dehydration step, was dermatologically examined on account of recurrent skin lesions that had persisted over a period of about 10 years. Patch tests yielded positive results with 0.01% (1+), 0.03% (2+) and 0.1% (3+) 1,2-epoxypropane in ethanol. The 10 control persons did not produce reactions to these preparations (Steinkraus and Hausen 1994).

Eczematous skin reactions on the fingers occurred twice in a female technician who had contact with 1,2-epoxypropane, epoxide resins and hardeners, glutaraldehyde and photochemicals in connection with her work using an electron microscope. Patch tests yielded positive results with 1% 1,2-epoxypropane and 1% epichlorohydrine (both substances in acetone) and to a cycloaliphatic epoxide resin (0.5% in petrolatum) after 48 and 96 hours. In 20 control persons, no reactions to the 1% 1,2-epoxypropane preparation were observed (Morris et al. 1998).

Another employee from a laboratory who used an electron microscope sought medical advice as a result of dermatitis on the hands that she had had for 8 years. Her work involved the preparation of tissue slides twice a day for about half an hour with either 50% or undiluted 1,2-epoxypropane. Patch tests yielded a marked positive result (no other details) with a 1% 1,2-epoxypropane preparation in 70% ethanol, which produced a slight reaction in only one of 16 control persons (van Ketel 1979).

An occlusive disinfectant dressing containing 1% 1,2-epoxypropane and 70% isopropanol was used to treat a patient for a skin burn. After a few days, an eczematous skin change developed over a wide area on the affected arm, which healed after discontinuing treatment. Later, an eczematous reaction was found on the fingers of the same patient who worked in a blood bank and for a longer period of time had used disinfectant swabs containing 1,2-epoxypropane and isopropanol while taking blood samples. After ceasing to use these swabs, also the dermatitis on his fingers healed. A further employee at the same blood bank used the disinfectant swabs to treat mycosis on the toes; a few days later an eczematous reaction developed on her toes and fingers. In patch tests with the swab material, both patients developed a 3+ reaction to 1% and 0.5% 1,2-epoxypropane in ethanol while one patient developed a 2+ reaction to 0.1% 1,2-epoxypropane and the other a 3+ reaction. There was no reaction to the highest 1,2-epoxypropane concentration in 25 control persons (Jensen 1981).

A physician, who had become sensitized after testing the irritating properties of epichlorohydrine in patch tests with 0.1%, 0.5% and 1% epichlorohydrine in ethanol, reacted in subsequent tests not only to 0.1% epichlorohydrine but also to 0.2% 1,2-epoxypropane in ethanol (Fregert and Gruvberger 1970).

4.4.2 Sensitizing effects on the respiratory tract

There are no data available.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

After 20 years of exposure to 1,2-epoxypropane, the number of chromosomal aberrations in the leukocytes was increased. However, these workers were exposed also to other epoxides, in particular ethylene oxide (Thiess et al. 1981 a).

The results of an investigation of chromosomal aberrations and micronuclei in the lymphocytes of 20 workers exposed to 1,2-epoxypropane during the production of alkylated starch are difficult to interpret, as no data for the control group were given (Högstedt et al. 1990).

An increase in the frequency of sister chromatid exchange (SCE) was found in a study with a small number of workers in China who were exposed to 1,2-epoxypropane concentrations of about 2 ml/m^3. The mean SCE frequency was 3.7 ± 2.11% (not significant) in exposed persons and 2.0 ± 0.52% in the control group (Czene et al. 2002, see Section 3.2). On account of the variance in the control group, the relevance of these results was regarded as questionable by the Scientific Committee for Occupational Exposure Limits (SCOEL 2010).

In this study, the number of 1-hydroxypropyl adenine adducts in the DNA was determined. A mean value of 0.66 ± 0.34 adducts per 10^9 nucleotides was determined in 7 of the 8 workers; no adducts were found in control persons. As this adduct makes up about 2% of the DNA adducts caused by 1,2-epoxypropane, this corresponds to a mean frequency of 3.3 N7-HPG adducts per 10^8 nucleotides for exposure to 1,2-epoxypropane concentrations of 2 ml/m^3 (SCOEL 2010).

4.7 Carcinogenicity

Several cohort studies (Hogstedt et al. 1979, 1986; Thiess et al. 1981 b) involving exposure to ethylene oxide also included persons exposed to 1,2-epoxypropane. As a result of the exposure to a mixture of substances, no conclusions can be drawn from these studies regarding the carcinogenicity of 1,2-epoxypropane. According to the IARC (1994), there is “inadequate evidence in humans” to be able to assess the carcinogenic potential of 1,2-epoxypropane.

5 Animal experiments and in vitro studies

5.1 Acute toxicity

There are no new relevant data available (see documentation "1,2-Propylene oxide" 1993).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Male Fischer 344 rats were exposed to 1,2-epoxypropane concentrations of 0, 10, 20, 50, 150 or 525 ml/m^3 for up to 4 weeks. The recovery period was also up to 4 weeks. Toxic effects and cell proliferation in the nose were determined. Respiratory epithelial cell hyperplasia, degeneration of the olfactory epithelium and cell proliferation in both epithelia were found to be dependent on the concentration and time, and reversible. A NOAEC (no observed adverse effect concentration) of 50 ml/m^3 was determined in this study (Eldridge et al. 1995).

Eleven male Wistar rats were exposed to 1500 ml/m^3 for 6 hours a day, on 5 days a week for 7 weeks. In the third week of exposure, staggering gait was observed in the exposed animals, and in the fifth week ataxia of the hind legs, although without vascular atrophy. Histologically, distal axonopathy with degeneration of the myelinated nerve fibres in the hind legs and fasciculus gracilis was found (Ohnishi et al. 1988; Ohnishi and Murai 1993;).

In the 2-year study in rats (Kuper et al. 1988; Section 5.7), a LOAEC (lowest observed adverse effect concentration) of 30 ml/m^3 for nest-like infolds (histopathologically the most sensitive effect) in the nasal epithelium was determined. A BMD calculated from the sums of the incidences of nest-like infolds for male and female animals after 28 months yielded a BMDL05 of 11 ml/m^3 (Figure 2).

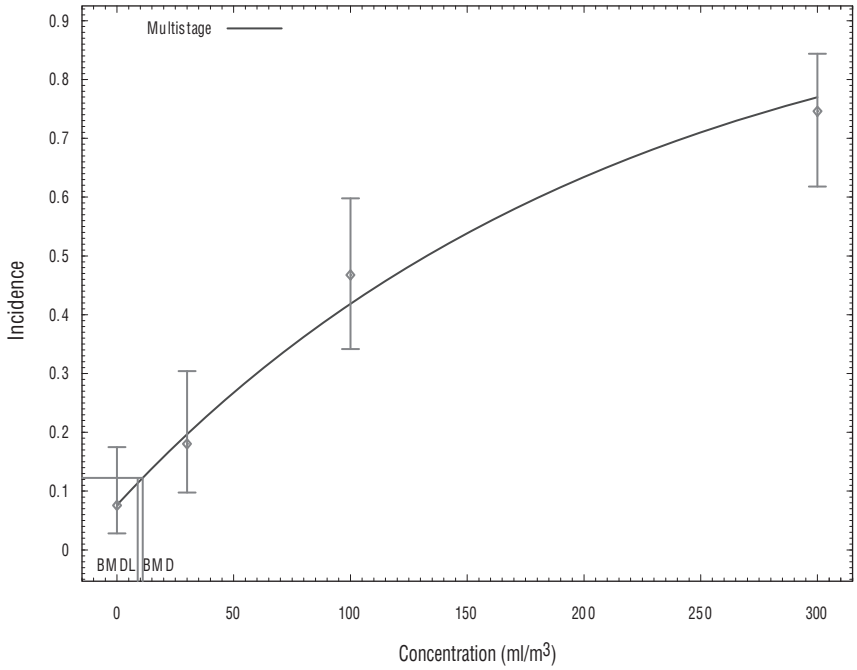

Figure 2 Calculation of the BMDL (multistage model with 95% confidence interval) for the end point "nest-like infolds" in male and female rats from the study of Kuper et al. (1988)

5.2.2 Ingestion

There are no new relevant data available (see documentation "1,2-Propylene oxide" 1993).

5.2.3 Dermal absorption

There are no new relevant data available (see documentation "1,2-Propylene oxide" 1993).

5.3 Local effects on skin and mucous membranes

There are no new relevant data available (see documentation "1,2-Propylene oxide" 1993).

5.4 Allergenic effects

Sensitizing effects on the skin

In a split adjuvant test, 100 µl of a 10% 1,2-epoxypropane preparation (vehicle not specified) was applied four times within 10 days under occlusive conditions to the skin of 10 Hartley guinea pigs. At the third application, the animals were also given an intradermal injection of Freund's complete adjuvant (FCA). The challenge treatment with 10% 1,2-epoxypropane took place after 2 weeks. No reactions were observed after either 24 or 48 hours (European Commission 2002).

Sensitizing effects on the respiratory tract

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no data available.

5.5.2 Developmental toxicity

In a 2-generation study, 30 male and 30 female Fischer 344 rats were exposed to 1,2-epoxypropane concentrations of 0, 30, 100 or 300 ml/m^3 for 6 hours a day. Both male and female animals were treated for 14 weeks before mating. From the 5th week after birth, the animals of the F_1 generation were exposed to concentrations of 0, 30, 100 or 300 ml/m^3 for 6 hours a day, on 5 days a week for 17 weeks before mating to produce the F_2 generation. Body weights were significantly (12%) reduced in the animals of the high concentration group in both sexes. No effects were observed on the mating and fertility indices, the litter size or the number of live pups on the day of birth and on postnatal days 4 and 28. Histological examinations did not reveal any unusual findings in the offspring of the F_1 or F_2 generations (Hayes et al. 1988).

From days 6 to 15 of gestation, groups of 25 Fischer 344 rats were exposed to 1,2-epoxypropane concentrations of 0, 100, 300 or 500 ml/m^3 for 6 hours a day. Necropsy took place on gestation day 20. Maternal body weight gains and food consumption were significantly reduced at 500 ml/m^3. No adverse effects on litter size, foetal resorptions or foetal weights were observed. The incidence of variations in the length of the 7th cervical rib was increased in the high-dose foetuses (13%), compared with that in the control group (2.8%) (Harris et al. 1989). The NOAEL (no observed adverse effect level) for developmental toxicity and maternal toxicity was 300 ml/m^3.

The following studies have already been described in the documentation from 1984 (see documentation "1,2-Propylene oxide" 1993): From gestation day 1 or 7 up to day 16, Sprague Dawley rats inhaled 1,2-epoxypropane concentrations of 0 or 500 ml/m^3 for 7 hours a day. The foetuses were examined on day 21. Both food consumption and the body weights of the dams were reduced during the treatment. Foetal growth was reduced compared with that of the controls. There were no treatment-related malformations, merely the incidence of wavy ribs was increased in the treated groups (Hardin et al. 1983).

From gestation day 1 or 7 up to day 19, female New Zealand rabbits inhaled 1,2-epoxypropane concentrations of 0 or 500 ml/m^3 for 7 hours a day. The foetuses were examined on day 30. Food consumption and the body weights of the dams were reduced. Fertility was not affected, and no developmental toxicity was observed (Hardin et al. 1983).

5.6 Genotoxicity

In vitro

1,2-Epoxypropane binds covalently to calf thymus DNA (Djuric et al. 1986; Randerath et al. 1981; Solomon et al. 1988). 1,2-Epoxypropane induces DNA damage and gene mutations in bacteria; it causes gene mutations in yeasts and fungi and mitotic gene conversion in Saccharomyces cerevisiae. In mammalian cells, 1,2-epoxypropane induces DNA damage, gene mutations, SCE and chromosomal aberrations (Albertini and Sweeney 2007; European Commission 2002; IARC 1994).

In vivo

In a study with Drosophila, 1,2-epoxypropane was found to be mutagenic in sex-linked recessive lethal mutation tests (IARC 1994).

An increased incidence of micronuclei, chromosomal aberrations and SCE in the bone marrow of mice after the intraperitoneal injection of 1,2-epoxypropane was found only in one study. No increases in the incidence of SCE and chromosomal aberrations were observed in monkeys after exposure to 1,2-epoxypropane concentrations of 100 or 300 ml/m^3 for 2 years. No dominant lethal mutations were detected in mice and rats after inhalation exposure to 1,2-epoxypropane (IARC 1994).

DNA adducts

Several studies showed that 1,2-epoxypropane can react with the nitrogen atoms on the ring of DNA bases, whereby hydroxypropyl adducts are formed mainly at the N7 position of guanine (N7-HPG) but also at the N3 and N1 positions of adenine (N3-HPA, N1-HPA), the N3 position of cytosine and the N3 position of thymine (Koskinen and Plna 2000; Osterman-Golkar et al. 2003; Solomon 1999). The N7-HPG and N3-HPA adducts themselves are not premutagenic lesions, but can

induce purine-free sites, as they destabilize the imidazole ring as a result of the positive charge. N7-HPG is the quantitatively most important DNA lesion caused by 1,2-epoxypropane. Normally, these purine-free lesions are rapidly repaired; the endogenous frequency of purine-free sites was determined to be 1 per 10^5 nucleotides (Albertini and Sweeney 2007). No difference was found between the number of purine-free sites in DNA found in the tissues of rats exposed to 500 ml/m^3 and that in the control animals (Ríos-Blanco et al. 2000).

N7-HPG was found in hydrolyzed samples of DNA in several organs of male mice after intraperitoneal injection of 1,2-epoxypropane (Svensson et al. 1991). After intraperitoneal or intravenous injection of 1,2-epoxypropane, 17 pmol/g DNA per mg 1,2-epoxypropane and per kg body weight was found in the liver of mice, 38 pmol in that of rats, and 17 pmol in that of dogs. In the same study, higher concentrations were determined in mice after inhalation (Segerbäck et al. 1994). Based on these data, a covalent binding index of 0.3 after intraperitoneal injection was calculated for mouse liver DNA (IARC 1994); this value was low compared with the values for other alkylating and carcinogenic substances.

In a study, the DNA adduct N7-HPG was quantitatively determined in nose and liver tissue of rats exposed to 1,2-epoxypropane concentrations of 500 ml/m^3 for 6 hours a day, on 5 days a week for 4 weeks. Using two different methods, this adduct was determined either immediately, 3 days or 4 weeks after the end of the exposure. In one method, the adduct was separated from the DNA by neutral thermal hydrolysis followed by electrophoretic derivatization and analysis with GC-HRMS (gas chromatography/high-resolution mass spectrometry). The second method used ^{32}P postlabelling to quantify this adduct. The values determined using GC-HRMS in the animals killed immediately after the end of exposure were 835.4 ± 80.1 pmol adduct/µmol guanine for respiratory mucosa, 296.8 ± 53.1 pmol adduct/µmol guanine for olfactory mucosa and 34.6 ± 3.0 pmol adduct/µmol guanine for liver tissue. These values were lower in the animals killed 3 days after the end of exposure: 592.7 ± 53.3 pmol adduct/µmol guanine for respiratory mucosa, 296 ± 32.6 pmol adduct/µmol guanine for olfactory mucosa and 23.2 ± 0.6 pmol adduct/µmol guanine for liver tissue. The following values were determined by ^{32}P postlabelling in the animals killed immediately after the end of exposure: 445.7 ± 8.0 pmol adduct/µmol guanine for respiratory mucosa, 301.6 ± 49.2 pmol adduct/µmol guanine for olfactory mucosa and 20.6 ± 1.8 pmol adduct/µmol guanine for liver tissue. In the animals killed 3 days after the end of exposure the following values were determined: 327 ± 21.7 pmol adduct/µmol guanine for respiratory mucosa, 185.3 ± 29.2 pmol adduct/µmol guanine for olfactory mucosa and 15.7 ± 0.9 pmol adduct/µmol guanine for liver tissue. In the control animals, no N7-HPG could be found as an endogenous DNA adduct. According to the authors, the results clearly show that nasal tissue, as the target organ of the carcinogenic effects of 1,2-epoxypropane, has a higher incidence of alkylation than the liver, which is not a target organ of carcinogenesis (Ríos-Blanco et al. 1997).

Rats were exposed to 5, 25, 50, 300 or 500 ml/m^3 for 3 days or 4 weeks. A concentration-dependent linear increase in N7-HPG in the DNA of the nasal epithelium, lungs and liver was observed. In the nasal epithelium the adduct level was 7 times higher than that in the lungs and 17 times higher than that in the liver. After concentrations of 5 ml/m^3, the adduct level was comparable with the reported number of endogenous adducts in humans and in animals not exposed (2 per 10^6 nucleotides). The authors emphasize that, in contrast to the linear increase of N7-HPG adducts, the incidence of nasal tumours in rats resulting from 1,2-epoxypropane was highly sublinear (Ríos-Blanco et al. 2003).

The 1-hydroxypropyladenine adduct is found less frequently after exposure to 1,2-epoxypropane; the concentrations detected made up 2% of the total DNA adducts (Plna et al. 1999; Segerbäck et al. 1998).

5.7 Carcinogenicity

5.7.1 Short-term studies

There are no new relevant data available (see documentation "1,2-Propylene oxide" 1993).

5.7.2 Long-term studies

In a long-term study, groups of 50 male Sprague Dawley rats were exposed to 1,2-epoxypropane concentrations of 435 or 870 ml/m^3 for 6 hours a day, on 5 days a week for 30 days, or to 1740 ml/m^3 for 8 days. A control group of 98 rats was exposed to clean air. The average lifespan was 613 days. No tumours were found in the region of the nose. Two animals in the medium concentration group developed pulmonary adenomas (Sellakumar et al. 1987).

Groups of 80 male Fischer 344 rats were exposed in whole-body chambers to 1,2-epoxypropane concentrations of 0, 100 or 300 ml/m^3 for 6 hours a day, on 5 days a week for 104 weeks. Mortality was significantly higher in the animals of the high concentration group, and a concentration-dependent increase in epithelial hyperplasia in the region of the nose was observed (0/76, 2/77, 11/78). An adenoma of the nasal mucosa was found in 2 of 78 animals in the high concentration group and an osteosarcoma in 1 animal. These types of tumour did not occur in the control group. In addition, adrenal phaeochromocytomas were significantly increased, although not in a concentration-dependent manner (8/78, 25/78, 22/80), while peritoneal mesotheliomas were not significantly increased (3/78, 8/78, 9/78) (Lynch et al. 1984).

In an NTP study, groups of 50 male and 50 female Fischer rats were exposed to 0, 200 or 400 ml/m^3 for 6 hours a day, on 5 days a week for 104 weeks. Concentration-dependent increases in epithelial hyperplasia and squamous metaplasia in the

region of the nose of the exposed animals were observed. The incidences of papillary adenomas of the nasal tissue in the females were 0/50, 0/50 and 3/50 and in the male animals 0/50, 0/50 and 2/50. In addition, in the female rats of the high dose group, increased C cell adenomas and carcinomas of the thyroid gland, and polyps and sarcomas of the endometrium were found; according to the NTP these effects are not substance-related (NTP 1985; Renne et al. 1986).

In the same study, groups of 50 male and 50 female B6C3F1 mice were exposed in whole-body chambers to 1,2-epoxypropane concentrations of 0, 200 or 400 ml/m^3 for 6 hours a day, on 5 days a week for 104 weeks. The number of surviving male mice was 42/50, 34/50 and 29/50 and of female mice 38/50, 29/50 and 10/50. In the female animals of the high concentration group, two adenomas were found in the nasal cavities, while in the males a squamous cell carcinoma and a papilloma were found. In addition, 10 of the 50 male mice developed haemangiomas or haemangiosarcomas. Three females of the high concentration group had haemangiomas and two had haemangiosarcomas in the nasal cavity (NTP 1985; Renne et al. 1986).

Groups of 100 male and 100 female Wistar rats were exposed to 1,2-epoxypropane concentrations of 0, 30, 100 or 300 ml/m^3 for 6 hours a day, on 5 days a week for 124 weeks (males) or 123 weeks (females). The incidences of mammary tumours in the female rats were 32/69, 39/71, 39/69 and 47/70 for fibroadenomas and 3/69, 6/71, 5/69 and 8/70 for tubulopapillary adenocarcinomas. No mammary gland tumours were observed in rats in the other studies. According to the authors, the reasons for this are possibly the shorter exposure period (104 weeks instead of 123 weeks) and a different strain of rat (Fischer 344 rats instead of Wistar rats). Degenerative and hyperplastic changes of the nasal mucosa were found to be more frequent in the animals of all exposure groups than in the control animals. Three malignant tumours occurred in the nasal cavity of treated males: an ameloblastic fibrosarcoma in one animal from the low concentration group, and a squamous cell carcinoma in one animal from the low concentration group and one from the high concentrations group. In 4 male rats from the high concentration group, a carcinoma was found in the larynx, trachea or lungs. No NOAEC for pre-neoplastic lesions of the nasal mucosa was obtained in this study. At 30 ml/m^3, nest-like infolds in the respiratory epithelium were found in 5, 11, 29 and 47 male rats and in 4, 8, 20 and 43 female rats (see Section 5.2.1) (Kuper et al. 1988).

6 Manifesto (MAK value/classification)

The critical effects are the carcinogenic and cytotoxic effects in the nasal epithelium.

Carcinogenicity. After inhalation exposure to concentrations of more than 300 ml/m^3, 1,2-epoxypropane induced tumours in the nasal epithelium of rats and mice and is therefore a locally active carcinogen. However, there are no reliable

studies on the carcinogenicity of 1,2-epoxypropane in humans. The carcinogenicity of 1,2-epoxypropane is based on its electrophilic reactivity resulting in DNA alkylation, mainly the alkylation of the N7 position of guanine. It is, however, only weakly genotoxic, as purine adducts at the N7 and N3 positions can be efficiently repaired. After the inhalation of 1,2-epoxypropane, increased cell proliferation in the nasal epithelial cells of the rat is observed; this is caused by GSH depletion with subsequent cytotoxicity.

Both DNA alkylation and cell proliferation are of importance for the carcinogenicity of the substance. Increased cell proliferation is needed for the increased conversion of the DNA adducts into mutations, thus leading to increased tumour formation. When cell proliferation is avoided, the formation of tumours is not to be expected. Since a MAK value can be derived at which cell proliferation would be avoided, 1,2-epoxypropane is classified in Carcinogen Category 4.

MAK value. For cell proliferation in nasal epithelial cells after 4-week exposure, a NOAEC of 50 ml/m^3 was determined in rats; for histopathological changes in the nasal turbinates, a LOAEC of 30 ml/m^3 was obtained. The BMDL05 (incidence increased by 5%) for this effect is 11 ml/m^3 (Section 5.2).

To apply this concentration into a value for humans, use was made of the PBPK model of Csanády and Filser (2007). It was calculated that the concentration in the nasal epithelia is the same in rats and in humans when the external exposure and time of duration are the same in both species. This applies, however, for a respiratory volume in humans of 3.6 m^3/8 hours. The results of this model depend a great deal on the respiratory minute volume. For 10 m^3/8 hour, therefore, a correction factor of 3 (10 m^3/3.6 m^3) must be used to reflect the higher respiration rate at the workplace. The model is conservative in two respects: it predicts higher DNA adduct concentrations in the nose of rats than those measured (Figure D from Csanády and Filser 2007), and a detoxifying metabolism via glutathione transferase and epoxide hydrolase in the nose is not assumed for humans. For this reason the BMDL05 was transferred directly to humans and only the shorter daily exposure time of the animals (6 hours) compared with exposure at the workplace (8 hours) and the increased respiratory activity of humans at the workplace, which is three times greater than the respiratory activity assumed for the PBPK model, were taken into account. A concentration of 11 ml/m^3 · 6 hours/8 hours/3 = 2.75 ml/m^3 was thus obtained. According to the preferred value approach, a MAK value for 1,2-epoxypropane of 2 ml/m^3 has, therefore, been established.

The NOAEC for the decrease in the GSH level in the nasal epithelia of rats is not clear, since the respective measurements were not statistically evaluated (Lee et al. 2005). At 5 ml/m^3, the GSH level was reduced by 10%. At 50 ml/m^3, the NOAEC for cell proliferation, the GSH level was reduced to 50%. On comparing the 3-day with the 4-week exposure, the depletion in GSH was not found to increase. A concentration of 2 ml/m^3 under workplace conditions with the increased respiratory volume of humans would thus correspond to about 6 ml/m^3 in the rat under resting conditions. This means a decrease in GSH by 10% could be expected. This reduc-

tion in GSH is, however, not of relevance for the carcinogenic effects, as increased cell proliferation first occurs at concentrations of 100 ml/m^3.

In workers exposed to 1,2-epoxypropane concentrations of 2 ml/m^3, no increase in the frequency of SCE in lymphocytes was found. After exposure to 2 ml/m^3, the mean frequency of N7-HPG was 3.3 per 10^8 nucleotides. In comparison, the corresponding value of 3.0 per 10^7 for the ethylene oxide adduct N7-(2-hydroxyethyl) guanine in the lymphocytes of non-smokers is ten times higher (Zhao and Hemminki 2002).

Peak limitation. 1,2-Epoxypropane is an irritating substance, and the critical effect is the local irritation in the nose. 1,2-Epoxypropane is therefore classified in Peak Limitation Category I. Cell proliferation is decisive for its carcinogenic effects. The NOAEC for cell proliferation in the rat is 50 ml/m^3. Transferred to workplace exposure, with three times the respiratory activity compared with under resting conditions (see above), this means 50 ml/m^3 / 3 = 16 ml/m^3 for humans. The nest-like infolds in the nasal epithelium, which were not found until after 28 months of exposure, therefore depend more on the duration of exposure than on the concentration or the excursion peaks. In the 2-year study with rats (Kuper et al. 1988), although the animals were examined for clinical symptoms, none were found. Histological correlates for inflammation were not found. Such correlates were observed, however, in another study with rats and mice at 200 ml/m^3 and above (NTP 1985). The NAEC (no adverse effect concentration) for inflammation in the nasal epithelium should therefore be in the range between 30 and 100 ml/m^3. There are no data available for irritation of the respiratory tract in humans. In the Chinese study (Czene et al. 2002), the workers were exposed to concentrations of up to 6.9 ml/m^3. As no irritating effects were reported in this study, it can be assumed that clearly apparent sensory irritation is not to be expected at this concentration. With an excursion factor of 2 therefore, the permissible peak concentration of 4 ml/m^3 is greatly below the NOAEC for cell proliferation and for biologically relevant GSH depletion, and therefore for the induction of carcinogenic effects in the nose. Because of the 10-fold margin between this and the NAEC for histologically detectable inflammation, irritating effects are not to be expected. In view of the carcinogenic effects, however, a higher excursion factor cannot be derived. Therefore, an excursion factor of 2 has been established for 1,2-epoxypropane.

Prenatal toxicity. Developmental toxicity studies with rats and rabbits revealed variations in the seventh cervical vertebra and wavy ribs in the rat at the maternally toxic 1,2-epoxypropane concentration of 500 ml/m^3, but no developmental toxicity in the rabbits. No malformations occurred. The NOAEC for toxic effects on prenatal development is 300 ml/m^3 for rats and 500 ml/m^3 for rabbits. As the 150 and 250-fold difference between this and the MAK value of 2ml/m^3 is sufficiently large, 1,2-epoxypropane is classified in Pregnancy Risk Group C.

Germ cell mutagenicity. 1,2-Epoxypropane induces DNA damage, gene mutations and chromosomal aberrations in bacteria and mammalian cells in vitro. Clastogenic effects were produced in vivo only after intraperitoneal injection. No genotoxic effects were found after inhalation in a test for chromosomal aberrations and

after oral administration in micronucleus and dominant lethal tests. For this reason, 1,2-epoxypropane is not classified in any of the categories for germ cell mutagens.

Sensitization. There are several reports of occupational contact sensitization to 1,2-epoxypropane from a very specific area of exposure—on workers in histology laboratories. The contact sensitizing potential of 1,2-epoxypropane has thus been confirmed, and although there is otherwise only one negative result from an experimental investigation in guinea pigs not carried out in accordance with currently valid test guidelines, 1,2-epoxypropane is designated with "Sh" (for substances which cause sensitization of the skin). As there are no data for respiratory sensitization available, the substance is not designated with "Sa" (for substances which cause sensitization of the airways).

Absorption through the skin. There are no data from experiments available for the absorption of 1,2-epoxypropane through the skin. Absorbed quantities of up to 443 µg after 8-hour exposure to 2 ml/m^3 can be derived from model calculations of dermal penetration from the gaseous phase. Under the same conditions, 48.2 mg would be absorbed via inhalation. Therefore, absorption through the skin from the gaseous phase is not expected to make a toxicologically relevant contribution to the internal exposure. In addition, as a result of the low boiling point and vapour pressure of the substance, any unnoticed skin contact with undiluted liquid 1,2-epoxypropane over an extended period is improbable under workplace conditions. As aqueous solutions of the compound are irritating to corrosive to the skin even in concentrations of below 10%, unnoticed long-term skin contact that could result in toxicologically relevant absorption is not to be expected. 1,2-Epoxypropane is therefore not designated with an "H" (for substances which penetrate the skin).

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