The MAK Collection for Occupational Health and Safety

2-Propoxyethanol (2-(Propyloxy)ethanol)

MAK Value Documentation, addendum – Translation of the German version from 2018

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2-Propoxyethanol (2-(Propyloxy)-ethanol)

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated 2-(propyloxy)ethanol (2-propoxyethanol) [2807-30-9] considering all toxicological end points. 2-(Propyloxy)ethanol is a haemolytic and irritant glycol ether, similar to the homologous 2-butoxyethanol. The haemolytic activity for both compounds is mediated by the corresponding alkoxy acid and is lower in human erythrocytes than in rat erythrocytes in vitro. The critical effect is the irritation seen in subchronic studies in rats at the lowest concentration tested of 100 ml/m^3. A NOAEC was not obtained. For 2-butoxyethanol the NOAEC for nasal effects in rats was 31 ml/m^3. Therefore, by analogy with the better investigated 2-butoxyethanol, the maximum concentration at the workplace (MAK value) of 2-(propyloxy)ethanol is lowered to 10 ml/m^3. This limit also protects from systemic toxicity. The assignment to Peak Limitation Category I with an excursion factor of 2 is retained.

A prenatal toxicity study in rats was re-evaluated by the Commission and the NOAEC for developmental toxicity of 400 ml/m^3 was confirmed. In rabbits, the NOAEC for developmental toxicity is 500 ml/m^3. Even after considering the increased respiratory volume at the workplace the differences of both NOAECs to the MAK value are sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is observed and 2-(propyloxy)ethanol remains assigned to Pregnancy Risk Group C.

2-(Propyloxy)ethanol is not genotoxic in vitro. In vivo studies as well as carcinogenicity studies are not available. Percutaneous absorption can contribute significantly to systemic toxicity and 2-(propyloxy)ethanol remains designated with an "H" notation. Results in animal studies do not point to a sensitization potential.

Keywords

2-propoxyethanol; 2-(propyloxy)ethanol; ethylene glycol mono-n-propyl ether; propyl cellosolve; n-propyl glycol; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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2-Propoxyethanol (2-(Propyloxy)-ethanol)

[2807-30-9]

Supplement 2018

MAK value (2017)	**10 ml/m³ (ppm) ≙ 43 mg/m³**
Peak limitation (2000)	**Category I, excursion factor 2**
Absorption through the skin (1996)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1996)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**

Vapour pressure at 25 °C	6.43 hPa (ECHA 2015)
log K_{OW}[1)] at 40 °C	0.673 (ECHA 2015)
Solubility	miscible with water (ECHA 2015)
1 ml/m³ (ppm) ≙ 4.32 mg/m³	**1 mg/m³ ≙ 0.231 ml/m³ (ppm)**

For 2-propoxyethanol there is documentation available from 1996 (documentation "2-Propoxyethanol" 1999) and a supplement from 2000 (supplement "2-(Propyloxy)-ethanol" 2000, available in German only). In addition, two unpublished subchronic inhalation studies are available under the REACH registration data (ECHA 2015), which are described in this supplement.

1 Toxic Effects and Mode of Action

The main effect of 2-propoxyethanol in rats is haemolysis caused by the metabolite propoxyacetic acid. In vitro studies have shown that humans are markedly less sensitive in this respect. This is known also from other alkoxyacetic acids. The substance

1) octanol/water partition coefficient

is irritating to the eyes and slightly irritating to the skin. In rats, after subchronic inhalation exposure, slight irritation was observed at concentrations of 100 ml/m^3 and above. At a concentration of 400 ml/m^3, a transient delay in body weight gains was observed. 2-Propoxyethanol is very well absorbed dermally and has no skin-sensitizing effects. Foetal toxicity and toxic effects on the testes, as are described for the homologous glycol ethers, 2-methoxyethanol and 2-ethoxyethanol, have not been found in studies with rats. The effect profile of 2-propoxyethanol is thus similar to that of 2-butoxyethanol, which has haemolytic effects rather than toxic effects on reproduction and whose main effect is irritation. In developmental toxicity studies, maternal toxicity occurred in rats at concentrations of 200 ml/m^3 and above in the form of haemolysis as well as a concentration-independent increase in skeletal variations and delayed ossification, but no malformations. In rabbits, no developmental toxicity was found up to the highest concentration tested of 500 ml/m^3. No genotoxicity was observed in gene mutation tests in bacteria or mammalian cells, or in the chromosomal aberration test in vitro. There are no studies available for the in vivo genotoxicity or the carcinogenicity of the substance.

2 Mechanism of Action

The haemolytic effect is due to the metabolite propoxyacetic acid (Boatman 1994). Other alkoxyacetic acids likewise induce this effect. The actual mechanism of action has been investigated mainly with butoxyacetic acid; however, it is not known in detail. Butoxyacetic acid presumably leads to an increased influx of calcium and sodium into the erythrocytes. The higher sodium level leads to increased water intake and osmotic lysis. At first, intracellular calcium delays the onset of haemolysis by activation of the calcium-dependent potassium channel, which facilitates the loss of potassium, but could subsequently activate proteases and additionally impair the function of the membrane (Udden and Patton 2005). Disturbance of the membrane transport proteins by butoxyacetic acid has also been suggested (Udden 2005).

There are marked species-specific differences in the severity of the haemolytic activity induced by alkoxyacetic acids, which have been well documented with the structurally analogous 2-butoxyethanol and its haemolytically active metabolite butoxyacetic acid (supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2010). The reasons for the lower sensitivity of human erythrocytes compared with rat erythrocytes are, however, not known. Species-specific differences in the membrane transport proteins and the calcium-dependent effects have been suggested (see above) (Udden and Patton 2005).

For propoxyacetic acid the lower sensitivity of human erythrocytes compared with rat erythrocytes is likewise well documented: in vitro, propoxyacetic acid concentrations of up to 5 mM led to 100% haemolysis of rat erythrocytes, but to virtually no haemolysis (about 3%) of human erythrocytes after incubation for up to 4 hours (Boatman 1994). In another study, rat erythrocytes, with an EC_{50} of 8.8 mM for haemolysis by propoxyacetic acid after 3-hour incubation, were twice as sensitive as human erythrocytes, with an EC_{50} of 18.3 mM (Starek et al. 2008). For butoxyacetic acid these authors found a 3-fold higher sensitivity of rat erythrocytes; other authors, however, report a 16-fold higher sensitivity of rat erythrocytes (0.5 mM) compared

with human erythrocytes (8 mM) on the basis of the LOAELs (lowest observed adverse effect levels) for haemolysis (supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2018). Unlike comparing the NOAELs (no observed adverse effect levels) or the LOAELs, the comparison of EC_{50} values is less suitable for the extrapolation between species because it does not take into account the slope of the dose–response relationship.

In rat erythrocytes in vitro, the haemolytic effect of propoxyacetic acid was found to be only half as high as that of butoxyacetic acid (Boatman 1994).

For 2-butoxyethanol there are comparative studies available of its haemolytic effects in humans and rats after inhalation exposure: increased osmotic fragility of the erythrocytes as a precursor to haemolysis was not observed after 4 to 8-hour exposure of volunteers up to the highest 2-butoxyethanol concentration tested of 195 ml/m^3. In contrast, 4-hour exposure to a 2-butoxyethanol concentration of 62 ml/m^3 led to increased osmotic fragility of the erythrocytes in rats (supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2010). The corresponding NOAEC (no observed adverse effect concentration) for rats was 32 ml/m^3 both for 2-butoxyethanol and for 2-propoxyethanol (Carpenter et al. 1956). Even after inhaling the substance itself, humans are markedly less sensitive than rats to developing a pre-stage of 2-butoxyethanol-induced haemolysis. There are no inhalation studies in humans available for 2-propoxyethanol, but, in view of the same NOAEC for both substances in the rat and the findings in in vitro investigations of haemolysis with the acid metabolites, similar results are to be expected for 2-propoxyethanol.

The NOAEC for haemolytic activity in subchronic studies with rats was found to be 100 ml/m^3 for 2-propoxyethanol, while the 2-butoxyethanol concentration of 31 ml/m^3 was already the LOAEC (lowest observed adverse effect concentration) and 25 ml/m^3 the NOAEC (supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2010). 2-Butoxyethanol is thus about four times more potent than 2-propoxyethanol. These differences were attributed to the inherently higher toxicity of butoxyacetic acid or the assumed higher level of elimination of propoxyacetic acid via glycine conjugation (ECHA 2015).

2-Butoxyethanol causes phaeochromocytomas in rats and hepatocellular adenomas and carcinomas as well as angiosarcomas of the liver in mice. These are very likely sequelae of the haemolysis, which lead to hypoxia (phaeochromocytomas) and oxidative DNA damage (liver tumours). Mechanistic explanations are available in particular for the development of the angiosarcomas in the liver of mice (supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2018). Both rats and mice develop haemolysis resulting in haemosiderosis of the liver, but liver tumours occur only in mice. This can be explained by the fact that rats have a higher antioxidative capacity (vitamin E) in the liver than mice and are thus better protected from oxidative damage caused by the accumulation of iron in the liver. For several reasons it is unlikely that humans develop liver tumours as a result of exposure to 2-butoxyethanol: the haemolytic effect and thus the potential deposition of haemosiderin in the liver caused by butoxyacetic acid is far less pronounced in humans than in the rat. When exposed to the same external concentration, humans form less butoxyacetic acid than rats and, according to PBPK (physiologically based pharmacokinetic) modelling, butoxyacetic acid concentrations causing haemolysis are only just attained even after exposure to a saturated vapour atmosphere of 2-butoxy-

ethanol (about 1160 ml/m³), taking into account dermal absorption of both gaseous and liquid 2-butoxyethanol. This means that, for toxicokinetic and toxicodynamic reasons, the body burden of humans is less than that of rats, which do not develop liver tumours. In addition, the antioxidative capacity in the liver of humans is 100 times higher than that in the mouse liver (supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2018).

In addition, in view of the irritant and CNS depressant effects at the concentration of 1160 ml/m³, it must be assumed that this concentration would not be tolerated long-term by the workers at the workplace, and therefore carcinogenic effects of 2-butoxyethanol at the workplace are very unlikely. For 2-propoxyethanol there are no carcinogenicity studies available; however, by analogy with 2-butoxyethanol, no relevant carcinogenic effects are to be expected in humans for 2-propoxyethanol, as although its vapour saturation concentration is 5 to 6 times as high (about 6200 ml/m³ calculated from the vapour pressure of 6.3 hPa), the haemolytic effect in the rat is only a quarter that of 2-butoxyethanol. Because of the irritation demonstrated for 2-propoxyethanol at concentrations in the range of 100 ml/m³, long-term exposure to the vapour saturation concentration of 2-propoxyethanol would, however, likewise not be tolerable for humans. To date, there is no PBPK model available for 2-propoxyethanol in humans.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

In Sprague Dawley rats exposed nose-only to a 2-propoxyethanol concentration of 175 ml/m³ for 6 hours, the propoxyacetic acid concentration in blood was > 0.6 mM. The elimination half-life of 2-propoxyethanol in blood was 0.133 hours and that of propoxyacetic acid 1.45 hours. After intravenous administration of 15 mg/kg body weight, the elimination half-life of the substance itself in the blood of Sprague Dawley rats was 0.12 hours and that of propoxyacetic acid 0.75 hours. After oral administration of 15 mg/kg body weight, the elimination half-life of propoxyacetic acid in the blood of Sprague Dawley rats was 1.32 hours. An oral dose of 150 mg/kg body weight resulted in a propoxyacetic acid concentration in the blood of about 1.2 mM. At this dose, elimination was saturated since the half-life was 2.37 hours (ECHA 2015).

The blood:air partition coefficient calculated according to the formula of Buist et al. (2012), is greater than 5. For the extrapolation of inhalation concentrations obtained in animal experiments to humans it has to be taken into account that the respiratory volume at the workplace is higher than under experimental conditions (see List of MAK and BAT Values, Section I c).

In rat skin and human stratum corneum, the absorption rates determined in vitro were 2.30 and 0.584 mg/cm² and hour, respectively. These values were about the level of those for 2-ethoxyethanol (Barber et al. 1992; documentation "2-Propoxyethanol" 1999). The dose was 300 µl undiluted 2-propoxyethanol and was applied to an area of 1.02 and 0.636 cm² in a static Franz cell (Barber et al. 1992).

A dose of 200 µl undiluted 2-propoxyethanol per cm² was applied to full thickness human skin with a thickness of 1 mm under occlusive conditions in a static Franz cell.

The receptor fluid was 0.9% aqueous sodium chloride solution. After 0.5, 1, 2, 4 and 8 hours the concentration of 2-propoxyethanol in the receptor fluid was analyzed and a flux of 0.394 mg/cm^2 and hour was determined. With a 50% solution the flux was 0.565 mg/cm^2 and hour (Venier et al. 2004). The content of the substance (which is potentially absorbable) in the skin, was not determined, since the dose in question was an infinite dose and, because 2-propoxyethanol is not lipophilic, the substance is not retained in the skin.

Assuming the exposure of 2000 cm^2 of skin for one hour, the fluxes found for human skin would correspond to the absorption of up to 1168 mg.

After the application of 50 mg 2-propoxyethanol/cm^2 to the skin of Sprague Dawley rats for 6 hours, an absorption rate of 1.15 mg/cm^2 and hour was determined (no other details; documentation "2-Propoxyethanol" 1999). In another unpublished study from 1998 in which 50 mg/cm^2 was applied to the skin of Sprague Dawley rats for 6 hours under occlusive conditions, an absorption rate of 0.73 mg/cm^2 and hour was given (ECHA 2015).

3.2 Metabolism

After oral, dermal and inhalation exposure of Sprague Dawley rats, 40% to 60% of the radioactively labelled 2-propoxyethanol was found in the urine as propoxyacetic acid, 26% to 37% was eliminated as *N*-(2-propoxyacetyl)glycine and 6% to 14% as ethylene glycol. Lesser amounts of glucuronide were identified in the urine and CO_2 in the exhaled air (documentation "2-Propoxyethanol" 1999; Boatman 1994).

The sometimes high conjugation rate of alkoxyacetic acids with amino acids (for example conjugation of butoxyacetic acid with glutamine) must be taken into account when estimating the exposure to glycol ethers by analyzing the corresponding acid conjugates in biological materials (documentation "2-Propoxyethanol" 1999).

4 Effects in Humans

Studies of irritation as the critical effect, as well as of allergenic effects and haemolysis in humans are still not available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The 6-hour LC_{50} for rats is greater than 2132 ml/m^3 (documentation "2-Propoxyethanol" 1999).

5.1.2 Oral administration

The LD_{50} in the rat after oral administration is 3090 mg/kg body weight (documentation "2-Propoxyethanol" 1999).

5.1.3 Dermal application

In rabbits, dermal LD_{50} values of 960 and 870 mg/kg body weight were determined. These values indicate that the substance is readily absorbed by the skin (documentation "2-Propoxyethanol" 1999).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Groups of 5 male and 5 female COBS/BD rats were exposed to concentrations of about 100, 200, 400 or 800 ml/m³ a total of 11 times (6 hours/day, 5 days/week) within 2 weeks. Haemoglobinuria was found in one male animal of the 400 ml/m³ group and in 2 male and 3 female animals at 800 ml/m³. In rats exposed to 400 and 800 ml/m³, the number of reticulocytes was increased; observed were also typical changes in the morphology of the erythrocytes and an increase in the absolute or relative spleen weights. At 400 ml/m³ and above, extramedullary haematopoiesis, congestion and haemosiderosis in the spleen occurred. These effects were interpreted as the result of haemolysis. No exposure-related effects occurred at the concentrations of 100 and 200 ml/m³. The authors gave a concentration of 800 ml/m³ as the NOAEC for effects on body weights. As no effects other than haemolysis and its consequences were observed at the two high concentrations, the NOAEC, excluding haemolysis, was the highest concentration tested of 800 ml/m³ (documentation "2-Propoxyethanol" 1999; Katz et al. 1984).

In a 14-week study from 1987, similar to OECD Test Guideline 413, groups of 15 male and 15 female Crj:CD(SD) rats were exposed whole-body to 2-propoxyethanol vapour concentrations of 0, 100, 200 or 400 ml/m³ for 6 hours per day, on 5 days per week. Once or twice during the study, lacrimation, nasal discharge containing porphyrin and an accompanying reddish or brownish discoloration of the facial fur—indicative of irritation—were observed in some animals of all treated groups. At concentrations of 200 ml/m³ and above, the erythrocyte count, haemoglobin and haematocrit were decreased, and haemoglobinuria was observed. In animals of the 200 and 400 ml/m³ groups, haemosiderin deposition in Kupffer cells of the liver (0 ml/m³: ♂: 4/15, ♀: 5/15; 100 ml/m³: ♂: 0/15, ♀: 5/15; 200 ml/m³: ♂: 4/15, ♀: 15/15; 400 ml/m³: ♂: 11/15, ♀: 15/15) and in the proximal renal tubules (0 ml/m³: ♂: 0/15, ♀: 0/15; 100 ml/m³: ♂: 0/15, ♀: 0/15; 200 ml/m³: ♂: 2/15, ♀: 14/15; 400 ml/m³: ♂: 11/15, ♀: 14/15) were found. Haemosiderosis in the splenic pulp of the male animals of these groups was more pronounced than in the control animals (♂: 0 and 100 ml/m³: minimal to slight; 200 ml/m³: minimal to moderate; 400 ml/m³: moderate; ♀: 0 and 100 ml/m³: slight to moderate; 200 ml/m³: predominantly moderate; 400 ml/m³: slight to moderate). In the female animals exposed to 200 ml/m³ and above, an increase in the reticulocyte count and polychromasia as well as increased absolute and relative spleen weights were determined. In the male animals, these effects occurred only at 400 ml/m³. At this concentration, the body weight gains were slightly retarded until day 7 of exposure. At 400 ml/m³, there was an increase in the number of female animals with Howell-Jolly bodies (pathological nuclear remnants in the normally nuclear-free erythrocytes) in the blood; these typically occur in the

case of haemolytic anaemia. However, the occurrence of Heinz bodies (oxidatively damaged and agglutinated haemoglobin in the erythrocytes) and of extramedullary haematopoesis in the spleen were not described. Some clinico-chemical parameters were significantly changed, but overall this was not pronounced, so that the authors did not interpret this as resulting from specific toxicity of the substance. The concentration of 100 ml/m³ was given as the NOAEC for effects on the erythrocytes and their consequences. The haematological and histopathological changes as well as the increased spleen weights were, in the opinion of the authors, due to the haemolytic activity of 2-propoxyethanol. The nasal mucosa of the control animals and the 400 ml/m³ group were subjected to histopathological examination. The incidences of acute inflammation in the controls and the 400 ml/m³ group were 2/15 and 4/15, respectively, in the male animals, and 5/15 and 9/15 in the female animals. The incidences of chronic inflammation of the nasal mucosa in exposed animals were, however, lower than those in the control animals (Eastman Kodak 1987). The authors of the study gave no interpretation of these results. Due to the numerically increased incidences of acute inflammation in the nasal mucosa, irritation of the nasal epithelium is to be assumed. A statistical evaluation, however, is not available. The NOAEC for systemic toxicity, apart from haemolytic effects and their consequences, is 200 ml/m³, since at 400 ml/m³ the body weight gains of the male animals were transiently delayed. Due to the clinical findings occurring in the animals even at the low concentration, no NOAEC for irritation was obtained.

A second 14-week study from 1989 according to OECD Test Guideline 413 to investigate neurotoxicity under the same exposure conditions as those in the study from 1987 (see above) was carried out in groups of 10 CD(SD)BR rats per sex and concentration. The results obtained in the first study were confirmed, and, in addition, no signs of neurotoxicity were observed in investigations using a functional observational battery. The above-described irritation was clinically observed at concentrations of 100 ml/m³ and above and limited to female animals at this concentration. The body weights of the male and female animals were slightly, but not significantly reduced at 400 ml/m³. In the animals of the 200 and 400 ml/m³ groups, haemosiderin deposits were found in Kupffer cells of the liver (200 ml/m³: ♂: 3/5, ♀: 5/5; 400 ml/m³: ♂: 4/5, ♀: 5/5) and in the proximal renal tubules (200 ml/m³: ♂: 5/5, ♀: 5/5; 400 ml/m³: ♂: 3/5, ♀: 5/5). In the splenic pulp of the animals of these groups such deposits were also more pronounced than in the control animals (0 ml/m³: ♂: 5/5 minimal, ♀: 5/5 slight; 100 ml/m³: ♂: 5/5 minimal, ♀: 5/5 slight; 200 ml/m³: ♂: 5/5 slight, ♀: 4/5 moderate; 400 ml/m³: ♂: 5/5 moderate, ♀: 5/5 moderate). No quantitative data were provided. The study pathologist attributed these deposits to haemolysis. There were no such findings at the concentration of 100 ml/m³. The noses of the animals were not examined histopathologically (Eastman Kodak 1989).

A NOAEC for clinical irritation was not obtained from either study, since such effects occurred to a slight extent even at the concentration of 100 ml/m³. In addition, the incidences of acute inflammation of the nasal mucosa were increased at 400 ml/m³; the animals of the lower exposure groups were, however, not examined histopathologically. Overall, the LOAEC was found to be 100 ml/m³.

5.2.2 Oral administration

There are no new data available.

5.2.3 Dermal application

There are no new data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

When applied in undiluted form under occlusive conditions for 24 hours, 2-propoxyethanol was slightly irritating to the skin of guinea pigs (documentation "2-Propoxyethanol" 1999).

5.3.2 Eyes

Studies carried out according to OECD test guidelines are not available. In two Draize tests the substance had an irritant effect on the eyes. Some of the effects were not reversible by day 7 (longest observation period) (documentation "2-Propoxyethanol" 1999). The legal classification "causes severe eye irritation" (ECHA 2015) is the same as that for the analogous substance 2-butoxyethanol (ECHA 2016).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

The two tests already described in the documentation of 1996 (documentation "2-Propoxyethanol" 1999) are again presented here. Undiluted 2-propoxyethanol had no sensitizing effects in a Buehler test carried out according to OECD Test Guideline 406 in only 10 female and 10 male Hartley guinea pigs (ECHA 2015). In another test not listed in the test guideline with intradermal injection ("footpad test") in male Hartley guinea pigs, a single dose of 0.05 ml of a 1% preparation of the substance in Freund's complete adjuvant did not result in sensitization. The challenge exposure took place one week later with a 1% preparation of 2-propoxyethanol in acetone/dioxane/guinea pig fat (7:2:1) (ECHA 2015).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no studies available for the effects of 2-propoxyethanol on fertility.

No adverse effects on the testes of rats were found after 2-week inhalation of concentrations of up to 800 ml/m³ (Katz et al. 1984; Section 5.2.1) nor in a 14-week inhalation study at concentrations of up to 400 ml/m³ (Eastman Kodak 1987; Section 5.2.1).

The NOAEL for the impairment of female fertility by the structurally analogous 2-butoxyethanol in a continuous breeding study with CD-1 mice was 720 mg/kg body weight and day (Heindel et al. 1990; ECHA 2016).

5.5.2 Developmental toxicity

There are no new data available.

In a pilot study with pregnant CD rats exposed to a concentration of 800 ml/m³, maternal toxicity in the form of decreased body weights and foetal resorptions (no other details) was found. In the following main study, groups of 24 to 29 CD rats were exposed to 2-propoxyethanol concentrations of 0, 100, 200, 300 or 400 ml/m³ from days 6 to 15 of gestation for 6 hours per day. In rats exposed to 200 ml/m³ and above, haemolytic effects in the dams and an increase in skeletal variations in the foetuses were seen. However, there was no evidence of selective foetal toxicity. The study showed pregnant rats, however, to be more sensitive to haemolytic effects (Krasavage and Katz 1985; documentation "2-Propoxyethanol" 1999). The study was re-evaluated by the Commission for this supplement. Concentration-independent increases in skeletal variations and delays in ossification, but no malformations were determined. The increased incidence of rudimentary 14th thoracolumbar ribs is not regarded as adverse. The NOAEC for developmental toxicity in rats is therefore 400 ml/m³.

In a study with groups of 12 to 15 pregnant New Zealand White rabbits exposed to 2-propoxyethanol concentrations of 0, 125, 250 or 500 ml/m³ from days 6 to 18 of gestation for 6 hours per day, no effects on the foetuses were found. One female animal exposed to 500 ml/m³ was found to have haemoglobinuria, and slightly reduced body weight gains were observed in the dams (documentation "2-Propoxyethanol" 1999). The NOAEC for developmental toxicity in rabbits is therefore 500 ml/m³.

5.6 Genotoxicity

5.6.1 In vitro

In Salmonella mutagenicity tests, 2-propoxyethanol was not mutagenic in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and in Escherichia coli WP2uvrA up to concentrations of 5 mg/ml with and without metabolic activation (ECHA 2015).

In a chromosomal aberration test in human lymphocytes, 2-propoxyethanol was not clastogenic at concentrations of up to 1 mg/ml with and without the addition of metabolic activation (ECHA 2015).

In a $TK^{+/-}$ test in L5178Y mouse lymphoma cells, 2-propoxyethanol was not genotoxic up to a concentration of 1 mg/ml with and without metabolic activation (ECHA 2015).

Cytotoxicity was not observed in any of the tests mentioned, the highest concentrations used, however, corresponded to the limit dose of the respective test guideline.

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

There are no data available.

6 Manifesto (MAK value/classification)

As regards the haemolytic effect, it was shown that human erythrocytes are markedly less sensitive than rat erythrocytes. The critical effect for humans is therefore local irritation, observed in rats at concentrations of 100 ml/m³ and above.

MAK value. In two subchronic studies, 2-propoxyethanol still caused clinical signs of slight irritation in rats at a concentration of 100 ml/m³. A NOAEC was not obtained.

The MAK value for 2-propoxyethanol was established in 1996 by analogy with the better investigated 2-butoxyethanol. Due to the local effects in the nose (hyaline degeneration of the olfactory epithelium) of rats, observed at a concentration of 31 ml/m³ in the 2-year study, the MAK value of 2-butoxyethanol has in the meantime been lowered from 20 to 10 ml/m³. The MAK value for 2-propoxyethanol has therefore likewise been set at 10 ml/m³ and thus protects against the irritation observed at the concentration of 100 ml/m³ in the subchronic studies in rats.

In the subchronic studies in rats, the NOAEC for systemic effects, apart from the haemolytic effects and their sequelae, was 200 ml/m³ based on the transiently reduced body weight gains at 400 ml/m³; 800 ml/m³ was the NOAEC for this effect after 2-week exposure. Taking into consideration the demonstrated amplification of this effect with the increasing duration of exposure (1:2), the higher respiratory volume at the workplace compared with the animal experiment (1:2; see Section 3.1) and the extrapolation of the data from the animal experiment to humans (1:2) at the workplace, a concentration of 25 ml/m³ is obtained from the NOAEC of 200 ml/m³ from the subchronic studies. On the basis of the NOAEC for haemolytic effects of 100 ml/m³ and taking into consideration the higher respiratory volume of humans at the workplace compared with that of the experimental animal at rest (1:2), the MAK value of 10 ml/m³ is confirmed even if an amplification of effects over time is assumed. Since humans are less sensitive to these effects than rodents, no additional margin is necessary for the extrapolation of the data from animal experiments to humans (1:2).

The MAK value of 10 ml/m³ thus also protects against systemic effects.

Peak limitation. By analogy with 2-butoxyethanol and because of the critical local effects, 2-propoxyethanol has been assigned to Peak Limitation Category I and, as for 2-butoxyethanol, an excursion factor of 2 has been set.

Prenatal toxicity. There are no new data available.

In rats, at concentrations of 200 ml/m³ and above, maternal toxicity in the form of haemolysis and a concentration-independent increase in skeletal variations and delays in ossification were found, but no malformations. The increased incidence of rudimentary 14th thoracolumbar ribs is not regarded as adverse. The NOAEC for developmental toxicity is 400 ml/m³ in rats and 500 ml/m³ in rabbits, which was the highest concentration tested in each case. Taking into consideration the increased respiratory volume (1:2), the NOAECs for developmental toxicity are therefore 20 to 25 times as high as the MAK value of 10 ml/m³. As variations and delays in ossification occurred in rats only at concentrations toxic to the dams, but there were no malformations, developmental toxicity was not observed in rabbits, and the margin between the NOAEC for developmental toxicity and the MAK value is sufficiently large, the classification of 2-propoxyethanol in Pregnancy Risk Group C has been confirmed.

Carcinogenicity. As there are no carcinogenicity studies with 2-propoxyethanol, the substance is not classified in one of the categories for carcinogens.

Comparison with the structurally analogous 2-butoxyethanol shows that carcinogenicity is not to be expected in humans (Section 2; supplement "Ethylene glycol monobutyl ether" 2018).

Germ cell mutagenicity. The substance is not genotoxic in vitro; in vivo data are not available. It is therefore not classified in one of the categories for germ cell mutagens.

Absorption through the skin. From an in vitro study (Section 3.1), dermal absorption of up to 1168 mg can be estimated for humans after exposure to undiluted 2-propoxyethanol, assuming the exposure of 2000 cm² of skin for one hour. From the NOAEC of 200 ml/m³ for systemic effects in rats, a corresponding concentration of 25 ml/m³ (108 mg/m³) was estimated for humans at the workplace (see above). Assuming a respiratory volume of 10 m³ in 8 hours and 100% absorption by inhalation, a systemically tolerable amount of 1080 mg is calculated. The amount absorbed through the skin is thus greater than 25% of the systemically tolerable amount, and the substance remains designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. No clinical findings are available for sensitization of the skin and airways. The results of experiments in guinea pigs with the Buehler test and from a study not carried out according to the test guidelines were negative, so that 2-propoxyethanol is not designated with either "Sh" (for substances which cause sensitization of the skin) or with "Sa" (for substances which cause sensitization of the airways).

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