The MAK Collection for Occupational Health and Safety

2-Isopropoxyethanol

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

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1130

2-Isopropoxyethanol / 2-Propane-2-yloxyethanol

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 the maximum concentration at the workplace (MAK value) and the Pregnancy Risk Group of 2-isopropoxyethanol [109-59-1].
As 2-isopropoxyethanol is irritating to rabbit skin and eyes an irritating potential for the respiratory tract of humans has to be assumed. In a poorly documented three-week inhalation study in rats, nasal irritations at 1000 ml/m^3 are reported, but the nose is not histopathologically investigated in any of the inhalation studies. A MAK value of 10 ml/m^3 for 2-isopropoxyethanol is derived by analogy with 2-butoxyethanol (ethylene glycol monobutyl ether) which shows a similar irritation potency. For rats, the critical effect in a 28-day inhalation study is the concentration dependent haemolytic anaemia at 100 ml/m^3 and above. The NOAEC is 30 ml/m^3. As humans are less sensitive than rats for this effect, which does not increase with prolonged exposure, the MAK value of 10 ml/m^3 should provide sufficient protection from haemolytic anaemia. Since a local effect is critical, Peak Limitation Category I is designated. By analogy with 2-butoxyethanol and 2-propoxyethanol an excursion factor of 2 is set.
The NOAEC for developmental toxicity in rats is 600 ml/m^3 and after considering the increased respiratory volume at the workplace because the blood:air partition coefficient of 2-isopropoxyethanol is > 5 (see List of MAK- and BAT Values, Sections I b and I c) the difference to the MAK value is sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is observed and 2-isopropoxyethanol remains assigned to Pregnancy Risk Group C.

Keywords

2-isopropoxyethanol; 2-propane-2-yloxyethanol; ethylene glycol isopropyl ether; ethylene glycol monoisopropyl ether; isopropyl ethylene glycol ether; isopropoxyethanol; beta-hydroxyethyl isopropyl ether; isopropyl cellosolve; isopropyl glycol; isopropyl glycol ether; 4-methyl-3-oxapentan-1-ol; 2-(1-methylethoxy)ethanol; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; 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-Isopropoxyethanol

[109-59-1]

Supplement 2018

MAK value (2016)	**10 ml/m³ (ppm) ≙ 43 mg/m³**
Peak limitation (2016)	**Category I, excursion factor 2**
Absorption through the skin (1991)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1991)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Vapour pressure at 25 °C	2.16 hPa (SRC 2013)
log K_{OW}[1)]	0.05 (SRC 2013)
1 ml/m³ (ppm) ≙ 4.32 mg/m³	**1 mg/m³ ≙ 0.23 ml/m³ (ppm)**

Documentation for 2-isopropoxyethanol (IUPAC name: 2-(propane-2-yloxy)ethanol) was published in 1991 (documentation "2-Isopropoxyethanol" 1993), followed by a supplement on peak limitation in 2001 (supplement "2-Isopropoxyethanol" 2001, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than that under experimental conditions. However, this does not apply to gases or vapours with a blood:air partition coefficient < 5 (see List of MAK and BAT Values). A blood:air partition coefficient of 9772 is calculated for 2-isopropoxyethanol using the formula of Buist et al. (2012). This supplement evaluates whether the MAK value for 2-isopropoxyethanol needs to be re-assessed because of the higher respiratory volume at the workplace.

New data from the REACH registration dataset (ECHA 2016) and the SIDS (Screening Information Dataset) Initial Assessment Report of the OECD (Organisation of Economic Co-operation and Development) (OECD 2009) were used in this assessment.

1) octanol/water partition coefficient

1 Toxic Effects and Mode of Action

2-Isopropoxyethanol was found to be only slightly toxic following a single exposure by inhalation or a single oral dose.

The substance is irritating to the rabbit skin and is assumed to induce local irritation also in the airways. After 3-week exposure to 1000 ml/m^3 by inhalation, irritation was observed in the rat nose.

There are no positive clinical findings for a sensitizing potential of 2-isopropoxyethanol. A maximization test in guinea pigs yielded no evidence of contact sensitization.

The haemolytic effect is the critical effect in rats. After exposure by inhalation, concentration-dependent haemolytic anaemia was observed in female rats at concentrations of 100 ml/m^3 and above. Haematuria was induced in female rats given gavage doses of 2-isopropoxyethanol of 30 mg/kg body weight and day and above for 41 to 48 days. Humans are markedly less sensitive to haemolytic effects than are rats.

In a developmental toxicity study in rats, no toxic effects on development were observed up to the highest concentration tested of 600 ml/m^3.

There are no carcinogenicity studies available for 2-isopropoxyethanol. The substance does not have mutagenic or clastogenic effects in vitro.

2 Mechanism of Action

Anaemia induced by 2-isopropoxyethanol in rats after inhalation and oral exposure was caused by a haemolytic effect that only develops in mature peripheral erythrocytes. Like 2-butoxyethanol, osmotic fragility of the erythrocyte membrane is increased and subject to intravascular lysis (ECETOC 2005; supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2010). The mechanism of the haemolytic effect has not been identified.

In the case of 2-propoxyethanol, the haemolytic effect is caused by the metabolite propoxyacetic acid. Although it has not been investigated, a similar mechanism is to be assumed for 2-isopropoxyethanol; the haemolytic effect is probably caused by the metabolite isopropoxyacetic acid.

The haemolytic effects of glycol ethers vary greatly depending upon the species. An earlier in vitro study of 2-isopropoxyethanol revealed a higher osmotic fragility, a precursor of hydrolysis, of rat erythrocytes in comparison with human erythrocytes (documentation "2-Isopropoxyethanol" 1993). In vitro and in vivo studies of the structurally related glycol ether 2-butoxyethanol and its metabolite butoxyacetic acid, which has a haemolytic effect, found that rats are more sensitive to this effect than humans (Carpenter et al. 1956; supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2010). A protein important for membrane integrity or membrane transport has been suggested as a potential target for 2-butoxyethanol (Udden 2005). Three transport pathways have been described for its transport into erythrocytes: 1. anion exchange mediated by the band 3 anion transport protein, which is responsible for transporting bicarbonate and chloride ions; 2. the monocarboxylate transporter, which carries lactate, pyruvate and glycolate and which is probably also relevant for isopropoxyacetic acid; and 3. non-ionic diffusion (Deuticke 1989).

Monocarboxylate transport is a potential target that has not been investigated for isopropoxyacetic acid, the metabolite of 2-isopropoxyethanol.

3 Toxicokinetics and Metabolism

There are no toxicokinetic investigations of the effects of inhalation or oral exposure available. As haemolytic effects were observed in rats in 28-day studies with exposure by inhalation to concentrations of 150 ml/m^3 and above, and changes in the number of different cell types were observed in the bone marrow of rats given oral doses of 30 mg/kg body weight and day and above, it can be assumed that 2-isopropoxyethanol is readily absorbed.

The dermal penetration of undiluted 2-isopropoxyethanol and a 50% aqueous solution of the substance was determined in human skin using an in vitro diffusion system. The test substance was applied occlusively to the skin at a concentration of 200 µl/cm^2 for periods of 0.5 or 1 hour and for 2, 4 or 8 hours. After application of the undiluted substance, a dermal flux of 240 ± 163 µg/(cm^2 × h), a permeation coefficient of 0.27 ± 0.18 × 10^{-3} cm/h and a total recovery of the test substance in the receptor fluid of 0.91% were determined. The respective values for the 50% aqueous solution were 246 ± 58 µg/(cm^2 × h), 0.44 ± 0.10 × 10^{-3} cm/h and 1.55% (Venier et al. 2004).

In rats, [1,2-^{14}C]-labelled 2-isopropoxyethanol was rapidly metabolized to isopropoxyacetic acid, *N*-isopropoxyacetylglycine and ethylene glycol after intraperitoneal injection of a dose of 0.993 mg/kg body weight. About 73% was eliminated with the urine, about 14% via the lungs and a small fraction with the faeces. The percentage of the metabolites isopropoxyacetic acid, *N*-isopropoxyacetylglycine and ethylene glycol eliminated with the urine was 30%, 46% and 13%, respectively. In rats, metabolism – catalysed by alcohol dehydrogenase in the liver – primarily occurs via the oxidation of 2-isopropoxyethanol to form isopropoxyacetic acid. Isopropoxyacetate can probably penetrate into the mitochondria, but does not undergo β-oxidation there. Instead, it is conjugated to glycine by glycine *N*-acyltransferase, forming *N*-isopropoxyacetylglycine. A further degradation pathway, which results in detoxification, involves the cleavage of the ether group by mixed-function oxidases, forming ethylene glycol. Urea, but not oxalic acid, was detected in the urine of rats. Unlike in rats, the metabolite ethylene glycol was not identified in the urine of dogs (Hutson and Pickering 1971). There are no data available for the distribution or for the half-life of the substance. The assumed metabolic pathway in rats is shown in Figure 1.

4 Effects in Humans

There are no data available.

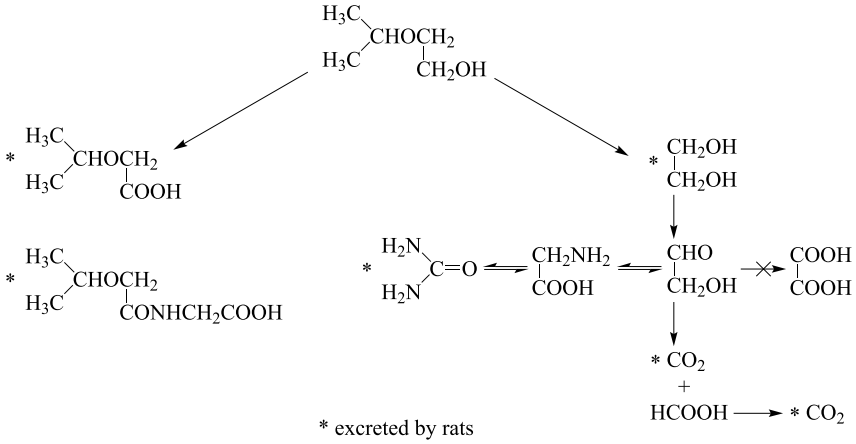

Figure 1 Metabolism of 2-isopropoxyethanol in rats (Hutson and Pickering 1971)

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In rats and mice, 4-hour and 7-hour LC_{50} values of about 4000 and 1930 ml/m³, respectively, were reported. Four-hour exposure of rats to a concentration of 80 ml/m³ induced haemolytic effects accompanied by kidney damage (no other details; documentation "2-Isopropoxyethanol" 1993).

5.1.2 Oral administration

In rats and mice, oral LD_{50} values of 500 to 5600 mg/kg body weight and of about 2200 mg/kg body weight, respectively, were reported. The main symptoms were depression of the central nervous system and dyspnoea; in addition, severe "haematuria" (probably haemoglobinuria, possibly intravascular haemolysis, but no other details) was observed with the associated findings in the kidneys, liver and spleen (no other details; documentation "2-Isopropoxyethanol" 1993).

A study carried out according to OECD Test Guideline 401, in which rats were exposed to 2-isopropoxyethanol in distilled water, reported an oral LD_{50} value of over 2000 mg/kg body weight. At this dose 2-isopropoxyethanol caused a decrease in body weight, reddish urine and a decrease in faecal volume (MHLW 2003 a; OECD 2009).

5.1.3 Dermal application

The dermal LD_{50} value in rabbits was about 1.6 ml/kg body weight (1445 mg/kg body weight) (no other details; documentation "2-Isopropoxyethanol" 1993; Smyth et al. 1969).

5.1.4 Subcutaneous injection

In groups of 5 male Wistar rats given a single subcutaneous injection of 2-isopropoxyethanol in saline in doses of 0, 0.625, 1.25 or 2.5 mmol/kg body weight (0, 65, 130 and 260 mg/kg body weight), haematological parameters were examined over a period of 0 to 600 hours. Abnormal clinical signs were not observed in any of the animals up to the high dose. The administration of 2-isopropoxyethanol resulted in a time-dependent and dose-dependent swelling of the erythrocytes. Initially, there was an increase in the packed cell volume and mean corpuscular volume. As haemolysis progressed, it was accompanied by a decrease in the erythrocyte count, the haemoglobin concentration and the packed cell volume. Subsequently, an increase in the haemoglobin concentration and the reticulocyte count was observed as a result of regeneration. In comparison to the effects induced by 2-phenoxyethanol, which was concurrently examined, those induced by 2-isopropoxyethanol occurred earlier and were about 10 times stronger (Starek et al. 2004).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

The studies that are relevant to the assessment are listed in Table 1.

In a 28-day inhalation study in Wistar rats carried out according to OECD Test Guideline 412, haemolytic anaemia in male and female animals and dose-dependent extramedullary haematopoiesis in the spleen of male animals were observed at the lowest concentration of 142 ml/m^3 and above. In addition, increased absolute and relative spleen weights and pigment deposits in the spleen were found with an increase in the concentration. Histopathological examination of the lungs, trachea and larynx did not reveal any unusual findings (Arts et al. 1992). In view of the irritation of the skin and eyes observed in rabbits (see Section 5.3), irritation of the respiratory tract is to be expected. However, this study did not include histopathological examination of the noses of the rats.

As a NOAEC (no observed adverse effect concentration) could not be derived, the same research group carried out another study with lower concentrations of the substance. 2-Isopropoxyethanol induced mild haemolytic anaemia in female rats at the highest concentration of 100 ml/m^3. After a 14-day recovery period, the values returned to the normal range. A NOAEC of 30 ml/m^3 was derived (Arts et al. 1992). Again, the study did not include histopathological examination of the nose.

A 3-week inhalation study (5 days a week, 6 hours a day) in rats reported pulmonary congestion after exposure to 2-isopropoxyethanol concentrations of 300 ml/m^3 and above and irritation of the nose at a concentration of 1000 ml/m^3 (no other details; Gage 1970). Again, histopathological examination of the nose was not performed.

Table 1 Effects of 2-isopropoxyethanol after repeated inhalation exposure

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 10 ♂ and 10 ♀	OECD Test Guideline 412, **28 days**, 0, 142, 441, 891 ml/m³, 5 days/week, 6 hours/day, vapour, whole-body, purity: 99.2%–99.3%	**no NOAEC**; **142 ml/m³ and above**: ♂, ♀: haemolytic anaemia; ♂: blood: RBC ↓, Hb ↓, MCV ↑, MCH ↑, MCHC ↓; spleen: extramedullary haematopoiesis (incidence and severity ↑); ♀: blood: RBC ↓, Hb ↓, MCV ↑, MCH ↑; **441 ml/m³ and above**: ♂: blood: PCV ↓, Ret ↑; spleen: absolute and relative weights ↑; pigment deposits (incidence ↑); ♀: blood: PCV ↓, Ret ↑; urine: pH ↓ (signs of compensated acidosis); spleen: absolute and relative weights ↑, extramedullary haematopoiesis (incidence and severity ↑); **891 ml/m³**: ♂: blood: WBC ↓; urine: pH ↓; ♀: blood: bilirubin ↓; heart: relative weights ↑; spleen: pigment deposits (incidence ↑); no mortality, no abnormal findings for body weight development or feed consumption	Arts et al. 1992
rat, Wistar, 10 ♂ and 10 ♀	OECD Test Guideline 412, **follow-up study to the above study**, **28 days**, 0, 10, 30, 100 ml/m³, 5 days/week, 6 hours/day, vapour, whole-body, purity: 99.2%–99.3%, recovery: 14 days, 5 ♂ and 5 ♀	**30 ml/m³**: **NOAEC**; **100 ml/m³**: ♀: slight haemolytic anaemia; blood: Hb ↓ (7%); recovery: effects reversible	Arts et al. 1992

Hb: haemoglobin; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; NOAEC: no observed adverse effect concentration; PCV: packed cell volume; RBC: red blood cells; Ret: reticulocyte count; WBC: white blood cells

The unpublished 26-week inhalation study from 1976 with exposure of rats, guinea pigs, rabbits and dogs that was included in the 1991 documentation (documentation "2-Isopropoxyethanol" 1993) is only available as a secondary source. This study reported haemolytic effects at concentrations of 25 ml/m^3 and above (no other details; ACGIH 2001).

5.2.2 Oral administration

Studies with oral administration are not included in the documentation published in 1991 (documentation "2-Isopropoxyethanol" 1993). Two recent studies are described in Table 2.

In a study carried out according to OECD Test Guideline 407, Sprague Dawley rats were given gavage doses of 2-isopropoxyethanol for 28 days. Changes in the bone marrow myelogram were already observed at the lowest dose of 30 mg/kg body weight and day and above. Effects on blood parameters, haemosiderin deposits in the spleen and extramedullary haematopoiesis were found at doses of 125 mg/kg body weight and day and above. A number of haematological parameters did not return to the normal range within the 14-day recovery period. The same is true for the histological changes in the spleen; these were, however, less pronounced. A NOAEL (no observed adverse effect level) could not be derived. The lowest dose of 30 mg/kg body weight and day is the LOAEL (lowest observed adverse effect level) for effects on the bone marrow (MHLW 2003 b; OECD 2009).

In another study in Sprague Dawley rats carried out according to OECD Test Guideline 421, gavage doses of 2-isopropoxyethanol were given to males for 48 days and to females for 41 to 47 days. Haematuria was observed in 1 female at 30 mg/kg body weight. At the highest dose of 125 mg/kg body weight and day, haematuria was induced in all the females and also in males, and increased absolute and relative spleen weights were found in animals of both sexes. Although the increase in the incidence of haematuria was not statistically significant in the females, it is considered an adverse, substance-induced effect. For this reason, a NOAEL of 8 mg/kg body weight and day was derived for haematuria in females and a NOAEL of 30 mg/kg body weight and day was established for haematuria and effects on the spleen in males (MHLW 2003 c; OECD 2009).

Summary

A NOAEL for rats cannot be derived from the 28-day gavage study. The LOAEL for effects on the bone marrow, changes in the myelogram, was 30 mg/kg body weight and day (MHLW 2003 b; OECD 2009). In the study carried out according to OECD Test Guideline 421 in which rats were given gavage doses for a longer exposure period (41 to 48 days), a NOAEL for haematuria of 8 mg/kg body weight and day was determined for females and of 30 mg/kg body weight and day for males (MHLW 2003 c; OECD 2009).

5.2.3 Dermal application

There are no data available.

Table 2 Effects of 2-isopropoxyethanol after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, groups of 5 or 10 ♂ and ♀	OECD Test Guideline 407, **28 days**, 0, 30, 125, 500 mg/kg body weight and day, gavage, dosing frequency: 7 days/week according to test guideline, vehicle: not specified by OECD 2009, purity: 99.5%, recovery: 14 days, only 0, 500 mg/kg body weight and day	**no NOAEL**; **30 mg/kg body weight and above**: ♂: bone marrow (myelogram, fraction of different cells): neutrophils ↓, eosinophils ↓, polychromatic erythroblasts ↑, ratio myeloid/erythroid cells ↓; ♀: bone marrow: myeloblasts ↓; **125 mg/kg body weight and above**: ♂: blood: % Ret ↑; bone marrow: total granulocytes ↓, total erythroblasts ↑; spleen: haemosiderin deposits (incidence ↑), extramedullary haematopoiesis (severity ↑); ♀: blood: RBC ↓, Hb ↓, MCHC ↓; bone marrow: eosinophilic myelocytes ↓, normoblasts ↑, increased erythropoiesis (incidence and severity ↑); spleen: relative weights ↑, haemosiderin deposits (severity ↑); **500 mg/kg body weight**: ♂, ♀: feed consumption ↓ (1st day); urine: reddish, protein ↑, bilirubin ↑, blood ↑ (reversible after 14-day recovery period); ♂: blood: RBC ↓, Hb ↓, HCT ↓, MCV ↑, MCH ↑, MCHC ↓; bone marrow: promyelocytes ↓, lymphocytes ↓, increased erythropoiesis (incidence and severity ↑); spleen: absolute and relative weights ↑, haemosiderin deposits (severity ↑); liver: relative weights ↑; kidneys: relative weights ↑; ♀: blood: HCT ↓, MCV ↑, MCH ↑, % Ret ↑; bone marrow: total granulocytes ↓, basophilic erythroblasts ↑, polychromatic erythroblasts ↑, total erythroblasts ↑, ratio myeloid/erythroid cells ↓; spleen: absolute weights ↑, extramedullary haematopoiesis (severity ↑); liver: relative weights ↑; **recovery 500 mg/kg body weight**: ♂: blood: MCV ↑, MCH ↑, MCHC ↓; thyroid: absolute and relative weights ↓; spleen: haemosiderin deposits (severity ↑); bone marrow: increased erythropoiesis (incidence ↑); ♀: body weights ↑, blood: MCV ↑, MCH ↑, WBC ↑; bone marrow: promyelocytes ↓, neutrophilic myelocytes ↑, total erythroblasts ↓, ratio myeloid/erythroid cells ↑; spleen: absolute weights ↑, haemosiderin deposits (severity ↑); liver: absolute weights ↑, relative weights ↓; kidneys: relative weights ↓; no mortality, no unusual findings for body weight development or water consumption	MHLW 2003 b; OECD 2009

Table 2 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 13 ♂ and 13 ♀	OECD Test Guideline 421, **♂: 14 days before and during mating for a total of 48 days**, **♀: 14 days before and during mating, during gestation, up to postnatal day 4 for a total of 41–47 days**, 0, 8, 30, 125 mg/kg body weight and day, gavage, dosing frequency: 7 days/week according to OECD Test Guideline 421, vehicle: not specified by OECD 2009, purity: 99.5%	**8 mg/kg body weight: NOAEL** ♀; **30 mg/kg body weight: NOAEL** ♂; **30 mg/kg body weight**: ♀: urine: haematuria (incidence: 1/13, no statistical significance); **125 mg/kg body weight**: ♂: feed consumption transiently ↓ (2 days); spleen: absolute and relative weights ↑; extramedullary haematopoiesis ↑ (incidence and severity ↑), pigment deposits (incidence and severity ↑); urine: haematuria (incidence: 7/13); ♀: spleen: absolute and relative weights ↑; urine: haematuria (incidence: 13/13); no mortality, no unusual findings for body weights or body weight development	MHLW 2003 c; OECD 2009

Hb: haemoglobin; HCT: haematocrit; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; NOAEL: no observed adverse effect level; RBC: red blood cells; Ret: reticulocyte count; WBC: white blood cells

5.2.4 Subcutaneous injection

Groups of 5 male Wistar rats were given subcutaneous injections of 2-isopropoxyethanol in saline in doses of 0, 0.25, 0.5, 0.75 or 1.25 mmol/kg body weight (0, 26, 52, 78 and 130 mg/kg body weight and day) on 5 days per week for 4 weeks. 2-Butoxyethanol (0, 0.25, 0.5, 0.75 and 1.25 mmol/kg body weight), 2-methoxyethanol and 2-ethoxyethanol (ethylene glycol monoethyl ether) (0, 1.25, 2.5 and 5.0 mmol/kg body weight, in each case) were used as reference substances and administered using the same pattern of treatment. All substances, with the exception of 2-methoxyethanol, resulted in a time-dependent and dose-dependent swelling of the erythrocytes, as evidenced by an increase in the mean corpuscular volume. Subsequently, the erythrocyte count, packed cell volume, haemoglobin concentration and mean corpuscular haemoglobin concentration decreased, followed by an increase in the mean corpuscular haemoglobin concentration and reticulocyte count. Haemolysis was induced by 2-isopropoxyethanol about as rapidly as by 2-ethoxyethanol and 2-butoxyethanol, but more rapidly than by 2-methoxyethanol. At the beginning of exposure, the haematological effects were somewhat less pronounced after treatment with 2-isopropoxyethanol than after treatment with 2-butoxyethanol. In spite of ongoing exposure, the haematological effects regressed, although the decrease in the erythrocyte count and the mean haemoglobin concentration and the increase in the mean corpuscular haemoglobin concentration and mean corpuscular haemoglobin were more persistent in rats treated with the high dose, probably as a result of the selective haemolysis of more mature erythrocytes. The development of tolerance to substance-induced haemolysis was observed after exposure to 2-isopropoxyethanol. At doses of 1.25 mmol/kg body weight and day (2-isopropoxyethanol: 130 mg/kg body weight and day; 2-butoxyethanol: 148 mg/kg body weight and day), 2-isopropoxyethanol caused a 35% decrease in the erythrocyte count, whereas 2-butoxyethanol caused a 61% decrease. On a molar level, the haemolytic effect of 2-butoxyethanol is therefore twice as strong as that of 2-isopropoxyethanol (Starek et al. 2008).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

2-Isopropoxyethanol caused irritation of the skin of rabbits only after prolonged contact (no other details; documentation "2-Isopropoxyethanol" 1993).

In a study in rabbits carried out according to a test protocol of the European Economic Community and the Draize method, a primary irritation index of 4.8 on a scale up to 8 was calculated for 2-isopropoxyethanol. There are no data available for reversibility (OECD 2009).

5.3.2 Eyes

A poorly documented study reported that undiluted 2-isopropoxyethanol caused iritis and corneal damage in the rabbit eye; these effects were reversible within 7 days (documentation "2-Isopropoxyethanol" 1993).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a very poorly documented maximization test, 2-isopropoxyethanol was not found to have a contact sensitizing effect. None of the 20 animals reacted to challenge treatment with a 1% 2-isopropoxyethanol preparation (no other details). The concentrations and vehicles used for intradermal induction treatment and epicutaneous induction treatment were not recorded (Zissu 1995).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a study carried out according to OECD Test Guideline 421 (reproduction/developmental toxicity screening test), a prolonged gestation period was observed in Sprague Dawley rats given gavage doses of 125 mg/kg body weight and day. No other unusual findings were reported. A NOAEL for fertility and foetotoxicity of 125 mg/kg body weight and day was derived (see Section 5.2.2; MHLW 2003 c; OECD 2009). 2-Methoxyethanol and 2-ethoxyethanol caused damage to the germinal epithelium of the testes (supplement "Ethylene glycol monoethyl ether" 2008; supplement "2-Methoxyethanol" 2009, available in German only); 2-isopropoxyethanol did not induce this effect.

5.5.2 Developmental toxicity

In a prenatal developmental toxicity study using a method similar to that of OECD Test Guideline 414, groups of 25 Sprague Dawley rats were exposed to 2-isopropoxyethanol concentrations of 0, 100, 300 or 600 ml/m^3 (purity: > 99.5%, whole-body, vapour) for 6 hours a day, on gestation days 6 to 15. The percentage of "damaged implantations" per litter was increased at the concentration of 600 ml/m^3. The term "damaged implantations" was used by the authors as a sum parameter that included both non-living (resorptions and late foetal deaths) and malformed foetuses. The changes in the individual parameters pre-implantation and post-implantation losses, number of resorptions, living foetuses and malformed foetuses per litter, sex ratio and foetal body weights were not statistically significant. Substance-induced teratogenic effects or increased incidences of variations were not observed at any concentration. Haematuria, delayed body weight development and reduced feed consumption were found in the dams at concentrations of 300 ml/m^3 and above. In addition, ruffled fur, reduced body weights and increased absolute and relative spleen weights were observed at 600 ml/m^3. According to the authors, the NOAEC for developmental toxicity was 300 ml/m^3 because of the increase in the sum parameter comprising non-living and malformed foetuses at 600 ml/m^3 and the NOAEC for maternal toxicity was 100 ml/m^3 (Union Carbide Corporation 1999). According to the Commission, the NOAEC for developmental toxicity is 600 ml/m^3, the highest concentration tested, because the individual parameters stipulated by OECD Test Guideline 414 are decisive for the derivation of a NOAEC for developmental toxicity.

In the above-mentioned study carried out according to OECD Test Guideline 421 (reproduction/developmental toxicity screening test), no unusual external changes were found in the offspring (see Sections 5.2.2, 5.5.1; MHLW 2003 c; OECD 2009). This test guideline does not include examination of the foetuses for visceral and skeletal malformations. For this reason, no conclusion can be drawn from this study as regards teratogenic effects. Foetotoxicity was not observed up to a dose of 125 mg/kg body weight and day.

5.6 Genotoxicity

5.6.1 In vitro

In bacterial mutagenicity tests carried out in Salmonella typhimurium TA98, TA100, TA1535 and TA1537 and E.coli WP2 uvrA according to OECD Test Guideline 471, 2-isopropoxyethanol was not found to be mutagenic up to 5000 µg/plate either with or without the addition of a metabolic activation system (MHLW 2003 d; OECD 2009).

In a study carried out according to OECD Test Guideline 473 in CHL/IU cells (Chinese hamster lung cells), 2-isopropoxyethanol did not cause an increase in the incidence of chromosomal aberrations or polyploid cells up to the concentration of 1050 µg/ml (MHLW 2003 e; OECD 2009).

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

There are no studies available.

6 Manifesto (MAK value/classification)

In view of the skin and eye irritation observed in rabbits, irritation of the respiratory tract in humans is to be assumed. The critical effect in rats is haemolytic anaemia; humans are less sensitive to this effect.

MAK value. In a 3-week inhalation study, irritation of the nose was observed in rats (no other details) exposed to a 2-isopropoxyethanol concentration of 1000 ml/m^3 (Gage 1970). Histopathological examination of the nose was not performed in either this study or any of the other inhalation studies.

According to the GHS (Globally Harmonized System of Classification and Labelling of Chemicals), 2-isopropoxyethanol, 2-propoxyethanol and 2-butoxyethanol are classified in category 2 for substances that cause eye irritation. For this reason, 2-butoxyethanol, which has been investigated more extensively and was used earlier as an analogous substance in the assessment of 2-propoxyethanol, is again included in the evaluation of 2-isopropoxyethanol.

The MAK value of **2-butoxyethanol** was lowered from 20 to 10 ml/m³ after a 2-year study in rats observed a local effect on the nose (hyaline degeneration in the olfactory epithelium) at a concentration of 31 ml/m³ (LOAEC) (supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2010). For this reason, a MAK value of 10 ml/m³ has been established also for 2-isopropoxyethanol.

In a 28-day inhalation study in Wistar rats carried out according to OECD Test Guideline 412, concentration-dependent haemolytic anaemia was observed in female rats after exposure to **2-isopropoxyethanol** concentrations of 100 ml/m³ and above; this effect was only slight at the low concentration. The NOAEC was 30 ml/m³ (Arts et al. 1992). On the basis of this NOAEC for haemolytic effects and taking into consideration the higher respiratory volume of humans at the workplace in comparison with test animals at rest (1:2) and the preferred value approach, the MAK value of 10 ml/m³ has been confirmed for 2-isopropoxyethanol. An additional margin for the extrapolation of data from animal studies to humans (1:2) is not considered necessary as humans are less sensitive to this effect than rodents.

As the severity of the haemolytic effect did not increase with time (Starek et al. 2008), haemolytic effects are unlikely to occur even after long-term exposure if the MAK value of 10 ml/m³ is not exceeded.

Peak limitation. As the MAK value for 2-isopropoxyethanol was derived on the basis of local effects, this substance has been classified in Peak Limitation Category I. There are no data available for the half-life. By analogy with 2-butoxyethanol and 2-propoxyethanol, an excursion factor of 2 has been established.

Prenatal toxicity. In a prenatal developmental toxicity study carried out according to a method similar to OECD Test Guideline 414, a higher percentage of non-living (resorptions and late foetal deaths) and malformed foetuses, considered together as a sum parameter, was found in Sprague Dawley rats exposed to 2-isopropoxyethanol vapour at a concentration of 600 ml/m³ on gestation days 6 to 15. Considered individually, the increase in each parameter was not statistically significant. Teratogenic effects were not observed. The NOAEC for maternal toxicity was 100 ml/m³ (Union Carbide Corporation 1999). According to the Commission, the NOAEC for developmental toxicity was 600 ml/m³, the highest concentration tested, as the individual parameters stipulated by OECD Test Guideline 414 are decisive for the derivation of a NOAEC for developmental toxicity. Taking into consideration the higher respiratory volume of humans at the workplace in comparison with test animals at rest (1:2), there is a 30-fold margin between the NOAEC for developmental toxicity of 600 ml/m³ and the MAK value of 10 ml/m³. This margin is sufficiently large to confirm classification in Pregnancy Risk Group C.

Unlike 2-isopropoxyethanol, shorter-chain glycol ethers such as 2-methoxyethanol and 2-ethoxyethanol have teratogenic potential (supplement "2-Methoxyethanol" 2009, available in German only; supplement "Ethylene glycol monoethyl ether" 2008). In contrast, the straight-chain 2-propoxyethanol and the longer-chain glycol ether 2-butoxyethanol and 2-phenoxyethanol are not teratogenic (documentation "2-Propoxyethanol" 1999; supplement "2-Butoxyethanol (Ethylene glycol monobutyl ether)" 2010; documentation "2-Phenoxyethanol" 1998, available in German only). The teratogenic effects of the shorter-chain glycol ethers decrease with increasing chain length and are very probably caused by the alkoxy acetic acids that are formed (ECETOC 2005).

Carcinogenicity. There are no carcinogenicity studies available. In vitro, the substance is neither mutagenic nor clastogenic. A genotoxic potential is not likely and is also not indicated by its structure. Therefore, the substance is not classified in one of the categories for carcinogens.

Germ cell mutagenicity. There are no data available for effects on germ cells. In vitro, 2-isopropoxyethanol is neither mutagenic nor clastogenic; therefore, the substance is not assumed to be a potential germ cell mutagen. For this reason, the substance is not classified in one of the categories for germ cell mutagens.

Absorption through the skin. In an in vitro penetration study with human skin, a dermal flux of 240 µg/(cm² × h) was calculated for 2-isopropoxyethanol (pure substance). This is equivalent to the total absorption of 480 mg 2-isopropoxyethanol after 1-hour exposure of both hands and forearms (about 2000 cm²). Taking into consideration the higher respiratory volume of humans at the workplace in comparison with test animals at rest (1:2), a concentration of 15 ml/m³ (66 mg/m³) is calculated from the NOAEC of 30 ml/m³ for haemolytic effects established from a 28-day inhalation study in Wistar rats. Assuming complete absorption and a respiratory volume of 10 m³, 660 mg 2-isopropoxyethanol is absorbed after exposure by inhalation. Even after taking into account that humans are much less sensitive to haemolytic effects than are rats, the substance is absorbed through the skin so readily that observation of the MAK value is not sufficient to prevent systemic effects after contact with the skin. As absorption through the skin is a very important route of absorption at the workplace, 2-isopropoxyethanol retains its "H" designation (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no positive clinical data for sensitizing effects on the skin or airways. A very poorly documented animal study did not find any evidence of contact sensitization. Therefore, 2-isopropoxyethanol has not been designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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