The MAK Collection for Occupational Health and Safety

Isopropyl alcohol

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

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Isopropyl alcohol / Propan-2-ol

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 isopropyl alcohol [67-63-0].

In carcinogenicity studies no tumours were observed in rats and mice up to 5000 ml/m³. From the LOAEC in rats and mice of 2500 ml/m³ where narcotic effects were observed, a MAK value of 200 ml/m³ is derived also considering the increased respiratory volume at the workplace because the blood:air partition coefficient of isopropyl alcohol is > 5 (see List of MAK and BAT Values, Sections I b and I c). Therefore, the MAK value of 200 ml/m³ is confirmed. At this concentration, no irritation is expected in humans based on the limited data in humans and animals.

Since a systemic effect is critical, Peak Limitation Category II is retained for isopropyl alcohol. Due to the half-life of up to 2 hours in rats, the excursion factor of 2 is confirmed.

In developmental toxicity studies, isopropyl alcohol does not result in teratogenicity but in fetotoxicity at maternally toxic doses in rats and rabbits. According to a PBPK model and considering the increased respiratory volume at the workplace, the NOAEL of 600 mg/kg body weight in rats is scaled to a concentration of 1000 ml/m³. There is no PBPK model for rabbits but due to the similar NOAEL for developmental toxicity in rabbits the same concentration is supposed. Because fetotoxicity was only observed at maternally toxic doses, the difference of the NOAEC for fetotoxicity and the MAK value is sufficient so that isopropyl alcohol remains assigned to Pregnancy Risk Group C.

Keywords

isopropyl alcohol; beta-hydroxypropane; dimethylcarbinol; isopropanol; 2-propanol; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Isopropyl alcohol

[67-63-0]

Supplement 2018

MAK value (1996)	**200 ml/m³ (ppm) ≙ 500 mg/m³**
Peak limitation (2001)	**Category II, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1996)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (1991)	**50 mg acetone/l blood or urine**

1 ml/m³ (ppm) ≙ 2.49 mg/m³ **1 mg/m³ ≙ 0.402 ml/m³ (ppm)**

For isopropyl alcohol, documentation from 1978 (documentation "iso-Propylalkohol/Isopropylöl" 1978, available in German only) and supplements from 1996 (supplement "Isopropyl alcohol" 2013a), 2001 (supplement "Isopropyl alcohol" 2013b) and 2012 (supplement "2-Propanol" 2012, available in German only) are available.

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 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, Sections I b and I c). The blood:air partition coefficient of isopropyl alcohol is 624 (Fiserova-Bergerova and Diaz 1986) or 848 (Clewell et al. 2001). This supplement evaluates whether the MAK value and the pregnancy risk group of isopropyl alcohol need to be re-assessed as a result of the higher respiratory volume at the workplace.

Toxicokinetics and Metabolism

After oral administration, isopropyl alcohol is absorbed almost completely within an hour in humans and animals. From data obtained with workers exposed to an iso-

propyl alcohol concentration of 260 ml/m³, a mean retention of 54% was calculated; isopropyl alcohol was not found in the blood at any point in time, but its metabolite acetone was detected up to a level of 15.6 mg/l blood. In women exposed to concentrations of 1 to 227 ml/m³ (2.5 to 570 mg/m³), isopropyl alcohol levels in blood of up to about 10 mg/l (mean value 1.7 mg/l) and blood acetone levels up to about 40 mg/l (mean value 16.3 mg/l) were determined at the end of the shift. The mean physiological blood acetone level was 2.9 mg/l. Only small quantities are absorbed dermally. After oral administration of 300 or 3000 mg isopropyl alcohol/kg body weight to rats, 81% to 89% of the dose was exhaled in the form of isopropyl alcohol (about 0–15%), acetone (about 40–55%) and carbon dioxide (about 16–30%). The half-life was 1 to 2 hours. Also in humans, isopropyl alcohol is eliminated mainly with the exhaled air with half-lives of 2.5 to 6.4 hours for isopropyl alcohol and of 11 to 22.4 hours for acetone (supplement "Isopropyl alcohol" 2013a).

According to a physiologically-based pharmacokinetic (PBPK) model (Clewell et al. 2001), an oral dose of 800 mg/kg body weight in rats corresponds to inhalation exposure at a concentration of about 2800 ml/m³ in the air for 6 hours. This concentration is independent of whether effects observed following isopropyl alcohol are caused by the concentration–time product (AUC = area under the curve) of isopropyl alcohol or acetone, or the maximum concentration (C_{max}) of acetone. The oral dose of 600 mg/kg body weight corresponds to about 2000 ml/m³ in the air.

As ethanol and isopropyl alcohol are frequently used as disinfectants on the skin, dermal absorption of the substances was investigated alone, in combination with each other and in a formulation. For this, 20 ml on a gauze dressing of 200 cm² was applied to the same skin area of 14 male volunteers and the concentration of these substances and of acetone in the blood was determined after 0, 15 and 60 minutes. No increased dermal absorption was found for any of the substances, and the mean blood concentrations did not differ significantly from each other at any time (Kirschner et al. 2009).

Effects in Humans

In the study described in the supplement of 1996 (supplement "Isopropyl alcohol" 2013a) with 60 women occupationally exposed to isopropyl alcohol concentrations of between 1 and 227 ml/m³ for 17 years, the determination of biological parameters and behavioural investigations did not reveal any pathological changes.

Studies with workers or volunteers not described before are listed below.

Single exposures

The exposure of 28 healthy male and 28 healthy female volunteers at rest to an isopropyl alcohol concentration of 150 ml/m³ for two hours produced no change in the blinking frequency during the entire exposure period. Lung function, swelling of the nasal mucosa, inflammation markers in the nasal lavage and colour vision were examined at the start of exposure and after three hours. No substance-related effects were found. The odour of the substance was perceived. Ten questions were asked regarding the subjective perception, for example, of irritation in the throat region; each question was answered by at least one person in the affirmative, describing it

as a symptom. The symptoms were overall only weak, attaining a value of 13.9 on a scale of 0 to 100, which corresponds to a verbal grading a little above "hardly at all". As regards subjective perception, women were slightly more sensitive than men to the acute irritant effects of the substance (Ernstgård et al. 2002).

In an experimental exposure study, 24 healthy male volunteers (mean age: 25.8 years) were exposed in a cross-over design to isopropyl alcohol concentrations of 35 or 190 ml/m^3 for 4 hours. There were no substance-related findings in the parameters describing sensory irritation and in the neuropsychological examination. At the higher concentration, the volunteers reported olfactory symptoms and increased tiredness (van Thriel et al. 2003). The tiredness was considered not to be a substance-related effect.

The exposure of 24 healthy male volunteers to isopropyl alcohol concentrations of 20 or 360 ml/m^3 for 2 or 4 hours in a study with cross-over design did not yield substance-related findings in a questionnaire evaluation of the intensity of discomfort, tiredness, irritation or breathing difficulties. Only the odour was perceived more clearly over time and described as unpleasant (Muttray et al. 1998).

Objectively measurable and subjectively perceived parameters of sensory irritation were investigated during 4-hour exposure to 400 ml isopropyl alcohol/m^3 in 12 naive controls and 12 workers occupationally exposed to isopropyl alcohol. The perception of the odour, the sensory irritation and the annoyance were all assessed as slight. The objective parameters measured were ocular hyperaemia, nasal congestion, nasal secretion and respiration. Of these objective parameters, only the respiratory frequency was slightly increased (Smeets et al. 2002), which may be evaluated as a weak indication of sensory irritation at 400 ml/m^3 (constant, for 4 hours).

In a study in which 20 healthy male volunteers aged 21 to 30 years were exposed once to an isopropyl alcohol concentration of 400 ml/m^3 for 8 hours, a non-significant deterioration in postural sway during bipedal standing was reported at noon, but not in the evening, and although monopedal standing was impaired in the evening, it was not at noon. In all further neuropsychological studies, no substance-related effects occurred (Sethre et al. 2000 a). It seems questionable whether the differently impaired balance (monopedal compared with bipedal) can be attributed to isopropyl alcohol, as it only occurred after 4 and 8 hours, respectively. Evaluations of balance while standing are subject to intrapersonal variability, which cannot be recorded in one single measurement. As the other neurobehavioural studies did not reveal substance-related effects, the investigation of balance while standing was carried out only once, did not include the intrapersonal variability, and did not reveal significant differences compared with the control conditions, these findings are not taken into account in deriving the MAK value.

Repeated exposure

In 21 workers at a foundry with exposure to isopropyl alcohol levels of between 6 and 73 ml/m^3 (median 28 ml/m^3) determined via personal air sampling, a research group found impaired monopedal or bipedal postural balance compared with a control group of workers at a dyeing factory with "very low solvent exposure" (Sethre et al. 1998). The results of these observations could not be reproduced in a follow-up study carried out by the research group at the same foundry, although a more specific examination was carried out (Sethre et al. 2000 b). The effects on postural balance are

possibly due to group differences, which could not be corrected statistically due to the low number of persons involved. Therefore, they are not regarded as substance-related and are not included in the derivation of the MAK value.

Summary: No substance-related toxic effects were observed in workplace studies up to a concentration of 227 ml/m³ and in several volunteer studies up to about 400 ml/m, and no sensory irritation was found up to 190 ml/m³.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

There are no new data available.

In the 13-week inhalation studies with rats and mice exposed to concentrations of 0, 100, 500, 1500 and 5000 ml/m³ described in the supplement of 1996 (supplement "Isopropyl alcohol" 2013a), encrustation of the nose was observed in the male rats at and above 500 ml/m³ and eye irritation in the female rats at 5000 ml/m³. It is doubtful that these findings have any toxicological relevance, particularly in view of the absence of microscopic changes. The changes in the kidneys in the form of hyaline droplets occurring in all exposed male rats, which were larger and more numerous than in the controls, are species-specific and sex-specific phenomena and therefore not used for the assessment. The relative liver weights were increased in the female mice at 1500 and 5000 ml/m³ and in the male and female rats at 5000 ml/m³. After exposure for 2 years, the testis weights were slightly increased in the rats at 500 ml/m³; the increase was statistically significant at 2500 ml/m³ and above. The incidence of interstitial cell adenomas of the testes was slightly increased. These findings are described by the authors of the study and in the ECHA database as hyperplasia and not as autonomous growth, and the barely significant incidence was not considered relevant to the assessment due to the particularly low incidence in the controls. In the 18-month study in mice, the relative testis weights were reduced at 500 ml/m³ and above, however without concentration dependency, and the absolute and relative liver weights were increased. Histologically, these organs were normal. During exposure to 2500 ml/m³ transient hypoactivity, loss of the startle reflex and narcosis (mice only) were observed in some rats and mice (supplement "Isopropyl alcohol" 2013a). The liver weight increases in mice—even the 16% increase at 2500 ml/m³—are not regarded as adverse, and did not always occur in both sexes. Thus, in the male rats, encrustations of the nose (13-week study) or not significantly increased testis weights (2-year study) and, in the male mice, reduced relative testis weights (18-month study) were found at 500 ml/m³. It is not possible at present to clarify the extent to which these findings have any relevance for humans.

Local effects on skin and mucous membranes

In rabbits, isopropyl alcohol is a strong eye irritant. The redness had in some cases not completely subsided within 14 days (ECHA 2016).

It is also reported in the supplement of 1996 (supplement "Isopropyl alcohol" 2013a) that isopropyl alcohol is irritating to corrosive to the eyes of rabbits, and that the effects were still present in some cases at the end of the recovery period of 21 days.

Reproductive and developmental toxicity

There are no new studies available since publication of the supplement of 2012 (supplement "2-Propanol" 2012, available in German only).

Isopropyl alcohol was not teratogenic in rats and rabbits.

Reduced foetal weights were observed only at maternally toxic doses (mortality) of 800 mg/kg body weight and day and above in a prenatal developmental toxicity study with rats (Tyl et al. 1994 in supplement "Isopropyl alcohol" 2013a). Postnatal mortality was found in a 1-generation study in rats after administration with the drinking water at the very high dose of 2768 mg/kg body weight and day, which had marked toxic effects in the dams (Faber et al. 2008; supplement "2-Propanol" 2012, available in German only). The NOAEL (no observed adverse effect level) for developmental toxicity was 596 mg/kg body weight and day in rats. At 1242 mg/kg body weight and day there was delayed ossification, a variation which was associated with the delayed foetal development and the observed maternal toxicity (Faber et al. 2008; supplement "2-Propanol" 2012, available in German only).

In rabbits, the NOAEL for developmental toxicity was the highest dose tested of 480 mg/kg body weight and day; at this dose maternal toxicity in the form of reduced food intake and body weight gains was found in these animals (Tyl et al. 1994 in supplement "Isopropyl alcohol" 2013a).

Manifesto (MAK value/classification)

The critical effect of isopropyl alcohol is its narcotic effect at high concentrations.

MAK value. In workplace studies, no substance-related toxic effects were found up to 227 ml/m^3. In several volunteer studies no substance-related toxic effects were found up to about 400 ml/m^3, and no sensory irritation up to 190 ml/m^3.

Encrustation of the nose was observed only in male rats after 13-week exposure to 500 ml/m^3 and above. However, this did not occur in the 2-year study. It is doubtful that this finding from the 13-week study has any toxicological relevance, also in view of the absence of microscopic changes. Narcotic effects were observed during the exposure at and above 2500 ml/m^3. The relevance for humans of the slight increase in the testis weights of rats and of the decrease in the testis weights without concentration dependency in mice found after chronic exposure to 500 ml/m^3 cannot be clarified at present. Therefore, on the basis of the LOAEC (lowest observed adverse effect concentration), a NAEC (no adverse effect concentration) of 833 ml/m^3 is calculated (1:3). Considering the extrapolation of the data from the animal study to humans (1:2) and the increased respiratory volume at the workplace (1:2), the previous MAK value of 200 ml/m^3 can be retained. This value is also supported by the MAK value of 500 ml/m^3 for acetone, the main metabolite of isopropyl alcohol. According to the studies of the irritancy of isopropyl alcohol in humans, no irritant effects are to be expected at this value.

Peak limitation. As the MAK value is derived from a systemic effect, the assignment of isopropyl alcohol to Peak Limitation Category II has been retained. Due to the short half-life of 1 to 2 hours in rats after inhalation and of 2.5 to 6.4 hours in humans as found in cases of oral poisoning, the excursion factor of 2 for isopropyl alcohol has been retained. At the permissible peak concentration of 400 ml/m³, no irritation is to be expected.

Prenatal toxicity. Isopropyl alcohol was not teratogenic in rats and rabbits. In a prenatal developmental toxicity study with rats, reduced foetal weights were found only at the maternally toxic doses (mortality) of 800 mg/kg body weight and day and above; postnatal mortality occurred in a 1-generation study with rats after administration with the drinking water at the very high dose of 2768 mg/kg body weight and day, which had marked toxic effects in the dams. The NOAEL for developmental toxicity in rats was 596 mg/kg body weight and day (drinking water) and that for rabbits was the highest dose tested of 480 mg/kg body weight and day (gavage); in rabbits, maternal toxicity was found at this dose in the form of reduced food intake and body weight gains (supplement "2-Propanol" 2012, available in German only).

The following toxicokinetic data are taken into consideration for the extrapolation of these NOAELs to a concentration in workplace air: the species-specific correction values (1:4 and 1:2.4) for rats and rabbits, the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the experimentally determined absorption of 54% by inhalation (supplement "Isopropyl alcohol" 2013a). The concentrations calculated from this are 1931 mg/m³ (776 ml/m³, rats) and 2592 mg/m³ (1040 ml/m³, rabbits).

According to a PBPK model (Clewell et al. 2001), an oral dose of isopropyl alcohol of 600 mg/kg body weight in the rat corresponds to a concentration of about 2000 ml/m³ for an exposure lasting 6 hours (see Section "Toxicokinetics"). The simplified estimate given above therefore results in a lower concentration (overestimation of inhalation toxicity). Taking into consideration the increased respiratory volume of humans, the oral NOAEL of about 600 mg/kg body weight and day in rats corresponds to a concentration in air of 1000 ml/m³. No PBPK model is available in the case of rabbits. According to the simplified extrapolation, the NOAEL for rabbits results in a concentration in air similar to that calculated from the NOAEL for rats (776 and 1040 ml/m³). It may therefore be assumed that with a PBPK model, a higher concentration in the workplace air would also be calculated from the NOAEL of the rabbit studies. The foetotoxic effects such as delayed ossification (variations) in rats are not to be considered as substance-specific, but secondary phenomena caused by the maternal toxicity. The MAK value has been retained, no teratogenic effects were found after exposure to isopropyl alcohol and higher concentrations at the workplace are calculated from the PBPK model than according to the simplified toxicokinetic extrapolation. This means that the difference between the NOAEL for developmental toxicity in rats and rabbits and the MAK value (around 5-fold) is even greater. The assignment of isopropyl alcohol to Pregnancy Risk Group C can therefore be retained.

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