Isopropyl alcohol

Supplement 1996	
MAK value (1996)	**200 ml/m³ (ppm)**
	490 mg/m³
Peak limitation (1983)	**Category II, 1**
Prenatal toxicity (1996)	**Pregnancy Risk Group C**
Synonyms	β-hydroxypropane
	dimethylcarbinol
	isopropanol
Chemical name (CAS)	2-propanol
CAS number	67-63-0
Structural formula	$(H_3C)_2$–CHOH
Molecular formula	C_3H_8O
Molecular weight	60.1
Melting point	– 89.5°C
Boiling point at 1013 hPa	82.4°C
Density at 20°C	0.786 g/cm³
Vapour pressure at 20°C	40 hPa
log K_{ow}[1)]	0.14
1 ml/m³ (ppm) ≙ 2.46 mg/m³	**1 mg/m³ ≙ 0.41 ml/m³ (ppm)**

The similarity of isopropyl alcohol to ethanol and its mode of action were used in 1977 as the basis for the previous MAK value of 400 ml/m³ (980 mg/m³). Since then, the database has greatly improved. The present documentation is based mainly on reviews of the toxicological data for isopropyl alcohol (DECOS 1994; WHO 1990).

1) *n*-octanol/water partition coefficient

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1 Toxic Effects and Mode of Action

Isopropyl alcohol is absorbed rapidly and in large amounts both by inhalation and via the gastrointestinal tract, and is distributed evenly in the body. The main metabolites are acetone, which can accumulate in the body as a result of its long elimination half-time, and CO_2. After the absorption of larger amounts of isopropyl alcohol, the symptoms are therefore similar to those after intoxication with acetone (see the 1994 MAK documentation "Acetone" 1996). Isopropyl alcohol causes only slight irritation of the skin, but in animal experiments has irritative to corrosive effects on the mucous membranes of the eyes. The acute systemic toxicity of isopropyl alcohol is low. Higher concentrations have narcotic effects. After long-term exposure to concentrations of 500 ml/m³ and above, increased testis weights and an increase in the incidence of interstitial cell adenomas of the testes were found in rats, and reduced testis weights and increased liver weights in mice. In the kidneys of male rats, the accumulation of hyaline droplets can be detected even at lower concentrations. At very high concentrations also the kidneys of the female rats and mice are damaged. Isopropyl alcohol is not genotoxic, does not have carcinogenic potential and does not cause teratogenic effects. Embryotoxic and foetotoxic effects are observed only at very high doses and concentrations that are also toxic for the dams.

2 Mechanism of Action

There are no studies available of the mechanism of action of isopropyl alcohol.

3 Toxicokinetics and Metabolism

Absorption and distribution

Isopropyl alcohol is absorbed rapidly and practically quantitatively by the gastrointestinal tract. This was seen, for example, after rats were given single isopropyl alcohol doses of 300 or 3000 mg/kg body weight. Also in humans the substance is rapidly absorbed. Thirty to 60 minutes after the ingestion of isopropyl alcohol in fruit juice (250–500 mg/kg body weight), the maximum levels of the substance in blood were determined. Dermal absorption has been demonstrated, but plays only a subordinate role at the workplace (DECOS 1994).

In workers exposed to maximum isopropyl alcohol concentrations of 260 ml/m³ (645 mg/m³), the average retention was calculated from the ratio of the alveolar isopropyl alcohol concentration to the isopropyl alcohol concentration in the ambient air and found to be 54%. Isopropyl alcohol could not be detected in the blood of these workers either during or after the shift. The authors suggested that a large

apparent distribution volume of isopropyl alcohol in the body may be the reason for this. The detection limit was also relatively high at 1 mg/l. The main metabolite, acetone, was detected in blood in concentrations of up to 15.6 mg/l (Brugnone et al. 1983). In women exposed to concentrations of 1 to 227 ml/m³ (2.5 to 570 mg/m³), blood isopropyl alcohol levels of up to about 10 mg/l (mean value 1.7 mg/l) and blood acetone levels of 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 (Triebig et al. 1989).

In mice, isopropyl alcohol rapidly reaches the blood after inhalation of the substance. After only 1 hour after the beginning of exposure (6 hours to ^{14}C-labelled isopropyl alcohol concentrations of 500 ml/m³), the maximum levels in blood were reached (radioactive equivalents of around 65 µg/g whole blood). The radioactive equivalents of the main metabolite, acetone, reached a maximum concentration in blood of about 190 µg/g whole blood at the end of the 6-hour exposure period. The same treatment in rats yielded maximum levels in blood at the end of the exposure period. With radioactive equivalent values of about 32 µg/g whole blood, the levels were around half those found in mice. The maximum radioactive equivalent concentration for acetone of about 100 µg/g whole blood was reached also at the end of the exposure (Slauter et al. 1994).

Isopropyl alcohol was distributed in rats and mice in all tissues and organs. Specific target organs were not found. There is no evidence that the substance accumulates (DECOS 1994).

Metabolism

Isopropyl alcohol is metabolized both in humans and in laboratory animals in a first, rate-limiting step by the alcohol dehydrogenase of the liver to form acetone. Evidence that metabolism becomes saturated was found in rats and mice after exposure to concentrations of 4000 to 5000 ml/m³, and in rats after oral doses of 3000 mg/kg body weight (DECOS 1994; Slauter et al. 1994). After previous or simultaneous administration of ethanol, the metabolism of isopropyl alcohol in humans and rodents is slower. Acetone is either eliminated directly with the exhaled air and urine or oxidized in a cytochrome P450-dependent reaction to form 1-hydroxy-2-propanone. Another important metabolite is carbon dioxide. In rats and mice, a third, non-identifiable metabolite was found in the urine in small amounts (DECOS 1994). Another research group found, in addition to the initial substance and acetone, also isopropyl glucuronic acid (< 5%) in the urine of mice and rats exposed for 6 hours via inhalation to isopropyl alcohol concentrations of 500 or 5000 ml/m³ (Slauter et al. 1994). In rabbits, around 10% (no other details) is found in glucuronidated form. Also in humans there are smaller amounts of conjugated isopropyl alcohol: sulfated in blood or glucuronidated in urine (DECOS 1994). In rats, short and long-term exposure to isopropyl alcohol led to an increase in the cytochrome P450 level in the liver.

Elimination

The elimination of isopropyl alcohol after inhalation exposure or intravenous injection was investigated in male and female rats and mice. The animals were given intravenous isopropyl alcohol doses of 300 mg/kg body weight or were exposed for 6 hours to concentrations of 500 or 5000 ml/m³ (nose only exposure in rats, whole animal exposure in mice). Rats were additionally given single or repeated oral isopropyl alcohol doses of 300 or 3000 mg/kg body weight. No noteworthy species or sex-specific differences in the amount eliminated or elimination route were observed. Rats exhaled 81% to 89% of the administered dose as isopropyl alcohol, acetone and carbon dioxide. In mice, 76% was exhaled after intravenous injection and 92% after inhalation. After intravenous and oral administration, the elimination products consisted of about 40% to 55% acetone, 16% to 30% carbon dioxide and 0% to 15% unchanged isopropyl alcohol. 3% to 8% of the administered dose was eliminated by rats and mice with the urine, and a maximum of 2% with the faeces. The half-times increased slowly with increasing dose. In rats and mice, these were given as 1 to 2 hours for isopropyl alcohol after 6-hour inhalation exposure to 500 and 5000 ml/m³ and after single or repeated oral doses of 300 mg/kg body weight. After single oral doses of 3000 mg/kg body weight, the half-time in male rats was given as 6.8 hours, in female rats as 4.0 hours (Slauter et al. 1994). The half-time for the main metabolite, acetone, after oral isopropyl alcohol doses of 200, 800 and 2000 mg/kg body weight was 4.0, 3.1 and 8.4 hours, respectively.

Also in humans the main elimination route is exhaled air. A half-time of 2.5 to 6.4 hours was reported for isopropyl alcohol, and of 11 to 22.4 hours for acetone (DECOS 1994). Determination of the acetone concentration in blood or urine is regarded as a suitable method for the biological monitoring of workers exposed to isopropyl alcohol. The BAT value is 50 mg acetone per litre blood or urine (Henschler and Lehnert 1990).

4 Effects in Humans

4.1 Single exposures

In cases of intoxication, mainly symptoms of alcohol intoxication are observed, such as nausea, vomiting, stomach ache, gastritis, hypotonia and hypothermia. The depressive effects of isopropyl alcohol on the central nervous system are twice as strong as those of ethanol and can lead, via unconsciousness, even to deep coma. The cause of death is then respiratory depression. Other substance-related effects are hyperglycaemia, an increase in the level of protein in the cerebrospinal fluid and disturbed alveolar functioning. Ingestion of amounts of 150 to 240 ml is potentially fatal. There are no quantitative data available for the toxicity of isopropyl alcohol after inhalation (DECOS 1994).

4.2 Repeated exposures

The daily ingestion of isopropyl alcohol doses of 2.6 and 6.4 mg/kg body weight over a period of six weeks did not lead to adverse effects in 8 healthy male volunteers (DECOS 1994).

In an epidemiological study with 60 women occupationally exposed to isopropyl alcohol (and nitro thinner) for up to 17 years (median: 4.5 years), the prevalence of toxic effects was not significantly higher than in 48 women not exposed to the substance. Also the determination of biological parameters and behavioural investigations did not reveal any pathological changes. At the time of the investigation, the individual exposure concentration was in the range between 1 and 227 ml/m^3 (median: 106 ml/m^3) (Triebig et al. 1989).

4.3 Local effects on skin and mucous membranes

After the application of isopropyl alcohol to the dry skin of the forearm, no irritation was observed. In addition, isopropyl alcohol was applied to the forearm after dipping it in lukewarm water for 10 minutes. The authors reported transient irritation of the treated area. In premature babies who came into contact with isopropyl alcohol in the clinic during treatment of the navel or ECG monitoring, irritation and blistering were observed after longer periods of contact with the substance (WHO 1990).

The irritative effects on the eyes, nose and throat were tested in 10 volunteers exposed to isopropyl alcohol concentrations of 200, 400 and 800 ml/m^3 for 3 to 5 minutes. The volunteers described the irritation at 400 ml/m^3 as weak, and at 800 ml/m^3 as not strong. 200 ml/m^3 was regarded as a tolerable concentration for an 8-hour working day (Nelson et al. 1943). In the light of present-day standards, this study is of only limited usefulness as a result of shortcomings in the study design.

In the epidemiological study with exposure concentrations up to 227 ml/m^3 described in section 4.2, there was no mention of irritation of the mucous membranes (Triebig et al. 1989).

4.4 Allergenic effects

In rare cases, allergic contact dermatitis was observed after exposure to isopropyl alcohol solutions. There were also reports of persons with alcohol hypersensitivity. Allergic reactions were observed in these cases to several primary and secondary alcohols, including isopropyl alcohol (WHO 1990).

4.5 Reproductive toxicity

There are no studies available of the reproductive and developmental toxicity of isopropyl alcohol.

4.6 Genotoxicity

There are no studies available of the genotoxicity of isopropyl alcohol.

4.7 Carcinogenicity

Several cohort studies were carried out with workers from various firms that produced isopropyl alcohol according to the strong acid procedure. There is sufficient evidence of an increase in the incidence of tumours of the upper respiratory tract. Non-Hodgkin's lymphomas were found in one study (DECOS 1994). The inducing agents were not regarded to be isopropyl alcohol, but initially isopropyl oils, which occur as byproducts with this procedure and contain mainly polypropylene and small amounts of various other compounds, and later diisopropyl sulfate (WHO 1990). On the other hand, there was no evidence that the production of isopropyl alcohol according to the weak acid procedure is associated with an increased incidence of tumours (DECOS 1994).

5 Animal Experiments and *in vitro* Studies

5.1 Acute toxicity

5.1.1 Inhalation

A NOAEC (no observed adverse effect concentration) of 770 ml/m³ (1925 mg/m³) was derived from the data for acute toxicity in the rat after inhalation of the substance. Changes were not observed during and after treatment with this concentration for 6 hours. At the next-higher concentration of 1500 ml/m³ (3750 mg/m³) tested in another study, slight transient behavioural changes were observed in male animals. After inhalation of isopropyl alcohol for 4 hours, an LC_{50} of 29040 ml/m³ (72600 mg/m³) was determined in rats (no details of sex). After inhalation of the substance for 8 hours, the LC_{50} in male rats was 18696 ml/m³ (46740 mg/m³), in female rats 22140 ml/m³ (55350 mg/m³). Assuming retention of 60% of the isopropyl alcohol, LD_{50} values of 6534, 8413 and 9963 mg/kg body weight were calculated (DECOS 1994).

Acute neurotoxic effects were investigated also in F344 rats exposed to isopropyl alcohol concentrations of 500, 1500, 5000 or 10000 ml/m³ for 6 hours. One hour after the end of exposure, transient signs of narcotic effects were observed in the high concentration group. Exhaustion and severe paralysis, difficult and laboured breathing, and the loss of reflexes were apparent even 6 hours after the end of exposure. Motor activity was also reduced at this time by 90%. In the 5000 ml/m³ group, sedation and the symptoms described above occurred, but to a lesser extent. Six hours after the end of exposure no effects were detectable. In the male animals of the 1500 ml/m³ group, merely motor activity was reduced by 15%. The NOEC (no observed effect concentration) was 500 ml/m³ (Gill et al. 1995).

Isopropyl alcohol caused weak sensory irritation of the upper respiratory tract. RD_{50} values of 5000 and 17693 ml/m³ (12500 and 44232 mg/m³) were determined in two different strains of mouse (DECOS 1994).

After guinea pigs inhaled isopropyl alcohol concentrations of 400 and 5500 ml/m³ for 24 hours, impairment of the mucociliary system and degeneration of the mucous membranes of the trachea and middle ear were observed. At the low isopropyl alcohol concentration, but not at the high concentration, the effects were reversible within 14 days (Ohashi et al. 1987 a, b).

5.1.2 Ingestion, dermal absorption, intravenous and intraperitoneal injection

In studies of the acute toxicity of isopropyl alcohol, mainly effects on the nervous system were observed. Oral LD_{50} values between 4475 and 7990 mg/kg body weight were determined for various animal species.

For the rabbit, a dermal LD_{50} value of 12 870 mg/kg body weight was determined.

After intravenous injection and intraperitoneal administration, LD_{50} values between 1000 and 2000, and 2800 and 4900 mg/kg body weight, respectively, were determined for various animal species (DECOS 1994).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In the concentration-finding study to the medium-term study described below, rats and mice inhaled isopropyl alcohol concentrations of 0, 1000, 5000, 10 000 and 15 000 ml/m³ on 9 of 11 days, for 6 hours a day. All the rats and mice of the high concentration group died after the first treatment. In the 10 000 ml/m³ group, 0% and 40% of the male and female rats, respectively, and 60% and 100% of the male and female mice died. The clinical symptoms observed were narcosis, ataxia, paresis, irritation of the eyes and a significant increase in body temperature. In the 5000 ml/m³ group, an atypical gait and a significant increase in body temperature

were observed. In the low concentration group, neither clinical nor functional changes were observed. Histological examination of the kidneys and liver of the rats of the two low concentration groups revealed hyaline droplets in the kidneys and cytoplasmic vacuolation in the liver of the male animals (Burleigh-Flayer et al. 1994 b; DECOS 1994).

In a medium-term study, rats and mice inhaled isopropyl alcohol concentrations of 0, 100, 500, 1500 and 5000 ml/m³ for 13 weeks (6 hours a day, 5 days a week). Narcotic effects were observed only during the inhalation of isopropyl alcohol and only in the two high concentration groups. Ataxia and hypoactivity were observed in a few rats and mice of the 5000 ml/m³ group directly after the exposure. The changes in body weights and body weight gains (decreased in the first week, increased in the following weeks) corresponded as a rule with the decrease and increase in food and water consumption. Behavioural and neuropathological investigations in rats did not reveal any substance-related changes apart from increased motor activity in the female rats of the high concentration group in weeks 9 and 13. In female rats of the high concentration group, eye irritation was much more frequent. Encrustation of the nose was observed in the male rats of the 500, 1500 and 5000 ml/m³ groups. Microscopic changes were not detected in either the eyes or the nasal cavity. In the high concentration group, the relative liver weights were increased in the male and female rats and the female mice, in the 1500 ml/m³ group only in the female mice. Evidence of liver damage was not found. The only microscopic changes were observed in the kidneys of the male rats of all concentration groups. The hyaline droplets present there were more numerous and larger than those in the controls. These changes are regarded as species and sex-specific and have no relevance for humans. The authors therefore gave a NOAEC for systemic effects in the rat and mouse of 1500 ml/m³. The NOAEC for irritation in the rat and mouse is 1500 ml/m³, if the encrustation of the nose observed only in male rats is excluded (Burleigh-Flayer et al. 1994 b).

Investigations of the chronic toxicity of isopropyl alcohol are described in Section 5.7.

5.2.2 Ingestion

Rats were given isopropyl alcohol with the drinking water for 27 weeks. In the male animals the average daily uptake was 600 or 2300 mg/kg body weight, in the females 1000 or 3900 mg/kg body weight. All the female animals survived the treatment, 2/5 males of the low dose group and 3/5 males of the high dose group died. At the end of the treatment period, growth retardation was determined in female animals, while the male animals were lighter than the controls up to the middle of the treatment period, and after that heavier. Investigations of food consumption and behaviour, and histopathological examinations did not reveal any differences between the treated animals and the controls (WHO 1990).

5.3 Local effects on skin and mucous membranes

In studies with guinea pigs and rabbits, isopropyl alcohol was not found to have skin-irritating potential. The compound caused eye irritation and corrosion in rabbits, however, in various studies, and the effects persisted in some cases for between 7 and more than 21 days (DECOS 1994).

5.4 Allergenic effects

There are no studies available of the allergenic effects of isopropyl alcohol.

5.5 Reproductive toxicity

As described in the MAK documentation "MAK-Werte und Schwangerschaft" (Begründung "Sammelkapitel Schwangerschaft" Henschler 1989, in German), isopropyl alcohol was classified in Pregnancy Risk Group D, although the isopropyl alcohol concentration in blood resulting from exposure to 400 ml/m^3 very probably cannot have any prenatal toxic effects. For classification in Group C, however, there were no studies with a second species available which confirmed the results found in rats. In the meantime, such studies have been carried out with rabbits and rats.

New Zealand White rabbits (15 per group) were given oral isopropyl alcohol doses of 120, 240 and 480 mg/kg body weight on days 6 to 18 after mating. 13, 15 and 11 rabbits per group were found to be pregnant. Doses of 120 and 240 mg/kg body weight were not toxic for the dams or embryos, and not teratogenic. Doses of 480 mg/kg body weight were toxic for the dams, but not for the embryos, and were not teratogenic. The rabbits treated with 480 mg/kg body weight consumed less food and their body weight development was retarded. Reddened and warm ears, a typical sign of alcohol intoxication, were observed. In addition, cyanosis, lethargy, laboured breathing and diarrhoea were observed. The authors note in particular that signs of prenatal toxicity were not seen at this high dose, although it was lethal for 27% of the dams (Tyl et al. 1994).

Sprague-Dawley rats (25 per group) were given oral isopropyl alcohol doses of 400, 800 and 1200 mg/kg body weight on days 6 to 15 after mating. 25, 23 and 22 rats per group were found to be pregnant. Doses of 400 mg/kg body weight were not toxic for the dams or embryos, and not teratogenic. 800 mg/kg body weight was lethal for one rat and 1200 mg/kg body weight for 2 rats between days 16 and 18 after mating. The mortality was regarded as treatment-related. The foetuses in these two dose groups were 5% and 6% lighter; this was regarded as a sign of prenatal toxicity. Other signs of prenatal toxicity were not seen after these maternally toxic doses of 800 and 1200 mg/kg body weight (Tyl et al. 1994).

These results are comparable to the findings of Nelson et al. (1988) in Sprague-Dawley rats exposed to isopropyl alcohol concentrations of 3500, 7000 and 10 000 ml/m^3 daily for 7 hours on days 1 to 19 after mating. Taking into consideration that the maximum retention of inhaled gases in the rat in general does not exceed a value of 60% (Johanson and Filser 1992), values of 720, 1440 and 2050 mg/kg can be estimated for the exposure-related amount inhaled daily. The effects observed in the foetuses at the low concentration (summarized in "MAK-Werte und Schwangerschaft" 1989 (a documentation containing 19 short reports. In German)) are in the same order of magnitude as those described above after oral doses of 800 mg/kg body weight and day. The higher concentrations caused toxic effects in the dams and led in the foetuses to a clear concentration-dependent increase in toxic effects.

It was also investigated whether isopropyl alcohol can cause neurotoxic damage, as known of short-chain alcohols such as ethanol, in young rats whose mothers were given oral doses of the substance during pregnancy and lactation. For this purpose, Sprague-Dawley rats were given oral isopropyl alcohol doses of 200, 700 and 1200 mg/kg body weight on day 6 after mating to day 21 after birth. The rats produced spontaneous litters. 35, 31 and 35 rats per group produced live offspring. On day 4 after birth, the litters were reduced to 4 male and 4 female rats per litter. On day 22 after birth, 2 animals per litter were killed. After perfusion, the central and peripheral nervous system was histopathologically examined in 6 animals per dose group. The offspring weaned from their mother were reared up to day 68 after birth and subjected to various behavioural tests. No maternally toxic effects were seen, apart from the death of one dam in the high dose group on day 15 after giving birth. Survival of the young and their body weight gains and behavioural development were not impaired. There was no evidence of neurotoxic disorders as a result of the treatment with isopropyl alcohol (Bates et al. 1994).

In a 2-generation study, Sprague-Dawley rats were given oral isopropyl alcohol doses of 100, 500 or 1000 mg/kg body weight and day. The treatment began at least 10 weeks before mating and was continued in the female animals until the end of lactation, and in the male animals until the birth of the offspring. In the middle and high dose groups, body weight gains were increased in the female animals during lactation, and the liver and kidney weights were increased in both sexes. Histopathological examination revealed only in the male animals accumulation of hyaline droplets in the kidneys and other slight changes.

In the F_1 generation of the high dose group, body weights were reduced and mortality in the early postnatal phase increased. Other clinical signs of substance-related toxicity were not observed.

The animals of the F_1 generation were treated as described above and also mated. In these parent animals the observed effects were more severe compared with those in the first parent generation. In addition, centrilobular hypertrophy was observed in the hepatocytes of some male animals. The body weights of the offspring in the high dose group were reduced.

There was a statistically significant ($p < 0.05$) reduction in the mating index of

the male animals of the F_1 generation from the high dose group compared with that for the controls (from 93.3% to 73.1%). In the offspring delivered by caesarian section in the F_1 and F_2 generations, no treatment-related effects were detected. Examination of the sexual organs and investigation of other sex-specific parameters also yielded no treatment-related effects. A NOEL (no observed effect level) for toxic effects on reproduction of 500 mg/kg body weight and day was obtained in this study (Bevan et al. 1995).

5.6 Genotoxicity

5.6.1 In vitro

Isopropyl alcohol was not found to be genotoxic in several *Salmonella* mutagenicity tests, in the SOS chromotest, in the HGPRT (hypoxanthine-guanine phosphoribosyl transferase) test and SCE (sister chromotid exchange) test (DECOS 1994). In a test to detect forward mutation (RK-mutatest) in a specially constructed strain of *Escherichia coli*, the mutation frequency was increased compared with that in the controls by 1.8 and 2.3 times after 10-minute incubation in a 9% and 10% isopropyl alcohol solution. Survival was reduced as a result of the treatment to 63% and 52% of the animals, respectively. A marked increased in the mutation frequency to 63 times the control value was obtained only with the cytotoxic concentration of 12.5% (survival 0.008%) (Hayes et al. 1990).

5.6.2 In vivo

In a valid micronucleus test with mice, isopropyl alcohol was found to be clearly non-genotoxic after intraperitoneal treatment with 350, 1173 or 2500 mg/kg body weight (DECOS 1994).

After rats were exposed for 4 months to concentrations of 1.0 and 10 mg/m^3 (0.4 and 4.1 ml/m^3) for 4 hours a day, a statistically significant increase in the number of mitotic aberrations in bone marrow cells was observed. After intragastral administration, the number of polyploid cells and cells with chromosomal aberrations was slightly increased in the bone marrow of rats. Chromosomal breaks were not observed. The results of both studies are, however, questionable because of shortcomings in the study design and the description of the methods. In cells from the tip of the root of *Allium cepa*, the number of mitotic aberrations was increased by 2.8 times after treatment with isopropyl alcohol. Such findings are generally not interpreted as evidence of genotoxic effects (DECOS 1994; WHO 1990).

5.7 Carcinogenicity

After inhalation exposure to isopropyl alcohol concentrations of 3080 ml/m³ (7700 mg/m³) for 5 to 8 months (3–7 hours a day, 5 days a week) and subcutaneous injection of 0.025 ml isopropyl alcohol once a week for 20 to 40 weeks, no significant increase in the number of lung tumours was found in the treated male mice from three different strains. Other organs were not investigated. The observation period was only 2 to 3 months, and the tumour incidence in the control group was high. No skin tumours were found in mice after the application of isopropyl alcohol to the shaved dorsal skin 3 times a week for 1 year (sex, dose and observation period not stated) (DECOS 1994).

In two valid studies with inhalation exposure of rats and mice, isopropyl alcohol was not found to have carcinogenic potential.

F344 rats of both sexes were given isopropyl alcohol concentrations of 0, 500, 2500 or 5000 ml/m³ for at least 104 weeks (6 hours a day, 5 days a week). The investigations included clinical observations, body and organ weights, examination of the eyes, clinical chemistry and pathology. In the animals of the two high concentration groups, narcotic effects were observed during the treatment. In the female animals of the high concentration group, eye irritation was observed outside the exposure period. In the male animals of the 5000 ml/m³ group, mortality was increased and the average lifespan reduced. During the whole study, the body weights and body weight gains in the two high concentration groups were higher than in the controls.

Significant changes in haematological parameters were not observed in any of the treated rats. Urinalysis revealed changes in the parameters in male animals of the 2500 ml/m³ group and in male and female animals of the 5000 ml/m³ group; this indicates impairments in kidney function, such as reduced osmolarity, an increase in the total protein and glucose levels and an increased volume. In the animals of this concentration group, increased liver and kidney weights were determined in addition. At the interim killing after week 73, a concentration-dependent increase in testis weights was observed. In male and female rats of the two high concentration groups, a series of non-neoplastic changes was observed. The most important were found in the kidneys and indicated chronic damage. In the male animals of the high concentration group which died or were sacrificed moribund, inflammation of the nasal mucosa, squamous metaplasia of the respiratory epithelium of the nasal cavity and iridocyclitis (inflammation of the iris and the ciliary body) were observed. In the female animals of the high concentration group which died or were sacrificed moribund, inflammation of the nasal mucosa and the nasolacrimal channel, squamous metaplasia of the respiratory epithelium of the nasal cavity and inflammation of the cornea were observed. Interstitial cell adenomas of the testes were the only neoplastic change and were observed in the control group and the 3 treated groups with incidences of 64.9%, 77.3%, 86.7% and 94.7%, respectively. The authors interpreted these changes, however, as hyperplasia and not as autonomous growth. The NOEC for toxic effects for rats of both sexes was given

as 500 ml/m³, the NOEC for carcinogenic effects as greater than 5000 ml/m³ (CMA 1994; Garman et al. 1995).

CD-1 mice of both sexes were given isopropyl alcohol concentrations of 0, 500, 2500 or 5000 ml/m³ for 18 months (6 hours a day, 5 days a week). The investigations included clinical observations, body and organ weights, haematology and pathology. During the treatment, narcotic effects were observed in the animals of the two high concentration groups, after the treatment only in the animals of the highest concentration group. The mortality, cause of death and average lifespan were comparable in the treated animals and controls. The body weights and body weight gains in the two high concentration groups were higher than in the controls. Changes in haematological parameters were not determined. In the female animals of the core group (exposure for 78 weeks) and the male animals of the recovery group (exposure for 54 weeks, recovery phase 24 weeks), a concentration-dependent increase in absolute and relative liver weights was observed. The absolute and relative brain weights of the female animals of the 5000 ml/m³ group were decreased. In the male animals of all concentration groups, increased frequencies of abnormal stomach contents were observed at the interim killing. At the end of exposure, the relative testis weights in all concentration groups were reduced. In all groups of exposed male and female animals, a slight increase in proteinosis in the kidney tubules was determined. In the female animals of the 5000 ml/m³ group, dilation of the kidney tubules was observed, in the male animals of the two high concentration groups dilation of the seminal vesicle. The authors do not exclude the possibility that the described effects are treatment-related, but regard them as not biologically relevant. An increase in the occurrence of neoplastic changes was not found in any group. As the changes in organ weights observed in some cases even in the 500 ml/m³ group were not connected with microscopic changes, the NOEC for toxic effects was given as 500 ml/m³ (Burleigh-Flayer et al. 1994°a; CMA 1993).

6 Manifesto (MAK value/classification)

Isopropyl alcohol is not responsible for the increase in the occurrence of tumours associated with the production of isopropyl alcohol according to the strong acid procedure. In workers employed in the production of isopropyl alcohol according to the weak acid procedure, no increased tumour incidence was observed. Also no carcinogenic potential can be deduced from carcinogenicity studies with rats and mice. The interstitial cell adenomas of the testes observed in rats were interpreted as hyperplasia and not as autonomous growth. Isopropyl alcohol proved not to be genotoxic in *in vitro* and *in vivo* investigations. The results in only a few studies that were regarded by the authors as positive are not seen as evidence of a genotoxic potential because of various shortcomings in these studies.

Results of studies of exposed persons which would be suitable for the derivation of a MAK value are not available. No substance-related toxic effects were observed in 60 women exposed at the workplace to isopropyl alcohol concentrations of 1 to 227 ml/m³.

In animal experiments, encrustation in the nose was observed only in male rats after medium-term exposure to concentrations of 500 ml/m³ and above. The toxicological relevance of this finding is questionable in particular because of the lack of microscopic changes. The changes in the kidneys observed also at this concentration and above in male rats are species and sex-specific occurrences. At the next-higher concentration of 1500 ml/m³, the relative liver weights were increased only in female mice. After long-term exposure, the testis weights and the incidence of interstitial cell adenomas of the testes were slightly increased in rats after concentrations of 500 ml/m³ and above. In mice, the relative testis weights were reduced after this concentration and above, and the absolute and relative liver weights increased, but not always in both sexes. Histological examination revealed no effects on these organs. The relevance for humans of the (in some cases only few or sex-specific) findings in rats and mice after concentrations of 500 ml/m³ cannot at present be decided.

The MAK value for isopropyl alcohol has, therefore, been provisionally lowered to 200 ml/m³. According to the few (and in some cases unreliable) findings for the irritative effects of isopropyl alcohol in humans and animals, irritative effects are no longer to be expected at this value.

The classification in Peak Limitation Category II, excursion factor 1 has been retained.

The available data indicate that designation with an "H" (for substances which can penetrate the skin) or "S" (for substances which cause sensitization) is not necessary.

The assumption in the MAK documentation "MAK-Werte und Schwangerschaft" (Begründung "Sammelkapitel Schwangerschaft" Henschler 1989, in German) deduced from studies with rats that the inhalation of 400 ml/m³ very probably cannot have prenatal toxic effects, has in the meantime been confirmed in another species and in other studies. Isopropyl alcohol is therefore classified in Pregnancy Risk Group C.

References

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