Isopropyl benzene / Cumene

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) for isopropyl benzene [98-82-8]. Critical effects after repeated inhalation exposure to isopropyl benzene are the induction of tumours in the lung of mice and in the nose of rats as well as effects on the liver in these species. The classification of isopropyl benzene in Category 3 B for carcinogenic substances is retained. Based on the increased liver weight in a 14-week inhalation study with rats, a MAK value of 10 ml/m^3 has been set. This value is now reaffirmed even considering the increased respiratory volume at the workplace (see List of MAK and BAT Values, Sections I b and I c). As there was a change in the Commissions evaluation on the adversity of increased liver weight, the new evaluation is based on the lower confidence limit of the benchmark dose (BMDL) of 42 ml/m^3 for nasal adenoma in male rats in a two-year inhalation study.
As there is no new data, Peak Limitation Category II with excursion factor of 4 is retained and isopropyl benzene remains assigned to Pregnancy Risk Group C. Isopropyl benzene also remains designated with an "H" (for substances that can be absorbed through the skin in toxicologically relevant amounts).

Keywords

isopropyl benzene; cumene; cumol; 2-phenylpropane; (1-methylethyl)benzene; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; genotoxicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Isopropyl benzene (Cumene)

[98-82-8]

Supplement 2018

MAK value (2012)	**10 ml/m³ ≙ 50 mg/m³**
Peak limitation (2002)	**Category II, excursion factor 4**
Absorption through the skin (1966)	**H**
Sensitization	**–**
Carcinogenicity (2012)	**Category 3B**
Prenatal toxicity (1996)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (2013)	**10 mg 2-phenyl-2-propanol/g creatinine**
Vapour pressure at 25 °C	6.0 hPa (SRC 2017)
log K_{OW}[1)]	3.66 (SRC 2017)
1 ml/m³ (ppm) ≙ 4.987 mg/m³	**1 mg/m³ ≙ 0.201 ml/m³ (ppm)**

Documentation for isopropyl benzene was published in 1996 (documentation "Cumene" 1999), followed by a supplement reviewing the peak limitation category in 2002 (supplement "iso-Propylbenzol" 2002, available in German only) and a supplement in 2013 that focused primarily on new data for the MAK value and carcinogenicity (supplement "Isopropyl benzene" 2013).

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 vapour 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 benzene is 37.0 (Sato and Nakajima 1979). This supplement evaluates whether the MAK value for isopropyl benzene needs to be re-assessed as a result of the higher respiratory volume at the workplace.

1) octanol/water partition coefficient.

Toxicokinetics and Metabolism

Absorption, distribution, elimination

The 1996 documentation (documentation "Cumene" 1999) reported that isopropyl benzene is absorbed through the skin; this was determined based on model calculations. Flux values of 0.004, 0.008 and 0.42 mg/cm^2 and hour were calculated for a saturated aqueous solution of isopropyl benzene according to the models of Wilschut et al. (1995), Guy and Potts (1993) and Fiserova-Bergerova et al. (1990). Based on these flux values, the dermal absorption of about 8, 16 or 834 mg, respectively, was estimated assuming exposure of the skin of both hands and forearms (2000 cm^2) for one hour. In addition, isopropyl benzene was found to penetrate the skin to the same extent as benzene, toluene, and *p*-xylene (no other details). The concentration of toluene in the air exhaled by test persons while and after washing both hands with toluene for five minutes was determined. A penetration rate of 0.5 mg/cm^2 and hour was calculated from the amount of exhaled toluene.

The flux values of between 2 and 3 mg/cm^2 and hour obtained from animal studies with the homologous compound ethylbenzene indicate that alkyl benzenes readily penetrate the skin (see also supplement "Ethylbenzene" 2012).

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

New data have not been published. Further to the study findings reported in the 2013 supplement (supplement "Isopropyl benzene" 2013), Table 1 provides a summary of the inhalation studies with isopropyl benzene in rats relevant to the evaluation and Table 2 the percentage changes in the relative organ weights of the liver and kidneys.

Summary

The Commission now considers an increase in relative liver weight to be adverse only if the increase is greater than 20%; 250 ml/m^3 is thus the NOAEC (no observed adverse effect concentration) for this effect. A NOAEC of 125 ml/m^3 was determined for the increased kidney weights in female rats after 14 weeks. There was no increase in the effect over the course of exposure.

Genotoxicity

In vitro

In the studies of isopropyl benzene available to date, genotoxic effects were neither detected in bacteria, nor in mammalian cells (Salmonella mutagenicity test, HPRT (hypoxanthine guanine phosphoribosyl transferase) test, chromosomal aberration

Table 1 Relevant inhalation studies with isopropyl benzene in rats (NTP 2009)

Species, strain, number per group	Exposure	Findings
rat, F344/N, 5 ♂, 5 ♀	**16 days**, 0, 250, 500, 1000, 2000, 4000 ml/m³, 6 hours/day, 5 days/week	**250 ml/m³ and above**: ♂: liver: absolute and relative weights ↑; kidneys: absolute and relative weights ↑, accumulation of hyaline droplets; ♀: liver: absolute and relative weights ↑; kidneys: absolute and relative weights ↑;
		1000 ml/m³ and above: ataxia, lethargy;
		2000 ml/m³ and above: mortality, body weights and body weight development ↓, absolute and relative thymus weights ↓
rat, F344/N, 10 ♂, 10 ♀ satellite group for haematology: 10 ♂, 10 ♀	**14 weeks**, 0, 62.5, 125, 250, 500, 1000 ml/m³, 6 hours/day, 5 days/week	**62.5 ml/m³ and above**: ♂, ♀: serum bile acids transiently ↑; ♂: serum: ALT activity ↓ (day 23 only); kidneys: relative weights ↑; liver: relative weights ↑;
		125 ml/m³ and above: ♂: kidneys: absolute weights and α_{2u}-globulin ↑; ♀: liver: relative weights ↑;
		250 ml/m³ and above: ♂, ♀: serum: ALT activity ↓ (after 14 weeks); ♂: serum: sorbitol dehydrogenase and AP activity ↓; liver: absolute weights ↑; kidneys: soluble protein and medullary granular casts ↑; ♀: kidneys: relative weights ↑;
		500 ml/m³ and above: ♂: serum: bile acids ↑; ♀: serum: sorbitol dehydrogenase and AP activity ↓;
		1000 ml/m³: ♂, ♀: serum: ALT activity ↓ (at all times); liver: absolute and relative weights ↑; kidneys: absolute and relative weights ↑; adrenal glands: absolute and relative weights ↑; blood: lymphocytes, thrombocytes and total leukocytes ↑, protein, albumin, globulin, calcium and phosphate levels ↑; ♂: kidneys: accumulation of hyaline droplets

ALT: alanine aminotransferase; AP: alkaline phosphatase

Table 2 Increase in relative organ weights [in %] of liver and kidneys in relevant inhalation studies with isopropyl benzene in rats (NTP 2009)

Concentration (ml/m³)	62.5	125	250	500	1000	2000
	16-day study					
relative liver weights (♂/♀)	–	–	15**/11*	18**/19**	45**/37**	87**/81**
relative kidney weights (♀)	–	–	16**	17**	17**	45**
	14-week study					
relative liver weights (♂/♀)	6*/5	4*/6*	10**/10**	21**/14**	28**/30**	–
relative kidney weights (♀)	3	2	5*	7**	11**	–

*: significant difference to the control group in the William's or Dunnett's tests ($p \leq 0.05$)
**: significant difference to the control group in the William's or Dunnett's tests ($p \leq 0.01$)

test, UDS test (test for unscheduled DNA synthesis)) (documentation "Cumene" 1999; supplement "Isopropyl benzene" 2013).

In a bacterial mutation assay using the Salmonella typhimurium strains TA98 and TA100 and the Escherichia coli strain WP2 uvrA (pKM101) with and without the addition of metabolic activation, negative results were obtained with doses of isopropyl benzene of 2.56 to 500 µg/plate. The expected results were achieved with the positive controls. Preincubation was carried out in closed vials because of the volatility of the test substance. Cytotoxicity was observed at the high doses of 250 or 500 µg/plate and above (NTP 2012).

In vivo

The 2013 supplement (supplement "Isopropyl benzene" 2013) describes a micronucleus test with isopropyl benzene given to rats by intraperitoneal injection (NTP 2009). Isopropyl benzene induced only a marginal increase in the number of micronuclei in the bone marrow, which was significant at only 2 of the 6 concentrations tested. For this reason, the results of the study cannot be regarded as unequivocally positive. Other micronucleus tests in mice after inhalation or oral administration of isopropyl benzene yielded negative results (documentation "Cumene" 1999; supplement "Isopropyl benzene" 2013).

To augment the data available, isopropyl benzene was administered orally to male F344 rats and male and female B6C3F1 mice. The leukocytes and cells from the liver, lungs and kidneys were analysed by alkaline comet assay and micronucleus tests were carried out with peripheral blood (see Table 3). The results of the comet assay were mainly negative. However, the findings in the livers of male rats and the lungs of female mice were considered positive in view of a significant trend and a significant increase in DNA damage in the high dose group compared with that in the control group. Micronucleus tests in rats and mice yielded negative results (NTP 2012).

Table 3 New in vivo studies of the genotoxic effects of isopropyl benzene

Test system		Dose	Findings	Comments	References
DNA single strand breaks, comet assay, alkaline, leukocytes, liver, lungs, kidneys	rat, F344, 6 ♂	0, 200, 400, 800 mg/kg body weight, in corn oil, gavage, 1× daily, for 4 days (0, 24, 48, 69 hours), examination after 72 hours, purity: > 99%	+ (liver)[a)] – (leukocytes, lungs, kidneys)	positive control: 200 mg EMS/kg body weight and day	NTP 2012
DNA single strand breaks, comet assay, alkaline, leukocytes, liver, lungs, kidneys	mouse, B6C3F1, 6 ♂ and 6 ♀	♂: 0, 312, 625, 1250 mg/kg body weight, ♀: 0, 250, 500, 1000 mg/kg body weight, in corn oil, gavage, 1× daily, for 4 days (0, 24, 48, 69 hours), examination after 72 hours, purity: > 99%	+ (♀: lungs)[a)] – (♂/♀: leukocytes, liver, kidneys; ♂: lungs)	positive control: 150 mg EMS/kg body weight and day	NTP 2012
micronucleus test, peripheral blood (PCE)	rat, F344, 6 ♂	0, 200, 400, 800 mg/kg body weight, in corn oil, gavage, 1× daily, for 4 days (0, 24, 48, 69 hours), examination after 72 hours, purity: > 99%	–	positive control: 200 mg EMS/kg body weight and day	NTP 2012
micronucleus test, peripheral blood (PCE)	mouse, B6C3F1, 6 ♂ and 6 ♀	♂: 0, 312, 625, 1250 mg/kg body weight, ♀: 0, 250, 500, 1000 mg/kg body weight, in corn oil, gavage, 1× daily, for 4 days (0, 24, 48, 69 hours), examination after 72 hours, purity: > 99%	–	positive control: 150 mg EMS/kg body weight and day	NTP 2012

[a)] significant trend and significant increase in the high dose group compared with the findings in the control group;
EMS: ethyl methanesulfonate; PCE: polychromatic erythrocytes

Summary

In the in vitro genotoxicity tests, negative results were obtained for isopropyl benzene in bacteria or mammalian cells. In vivo, the comet assay, an indicator test, yielded positive results in the liver of male rats and the lungs of female mice, while analyses of other tissues (leukocytes and kidneys) yielded negative results. The results of two micronucleus tests in mice after oral administration and one after inhalation exposure were negative. The results of a micronucleus test with isopropyl benzene given to rats by intraperitoneal injection were not unequivocal and are therefore not to be regarded as positive. This conclusion is confirmed by the negative results obtained in a new micronucleus test in which isopropyl benzene was administered orally to rats.

Manifesto (MAK value/classification)

In animals, isopropyl benzene is slightly irritating to the skin, eyes and respiratory tract. The critical effects after repeated inhalation were the tumour-inducing effects on the lungs of mice and the nose of rats and the effects on the liver of mice and rats.

Carcinogenicity. There are no new data available for the carcinogenic effects of isopropyl benzene. For this reason, isopropyl benzene remains classified in Carcinogen Category 3B.

Germ cell mutagenicity. There are no studies available of the germ cell mutagenicity of the substance. In vitro studies of genotoxicity yielded negative results. Negative results were likewise obtained from two micronucleus tests in mice after oral administration and one after inhalation exposure. The results of a micronucleus test with isopropyl benzene given to rats by intraperitoneal injection were not unequivocal and are therefore not to be regarded as positive (supplement "Isopropyl benzene" 2013). This conclusion is confirmed by the negative results obtained from a new micronucleus test in which isopropyl benzene was administered orally to rats. The comet assay, an indicator test, yielded positive results in the liver of male rats and the lungs of female mice; these are the target organs of isopropyl benzene. However, these positive results are not sufficient to prove that isopropyl benzene has genotoxic potential because the negative results obtained from micronucleus tests indicate that the substance does not induce direct clastogenic effects. For this reason, isopropyl benzene is not classified in one of the categories for germ cell mutagens.

MAK value. In the 2013 supplement (supplement "Isopropyl benzene" 2013), a MAK value of 10 ml/m^3 was derived from the BMDL of 35 ml/m^3 for the increased liver weights (increase by one standard deviation from the control value) determined in the 14-week study in rats and from the $BMDL_{05}$ of 42 ml/m^3 for nasal adenomas determined in the 2-year study in male rats. No new data have become available. The nasal adenomas can be considered a systemic effect because isopropyl benzene causes only very slight irritation. Based on the $BMDL_{05}$ for nasal adenomas and after applying the revised procedure of the Commission (see List of MAK and BAT Values, Section I c), the MAK value does not need to be lowered

after extrapolation of the findings from animal studies to humans (1:2) and taking into consideration the increased respiratory volume of the person at the workplace compared with that of the test animal at rest (1:2). The Commission now considers an increase in relative liver weights to be adverse only if the increase is greater than 20%; 250 ml/m^3 is thus the NOAEC for this effect. After 14 weeks, a NOAEC of 125 ml/m^3 was observed for other systemic end points such as increased kidney weights in female rats and changes in clinico-chemical parameters; there was no increase in the effects over the course of exposure. After extrapolation of the findings from animal studies to humans (1:2) and taking into consideration the increased respiratory volume of the person at the workplace compared with that of the test animal at rest (1:2), a concentration of 31 ml/m^3 is obtained. Therefore, the MAK value of 10 ml/m^3 does not need to be adjusted in view of these systemic effects.

Peak limitation. As no new data are available, the substance continues to be classified in Peak Limitation Category II with an excursion factor of 4.

Prenatal toxicity. There are no new data available for the toxic effects on development of isopropyl benzene.

In the studies already cited in the documentation from 1996 (documentation "Cumene" 1999), no foetotoxic or teratogenic effects were found in rats and rabbits after exposure to isopropyl benzene up to maternally toxic concentrations of 1200 and 2300 ml/m^3, respectively. Even taking the increased respiratory volume (1:2) into consideration, the 60 to 115-fold margin between the NOAEC for developmental toxicity and the MAK value of 10 ml/m^3 is sufficiently large; isopropyl benzene therefore remains classifed in Pregnancy Risk Group C.

Absorption through the skin. No data from studies of the absorption of isopropyl benzene through the skin are available. For this reason, the absorption of the substance through the skin was estimated using mathematical models (Wilschut et al. 1995; Guy and Potts 1993; Fiserova-Bergerova et al. 1990). Model calculations yielded flux values of up to 0.42 mg/cm^2 and hour. As the results for other aromatic alkyls obtained using the model of Fiserova-Bergerova et al. (1990) coincide better with the in vivo data available for these substances, this model is used to assess the dermal absorption of this group of substances. Assuming a penetration rate of 0.42 mg/cm^2 and hour, the dermal absorption of about 830 mg has been estimated after exposure of both hands and forearms (2000 cm^2) to a saturated aqueous solution of isopropyl benzene for one hour. Assuming 60% absorption by inhalation, as is the case for ethylbenzene (supplement "Ethylbenzene" 2012), an inhalation absorption of 300 mg is estimated after 8-hour exposure at the level of the MAK value of 10 ml/m^3 (respiratory volume of 10 m^3). Thus, the contribution of dermal absorption to systemic exposure is toxicologically relevant and isopropyl benzene remains designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

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