The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Isopropyl benzene (cumene) – Evaluation of a BAT value

Assessment Values in Biological Material – Translation of the German version from 2001

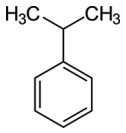
U. Knecht[1]

[1] *Institute and Outpatient Clinic for Occupational and Social Medicine, University Hospital Gießen and Marburg, Aulweg 129, 35392 Gießen, Germany*

email: MAK Commission (arbeitsstoffkommission@dfg.de)

Keywords:

cumene, isopropyl benzene, BAT value, biological tolerance value, biomonitoring, 2-phenyl-2-propanol

BAT value (2000)	**50 mg 2-phenyl-2-propanol (after hydrolysis)/g creatinine**[a)] Sampling time: end of exposure or end of shift **2 mg isopropyl benzene/l blood**[a)] Sampling time: end of exposure or end of shift
MAK value (1966, 1996)	**50 ml/m³ (ppm) ≙ 250 mg/m³** [b)]
Synonyms	cumol 2-phenylpropane
Chemical name (CAS)	(1-methylethyl)benzene
CAS number	98-82-8
Formula	 C_9H_{12}
Molar mass	120.2 g/mol
Melting point	−97 °C
Boiling point	152.4 °C
Density at 25 °C	0.86 g/cm³
Vapour pressure at 20 °C	5.3 hPa
Odour threshold	0.06 mg/m³
Solubility in water at 20 °C	50 mg/l

[a)] No longer valid. For the current value see Klotz and Knecht (2021).

[b)] No longer valid. For the current value see Hartwig and MAK Commission (2018).

Citation Note:
Knecht U. Isopropyl benzene (cumene) – Evaluation of a BAT value. Assessment Values in Biological Material – Translation of the German version from 2001. MAK Collect Occup Health Saf. 2021 Dec:Doc920. DOI: https://doi.org/10.34865/bb9882eoj21_1or

Manuscript completed:
19 Jan 2000

Publication date:
14 Dec 2021

Isopropyl benzene (cumene) is a colourless hydrocarbon. It is insoluble in water and has an aromatic, gasoline-like odour. Isopropyl benzene is miscible to an unlimited extent with other solvents such as acetone, alcohol, ether or benzene. Isopropyl benzene vapours together with air form an explosive mixture. The approx. 800 000 tonnes per year produced in Germany at present are almost exclusively used in the manufacture of phenol, acetone and alpha-methylstyrene. In addition, isopropyl benzene is used as a feedstock in the detergent and chemical industry, in the manufacture of plastic materials, resins, pesticides and insecticides, as metal cleaner and especially in the solvents industry for paints, printing colours, coatings and ink. Furthermore, it is used in gasoline (Falbe and Regitz 1999; Voges 1989, p. 257–258; Weissermel and Arpe 1994). The maximum workplace concentration (MAK value) of 50 ml/m³ for isopropyl benzene established in 1966 has been confirmed in 1996 (translated in Greim 1999).

1 Toxicokinetics

1.1 Absorption and distribution

When handling isopropyl benzene, the substance can basically be taken up by inhalation, dermal and oral absorption. From the viewpoint of occupational health and environmental medicine inhalation and percutaneous absorption are the main routes of uptake. To estimate the absorbed amount of the substance, pulmonary retention can be used which shows the difference in concentration between exhaled air and inhaled air in % of the inhaled concentration (Bolt and Drexler 1994). In experiments with inhalation exposure of humans to concentrations of 240, 480 and 720 mg isopropyl benzene/m³ the pulmonary retention was, independent of concentration, initially 64% and decreased to 45% after 8-hour exposure (Seńczuk and Litewka 1976). Percutaneous absorption of isopropyl benzene is conceivable both via direct skin contact and via ambient air. Dermal absorption depends on many factors. These include especially the working in a hot environment with increased skin circulation or in a humid environment with changes in the horny layer. Based on its physico-chemical properties, the skin penetration rate of isopropyl benzene was predicted to be 0.34 mg/cm² per hour for a saturated aqueous isopropyl benzene solution (Fiserova-Bergerova et al. 1990).

Although oral absorption is conceivable in the case of accidents at work, it is hardly of any significance in the actual working life.

To date, there are no studies available for the distribution and accumulation of isopropyl benzene in human tissues. The partition coefficients water:air, blood:air and oil:air of 1.4, 37 and 6215, respectively, of oil:water of > 4300 and oil:blood of 168, however, suggest that isopropyl benzene is distributed in the whole organism – especially in the adipose tissue (Gerarde 1959; Sato and Nakajima 1979).

In blood, 85% of isopropyl benzene is bound to proteins (Fabre et al. 1985; Lam et al. 1990).

1.2 Metabolism

Biotransformation of isopropyl benzene takes place via stepwise oxidation, predominantly in the liver (Pyykkö et al. 1987; Robinson et al. 1955).

The oxidative metabolism of isopropyl benzene starts at the isopropyl group. The biotransformation process is shown in Figure 1.

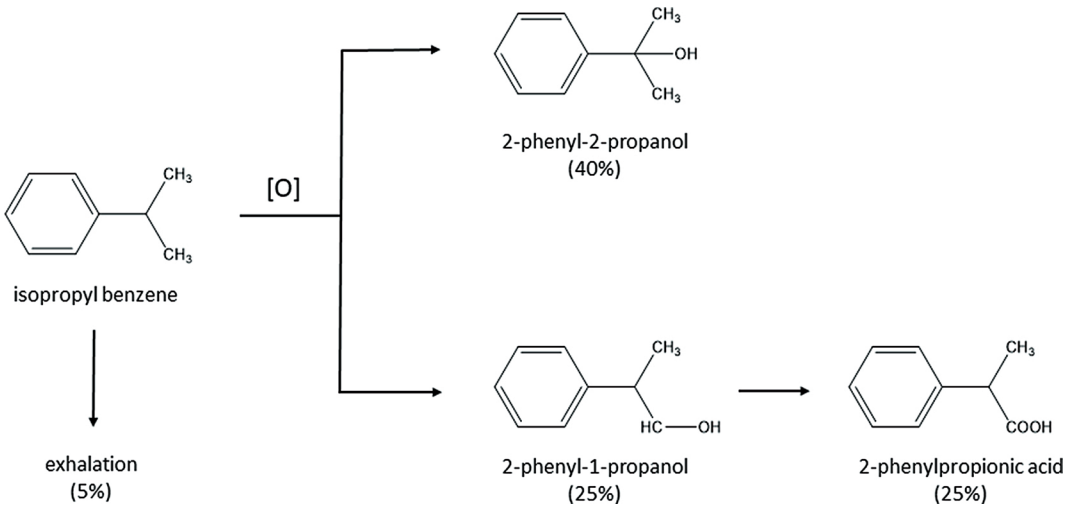


Fig. 1 Metabolism of isopropyl benzene (cumene). The excretion rates given are based on animal experiments (Robinson et al. 1955).

The spectrum of metabolites includes 2-phenyl-2-propanol (main metabolite), 2-phenyl-1-propanol and 2-phenylpropionic acid. The metabolites are bound to glucuronic acid or glycine (Bakke and Scheline 1970; Robinson et al. 1955; Sencczuk and Litewka 1976).

1.3 Elimination

Isopropyl benzene is eliminated in small quantities as unchanged substance by exhalation via the lungs. Elimination thus depends on the isopropyl benzene concentration in blood and the vapour pressure. The greater portion, however, independent of the route of uptake, is excreted with the urine in the form of water soluble, biotransformed metabolites. Due to its poor solubility in water, pure isopropyl benzene is not renally eliminated.

In rabbits, after oral administration, isopropyl benzene was transformed to 2-phenyl-2-propanol (approx. 40%), to 2-phenyl-1-propanol (25%) and to 2-phenylpropionic acid (25%) (Robinson et al. 1955). After oral administration (100 mg isopropyl benzene/kg body weight) to rats mainly 2-phenyl-1-propanol was found, 2-phenyl-2-propanol to a lesser extent. Unlike in other aromatic hydrocarbons, degradation via phenol derivatives could not be demonstrated, which is thought to be the reason for the lack of toxicity to the bone marrow (Bakke and Scheline 1970). Studies with mice could only demonstrate the excretion of 2-phenyl-2-propanol (Goenechea et al. 1986). In inhalation studies in humans 35% of the inhaled isopropyl benzene was biphasically eliminated as 2-phenyl-2-propanol (Sencczuk and Litewka 1976).

2 Critical Toxicity

2.1 Acute toxicity

The main effect of aromatic hydrocarbons is local irritation. Manifestation and severity of the irritation are determined by the chain length. Isopropyl benzene mainly causes irritation to the skin, eyes and respiratory tract: conjunctivitis, irritation of the respiratory tract and dermatitis have been described; acute liver damage is also possible.

Independent of their chemical structure aromatic hydrocarbons are inhalation anaesthetics. This non-specific central depressive effect is caused by the unchanged substance. Vapour concentrations markedly above the current MAK value of 250 mg/m³ can, in addition to the mentioned local irritation, have effects on the central nervous system with the risk of central respiratory paralysis. Other symptoms of central nervous effects are a feeling of being unwell, concentration disorders, dizziness, drowsiness, nausea, abdominal pain, dyspnoea. Overall, the acute systemic toxicity is however to be regarded as rather low. Impurities with isopropyl benzene hydroperoxide, which is formed during oxidation of isopropyl benzene, can induce haemolytic effects (Sandmeyer 1994). An 18-hour exposure of rats to 1000 and 616 ml/m³ caused hyperaemia in lungs and liver, spleen enlargement and haemorrhagic kidney changes as early as one day after the exposure. Histopathology revealed kidney damage. In mice, the inhalation LC_{50} was determined to be approx. 2000 ml/m³ after 7-hour exposure.

2.2 Chronic toxicity

After chronic exposure to isopropyl benzene mainly general symptoms like tiredness, weakness, headaches, nausea and alcohol intolerance were observed. These central nervous symptoms are due to the special affinity of isopropyl benzene to the nerve cells. Interaction of the hydrophobic substance with neuronal membranes leads to changes in the cell permeability and metabolic processes in the brain (Jenkins et al. 1970; Nau et al. 1966; Smyth et al. 1951). In addition to irritation, the main effects of its critical toxicity are impairment of central nervous functions. Complaints and symptoms are caused by the non-metabolised substance.

3 Exposure and effects

3.1 Relationship between external and internal exposure

At the moment, there are no results available from field studies for the relationship between external and internal exposure. Knecht and Ulshöfer (1996) carried out a study with 18 test persons at external isopropyl benzene exposure concentrations between 15 and 50 ml/m³. Exposure duration was eight hours in total, with a ten minute physical exercise of 75 Watt per hour on a bicycle ergometer. Exposure was interrupted after four hours by a 45-minute break outside the chamber. The concentrations of isopropyl benzene were analysed in blood and alveolar air, as well as those of the metabolites normally excreted with the urine, i.e. 2-phenyl-1-propanol, 2-phenyl-2-propanol and 2-phenylpropionic acid.

The isopropyl benzene concentrations in blood are shown in Table 1.

Tab. 1 Isopropyl benzene concentrations in air and blood samples during and after 8-hour standardised exposure to 15–50 ml/m³ isopropyl benzene

Isopropyl benzene in air	Test persons	Isopropyl benzene in blood [mg/l]	
[ml/m³]	[n]	after 4-hour exposure	after the end of exposure
45–50	8	1.18 ± 0.44	1.54 ± 0.33
35–40	5	0.75 ± 0.27	0.79 ± 0.26
25–30	2	0.51 ± 0.03	0.64 ± 0.14
15	2	0.56 ± 0.13	0.59 ± 0.06

Using further blood samples obtained at short intervals after the end of exposure, the elimination kinetics of isopropyl benzene could be determined (Figure 2).

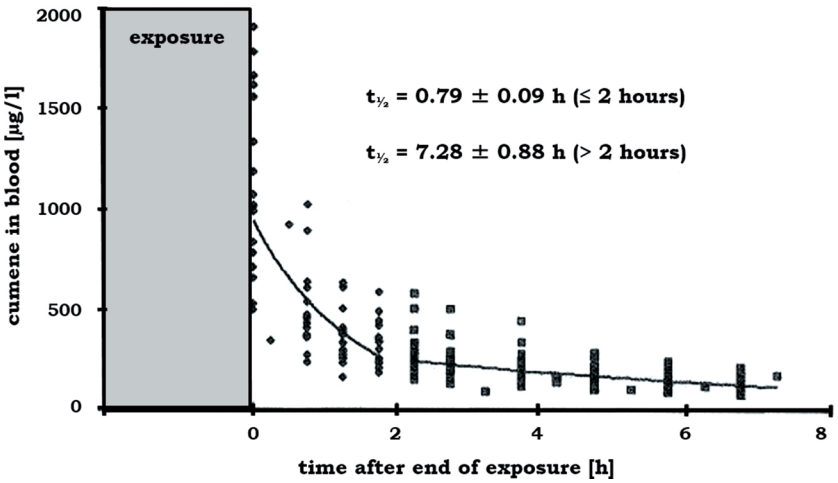


Fig. 2 Biphasic elimination kinetics of isopropyl benzene (cumene) in blood

The isopropyl benzene concentrations in alveolar air are closely correlated with the blood levels. The results of the measurements in alveolar air are shown in Table 2.

From the alveolar air samples taken at the end of exposure parallel to the blood samples individual mean half-lives can be calculated, which also show biphasic elimination kinetics. During the first two hours after the end of exposure a half-life of $t_{1/2} = 0.87 \pm 0.26$ hours is obtained which, in the further course, increases to $t_{1/2} = 8.15 \pm 0.74$ hours.

Separate investigations of the pulmonary retention of isopropyl benzene during a 4-hour exposure to 50 ml isopropyl benzene/m^3 revealed an initial retention of 50.1%, which decreased to 37.8% toward the end of exposure.

Tab. 2 Isopropyl benzene concentrations in air and alveolar air samples during and after 8-hour standardised exposure to 15–50 ml isopropyl benzene/m^3

Isopropyl benzene in air	Test persons	Isopropyl benzene in alveolar air [µg/l]	
[ml/m^3]	[n]	after 4-hour exposure	after the end of exposure
45–50	7	12.84 ± 4.41	16.05 ± 4.08
35–40	4	8.97 ± 1.38	8.37 ± 0.82
25–30	3	5.69 ± 0.47	7.06 ± 1.67
15	2	3.86 ± 0.49	5.60 ± 1.35

Table 3 shows the average renal excretion rates of the isopropyl benzene metabolites in relation to external exposure.

Tab. 3 Average concentrations of the isopropyl benzene metabolites in urine [mg/g creatinine] immediately after the end of exposure (up to approx. 2 hours thereafter)

Isopropyl benzene in air	Number of samples	2-Phenyl-2-propanol	2-Phenyl-1-propanol	2-Phenylpropionic acid
[ml/m^3]	[n]	[mg/g creatinine]	[mg/g creatinine]	[mg/g creatinine]
45–50	20	35.8 ± 13.2[a)]	1.3 ± 0.4	8.3 ± 5.3
35–40	12	32.8 ± 14.2	0.8 ± 0.2	7.1 ± 3.3
25–30	9	20.1 ± 4.3	0.6 ± 0.2	4.8 ± 2.4
15	5	7.5 ± 2.0	0.4 ± 0.1	2.6 ± 0.7

[a)] 95th percentile 51.2 mg/g creatinine

Figure 3 shows in an exemplary manner the cumulative elimination kinetics of 2-phenyl-2-propanol over a period of about 50 hours after the start of exposure. It can be seen that 50% of this metabolite has been eliminated about 9.5 hours after the start of exposure. From this kinetics no strong accumulation properties can be concluded. Irrespective of the external exposure the calculated half-lives were $t_{1/2} = 6.4 \pm 1.0$ hours. The same interpretation applies to the excretion behaviour of 2-phenyl-1-propanol. The resulting average half-life is $t_{1/2} = 8.8 \pm 0.6$ hours. In the case of 2-phenylpropionic acid 50% has been excreted in urine 4 hours after the end of exposure with an average half-life of $t_{1/2} = 10.8 \pm 2.3$ hours.

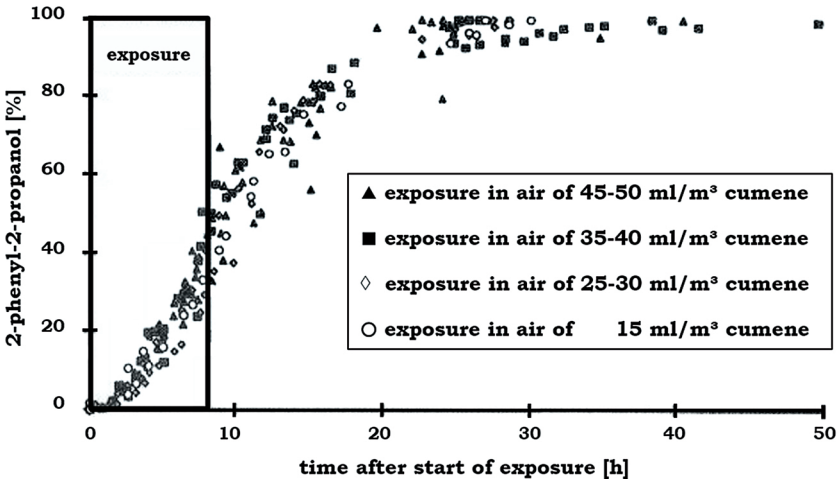


Fig. 3 Cumulative urinary excretion of the isopropyl benzene metabolite 2-phenyl-2-propanol following exposure to 15–50 ml isopropyl benzene (cumene)/m^3

In a laboratory study carried out by Sećzuk and Litewka (1976) isopropyl benzene exposure concentrations clearly above the level of the MAK value were used. Therefore, these were not considered any further in the evaluation of the biological tolerance value (BAT value).

4 Selection of the indicators

Basically, the following parameters are available for the biomonitoring of isopropyl benzene-exposed workers:

- determination of the isopropyl benzene concentration in alveolar air,
- determination of the isopropyl benzene concentration in blood,
- determination of 2-phenyl-2-propanol in urine,
- determination of 2-phenyl-1-propanol in urine, and
- determination of 2-phenylpropionic acid in urine.

As the critical toxicity is related to the hazardous substance itself, the isopropyl benzene determinations in alveolar air and blood are primarily suited to estimate internal exposure. Alveolar air sampling can only be carried out with standardised sampling techniques (breath sampler). This limits the use of the method. Available results, however, show that the advantages of this non-invasive procedure are not to be ignored.

Using standardised exposures it could be demonstrated that the determination of isopropyl benzene in blood is an effective parameter reflecting the external exposure in a representative way. The isopropyl benzene level in blood quickly responds to changing external exposure situations.

Apart from the determination of unmetabolised isopropyl benzene, the determination of its selective metabolites 2-phenyl-2-propanol, 2-phenyl-1-propanol and 2-phenylpropionic acid are suited as indicators. Priority should be given to the parameter 2-phenyl-2-propanol in so far as its excretion rates are the highest.

At present, no parameters for effect monitoring are known.

5 Analytical Methods

A suitable and proven procedure for the determination of isopropyl benzene in blood is the gas chromatographic head-space method (Goenechea and Machata 1983). For the determination of the isopropyl benzene metabolites, gas chromatographic, but also HPLC procedures are suitable analytical methods.

6 Evaluation of the BAT value

On the basis of a laboratory study by Knecht and Ulshöfer (1996), it is possible to establish correlations between an external exposure to 15 to 50 ml isopropyl benzene/m^3 and the resulting isopropyl benzene levels in blood. For the evaluation of a **BAT value** it seems to be essential that exposure by direct skin contact can be excluded. A ten minute exercise of 75 Watt per hour on a bicycle ergometer in each case corresponds to a medium-heavy physical activity. The resulting increase in the respiratory minute volume can have a significant impact on the rate of absorption. This appears to be of relevance in so far as the partition coefficient of isopropyl benzene between blood and air is given to be 37 (Gerarde 1959; Sato and Nakajima 1979).

From the results of the study by Knecht and Ulshöfer (1996) and taking into consideration the 95th percentile

a BAT value of 2 mg isopropyl benzene/l blood

can be derived. This relates to sampling carried out immediately after the end of a shift. For later samplings an initial half-life of about 0.8 hours for the elimination of isopropyl benzene from blood has to be taken into account.

Analysis of isopropyl benzene in alveolar air should only be used if samples can be taken in a standardised way. Under these conditions, the efficiency of detection in alveolar air is similar to that in blood.

There are quantitative differences in renal excretion of the individual isopropyl benzene metabolites. While 2-phenyl-2-propanol has the highest excretion rates, those of the corresponding carbonic acid and 2-phenyl-1-propanol are clearly lower.

The laboratory investigations by Knecht and Ulshöfer (1996) allow to establish a relationship between isopropyl benzene concentration in ambient air and 2-phenyl-2-propanol in urine. According to these, an eight hour exposure to isopropyl benzene at the level of the present MAK value of 50 ml/m^3 corresponds, at the end of exposure, to a renal excretion of

50 mg 2-phenyl-2-propanol/g creatinine

released from the conjugates.

This value is established as **BAT value**. It is the 95th percentile of the renal excretion. It should be noted that sampling can be carried out immediately after the end of shift up to approx. two hours thereafter.

Note: These BAT values are no longer valid. For updates please refer to Klotz and Knecht (2021).

7 Interpretation of analytical data

Analysis of blood levels is best suited to show highly variable external isopropyl benzene exposures.

As could be demonstrated in investigations with other aromatics, serious interactions have to be expected for the toxicokinetics of isopropyl benzene in the case of simultaneous alcohol consumption. This effect leads to a changed metabolite spectrum with regard to level and chronological sequence. In addition, there might be an effect on the level of the isopropyl benzene concentration in blood, since markedly higher levels can result from alcohol consumption.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

References

Bakke OM, Scheline RR (1970) Hydroxylation of aromatic hydrocarbons in the rat. Toxicol Appl Pharmacol 16(3): 691–700. DOI: 10.1016/0041-008x(70)90074-8

Bolt HM, Drexler H (1994) Biologische Arbeitsstoff-Toleranzwerte (Biomonitoring). Teil III: Toxikokinetische Grundlagen. (Aufnahme, Verteilung, Stoffwechsel, Ausscheidung). Arbeitsmed Sozialmed Umweltmed 29: 206–208

Fabre R, Truhaut R, Laham S, Peron M (1985) Recherches toxicologiques sur les solvents de remplacement du benzène. II. Etude du toluène [Toxicological research on solvents substituted for benzene. II. Study of toluene]. Arch Mal Prof 16(3): 197–215

Falbe J, Regitz M (eds) (1999) Römpp Lexikon Chemie, 10th ed. Thieme, Stuttgart

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med 17(5): 617–635. DOI: 10.1002/ajim.4700170507

Gerarde HW (1959) Toxicological studies on hydrocarbons. III. The biochemorphology of the phenylalkanes and phenylalkenes. AMA Arch Ind Health 19(4): 403–418

Goenechea S, Machata G (1983) Isopropylbenzol (Cumol). In: Angerer J, Schaller KH, Henschler D (eds) Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Bd 2: Analysen in biologischem Material, 7. Lieferung. VCH, Weinheim. Also available from DOI: 10.1002/3527600418.bi9882d0007

Goenechea S, Rücker G, Hoffmann G, Neugebauer M, Langer M (1986) Spaltung von 2-Phenylpropan-1-ol- und 2-Phenylpropan-2-ol-Glucuronid, zweier Metaboliten des Isopropylbenzol (Cumol). Z Rechtsmed 97: 83–88

Greim H (ed) (1999) Cumene. MAK Value Documentation, 1996. In: Occupational Toxicants, vol 13. Wiley-VCH, Weinheim, 118–128. Also available from DOI: 10.1002/3527600418.mb9882e0013

Hartwig A, MAK Commission (2018) Isopropyl benzene/Cumene. MAK Value Documentation, 2018. MAK Collect Occup Health Saf 3(4): 1909–1917. DOI: 10.1002/3527600418.mb9882e6418

Jenkins LH, Jones RA, Siegel J (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol 16(3): 818–823. DOI: 10.1016/0041-008x(70)90088-8

Klotz K, Knecht U (2021) Cumene (iso-propylbenzene) – Addendum for re-evaluation of the BAT value. Assessment Values in Biological Material – Translation of the German version from 2014. MAK Collect Occup Health Saf: Doc921. DOI: 10.34865/bb9882eoj21_1ad

Knecht U, Ulshöfer A (1996) Bio-Monitoring nach iso-Propylbenzol-Einwirkung. In: DGAUM (ed) 36. Wissenschaftliche Jahrestagung 1996. Rindt, Wiesbaden, 225–227

Lam C-W, Galen TJ, Boyd JF, Pierson DL (1990) Mechanism of transport and distribution of organic solvents in blood. Toxicol Appl Pharmacol 104(1): 117–129. DOI: 10.1016/0041-008x(90)90287-5

Nau CA, Neal J, Thornton M (1966) C9–C12 Fractions obtained from petroleum distillates. An evaluation on their potential toxicity. Arch Environ Health 12(3): 382–393. DOI: 10.1080/00039896.1966.10664385

Pyykkö K, Paavilainen S, Metsä-Ketelä T, Laustiola K (1987) The increasing and decreasing effects of aromatic hydrocarbon sovents in pulmonary and hepatic cytochrome P-450 in rat. Pharmacol Toxicol 60(4): 288–293. DOI: 10.1111/j.1600-0773.1987.tb01754.x

Robinson D, Smith JN, Williams RT (1955) Studies in detoxication. 60. The metabolism of alkylbenzenes: isopropylbenzene (cumene) and derivatives of hydratropic acid. Biochem J 59(1): 153–159. DOI: 10.1042/bj0590153

Sandmeyer EE (1994) Aromatic hydrocarbons. In: Clayton GD, Clayton FE (eds) Patty's industrial hygiene and toxicology, vol 2, pt B, 4th ed. John Wiley & Sons, New York, NY

Sato A, Nakajima T (1979) Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br J Ind Med 36(3): 231–234. DOI: 10.1136/oem.36.3.231

Seńczuk W, Litewka B (1976) Absorption of cumene through the respiratory tract and excretion of dimethylphenylcarbinol in urine. Br J Ind Med 33(2): 100–105. DOI: 10.1136/oem.33.2.100

Smyth HF Jr, Carpenter CP, Weil CS (1951) Range-finding toxicity data: list IV. Arch Ind Hyg Occup Med 4(2): 199–122

Voges H-W (1989) Cumene. In: Elvers B, Hawkins S, Ravenscroft M, Schulz G (eds) Ullmann's encyclopedia of technical chemistry, vol A13, 5th ed. VCH, Weinheim

Weissermel K, Arpe H-J (1994) Industrielle Organische Chemie, 4th ed. Wiley-VCH, Weinheim