European Commission

SCOEL/REC/029
2-Phenylpropane (Cumene)

Recommendation from the
Scientific Committee on Occupational Exposure Limits

Scientific Committee
on Occupational Exposure Limits

H.M. Bolt, G. Nielsen, D. Papameletiou, C. L. Klein
Adopted 23 September – 2015; Corrigendum 5 December -2017

EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B — Employment
Unit B.3 — Health and Safety

Contact: Dr. Christoph Klein

E-mail: *EMPL-SCOEL@ec.europa.eu*
Christoph.Klein@*ec.europa.eu*

European Commission
B-1049 Brussels

SCOEL/REC/029
2-Phenylpropane (Cumene)

Recommendation from the
Scientific Committee on Occupational Exposure Limits

Corrigendum (5 December -2017):

- *In Chapter 3 (page 13) of the REC the following sentence has been deleted: '2-Phenylpropane is considered a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC.'*
- *In Chapter 7.6 (page 26) the word NMP has been substituted with 2-phenylpropane.*

Directorate-General for Employment, Social Affairs and Inclusion
Scientific Committee on Occupational Exposure Limits

2016

Europe Direct is a service to help you find answers to your questions about the European Union.

Freephone number (*)**:**

00 800 6 7 8 9 10 11

(*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Luxembourg: Publications Office of the European Union, 2016

ISBN 978-92-79-77248-1
doi: 10.2767/120149

PRINTED IN LUXEMBOURG

PRINTED ON ELEMENTAL CHLORINE-FREE BLEACHED PAPER (ECF)

CONTENTS

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR 2-PHENYLPROPANE (CUMENE)

8-hour TWA:	50 mg/m^3 (10 ppm)
STEL:	250 mg/m^3 (50 ppm)
BLV:	7 mg 2-phenyl-2-propanol/g creatinine (sampled within 2 hours post shift)
Additional categorisation:	SCOEL carcinogen group D (non-genotoxic carcinogen) with Mode of Action-based threshold
Notation:	skin

This evaluation is an update of an earlier assessment by this committee from (SCOEL1993) and is based on Gardner (1994), Greim (1996), EPA (1997), WHO (1999), ECB (2000), ECB (2001), ACGIH (2001), NTP (2009, 2012a,b, 2013), IARC (2012), the references cited in these reviews and a literature survey by SCOEL performed in 2014.

The present Recommendation was adopted by SCOEL on 2015-09-23; corrigendum 2017-12-05.

RECOMMENDATION EXECUTIVE SUMMARY

The acute toxicity of 2-phenylpropane is low and mostly related to pre-narcotic solvent effects. For neurobehavioural effects, a NOAEC of 100 ppm has been reported (see Section 7.2.2).

For the question of recommending an OEL, the critical effect of 2-phenylpropane, carcinogenicity, as experimentally demonstrated in animals, must be considered. Under conditions of a 2-year inhalation bioassay (NTP 2009, see Section 7.7.2), increased incidences in male and female F344/N rats of (benign) respiratory epithelial adenoma in the nose and in males renal tubule adenoma or carcinoma (combined) were observed. In male and female B6C3F1 mice, evidence of carcinogenic activity was based on increased incidences of alveolar/bronchiolar neoplasms. Also, increased incidences of hepatocelullar adenoma or carcinoma (combined) in female mice were related to the exposure.

In mutagenicity/genotoxicity assays, both *in vitro* and *in vivo*, 2-phenylpropane was overwhelmingly negative (for details, see Section 7.6); dose-related increases in DNA damage were observed in male rat liver cells and female mouse lung cells, but not in other tissues. Although metabolites of potential genotoxicity might be formed, the mode of action of 2-phenylpropane appears to be non-genotoxic.

As explained in Section 7.9, the observed difference between rats and mice in lung carcinogenicity may be explained by differences in the local metabolism, as there are more Clara cells in mice than in rats, which contain the ring-oxidising cytochromes P-450 CYP2F and CYP2E1 (Sections 7.1.2./7.9.). As in humans there are even less Clara cells than in rats. A very low susceptibility of humans may be reasonably anticipated. By analogy to other solvents, e.g. phenylethane (ethyl benzene), the renal effects of 2-phenylpropane in male rats (tubular adenomas/carcinomas) may reasonably be related to the specific $\alpha 2_u$-globulin-nephropathy, which is not relevant to humans. In the case of 2-phenylpropane, this is supported by measurements of $\alpha 2_u$-globulin in kidneys of rats exposed subchronically (NTP 2009, NTP 2012b; see Section 7.3.2). Damage to rat nasal tissue was not observed in subchronic studies at all concentrations tested, up to 500 ppm 2-phenylpropane (Section 7.3.2). In the 2-year study by NTP (2009), there were signs of chronic inflammation in the nasal epithelium of rats in conjunction with the occurrence of adenomas of the respiratory epithelium (Section 7.7.2). Based on these arguments, the existence of a threshold for the experimentally observed carcinogenic effects of 2-phenylpropane is very likely. In total, the data suggest that 2-phenylpropene is an overwhelmingly non-genotoxic carcinogen. In consequence, the compound is grouped into *SCOEL carcinogenicity group D, for which a health-based OEL may be derived*.

The NOAEC in rats, based on the studies of Cushman *et al* (1995) and NTP (1999) is 50 ppm (Section 7.3.2). This NOAEC is primarily based on hepatic effects. As discussed in Section 7.7.2, there is evidence that the formation of liver tumours in (female) mice cannot be translated to humans based on kinetic and dynamic arguments. But it appears safe to base the OEL derivation on this NOAEC, as this will provide an in-built margin of safety. The derived OEL will therefore in any case be protective against carcinogenic effects seen in animal experiments. The OEL evaluation is based on experimental studies with inhalation exposure. Starting from the NOAEC of 50 ppm an uncertainty factor of 5 is applied accounting for the nature of the effect and the remaining uncertainties due to inter- and intra-species differences. Therefore, a health-based *OEL of 10 ppm is recommended, based on the preferred value approach*. Together with the above mentioned in-built margin of safety, this OEL will provide a sufficient distance to reported adverse effects. *A STEL of 50 ppm can be recommended* to protect against possible short-term behavioural effects and is also protective against local irritation.

Biological Monitoring

The database for human biological monitoring has been described in Section 7.1.4. Because of non-invasiveness, the excretion of the metabolite 2-phenyl-2-propanol in the urine appears as an appropriate parameter, with a sampling time not later than 2 hours after a shift. Based on the human volunteer exposure data by Knecht and Ulshöfer

(1996, see Section 7.1.4), *a BLV is recommended of a urinary excretion 7 mg 2-phenyl-2-propanol per g creatinine*. This BLV is equivalent to the proposed OEL.

Other assignments

No consistent information is given on the dermal absorption of this compound through the intact skin. 2-Phenylpropane did not clearly show skin absorption in two older studies (Valette *et al* 1954, Wolf *et al* 1956), but it caused severe systemic effects in another investigation (Monsanto Co. 1978). Because of its high lipophilicity and its analogy to benzene and xylene, a relevant skin penetration can be assumed. Fiserova-Bergerova *et al* (1990) calculated a human skin penetration rate of about 0.34 mg/cm^2/hour for a saturated aqueous solution of 2-phenylpropane. Therefore, a *"skin notation" is recommended*, which is also in line with current assessments of the European Union Risk Assessment Report (ECB 2001), the UK Health and Safety Executive (Gardner and Delic 1994) and the German MAK Commission (Greim 1996).

As there were no experimental signs of ototoxicity of 2-phenylpropane (Cushman *et al* 1995, Section 7.3.2), there is no need of a "noise notation".

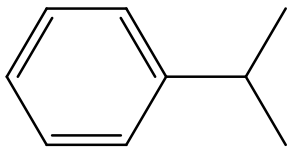
Measurement and measurement systems

Analytical measurement systems exist to determine the recommended levels with an appropriate level of precision and accuracy. Standard methods for determination of solvents can be applied. For the determination of the metabolite 2-phenyl-2-propanol in urine, an established analytical method is available (Knecht 2013).

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

2-Phenylpropane is a clear, colourless liquid with a strong aromatic odour. The boiling point of the substance is 152.7 °C and the vapour pressure is 4.96 hPa at 20 °C. 2-Phenylpropane is almost insoluble in water, but it is soluble in most organic solvents. The log P_{OW} is 3.55. The substance has a flash point of 39 °C (closed cup) and a density of 0.86 g/cm^3 at 20 °C (ACGIH 2001; ECB 2000).

Name:	2-phenylpropane
Synonyms:	cumene; propylbenzene; isopropylbenzene (1-methylethyl) benzene
Molecular formula:	C9H12
Structural formula:	
EC No.:	202-704-5
CAS No.:	98-82-8
Molecular weight:	120.19 g/mol
Boiling point:	152.7 °C
Melting point:	-96.0 °C
Vapour pressure (20° C)	4 hPa
Conversion factors	1 ppm = 5 mg/m^3
(20 °C, 101.3kPa)	1 mg/m^3 = 0.2 ppm

2. EU HARMONISED CLASSIFICATION AND LABELLING

EU classification:

Flam. Liq. 3 H226 Flammable liquid and vapour

Asp. Tox. 1 H304 May be fatal if swallowed and enters airways

STOT SE 3 H335 May cause respiratory irritation

Aquatic Chronic 2 H411 Toxic to aquatic life with long lasting effects

Information about the EU harmonised classification and labelling for 2-Phenylpropane (cumene) is provided by ECHA, as summarised in Tables 1 and 2.

Table 1: 2-Phenylpropane/cumene: Classification according to part 3 of Annex VI, table 3.1 (list of harmonised classification and labelling of hazardous substances of Regulation (EC) No1272/2008; Source: ECHA (2015)

Index no.	International Chemical Identification	EC no	CAS no.	Classification		Labelling			Spec. Conc. Limits M-factors	Notes
				Hazard Class & Category Code (s)	Hazard statement code (s)	Picto-gram Signal Word Code (s)	Hazard statement code (s)	Suppl. Hazard statement code (s)		
601-024-00-X	2-phenylpropane	202-704-5	98-82-8	flam. liq. 3 asp. Tox. 1 STOT SE 3 aquatic chronic 2	H226 H304 H335 H411	GHS07 GHS02 GHS09 GHS08 Dgr	H226 H304 H335 H411			Note C

Table 2: 2-Phenylpropane/cumene: Classification according to part 3 of Annex VI, table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC of Regulation (EC) No1272/2008; Source: ECHA (2015)

Classification	Risk Phrases	Safety Phrases	Indication of danger	Concentration Limits	
				Concentration	Classification
				-	-
R10	10	24			
Xn; R65	37	37	Xn		
Xi; R37	51/53	61	N		
N; R51-53	65	62			

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

2-Phenylpropane is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits for 2-phenylpropane (cumene) exist in a number of countries, as shown in the table below. The values presented below represent examples and are not an exhaustive listing of all limit values within the EU and other countries.

Table 3: Existing OELs for 2-phenylpropane (cumene); adapted from the GESTIS database (GESTIS, 2015).

EU-countries	TWA (8 hrs)		STEL (15 min)		
	ppm	mg/m³	ppm	mg/m³	References
Austria	20	100	50	250	GKV (2011)
Belgium	20	100	50	250	Royal Decision (2014)
Denmark	20	100	50	250	BEK (2011)
European Union	20	100	50	250	SCOEL (2009)
Finland	20	100	50	250	GESTIS (2015)
France	20	100	50	250	INRS (2012)
Germany (AGS)	10	50	40	200	BAUA (2006)
Germany (DFG)	10	50	40	200	DFG (2015)
Hungary		100		250	MHSFA (2000)
Italy	20	100	50	250	SSL (2008)
Ireland	20	100	50	250	HSA (2011)
Latvia	20	100	50	250	GESTIS (2015)
Poland		100		250	MLSP (2002)
Spain	20	100	50	250	INSHT (2011)
Sweden	25	120	35	170	SWEA (2011)
The Netherlands		100		250	DLPLV (2007)
United Kingdom	25	125	75	375	HSE (2011)
Non EU-countries	ppm	mg/m³	ppm	mg/m³	
Australia	25	125	75	375	Safe Work Australia (2011)
Canada (Ontario)	50				Ontario Ministry of Labour (2013)
Canada	50	246			IRSST(2010)

(Québec)					
New Zealand	25	125	75	375	HS (2013)
Norway	25	125			NLIA (2011)
Singapore	50	246			GESTIS (2015)
South Korea	50	245			GESTIS (2015)
Switzerland	20	100	80	400	SUVA (2015)
USA (NIOSH)	50	245			NIOSH (2007)
USA (OSHA)	50	245			OSHA (2006)

In addition to the above OELs, in Germany for biological monitoring the following BAT value ("*Biologischer Arbeitsstoff-Toleranz-Wert*" has been established (DFG 2015):

BAT=10 mg/l measured as mg 2-phenyl-2-propanol (after hydrolysis) per liter of urine, measured at the end of exposure or end of shift.

5. Occurrence, Use and Occupational Exposure

5.1. Occurrence and use

2-Phenylpropane (cumene) is a natural constituent of crude oil and occurs naturally in the environment in plants, marsh grasses and foodstuff (HSDB, 2005). Further it is found in gasoline, solvents, plants (essential oils), food and cigarette smoke. Other sources include vulcanization of rubber, jet engine exhaust, outboard motor operation, solvent use, paint, iron and steel manufacturing, moreover it is used in pharmaceutical production, textile plants, paving and roofing, mining, organics and plastics manufacturing, electroplating and pulp and paper production (HSDB 2005).

2-Phenylpropane is mainly used as an intermediate in the synthesis of acetone (95%) and phenol, and is also used as a catalyst for acrylic polyester resins and as a solvent in the automobile and printing industries. It has been recommended as a substitute for benzene for many industrial applications (NTP 2009). Other uses include the synthesis of α-methylstyrene, acetophenone and detergents, synthesis of di-isopropylbenzene and catalyst for acrylic polyester-type resins (NTP 2013; Hwang and Chen 2010)

In the atmosphere, 2-phenylpropane exists as a vapor and is primarily degraded by reactions with hydroxyl radicals; it is not readily susceptible to photolysis or ozone oxidation. 2-Phenylpropane is adsorbed strongly to soils and is unlikely to leach to groundwater. It will volatilize from dry soil surfaces or undergo aerobic biodegradation within the soil. In water, 2-phenylpropane will undergo volatilization from the surface or bind to sediment and undergo aerobic biodegradation.

There is a potential for 2-phenylpropane to bio-accumulate in fish (ECB 2001).

5.2. Production and use information

2-Phenylpropane/cumene was first synthesized in large quantities during World War II as a blending agent for aviation fuels. However, despite its high heating value and a high octane number, the use of 2-phenylpropane in fuels is considered today as economically

not attractive. Its presence in gasoline now is incidental, being an inevitable minor reaction product of refinery processes such as catalytic reforming and steam cracking (Hwang and Chen 2010).

Nowadays, commercial production of 2-phenylpropane is carried out by Friedel–Crafts alkylation of benzene with propylene. It is driven by the demand for phenol in the manufacturing of polycarbonates, which is accelerating, owing to the broadening applications of polycarbonates in the electronic, healthcare, and automobile industries. In quantitative terms, 2-phenylpropane synthesis uses approximately 20% of the global production of benzene (Ceresana 2001).

The alkylation reaction for synthesis of 2-phenylpropane is promoted by acid-type catalysts. The synthesis can be performed in gas or liquid phase. Liquid - phase processes with solid phosphoric acid (SPA) – alumina catalysts prevailing in the 1990's, were increasingly substituted in recent years by zeolite-based systems (Dimian and Bildea 2008; Hwang and Chen 2010; Perego and Ingallina 2002).

Worldwide, 2-phenylpropane production capacity was in 2002 around 8 million tonnes per year, distributed over around 40 plants (Perego and Ingallina 2002). In 2010, 50 producers were reported worldwide: eight in the People's Republic of China, 12 in East Asia, two in India, 18 in Europe, two in South and Central America and nine in the USA (Chemical Economics Handbook 2010). According to CIEC (2001) the 2-phenylpropane production at world-scale was distributed in 2001 as follows:

- Western Europe: 31%
- Eastern Europe: 8%
- North America: 41%
- South America: 2%
- Asia/Pacific: 18%

Available quantitative data about production volumes in the European Union (EU) are quite old:

- between 850 000 and 4 100 000 tonnes in 1992–93 (ECB 2001)
- 2 million tonnes in 2001 (CIEC 2001).

In 2013, the regional distribution of 2-phenylpropane consumption was as follows (Chemical Economics Handbook 2014):

- Northeast Asia including China, Japan, Taiwan, the Republic of Korea (39%)
- North America (24%)
- Western Europe (23%)

In quantitative terms, the 2-phenylpropane consumption in Europe was in 2012 around 3.8 million tonnes (Micromarket Monitor 2015). Germany was the leading consumer of 2-phenylpropane in the region, consuming about 28.9% of the total regional demand, with Belgium as the second largest consumer.

2-Phenylpropane is used primarily (95%) as an intermediate in the production of phenol and acetone. Other uses include: the manufacture of styrene, α-methylstyrene, acetophenone, detergents and di-isopropylbenzene; as a catalyst for acrylic and polyester-type resins; as a thinner for paints, enamels and lacquers; as a solvent for fat and resins; and in printing and rubber manufacture. Minor amounts are used in gasoline blending and as a component of high-octane aviation fuel (IARC 2012).

5.3. Occupational exposure

Occupational exposure, primarily *via* inhalation, occurs during its production and use, or the use of products that contain 2-phenylpropane. 2-Phenylpropane is typically produced under closed conditions, and most reported levels of occupational exposure are low (IARC 2012, ECB 2001).

5.4. Routes of exposure and uptake

The major route of potential occupational exposure to 2-phenylpropane is inhalation. Dermal exposure may occur but is predicted to be low (ECB 2001).

2-Phenylpropane is primarily released into the environment during its production and use, and from emissions from gasoline engines. It can also be released during the transportation and distribution of fossil fuels or accidental spills of fuel. 2-Phenylpropane has also been detected in cigarette smoke. The major source of exposure of the general public is through inhalation of contaminated air.

6. MONITORING EXPOSURE

2-Phenylpropane can be monitored in the air of the workplace by applying the following methods (see Table 4):

- OSHA method PV2137
- NIOSH method 1501
- MAK method 1
- MAK method 2
- MAK method 6

In all five methods 2-phenylpropane is sampled from the air in the workplace by adsorption onto a solid sorbent, followed by extraction of 2-phenylpropane with an organic solvent. The 2-phenylpropane-containing extract can then be analysed by gas chromatography (GC), using flame ionisation detection (FID) or mass spectrometry (MS) as shown in Table 4.

Table 4: Overview of sampling and analytical methods for monitoring 2-phenylpropane in the workplace air.

Method	Sorbent	Desorption solution	Analysis	Recovery (%)	LOQ	Concentration range	References
OSHA method PV2137	Coconut shell charcoal	Carbon disulphide N,N-dimethylfor-mamide (99:1)	GC-FID	100.3	41 µg/m^3	n.d.	OSHA (2015)
NIOSH method 1501	Coconut shell charcoal	Carbon disulfide	GC-FID	n.d	0.6 µg/sample	0.039-3.46 mg	NIOSH (2003)
MAK method 1	Active charcoal	CS_2	GC-FID	101	0.5 mg/m^3	0.1 to 2 times the DFG set limit value	Kraemer (2014)
MAK method 2	Active charcoal	CH_2CL_2/CS_2/MeOH (60:35:5)	GC -FID	95	1 mg/m^3	n.d.	Schneider and Breuer (2014)
MAK method 6	Chromo-sorb 106	Thermal desorption	GC-FID GC/MS	>95%	0.7 mg/m^3	0.1 to 2 times the limit value set by DFG	Tschickardt (2014)

OSHA method PV2137 is a partially evaluated method, which means that this method hasbeen subjected to established evaluation procedures of the methods development team and is presented for information and trial use.

2-Phenylpropane and 2-phenyl-2-propanol (the main metabolite of 2-phenylpropane), can be monitored in blood or urine by applying the following methods (see Table 5):

- MAK biomonitoring method 1
- MAK biomonitoring method 2

Table 5: Overview of sampling and analytical methods for monitoring 2-phenylpropane in the biological samples (blood and urine).

Method	Application	Analysis	Standard deviation (rel)(*Sw*) *	Prognostic range(*u*)*	Recovery (%)	Detection limit	References
MAK method 1	Determination of 2-phenylpropane in blood	GC- FID	7.0-1.2%	15.8-2.7%	82-100	0.086 mg/l 2-phenylpropane in blood	Goenechea (1983)

MAK method 2	Determination of 2-phenyl-2-propanol in urine	GC-FID	6.5%-8.6%	14.5%-19.2%	91.9-109	0.5 mg 2-phenyl-2-propanol per litre of urine	Knecht (2013)

* Within day precision

7. HEALTH EFFECTS

The acute toxicity of 2-phenylpropane is low and mostly related to pre-narcotic solvent effects. Target organs, upon repetitive dosing to experimental animals, are kidneys, liver and the respiratory tract (Greim 1996).

7.1. Toxicokinetics (absporption, distribution, metabolism, excretion)

2-Phenylpropane is a highly lipophilic substance, which is well distributed in the whole body with partition coefficients of 1.44 (water/air), 37 (blood/air) and 6 215 (oil/air) (Sato and Nakajima 1979). These data also indicate a possible accumulation of 2-phenylpropane in adipose tissue (ECB 2001).

7.1.1. Human data

2-Phenylpropane is well absorbed through the respiratory tract. Ten healthy subjects (5 per sex) were exposed once for 8 hours to 2-phenylpropane vapour concentrations of 240, 480 and 720 mg/m^3 (48, 96 and 144 ppm), including two breaks of 30 min. Pulmonary retention was about 64 % at the beginning of the exposure and diminished to about 45 % at the end of the exposure (Senczuk and Litewka 1976). Investigation of non-occupationally exposed hospital (n = 58) and chemical workers (n = 28) revealed pulmonary retentions of about 70.4 and 77.8 %, respectively (Brugnone *et al* 1989).

Though no adequate human study is available, owing to its lipophilic properties it can be assumed that 2-phenylpropane is well absorbed through the gastro-intestinal tract and through the skin, by structural and physico-chemical analogy with toluene and xylene (ECB 2001).

2-Phenylpropane is metabolised to 2-phenyl-2-propanol (40 %) and to 2-phenyl-1-propanol (25 %), which is further transformed into 2-phenylpropionic acid. About 5 % of 2-phenylpropane is exhaled. Half of the metabolite 2-phenyl-2-propanol is excreted within 9.5 hours. 2-Phenylpropionic acid is eliminated with a biological half-life of 10.8 ± 2.3 hours (Lehnert and Greim 2001).

7.1.2. Animal data

As shown in different animal studies, 2-phenylpropane is well absorbed through the respiratory tract and the gastrointestinal tract (see below). No pharmacokinetic data were available for dermal absorption. Two older studies did not clearly indicate skin absorption (Valette and Cavier 1954, Wolf *et al* 1956). However, topically applied 2-phenylpropane caused severe systemic damages in rabbits (Monsanto Co. 1978; see Section 7.2.2). Thus, it is at least partly absorbed by the skin.

^{14}C-Labelled 2-phenylpropane was readily absorbed by rats after inhalation exposure (nose-only, 6 hours) and after a single oral administration (Research Triangle Institute 1989). Blood levels increased in a concentration-dependent manner. Some radioactivity

was still observed in several tissues after 72 hours, mostly in the liver (liver/blood ratio = 5) and in fat (fat/blood ratio = 4.5) indicating the high lipophilicity of this substance.

Inhalation exposure of rats to 509 ppm (2 545 mg/m^3) 2-phenylpropane for 10–150 days (8 hours/day) resulted in high amounts of this compound in the CNS, endocrine glands, bone marrow, spleen and liver (Fabre *et al* 1955). A large fraction (85 %) of the substance in blood was bound to proteins (Lehnert and Greim 2001). Tissue levels of 2-phenylpropane decreased slowly during an observation period of 48 hours after the end of exposure. Identified metabolites in the urine were 2-phenylpropane-2-ol and its glucuronide or sulphate conjugates, 2-propane-1,2-diol, 2-phenylpropionic acid and phenolic compounds (not further specified). These metabolites were also detected after administration of ^{14}C-2-phenylpropane to rats either orally or by inhalation (Research Triangle Institute 1989). Within 72 hours, about 90 % of the ^{14}C-labelled compounds were excreted in the urine and about 5 % were exhaled or excreted in the faeces. Significant amounts of radioactivity were still measured in different organs, with highest quantities in adipose tissue (see above). The exhaled ^{14}C-fraction was unchanged 2-phenylpropane, the relative amount increasing with increasing dose. About 50 % of the renally excreted radioactive compounds was 2-phenylpropan-2-ol (free or conjugated as glucuronide or sulphate) (Research Triangle Institute 1989).

Similar to inhalation exposure, about 90 % of the radiolabelled compounds were eliminated within 72 hours after oral administration, a minimum of 70 % being excreted in the urine and only 3 % in the faeces. The amount of exhaled radioactivity increased at higher doses (5 % at 33 mg/kg and 13 % at 1 323 mg/kg). The elimination half-life of 2-phenylpropane was calculated to be 7.3–8.6 hours (ECB 2001).

Furthermore, the absorption, distribution, metabolism and excretion of ^{14}C-2-phenyl-propane were studied in male rats and mice of both sexes after oral or intravenous administration (Chen *et al* 2011). In both species and sexes, urine accounted for the majority of the excretion (typically ≥ 70 %) by oral and intravenous administration. Enterohepatic circulation of 2-phenylpropane and/or its metabolites was indicated because 37 % of the total dose was excreted in bile in bile duct-canulated rats with little excreted in normal rats. The highest tissue ^{14}C-levels in rats were observed in adipose tissue, liver and kidney with no accumulation observed after repeat dosing up to 7 days. In contrast, mice contained the highest concentrations of ^{14}C at 24 hours after dosing in the liver, kidney and lung, with repeat dosing accumulation of ^{14}C observed in these tissues as well as in the blood, brain, heart, muscle and spleen. Following administration of ^{14}C-labelled 2-phenylpropane, ^{14}C concentrations in lung tissue were highest in female mice after seven consecutive daily doses but did not increase with repeated dosing in rats. The metabolites in the expired air, urine, bile and microsomes were characterised with 16 metabolites identified. The volatile organics in the expired air comprised mainly 2-phenylpropane and up to 4 % α-methylstyrene. The major urinary and biliary metabolite was 2-phenyl-2-propanol glucuronide, which corresponded with the main microsomal metabolite being 2-phenyl-2-propanol.

The different distribution patterns of metabolites in the lungs between rats and mice are ascribed to differential local metabolism. There are more Clara cells in mice than in rats containing ring-oxidising CYP2E1 and CYP2F (CYP2F2 in mice, CYP2F4 in rats). Moreover, the human CYP2F1 is much less prevalent in these tissues and therefore much less effective at metabolising 2-phenypropane, compared to the situation in rodents (Chen *et al* 2011, Cruzan *et al* 2009, 2012).

7.1.3. In vitro data

Henne *et al* (2001) investigated the active site topography of rabbit CYP4B1 relative to rat CYP2B1 and bacterial CYP102 in vitro using 2-phenylpropane and several other aromatic substrates. CYP4B1 is primarily an extrahepatic monooxygenase and does not have a clearly defined endogenous substrate. Each of these cytochromes metabolised 2-phenylpropane to hydroxylated products. CYP2B1 and CYP102 preferentially formed

2-phenyl-2-propanol; however, reaction with CYP4B1 preferentially formed 2-phenyl-1-propanol along with a relatively small amount of 2-phenyl-2-propanol. CYP102 was the only enzyme that formed significant amounts of isopropylphenol, a ring-hydroxylated metabolite. α-Methylstyrene was not a significant metabolite for any of the enzyme preparations (NTP 2013). In vitro studies with mouse and rat lung and liver microsomes demonstrated that mouse lung microsomes were the most efficient at metabolising 2-phenylpropane, which is consistent with accumulation of cumene metabolites in mouse lung (NTP 2013).

Based on the physico-chemical properties of 2-phenylpropane, Fiserova-Bergerova *et al* (1990) calculated a human skin penetration rate of about 0.34 mg/cm^2 per hour for a saturated aqueous solution.

7.1.4. Biological monitoring

Eighteen persons were exposed by inhalation to 2-phenylpropane for 8 hours at concentrations ranging from 15 to 50 ppm. There was a moderate bicycle exercise of 75 W for 10 min every hour. 2-Phenylpropane was measured in exhaled breath and in blood. 2-Phenyl-1-propanol, 2-phenyl-2-propanol and 2-phenylpropionic acid were measured in urine. The major urinary metabolite was 2-phenyl-2-propanol. The experiment was published in abridged form of a congress report by Knecht and Ulshöfer (1996). Additional data of this experiment were later retrieved by Lehnert and Greim (2001), based on the original experimental data set. The measured parameters provided good correlations with the airborne 2-phenylpropane concentrations.

In this experiment, the highest airborne concentration tested of 45–50 ppm 2-phenylpropane corresponded to 35.8 ± 13.2 mg 2-phenyl-2-propanol/g creatinine (n = 20). At 35–40 ppm 32.8 ± 14.2 mg/g (n = 12), at 25–30 ppm 20.1 ± 4.3 mg/g (n = 9) and at 15 ppm 7.5 ± 2 mg/g (n = 5) were found. 2-Phenylpropane blood concentrations at the end of shift were 1.54 ± 0.33 mg/l at 45–50 ppm 2-phenylpropane in air, 0.79 ± 0.26 mg/l at 35–40 ppm, 0.64 ± 0.14 mg/l at 25–30 and 0.59 ± 0.06 mg/l at 15 ppm. Because of the rapid metabolite excretion (Section 7.1.1) urine sampling for biological monitoring should not be later than two hours after shift. No correlation between health effects and concentrations of 2-phenyl-2-propanol in urine or 2-phenylpropane in blood has been established.

These values (the mean urinary excretion levels of the main metabolite, 2-phenyl-2-propanol, immediately after experimental exposure to 2-phenylpropane) are shown in Figure 1. As there is no physiological background excretion of 2-phenyl-2-propanol, the curve in this figure is forced through the origin. Overall, the data suggest a urinary excretion of 7 mg 2-phenyl-2-propanol/g creatinine as a plausible biological equivalent to an 8-hour TWA exposure to 2-phenylpropene of 10 ppm (see Chapter 4).

For analysis of 2-phenyl-2-propanol, after addition of internal standard, 2-(4-fluorophenyl)ethanol, the urine is subjected to hydrolysis using hydrochloric acid. The analyte is enriched using liquid-liquid-extraction and simultaneously separated from matrix components. After separation by capillary gas chromatography, quantitation is done using flame ionisation detection (Knecht 2013).

mg 2-phenyl-2-propanol/g creatinine

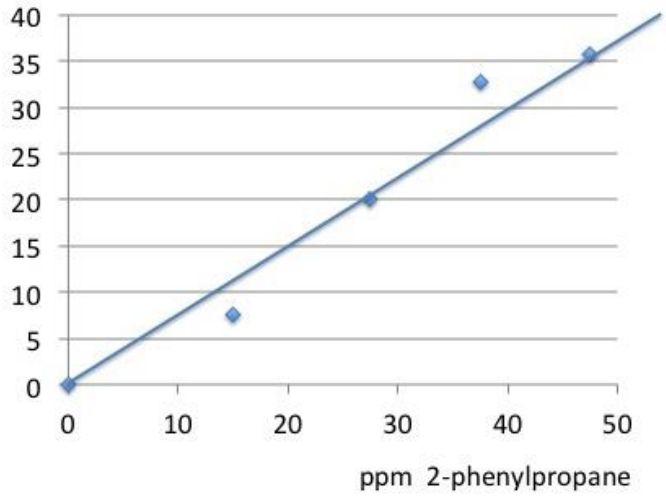


Figure 1. Mean 2-phenyl-2-propanol after experimental human exposure to 2-phenylpropane (experiment of Knecht and Ulshöfer 1996; linear function forced through the origin).

7.2. Acute toxicity

7.2.1. Human data

According to the US EPA, inhalation exposure of humans to 2-phenylpropane can cause headache, dizziness, drowsiness, slight ataxia and unconsciousness (EPA 2000) (no further details given).

7.2.2. Animal data

Inhalation

Inhalation exposure of rats to 2-phenylpropane resulted in LC_{50} values of 8000 ppm (40 000 mg/m^3)/4 hours (Smyth 1951) and > 3520 ppm (17600 mg/m^3)/6 hours (Monsanto Co. 1985, cited in ECB 2000), while LC_{50} values in mice were 5000 ppm (25000 mg/m^3)/2 hours (Solomin 1971) and 2000 ppm/7 hours (10000 mg/m^3; unpublished report, Huels AG 1994, cited in ECB 2000).

Exposure-related behavioural changes, indicating CNS depression, occurred in CFW mice after single exposures to 2000–8 000 ppm (10000–40000 mg/m³) 2-phenylpropane for 20 min (Tegeris and Balster 1994). Histopathological investigations of rats after inhalation exposure to 2000 and 5000 ppm (10000 and 25000 mg/m³) for 5 consecutive days (6 hours/day) revealed congestion of many tissues, red fluid filled bladders, abnormal contents in the intestine as well as excessive ocular and nasal accumulations (Gulf Oil Corp. 1985a, cited in ECB 2000). A single inhalation exposure of F344 rats to 100, 500 and 1 200 ppm (500, 2500 and 6000 mg/m^3; 6 hours) led to lowering of the rectal temperature and changes in a functional observational battery (at 500 ppm), which disappeared after 24 hours (Bushy Run Research Center 1989; Cushman *et al* 1995). The NOAEC for CNS effects was 100 ppm.

Acute toxic symptoms observed in mice were unconsciousness, ataxia, loss of reflexes and depression of the breathing frequency finally leading to death (Gardner and Delic 1994). Steatosis in liver and kidney as well as phagocytosis in the reticular cells of the follicles of the spleen occurred. 2-Phenylpropane caused sensory irritation of the respiratory mucosa in mice (for details, see Section 7.4.2).

Oral exposure

Oral LD_{50} values of 1400–8620 mg/kg have been reported in different rat strains (Gerarde 1959; Monsanto Co. 1978, cited in ACGIH 2001; Smyth *et al* 1951; Wolf *et al* 1956). Clinical signs after oral application of 2-phenylpropane were sluggishness, prostration and narcosis. Autopsy of the rats revealed pneumonitis, pulmonary oedema, haemorrhage, inflammation of the gastrointestinal tract and liver discoloration (Monsanto Co. 1978, cited in ACGIH 2001).

Dermal exposure

The dermal LD_{50} values ranged from > 3160 mg/kg up to 10600 mg/kg in rabbits (ECB 2001; Smyth *et al* 1951). Signs of toxicity included weakness, weight loss and collapse. Furthermore, discoloration of liver, kidney and spleen as well as inflammation of the gastrointestinal tract and lung haemorrhage occurred (Monsanto Co. 1978, cited in ACGIH 2001).

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

No data were available

7.3.2. Animal data

Inhalation

Cushman *et al* (1995) performed two 13-week inhalation studies with 2-phenylpropane in F344 rats. In the first study, rats (n = 21 per sex and group) were exposed to concentrations of 0, 100, 500 and 1200 ppm (0, 500, 2500 and 6000 mg/m^3) 2-phenylpropane (6 hours/day, 5 days/week). The second study was a repeat of the first study (n = 15 per sex and group) with the exception that one group of animals exposed to 50 ppm (250 mg/m^3) was added and all animals of this second study were allowed to recover for 4 weeks subsequently to exposure.

No exposure-related changes in the functional observational battery occurred in any of the experiments. In the first study at 500 ppm, total motor activity was decreased at week 13 and ambulatory activity was statistically decreased at weeks 4, 9 and 13. These findings were not replicated in the second study. The development of cataracts in the eyes of both control and exposed animals, also occurring only in the first experiment, was not interpretable because of the high incidence in the control group.

Measurement of the auditory brain stem response revealed no changes in the auditory function indicating that 2-phenylpropane is not ototoxic. Haematological examinations revealed exposure-related increases in total leukocytes, lymphocytes and platelets at 500 ppm (both sexes). Furthermore, 2-phenylpropane caused increases in total protein, albumin, globulin, calcium and phosphorous levels in rats of both sexes (500 ppm) and lower serum glucose levels in female rats (1200 ppm).

The organ weights of liver, kidney and adrenal gland were significantly increased at 500 ppm in both male and female rats of either study. The persistence of the increases of organ weights after 4 weeks of recovery in the second study indicated limited reversibility of this effect. In male rats, the incidences of hypertrophy and hyperplasia of

the proximal tubules and interstitial nephritis were increased at 500 ppm due to a greater amount of hyaline droplets. However, this effect was closely linked to the male rat specific nephropathy. No such effect occurred at 100 ppm. Kidney and liver weights were not affected at 50 and 100 ppm in both studies, on an absolute and relative basis. At 500 ppm, liver weights increased in females (abs 7 %, rel 11 %) and males (abs 20 %, rel 17 %) in the first study. In the second study (including the post-exposure period) liver weights increased in females (abs 13 %, rel 11 %) and males (only abs 11 %); relative kidney weights in males increased by 6 %. No pathological changes were reported in nasal tissues. Clinical chemistry parameters were not affected at 100 ppm. A NOAEC of 100 ppm was derived from these studies (Cushman *et al* 1995; full reports: Bushy Run Research Center 1989, 1991).

A 4-week study on rats (0, 100, 300 and 600 ppm = 0, 500, 1500 and 3000 mg/m^3) performed by Monsanto Company (1986, cited in EPA 1997) revealed similar effects. Renal changes occurred only in male rats and were related to male rat specific nephropathy. A LOAEC of 100 ppm was established on the basis of cage-side observations of head tilt and head movements, which were associated with CNS perturbation. However, the authors noted that these head movements were not observed in several other studies.

Continuous inhalation exposure of rats, guinea pigs, dogs and monkeys to 3.7 and 30 ppm (18.5 and 150 mg/m^3) 2-phenylpropane for 90 days did not cause any exposure-related effects (Jenkins *et al* 1970). The body weights of the animals were within the normal range and the limited histopathological and haematological examinations performed did not reveal any changes. Also, inhalation exposure (8 hours/day, 5 days/week) of the same animal species to 244 ppm (1 220 mg/m^3) 2-phenylpropane for 6 weeks did not produce histopathological and haematological changes. The only effect observed was a marked reduction in the body weight gain of guinea pigs.

The effect of acute and subacute exposure of 2-phenylpropane on expressions of synaptophysin and glial fibrillary acidic protein (GFAP) in the hippocampi was investigated by Lee *et al* (2009). Sprague-Dawley male rats were exposed to 2-phenylpropane (0, 8, 80 and 800 ppm) by inhalation for 1, 14, 28 and 90 days. In Western blot analysis, the expression levels of synaptophysin in the hippocampi were significantly increased at 800 ppm on day 14 and significantly decreased at 8 ppm on day 28. Levels of GFAP were significantly increased in hippocampi at 1, 14 and 28 days after 2-phenylpropane exposure when compared to the control group. 2-Phenylpropane inhalation changed the expression of synaptophysin and GFAP in hippocampus, even at a dose of 8 ppm. It is not clear whether this represents an adverse health effect or a physiological adaptive response.

In a study by NTP (2009), 2-phenylpropane was studied with the primary intention to determine if it caused cancer in rats or mice. Male and female F344/N rats and B6C3F1 mice were exposed to 2-phenylpropane (greater than 99.9 % pure) by inhalation for two weeks, 3 months, or 2 years. In the following, a summary of the results from the shorter range-finding studies is given. The 2-year carcinogenicity study is reported in Section 7.7.2.

Groups of 5 male and 5 female rats were exposed to 2-phenylpropane vapour at concentrations of 0, 250, 500, 1000, 2000 or 4000 ppm, 6 hours per day, 5 days per week for 16 days. All rats exposed to 4000 ppm died on day 1, and two male and three female rats exposed to 2 000 ppm died by day 4. Mean body weights of 2000 ppm rats were significantly less than those of the chamber controls. Rats exposed to 2000 ppm that died early were severely lethargic following daily exposure. Liver and kidney weights of all exposed groups were increased. Accumulation of minimal to mild hyaline droplets was observed in the renal tubular cortex of males exposed to concentrations of 250 to 2000 ppm.

Groups of 5 male and 5 female mice were exposed to 2-phenylpropane vapour at concentrations of 0, 250, 500, 1000, 2000 or 4000 ppm, 6 hours per day, 5 days per week for 17 days. All mice exposed to 4000 ppm died on day 1; all mice exposed to 2 000 ppm died on day 2, and four female mice exposed to 1 000 ppm died by day 4.

Mean body weights of all exposed groups were similar to those of the chamber controls. Mice exposed to 2000 ppm were severely lethargic after the first exposure. The 4 female mice exposed to 1000 ppm that died early exhibited signs of lethargy and ataxia. Liver weights, both relative and absolute, were increased in all groups of surviving males and in 250- and 500-ppm female groups.

Groups of 10 male and 10 female rats were exposed to 2-phenylpropane vapour at concentrations of 0, 62.5, 125, 250, 500 or 1000 ppm, 6 hours per day, 5 days per week for 14 weeks. Additional clinical pathology groups of 10 male and 10 female rats were exposed to the same concentrations for 23 days. All rats survived to the end of the study, and mean body weights of all exposed groups were similar to those of the chamber controls. Kidney and liver weights of 250-ppm or greater males and liver weights of 1000-ppm females were significantly greater than those of the chamber controls. There were significant differences between exposed and chamber control females in the relative length of time spent in the oestrous stages. The amount of $\alpha 2_{\mu}$-globulin in the right kidneys was significantly increased in male rats exposed to 125 ppm or greater. The incidences of medullary granular casts in males exposed to 250 ppm or greater were significantly increased. The severities of renal tubule cortex hyaline droplet accumulation and regeneration increased with increasing exposure concentration in male rats.

Groups of 10 male and 10 female mice were exposed to 2-phenylpropane vapour at concentrations of 0, 62.5, 125, 250, 500 or 1000 ppm, 6 hours per day, 5 days per week for 14 weeks. Eight 1000-ppm females died during week 1 of the study. Mean body weights of males exposed to 500 or 1000 ppm were significantly less than those of the chamber controls. The eight 1000-ppm female mice that died during the first week of the study exhibited clinical signs of acute toxicity, including lethargy or ataxia. Liver weights of mice exposed to 500 or 1000 ppm were significantly increased. The weight of the cauda epididymidis and the spermatid count were significantly decreased in 1000-ppm males.

With regard to assessment of a NOAEC or LOAEC, the lowest tested concentration in the 3-month study by NTP was 62.5 ppm. This caused a reported elevation of relative liver and kidney weights in male rats and an increased incidence of chronic focal inflammation in the livers of female mice. However, the relative liver weight in male rats exposed under these conditions increased only marginally, by about 5–6 %; absolute organ weights were not affected. In female rats, relative kidney weight was increased at 250 ppm and higher, but histopathological changes were not observed. In female mice, the incidences of chronic focal hepatic inflammation showed the following pattern: 10, 10 and 9 (of 10) animals at 62.5, 125 and 250 ppm, respectively. At 500 ppm, 7 (of 10) showed chronic focal inflammation, while this was seen in 2 (of 2) at 1 000 ppm. Liver necrosis was seen in 2 (of 10) animals at 500 ppm and in 1 (of 10) of the controls. The chronic inflammation reported in the liver of female mice in the 90-day study was of minimal grade and is a normal finding in the liver of mice and rats. Therefore, this liver lesion is seen by SCOEL to represent a normal background variation that does not carry much scientific weight. With regard to kidney toxicity, hyaline droplet formation was increased *vs.* controls at 125 ppm and higher in male rats, and at this concentration minimal granular casts in the renal tubules of the medulla were observed, with greater severity at the higher concentrations. The granular casts and renal tubular regeneration were considered indicative of renal tubule epithelium damage. A relevance of these findings in male rats for humans is not likely, in view of $\alpha 2_{u}$-nephropathy discussed in chapter 7.9.

In consequence, the NOAEC based on this subchronic study amounts to 62.5 ppm. This level is supported by the above mentioned subchronic study of Cushman *et al* (1995) that provided an NOAEC for rats of 50 ppm. Taking together both studies, SCOEL considers a *NOAEC for rats of 50 ppm*. With regard to liver changes, the evaluation is in accordance with conclusions reached at the 3rd International ESTP (European Society of Toxicologic Pathology) Expert workshop (Hall *et al* 2012).

Oral exposure

Oral application of 8.47 mmol/kg [1018 mg/kg] per day of 2-phenylpropane (gavage) on 5 days/week for 2 weeks did not produce ototoxicity in SD rats (Gagnaire and Langlais, 2005). Groups of 10 rats per dose were given 0, 154, 462 and 769 mg/kg per day of 2-phenylpropane by gavage over a period of 6 months (5 days/week) (Wolf *et al* 1956). The only effect detected was a significant increase of average kidney weights at 462 mg/kg per day. From these data, a NOAEL of 154 mg/kg per day and a LOAEL of 462 mg/kg per day can be estimated for oral application of 2-phenylpropane.

Dermal exposure

A 10% solution of a mixture containing 30% 2-phenylpropane, 58% glycol ether and 12% "Busan 72" was topically applied to the shaved dorsal skin (approximately 10% of the body surface) of New Zealand white rabbits on 5 days/week for 28 days (2 ml/kg per day of the 10% mixture, corresponding to approximately 57 mg/kg per day of 2-phenylpropane; unpublished results, Procter & Gamble Comp. 1985). Skin oedema, fissuring and moderate to severe erythema as well as dermatitis, acanthosis and hyperkeratosis occurred. However, dermal application of 2-phenylpropane did not cause systemic toxicity in these animals.

7.3.3. In vitro data

There are no relevant data.

7.4. Irritancy and corrosivity

7.4.1. Human data

An odour threshold limit value of 0.088 ppm (0.43 mg/m^3) was reported by Amoore and Hautula (1983). There is no indication of local irritancy in this report.

Experience in handling 2-phenylpropane indicates that painful irritation of the eyes and the respiratory tract occurs at concentrations of approximately 300–400 ppm (1500–2000 mg/m^3) (ECB 2001). No further details were given.

7.4.2. Animal data

Skin

Unspecified amounts of undiluted 2-phenylpropane were applied (10–20 times) to the ear or to the shaved skin of the abdomen of white rabbits over a period of 2–4 weeks (Wolf *et al* 1956). Moderate irritation and slight necrosis resulting in exfoliation occurred. According to the authors, there was no indication that 2-phenylpropane was well absorbed through the skin.

Open or semi-occlusive application of unspecified doses of 2-phenylpropane to the shaved skin of the inner ear and on the shaved abdomen of rabbits for 2–4 weeks (once per day) caused slight necrosis, erythema and exfoliation of the skin (Wolf *et al* 1956). The effects observed after topical application of pure 2-phenylpropane persisted for 21 days, while the effects produced by a 10% aqueous solution applied daily over a period of 9 days completely disappeared within 21 days (Dow Chemical Company 1985, cited in Greim 1996).

Dermal exposure of New Zealand rabbits to 0.5 ml 2-phenylpropane for 24 hours resulted in slight defatting and flaking of the skin (Monsanto Co. 1978, cited in ACGIH 2001).

Application of 10 ml 2-phenylpropane to shaved strips on the back of calves produced severe cracking or sloughing of the skin (Turner *et al* 1962).

Eyes

Instillation of two drops of undiluted 2-phenylpropane into the rabbit eye caused only slight conjunctival irritation but no corneal injury (Wolf *et al* 1956). Only minor reactions were observed in several other studies (Huntingdon Research Center 1979, cited in ECB 2000; Monsanto Co. 1985, cited in ECB 2000; Smyth *et al* 1951; Union Carbide Corporation 1985, cited in ECB 2000).

Respiratory tract

The RD_{50} (concentration causing a 50% depression of the respiratory rate due to sensory irritation of the respiratory tract) of 2-phenylpropane was 2490 ppm (12450 mg/m³) in Swiss-Webster mice (Nielsen and Alarie 1982) and 2058 ppm (10290 mg/m^3) in CF1 mice (Kristiansen *et al* 1986).

7.4.3. In vitro data

No relevant in vitro data have been found

7.5. Sensitisation

7.5.1. Human data

No data were available.

7.5.2. Animal data

2-Phenylpropane was not sensitising in a Guinea pig maximisation test performed according to OECD guideline 406 (Huels AG 1988, cited in ECB 2000).

7.5.3. In vitro data

No data were available.

7.6. Genotoxicity

7.6.1. Human data

There are no human studies on genotoxicity of 2-Phenylpropane.

7.6.2. Animal data

A micronucleus test with CDR-1 BR Swiss mice (10 per sex and group) indicated no clastogenic potential after oral application of 250, 500 and 1 000 mg/kg per day of 2-phenylpropane on 2 consecutive days (Gulf Oil Corp. 1985c, cited in ECB 2000).

In recent studies conducted by NTP (NTP 2009, 2012a, b), male Fisher 344 rats and male and female B6C3F1 mice (6 animals/dose group) were administered vehicle (corn oil), 2-phenylpropane or (as positive control) ethyl methanesulphonate by gavage, once daily for 4 consecutive days. The top doses of 2-phenylpropane used in these studies (800 mg/kg/day for male rats; 1 250 and 1 000 mg/kg/day for male and female mice,

respectively) were selected on the basis of the setting studies. The final (4th) dose was administered 21 hours following the previous dose; 3 hours later, peripheral blood and liver, lung and kidney tissues were collected from each animal. Blood samples were prepared for micronuclei analysis, while blood and the tissue samples were processed for the comet assay. Frequencies of micronucleated polychromatic erythrocytes were measured using flow cytometry. Cells from the kidney, liver and lung, as well as blood leukocytes, were analysed for extent of DNA migration (DNA damage) using the alkaline (pH > 13) Comet assay. Micronuclei and COMET assay data were evaluated. Results of the micronucleus tests for 2-phenylpropane in both rats and mice were negative. Results of the comet assay for all tissues in all species/sexes were negative with two exceptions: results in female mouse lung and male rat liver were judged to be positive based on the presence of a significant trend and a significant increase in DNA damage at the highest dose tested in both tissues, compared with the concurrent vehicle control group.

It was concluded (NTP 2012b) that 2-phenylpropane did not show evidence of bacterial mutagenicity or evidence of chromosomal breakage in pro-erythrocytes of male and female mice, and male rats. Dose-related increases in DNA damage were observed in male rat liver cells and female mouse lung cells at repeated doses of 800 mg/kg (or higher); none of the other tissues sampled in mice and rats showed evidence of DNA damage.

7.6.3. In vitro

In earlier studies, 2-phenylpropane was not mutagenic in several bacterial tests performed with *Salmonella typhimurium* (TA97, TA98, TA100, TA1535, TA1537) with and without metabolic activation (summarised in ECB 2000). It gave negative results in a chromosome aberration assay with Chinese hamster ovary (CHO) cells (Putman 1987a), in two HGPRT mutation assays with CHO cells (Yang 1987, Gulf Oil Corp. 1985b, cited in ECB 2000) and in an unscheduled DNA synthesis (UDS) test using rat hepatocytes (Curren 1987). 2-Phenylpropane was weakly positive regarding DNA repair activity in primary rat hepatocytes (Gulf Oil Corp. 1984, cited in WHO 1999). This test prompted a repeat with clearly negative result (WHO 1999). A morphological cell transformation assay with BALB/3T3 mouse embryo cells was negative after application of 50, 100, 150 and 200 µg/ml of 2-phenylpropane (Putman 1987b).

Because of concern regarding the volatility of 2-phenylpropane, the compound was again subjected to a battery of genotoxicity tests within the frame of the US National Toxicology Program (NTP 2009, 2012a, b). It was tested in the bacterial reverse mutation assay using *Salmonella typhimurium* strains TA98 and TA100 and *Escherichia coli* strain WP2 *uvrA* (pKM101) in the pre-incubation method with and without metabolic activation (10 % phenobarbital/benzoflavone induced rat liver S9). This was addressed as the standard protocol employed by NTP for bacterial mutagenicity assessment, and these three strains of bacteria permit detection of the vast majority of bacterial mutagens, including chemicals that induce base substitutions, frame-shifts, and oxidative damage. Pre-incubation was conducted in sealed tubes to maximise exposure of the bacteria. In dose range finding tests, toxicity was observed at 250 or 500 µg/plate; therefore, the highest dose tested was 250 or 500 µg/plate. The observation of toxicity at 250 or 500 µg/plate confirmed that exposure to 2-phenylpropane had occurred. Under these test conditions, 2-phenylpropane did not induce increases in revertant counts up to dose levels that induced toxicity.

7.7. Carcinogenicity

7.7.1. Human data

There are no published data on carcinogenicity in humans (IARC 2012).

7.7.2. Animal data

In a recent study (NTP 2009), male and female F344/N rats and B6C3F1 mice were exposed to 2-phenylpropane (greater than 99.9 % pure) by inhalation for 2 years. In the following, a summary of the results is given. The range-finding studies of shorter duration are reported in Section 7.3.2.

Groups of 50 male and 50 female rats were exposed to 2-phenylpropane vapour at concentrations of 0, 250, 500 or 1000 ppm, 6 hours per day, 5 days per week for 105 weeks. Survival of all exposed groups of rats was similar to that of the chamber controls. Mean body weights of 1000-ppm females were slightly less than those of the chamber controls during the second year of the study but were similar to the chamber controls at the end of the study.

Incidences of adenoma of the respiratory epithelium in the nose occurred with a positive trend in males and were significantly increased in all exposed groups of males and in 250-ppm females. Incidences of hyperplasia of basal cells in the olfactory epithelium in the nose of all exposed groups and hyperplasia of the respiratory epithelium in the nose of all exposed groups of males and 1000-ppm females were significantly increased.

The incidences of renal tubule adenoma in all exposed groups of males, renal tubule carcinoma in 500- and 1000-ppm males, and renal tubule adenoma or carcinoma (combined) in all exposed groups of males were increased; the difference from chamber controls for the combined incidence was significant at 500 ppm. The incidences of hyperplasia of the renal tubule and transitional epithelium of the renal pelvis in 500- and 1 000-ppm males and mineralisation of the renal papilla in all exposed groups of males were significantly greater than those of the chamber controls.

Groups of 50 male and 50 female mice were exposed to 2-phenylpropane vapour at concentrations of 0, 125 (female mice only), 250, 500 or 1000 (male mice only) ppm, 6 hours per day, 5 days per week for 105 weeks. An exposure concentration-related decrease in survival occurred in male mice, and the survival of 1000-ppm males was significantly less than that of the chamber controls. Mean body weights of 1000-ppm males were generally less than those of the chamber controls after week 8 of the study, and those of 500-ppm females were less from week 28 until week 76 of the study.

The incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) in all exposed groups of mice occurred with positive trends and were significantly greater than those in the chamber controls. The incidences of alveolar epithelial bronchiole metaplasia and bronchiole hyperplasia were significantly increased in all exposed groups of mice. *p53* and *K-ras* mutations were found in 52 % and 87 % of lung neoplasms in exposed mice compared to 0 % and 14 % in the chamber controls, respectively.

In female mice, the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with positive trends and were significantly increased in the 500-ppm group. In male mice, there were significant increases in the incidences of eosinophilic foci of the liver.

In the nose, the incidences of olfactory epithelium atrophy, basal cell hyperplasia of the olfactory epithelium, atypical hyperplasia of the olfactory epithelium, hyperplasia of olfactory epithelium glands, and suppurative inflammation were generally significantly increased in 500- and 1000-ppm males and 500-ppm females. The incidences of squamous metaplasia of the respiratory epithelium were significantly increased in 500-ppm females. The incidence of basal cell hyperplasia was also significantly increased in 250-ppm females.

The incidences of epithelial hyperplasia of the forestomach in the 500- and 1000-ppm groups of males and the incidences of ulceration and inflammation of the forestomach in 1000-ppm males were significantly increased.

All groups of animals exposed to 2-phenylpropane exhibited hyperplasia of the epithelial tissues of the nose, and exposed male and female mice experienced metaplasia and hyperplasia of the lung.

Carcinogenic activity of a metabolite

There has been a discussion of the involvement of the metabolite α-methylstyrene in the experimental carcinogenicity of 2-phenylpropane (IARC 2013; NTP 2013).

Male and female F344/N rats and B6C3F1 mice were exposed to α-methylstyrene (99.5 % pure), which is one of the metabolites of 2-phenylpropane, by inhalation for two years (NTP 2007). Groups of 50 male and 50 female rats and groups of 10 male and 10 female mice were exposed by whole body inhalation to α-methylstyrene at concentrations of 0, 100, 300 and 1000 ppm (rats) or 600 ppm (mice) for 6 hours per day, 5 days per week, except holidays, for 105 weeks. It was concluded that, under the conditions of this inhalation study, there was "some evidence of carcinogenic activity" of α-methylstyrene in male F344/N rats based on increased incidences of renal tubule adenomas and carcinomas (combined). Exposure of rats to α-methylstyrene resulted in kidney toxicity, which in males exhibited features of $\alpha_{2\mu}$-globulin nephropathy. There was an increased incidence of mononuclear cell leukaemia in 1000-ppm male F344/N rats, which may have been related to α-methylstyrene exposure. There was no evidence of carcinogenic activity of α-methylstyrene in female F344/N rats exposed to 100, 300 or 1000 ppm. There was "equivocal evidence of carcinogenic activity" of α-methylstyrene in male B6C3F1 mice based on marginally increased incidences of hepatocellular adenoma or carcinoma (combined). There was "clear evidence of carcinogenic activity" of α-methylstyrene in female B6C3F1 mice based on increased incidences of hepatocellular adenomas and carcinomas in all dosed groups. Exposure to α-methylstyrene resulted in non-neoplastic lesions of the nose in male and female rats and mice and of the liver and kidney in female mice.

α-Methylstyrene is not mutagenic in bacterial test systems, but may cause chromosomal damage in cultured rodent and human cells. Its epoxide metabolite, α-methylstyrene oxide, is mutagenic in bacteria (NTP 2013).

7.8. Reproductive toxicity

7.8.1. Human data

No data were available.

7.8.2. Animal data

Fertility

No compound-related differences in the counts of testicular sperm heads or epididymal spermatozoa occurred in rats after inhalation exposure to 50, 100, 500 and 1200 ppm (250, 500, 2500 and 6000 mg/m^3) 2-phenylpropane for 13 weeks (6 hours/day, 5 days/week) (Cushman *et al* 1995). Also, the morphology and stages of spermatogenesis were normal in all groups.

Developmental toxicity

Pregnant Sprague-Dawley rats (gestational day 6–15, n = 25 per group) and New Zealand white rabbits (gestational day 6–18, n = 15 per group) were exposed for 6 hours/day by inhalation to 2-phenylpropane at concentrations of 0, 100, 500 and 1200 ppm (rats; 0, 500, 2500 and 6000 mg/m^3) and 0, 500, 1200 and 2300 ppm (rabbits; 0, 2500, 6000 and 11500 mg/m^3) (Darmer *et al* 1997). At 1200 ppm, the body weight gain of the rats was decreased and the relative liver weights were increased. Feed consumption of both rats and rabbits was decreased at 500 ppm. The liver weights of rabbits exposed to 2 300 ppm were significantly increased and 2 rabbits of this exposure group died. According to the authors, the NOAEC for maternal toxicity in rats was 100 ppm and no NOAEC for maternal toxicity in rabbits could be derived from this study. Despite of maternal toxicity in animals of both species there were no statistically significant alterations in gestational parameters, including the number of corpora lutea, the number of resorptions and stillborns, the number of live pups, the sex ratio and the foetal body weight, at any concentration tested (the analysis by EPA (1997) of the original report identified "non-significant increases in nonviable implants, and early resorption and a non-significant decrease in the percent of live foetuses" at the highest concentration). In rats, no significant changes in the incidences of any malformations or variations occurred, indicating a NOAEC for developmental toxicity of 200 ppm.

In rabbits, there were also no significant differences in the incidences of malformations, but one variation (ecchymosis on the head, i.e. haemorrhagic areas of the skin) was significantly increased in the 500-ppm group (not concentration-related). However, since the incidence of this variation was in the range of historical control values, the authors did not consider it to be a treatment-related effect. In conclusion, the authors derived a NOAEC of 2300 ppm for the developmental toxicity of 2-phenylpropane in rabbits. However, though the alterations in gestational parameters were not statistically significant (see above), EPA (1997) regarded these findings as potential developmental effects. Thus, these authors considered 1200 ppm to be the NOAEC for both developmental and maternal effects.

7.9. Mode of action and adverse outcome pathway considerations

For matters of setting an OEL for 2-phenylpropane, the principal aspect is carcinogenicity. The NTP panel (NTP 2009) concluded that, under the conditions of the NTP 2-year inhalation studies, there was clear evidence of carcinogenic activity of 2-phenylpropane in male F344/N rats based on increased incidences of respiratory epithelial adenoma in the nose and renal tubule adenoma or carcinoma (combined). Some evidence of carcinogenic activity of 2-phenylpropane was seen in female F344/N rats based on the incidences of respiratory epithelium adenoma in the nose. Clear evidence of carcinogenic activity of 2-phenylpropane was seen in male B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms. Clear evidence of carcinogenic activity of 2-phenylpropane was seen in female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms. Increased incidences of hepatocellullar adenoma or carcinoma (combined) in female mice were also considered related to exposure to 2-phenylpropane. Exposure to 2-phenylpropane resulted in non-neoplastic lesions in the nose and kidney of male rats; the nose of female rats; the lung, nose, liver and forestomach of male mice; and the lung and nose of female mice. The incidences of alveolar/bronchiolar adenomas and carcinomas in 2-phenylpropane-treated B6C3F1 mice were significantly greater than those of the control animals (Hong *et al* 2008). Lung neoplasms were evaluated for point mutations in the *K-ras* and *p53* genes that are often mutated in humans. *K-ras* mutations were detected in 87 % of 2-phenylpropane-induced lung neoplasms. *p53* protein expression was detected by immunohistochemistry in 56 % of 2-phenylpropane-induced neoplasms, and mutations were detected in 52% of neoplasms. No *p53* mutations and 1 of 7 (14%) *K-ras* mutations were detected in spontaneous neoplasms. 2-Phenylpropane-induced lung carcinomas showed loss of heterozygosity (LOH) on chromosome 4 near the *p16* gene (13%) and on chromosome 6 near the *K-ras* gene (12%). No LOH was observed in spontaneous carcinomas or normal lung tissues examined. The pattern of mutations identified in the

lung tumours suggests that DNA damage and genomic instability may be contributing factors to the mutation profile and development of lung cancer in mice exposed to 2-phenylpropane (NTP 2009).

With respect to the observed mouse lung tumours, the following mechanistic investigations have been reported. Wakamatsu *et al* (2008) performed global gene expression analysis to distinguish patterns of gene regulation between 2-phenylpropane-induced tumours and normal lung tissue and to look for patterns based on the presence or absence of *K-ras* and *p53* mutations in the tumours. Principal component analysis segregated the carcinomas into groups with and without *K-ras* mutations, but failed to separate the tumours based on *p53* mutation status. Gene expression analysis also suggested that 2-phenylpropane-induced carcinomas with *K-ras* mutations have greater malignant potential than those without mutations. The gene expression analysis suggested the formation of alveolar/bronchiolar carcinomas in 2-phenylpropane-exposed mice typically involves mutation of *K-ras*, which results in increased Erk MAP kinase signalling and modification of histones. Hoenerhoff *et al* (2009) evaluated spontaneous and 2-phenylpropane-induced lung neoplasms for mutations in *K-ras* and *Tp53* genes, as well as chemical-specific mutations that could function as biomarkers of chemical exposure with potential human health importance. Results suggest that in 2-phenylpropane-induced pulmonary tumours in mice, DNA damage and genomic instability leading to *K-ras* and *Tp53* dysregulation leads to up-regulation of pathways associated with the development of lung cancer in 2-phenylpropane-exposed mice and that tumours resulting from mutations in *K-ras* possess a gene expression associated with a greater degree of malignancy. These findings were interpreted by NTP (2013) to suggest an involvement of local DNA damage (including indirect damage through reactive oxygen species) and genomic instability in the tumour induction by 2-phenylpropane.

With regard to species-specificity of the *mouse lung tumours*, data from chemically related compounds can be combined to reinforce confidence in the "CYP2F toxicity hypothesis". In particular for styrene, a coherence of toxicity with the local presence of CYP2F2 has been demonstrated. Rat CYP2F4 appears to be equally active in metabolising such chemicals compared to mice; however, CYP2F4 occurs to a much lower extent in rat Clara cells, and levels of metabolites produced are therefore not sufficient to cause lung cytotoxicity. Human lungs contain even far fewer of Clara cells than rats or mice, and human lung microsomes failed to, or only marginally, metabolise these substrates. In addition, the human lung differs markedly from the mouse lung in the morphology of its Clara cells, which make humans much less sensitive than mice to toxicity due to reactive metabolites (Cruzan *et al* 2009, 2012). In total, it appears that species-specific metabolism by the cytochrome P450 isoform CYP2F2 in Clara cells of the mouse lung results in the production of cytotoxic metabolites that is essentially connected with the evolvement of tumours.

With regard to *renal carcinogenicity* of 2-phenylpropane in male rats, the available data are consistent with an α2u-globulin nephropathy mechanism of action in kidney-tumour formation. This is generally accepted to be a species-specific mechanism that does not operate in humans.

The formation of *hepatocellular tumours*, especially in mice, by phenobarbital-like CYP inducers can also not be translated to the conditions in humans, based on analysis of toxicokinetic and toxicodynamics parameters. Such liver tumours are formed as a result of species-specific sustained cytotoxicity and regenerative proliferation (for details, see Holsapple *et al* 2006).

The *nose respiratory epithelial tumours* observed in rats were benign adenomas and apparently related to inflammatory processes, as there is no indication of a genotoxic action on the nasal epithelium.

Interpretation by SCOEL: SCOEL considers 2-phenylpropane to be primarily a non-genotoxic carcinogen, which allows setting of a health-based Occupational Exposure

Limit. For the induction of observed lung, kidney and liver tumours species-specific mechanisms appear to be decisive.

7.10. Lack of specific scientific information

In general, 2-phenylpropane is a well-investigated compound experimentally. However, epidemiological studies on exposed industrial populations are lacking.

8. GROUPS AT EXTRA RISK

There is no specific information on population groups at extra risk from 2-phenylpropane.

9. REFERENCES

ACGIH, American Conference of Governmental Industrial Hygienists (2001). Cumene. In: Threshold limit values for chemical substances and physical agents and biological exposure indices, 2004. ACGIH, Cincinnati, Ohio, USA.

Alarie Y, Nielsen GD, Schaper MM (2001). Animal bioassays for evaluation of indoor air quality. Chapter 23. In: Spengler JD, McCarthy JF, Samet JM. Indoor air quality handbook. McGraw-Hill, 23.1-23.49.

Amoore JE, Hautala E (1983). Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3:272-290, cited in WHO 1999.

BAUA, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (2006). TRGS 900 "Arbeitsplatzgrenzwerte". , BAUA, Germany, http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/TRGS-900.html

BEK (2011). Bekendtgørelse om ændring af bekendtgørelse om grænseværdier for stoffer og materialer, BEK nr 1134 af 01/12/2011 (Gældende), Beskæftigelsesministeriet, Arbejdstilsynet, j.nr. 2011007144, Denmark, https://www.retsinformation.dk/pdfPrint.aspx?id=139131

Brugnone F, Perbellini L, Faccini GB, Pasini F, Maranelli G, Romeo L, Gobbi M, Zedde A (1989). Breath and blood levels of benzene, toluene, cumene and styrene in non-occupational exposure. Int Arch Occup Environ Health 61:303-311.

Bushy Run Research Center (1989). Cumene (isopropylbenzene) fourteen-week vapor inhalation study in rats with neurotoxicity evaluation. Project Report 52-628. OTS 0525881, Doc ID 408991272.

Bushy Run Research Center (1991). Cumene (isopropylbenzene) thirteen-week vapour inhalation study in rats. Project Report 53-611. OTS 0206782, Doc ID 86910001018.

Ceresana Market Intelligence. Consulting (2001) Market Study: Benzene (2nd edition), http://www.ceresana.com/en/market-studies/chemicals/benzene/

Chakraborty J, Smith JN (1967). Enzymic oxidation of some alkylbenzenes in insects and vertebrates. Biochem J 102:98-503, cited in ECB 2001.

Chemical Economics Handbook (2010). Cumene, CEH Marketing Research Report. Menlo Park, CA: SRI Consulting International,cited in IARC 2012.

Chemical Economics Handbook (2014). Cumene. https://www.ihs.com/products/cumene-chemical-economics-handbook.html

Chen L-J, Wegerski CJ, Kramer DJ, Thomas LA, McDonald JD, Dix KJ, Sanders JM (2011). Disposition and metabolism of cumene in F344 rats and B6C3F1 mice. Drug Metab Dispos 39(3):488-509.

CIEC, Chemical Industry Education Centre (2001). Phenol Annual Production. Essential Chemical Industry Book Greener Industry Website, United Kingdom (2001), accessed October 2015, http://www.greener-industry.org.uk/pages/phenol/1PhenolAnnualProd.htm

CMA, Chemical Manufacturers Association (1992). Letter from Chemical Manufacturers Association to USEPA submitting two studies on cataract formation in rats with cumene & one study identifying an unknown urinary metabolite of cumene. OTS 0540104, New Doc ID 86-920000974, cited in Greim 1996.

Cruzan G, Bus J, Banton M, Gingell R, Carlson G (2009). Mouse specific lung tumors from CYP2F2-mediated cytotoxic metabolism: an endpoint/toxic response where data from multiple chemicals converge to support a mode of action. Regul Toxicol Pharmacol 55(2):205-218.

Cruzan G, Bus J, Hotchkiss J, Harkema J, Banton M, Sarang S (2012). CYP2F2-generated metabolites, not styrene oxide, are a key event mediating the mode of action of styrene-induced mouse lung tumors. Regul Toxicol Pharmacol 62(1):214-220.

Curren RD (1987). NTIS [National Technical Information Service]/OTS 0522853, cited in ECB 2000.

Cushman JR, Norris JC, Dodd DE, Darmer KI, Morris CR (1995). Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. J Am Coll Toxicol 14:129-147.

Darmer KI, Neeper-Bradley TL, Cushman JR, Morris CR, Francis BO (1997). Developmental toxicity of cumene vapor in CD rats and New Zealand White rabbits. Int J Toxicol 16:119-139.

DFG, Deutsche Forschungsgemeinschaft (2015). List of MAK and BAT Values 2015: Maximum Concentrations and Biological Tolerance Values at the Workplace. Chapter II List of Substances. DFG, Germany. Wiley-VCH, Weinheim, http://onlinelibrary.wiley.com/book/10.1002/9783527695539

Dimian AC, Bildea CS (2008). Chemical process design: Computer-aided case studies, chapter 6: Alkylation of benzene by propylene to cumene. ISBN: 978-3-527-31403-4, http://tekim.undip.ac.id/staf/istadi/files/2009/05/topik2.pdf

DLPLV, Dutch Legal Public Limit Values (2007). Nationale wettelijke publieke grenswaarden, DLPLV, Dutch Law on Labour Conditions, The Netherlands, http://www.ser.nl/nl/themas/grenswaarden/procedure%20tot%202007.aspx

Dow Chemical Company (1985). Results of range finding toxicological tests on Dowell A-121. OTS 0206726, Doc ID 878214936, cited in Greim 1996.

ECB, European Chemicals Bureau (2000). IUCLID, International Uniform Chemical Information Database. Edition II. EUR 19559 EN, European Commission.

ECB, European Chemicals Bureau (2001). European Union Risk Assessment Report: Cumene. 1st Priority List, Vol. 6. EUR 19726 EN. European Commission. Joint Research Centre, http://echa.europa.eu/documents/10162/c44474a0-e926-451d-9efd-810b230008f4

EPA, Environmental Protection Agency (1997). Toxicological review of cumene. In support of summary information on the integrated risk information system. US Environmental Protection Agency, Washington DC.

EPA, Environmental Protection Agency (2000). Cumene. Hazard summary-created in April 1992; revised in January 2000. US Environmental Protection Agency, Washington DC, http://www.epa.gov/ttn/atw/hlthef/cumene.html.

Fabre R, Truhaut R, Bernuchon J, Loisillier F (1955). Toxicological studies on solvents replacing benzene. III. Study of isopropylbenzene or cumene. Archives Maladies Professionelles 16:285-299, cited in Gardner and Delic 1994.

Fiserova-Bergerova V, Pierce JT, Droz P-O (1990). Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med 17:617-635.

Florin I, Rutberg L, Curvall M, Enzell CR (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15:219-232.

Gagnaire F, Langlais C (2005). Relative ototoxicity of 21 aromatic solvents. Arch Toxicol 79:46-354.

Gardner R, Delic J (1994). Criteria document for an occupational exposure limit. Cumene. HSE Books, Sudbury, Suffolk, UK.

Gerarde HW (1959). Toxicological studies on hydrocarbons. III. The biochemorphology of the phenylalkanes and phenylalkenes. AMA Arch Ind Health 19:403-418, cited in ACGIH 2001.

GESTIS (2015). Cumene. GESTIS database on hazardous substances. IFA [Institut für Arbeitssicherheit der Deutschen Gesetzlichen Unfallversicherung], St. Augustin. http://limitvalue.ifa.dguv.de/ accessed August 2015

GKV (2011). BGBl. II Nr. 429/2011. Verordnung des Bundesministers für Arbeit, Soziales und Konsumentenschutz über Grenzwerte für Arbeitsstoffe sowie über krebserzeugende und über fortpflanzungsgefährdende (reproduktionstoxische) Arbeitsstoffe, Grenzwerteverordnung (DKV), Austria, http://www.arbeitsinspektion.gv.at/NR/rdonlyres/F173280B-D4FB-44D2-8269-8DB2CB1D2078/0/GKV2011.pdf.

Goenechea S (1983). Isopropylbenzol (Cumol). In: Angerer J, Schaller KH, Henschler D (eds.), Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 2: Analysen in biologischem Material (Biomonitoring Methods in German language), 7. Lieferung, VCH Weinheim. http://onlinelibrary.wiley.com/doi/10.1002/3527600418.bi9882d0007/full

Greim H (ed.) (1996). iso-Propylbenzol (Cumol). Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, 22. Lfg., VCH Weinheim. http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics.

Gulf Oil Corporation (1984). Hepatocyte primary culture/DNA repair test of cumene NTIS/OTS 0509712, cited in WHO 1999.

Gulf Oil Corporation (1985a). Five-day repeated dose inhalation toxicity study in rats of cumene. NTIS/OTS 0206783, cited in ECB 2001.

Gulf Oil Corporation (1985b). NTIS [National Technical Information Service]/OTS 0206775, cited in ECB 2000.

Gulf Oil Corporation (1985c). NTIS [National Technical Information Service]/OTS 0206782, cited in ECB 2000.

Hall AP, Elcombe CR, Foster JR, Harada T, Kaufmann W, Knippel A, Küttler K, Malarkey DE, Maronpot PR, Nishikawa A, Nolte T, Schulte A, Strauss V, York MJ (2012). Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes – conclusions from the 3rd International ESTP Expert Workshop. Toxicol Pathol 40: 971-994. http://tpx.sagepub.com/content/40/7/971.

Henne KR, Fisher MB, Iyer KR, Lang DH, Trager WF, Rettie AE (2001). Active site characteristics of CYP4B1 probed with aromatic ligands. Biochemistry 40(29): 8597-8605.

Hoenerhoff MJ, Hong H-H, Ton T-V, Lahousse SA, Sills RC (2009). A review of the molecular mechanisms of chemically induced neoplasia in rat and mouse models in National Toxicology Program bioassays and their relevance to human cancer. Toxicol Pathol 37:835-848.

Holsapple MP, Pitot HC, Cohen SM, Boobis AR, Klaunig JE, Pastoor T, Dellarco VL, Dragan YP (2006). Mode of action in relevance of rodent liver tumors to human cancer risk. Toxicol Sci 89(1):51-56.

Hong H-HL, Ton T-VT, Kim Y, Wakamatsu N, Clayton NP, Chan P-CC, Sills RS, Lahousse SA (2008). Genetic alterations in K-ras and p53 cancer genes in lung neoplasms from B6C3F1 mice exposed to cumene. Toxicol Pathol 36 (5):720-726.

HS, Health and Safety (2013). Workplace Exposure Standards and Biological Exposure Indices Effective from February 2013, 7th Edition. HS, The Ministry of Business, Innovation and Employment, New Zealand, http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/workplace-exposure-standards-and-biological-exposure-indices/workplace-exposure-standards-and-biological-indices-2013.pdf

HSA, Health and Safety Authority (2011). 2011 Code of Practice for the Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001 (S.I. No. 619 of 2001), HAS, Ireland.

HSDB, Hazardous Substances Database (2005). Cumene. National Library of Medicine. Complete update: 2005, last reviewed: 2000. http://toxnet.nlm.nih.gov/cgibin/sis/htmlgen?HSDB

HSE, Health & Safety Executive (2001). Consultation Document - European Commission Directive 2000/39/EC establishing a first list of Indicative Occupational Exposure Limit Values at European Community level in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. http://www.hse.gov.uk/consult/condocs/cd166.htm.

HSE, Health and Safety Executive (2011). EH40, Second edition, HSE, UK, http://www.hse.gov.uk/pUbns/priced/eh40.pdf

Huels AG (1988). Huels Report No. 1219 (unpublished), cited in ECB 2000.

Huels AG (1994). Huels Report No. 1219 (unpublished) (1988). As reported in dossier prepared by ICI Chemicals and Polymers, Ltd (May 27, 1994), cited in ACGIH 2001.

Huntingdon Research Center (1979). Report No. 325b (unpublished), cited in ECB 2000.

Hwang SY, Chen SS (2010). 2-Phenylpropane, Kirk-Othmer Encyclopedia of Chemical Technology. Published Online: 17 Sept 2010, DOI: 10.1002/0471238961.0321130519030821.a01.pub3

IARC, International Agency for Research on Cancer (2011). Carcinogenicity of chemicals in industrial and consumer products, food contaminants and flavourings, and water chlorination byproducts. Oncology 12:328-329.

IARC, International Agency for Research on Cancer (2012) Cumene. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 101:325-348. IARC, Geneva, CH http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-009.pdf

ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2010). ICH Harmonised tripartite guideline. ICH Q3C(R5): Impurities: guideline for residual solvents. Revision of the ICH Q3C(R4) guideline to account for new toxicity data related to cumene.

INRS, Institut National de Recherche et de Sécurité (2012).Valeurs limites d'exposition professionnelle aux agents chimiques en France, INRS, France, http://www.inrs.fr/media.html?refINRS=ED%20984

INSHT, Instituto Nacional de Seguridad e Higiene en el Trabajo (2011). Limites de Exposicion profesional para agentes quimicos en Espana. INSHT, Spain, http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_Limite/limites2011/Limites2011web.pdf

IRSST, Institut de Recherche Robert Sauvé en Santé et en Sécurité du Travail Canada (2010). IRSST, Québec, Canada, http://www.irsst.qc.ca/en/-RSST62-53-3.html

HSDB, Hazardous Substances Database (2005). 2-Phenylpropane. HSDB. National Library of Medicine. Complete update: 2005, last reviewed: 2000. http://toxnet.nlm.nih.gov/cgibin/sis/htmlgen.

Jenkins LJ, Jones RA, Siegel J (1970). Long-term inhalation screening studies of benzene, toluene, p-xylene and cumene on experimental animals. Toxicol Appl Pharmacol 16:818-823, cited in ECB 2001 and HSE 2001.

Knecht U (2013). 2-Phenyl-2-propanol in urine. In: Göen Th, Hartwig A (eds.), The MAK-collection for Occupational Health and Safety, Part IV: Biomonitoring methods, Vol. 13, pp. 163-177, Wiley-VCH Weinheim. http://onlinelibrary.wiley.com/doi/10.1002/3527600418.bi9882e0013/full

Knecht U, Ulshöfer A (1996). Bio-Monitoring nach *iso*-Propylbenzol-Einwirkung. In: Münzberger E. Die Stellung der Arbeitsphysiologie in der heutigen Arbeitsmedizin. Begutachtung in der Arbeitsmedizin und Umweltmedizin. 36. Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin vom 6. bis 9. Mai 1996 in Wiesbaden. Rindt-Druck, Fulda, 225-227.

Kraemer M (2014). Solvent mixtures. Method number 1 (Lösemittelgemische; Air Monitoring Methods in German language). In: Parlar H, Hartwig A (eds), Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 1, Luftanalysen, 18. Lieferung, Wiley-VCH, Weinheim. http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0lmix001d0018/pdf

Kristiansen U, Hansen L, Nielsen GD, Holst E (1986). Sensory irritation and pulmonary irritation of cumene and n-propanol: mechanisms of receptor activation and desensitization. Acta Pharmacol Toxicol 59:60-72, cited in Greim 1996 and HSE 2001.

Lee KY, Cho ES, Kang MG, Lee SB, Kim HY, Son HY (2009). Effects of cumene exposure on synaptophisin and GFAP expressions in hippocampus of rat. Lab Anim Res 25(4):303-309.

Lehnert G, Greim H (eds.) (2001). *iso*-Propylbenzol. Biologische Arbeitsstoff-Toleranz-Werte (BAT-Werte) und Expositionsäquivalente für krebserzeugende Arbeitsstoffe (EKA), Arbeitsmedizinisch-toxikologische Begründungen, 10. Lfg., Wiley-VCH Weinheim. http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics.

MHSFA, Ministry of Health, Social and Ministry of Family Affairs, Hungary (2000). 25/2000. (IX. 30.) EüM-SzCsM együttes rendelet a munkahelyek kémiai biztonságáról, MHSFAHungary, http://net.jogtar.hu/jr/gen/hjegy_doc.cgi?docid=A0000025.EUM

MLSP, Ministry of Labour and Social Policy Poland (2002). The Ordinance of the Minister of Labour and Social Policy on the Maximum Admissible Concentrations and Intensities of Harmful to Health Agents in the Working Environment. Rozporzñdzenie ministra pracy i polityki spo¸ecznej Z dnia 29 listopada 2002 r, MLSP, Poland, http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/legaldocument/wcms_151572.pdf

Micromarket Monitor (2015). Europe Cumene Market Report. http://www.micromarketmonitor.com/market/europe-2-Phenylpropane-7444892924.html

Monsanto Company (1978). TSCA Section 8(d) Submission. Cumene health studies Y-78-213. Acute toxicity, eye and skin irritation. EPA/TS Document No. 40-8592034. US Environmental Protection Agency (1978). Office of Toxic Substances, Washington DC, cited in ACGIH 2001.

Monsanto Company (1985). NTIS [National Technical Information Service]/OTS 0512312, cited in ECB 2000.

Monsanto Company (1986). One-month study of cumene vapor administered to male and female Sprague-Dawley rats by inhalation. US EPA/OTS Public Files, 8D submission. Microfiche No. OTS0513229, cited in EPA 1997.

MoSH, Ministry of Social Affairs and Health Finland (2012). HTP-värden 2012. Koncentrationer som befunnits skadliga. Social- och halso vardsministeriets publikationer 2012:6, MoSH, Finland, http://www.ttk.fi/files/2610/STM_2012_6_HTP_SWE_web.pdf

NIOSH (2003). Hydrocarbons, aromatic: Method 1501, Issue 3, March 2003. NIOSH Manual of Analytical Methods, 4th ed., Cincinnati, OH: National Institute for Occupational Safety and Health, United States Department of Health and Human Services.
http://www.cdc.gov/niosh/docs/2003-154/pdfs/1501.pdf

NIOSH (2007). Pocket guide to chemical hazards. Department of Health and Human Services. Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH), USA, http://www.cdc.gov/niosh/docs/2005-149/pdfs/2005-149.pdf

NIOSH (2011). Pocket guide to chemical hazards. Cumene. Accessed 1/10/2015. http://www.cdc.gov/niosh/npg/npgd0159.html

NLIA, Norwegian Labour Inspection Authority (2011). Administrative normer for forurensning i arbeidsatmosfære, NLIA, Norway, http://www.arbeidstilsynet.no/binfil/download2.php?tid=77907

NTP, National Toxicology Program (2007). NTP Toxicology and carcinogenesis studies of alpha-methylstyrene (CAS No. 98–83–9) in F344/N rats and B6C3F1 mice (inhalation studies). Natl Toxicol Program Tech Rep Ser 543:1–210. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr543/index.html

NTP, National Toxicology Program (2009). NTP Toxicology and carcinogenesis studies of cumene (CAS No. 98–82–8) in F344/N rats and B6C3F1 mice (inhalation studies). Natl Toxicol Program Tech Rep Ser 542:1–200.

NTP, National Toxicology Program (2012a). Report on Carcinogens (RoC) Concept: Cumene (Aug 2012, accessed 31 Dec 2012). http://ntp.niehs.nih.gov/NTP/roc/thirteenth/Concepts/CumeneConcDocRoC8-30-12508.pdf.

NTP, National Toxicology Program (2012b). Final report on the cumene (CASRN 98-82-8) genotoxicity studies. Oct 29, 2012. US Department of Health and Human Services, Washington DC.

NTP, National Toxicology Program (2013). Report on Carcinogens (RoC), Monograph on 2-Phenylpropane. National Toxicology Program (NTP), US Department of Health and Human Services (HHS), September 2013, NIH Publication No. 13-5983 ISSN 2331-267X
http://ntp.niehs.nih.gov/ntp/roc/thirteenth/monographs_final/2-Phenylpropane_508.pdf

Nielsen GD, Alarie Y (1982). Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: prediction of safe industrial exposure levels and correlation with their thermodynamic properties. Toxicol Appl Pharmacol 65:459-477.

Ontario Ministry of Labour (2013). Current Occupational Exposure Limits for Ontario Workplaces Required under Regulation 833, Canada, http://www.labour.gov.on.ca/english/hs/pdf/ontario_oels.pdf

OSHA, Occupational Safety and Health Administration (2006). Air Contaminants. OSHA, USA, https://www.osha.gov/dsg/annotated-pels/tablez-1.html

OSHA, Occupational Safety and Health Administration (2015). OSHA method for air sampling of 2-Phenylpropane method No. PV2137 accessed 7-10-2015. https://www.osha.gov/dts/sltc/methods/partial/pv2137/pv2137.html

Perbellini L, Pasini F, Faccini GB, Danzi B, Gobbi M, Zedde A, Cirillo P, Brugnone F, (1988). Determination of industrially used solvents in blood, alveolar air and urine in a group of blood donors. Med Lav 79:460-467, cited in ECB 2001.

Perego C, Ingallina P (2002). Recent advances in the industrial alkylation of aromatics: new catalysts and new processes. Catalysis Today 73: 3-12 http://www.researchgate.net/publication/222527979_Recent_advances_in_the_industrial_alkylation_of_aromatics_New_catalysts_and_new_processes

Procter & Gamble Company (1985). 28-Day subacute percutaneous toxicity with cover letter. OTS 0206749, Doc ID 878215029, cited in Greim 1996.

PubChem (2015). Cumene, National Center for Biotechnology Information (NIH). PubChem Compound Database; CID=7406, (accessed Oct. 28, 2015), http://pubchem.ncbi.nlm.nih.gov/compound/2-Phenylpropane

Putman DL (1987a). NTIS [National Technical Information Service]/OTS 0522852, cited in ECB 2000.

Putman DL (1987b). NTIS [National Technical Information Service]/OTS 0522854, cited in ECB 2000.

Research Triangle Institute (1989). Metabolism, disposition and pharmacokinetics of cumene in F-344 rats following oral, i.v. administration or noise-only inhalation exposure. RTI Study Number 3543, cited in Gardner and Delic 1994 and WHO 1999.

Royal Decision (Koninklijk besluit) (2014). Revised version valid for after July 2014. In dutch. Koninklijk besluit van 11 maart 2002 betreffende de bescherming van de gezondheid en de veiligheid van de werknemers tegen de risico's van chemische agentia op het werk, Belgium, https://www.google.it/?gfe_rd=cr&ei=2v00Vb7xC6fD8ges7oHQAw&gws_rd=ssl#q=Koninklijk+besluit+van+11+maart+2002+betreffende+de+bescherming+van+de+gezondheid+en+de+veiligheid+van+de+werknemers+tegen+de+risico%E2%80%99s+van+chemische+agentia+op+het+werk

Safe Work Australia (2011). Workplace exposure standards for airborne contaminants date of effect: 22 December 2011, Australia, http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/639/Workplace_Exposure_Standards_for_Airborne_Contaminants.pdf

Sato A, Nakajima T (1979). Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br J Ind Med 36:231-234, cited in Greim 1996.

Schneider W, Breuer D (2014). Solvent mixtures. Method number 2 (Lösemittelgemische; Air Monitoring Methods in German language). In: Parlar H, Hartwig A (eds), Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 1, Luftanalysen, 18. Lieferung, Wiley-VCH, Weinheim. http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0lmix002d0018/pdf

SCOEL (1993). SUM 29 - Cumene CAS 98-82-8. Recommendation adopted in 1993. Available via http://ec.europa.eu/social/keyDocuments.jsp?type=0&policyArea=82&subCategory=153&country=0&year=0&advSearchKey=recommendation&mode=advancedSubmit&langId=enhttp://ec.europa.eu/social/keyDocuments.jsp?advSearchKey=cumene&mode=advancedSubmit&langId=en&policyArea=&type=0&country=0&year=0

Schaper M (1993). Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am Ind Hyg Assoc J 54(9):488-544.

Senczuk W, Litewka B (1976). Absorption of cumene through the respiratory tract and excretion of dimethylphenylcarbinol in urine. Br J Ind Med 33:100-105, cited in Greim 1996.

Simmon VF, Kauhanen K, Tardiff RG (1977). Mutagenic activity of chemicals identified in drinking water. In: Scott D, Bridges BA, Sobels FH. Progress in genetic toxicology: Proceedings of the second international conference on environmental mutagens, Edinburgh, July 11-15, 1977. Elsevier/North Holland Biomedical Press, Amsterdam, 249-258.

Smyth HF, Carpenter CP, Weil CS (1951). Range-finding toxicity data: List IV. AMA Arch Ind Hyg and Occup Med 4:119-122.

Solomin GI (1979). Toxic effect of chemical substances in the altered gas environment of sealed spaces. Kosm Biol Aviakosm Med 13:83-84, cited in ECB 2000.

SSL [Salute e Sicurezza sul Lavoro, Italy] (2008). D.lgs. 9 aprile 2008, n. 81 Testo coordinato con il D.Lgs. 3 agosto 2009, n. 106, SSL, Italy, http://www.lavoro.gov.it/SicurezzaLavoro/MS/Normativa/Documents/TU%2081-08%20-%20Ed.%20Maggio%202014.pdf

SUVA, Schweizerische Unfallversicherungsanstalt (2015). SUVA, Grenzwerte am Arbeitsplatz 2015. MAK-Werte, BAT-Werte, Grenzwerte für physikalische Einwirkungen, Switzerland, https://extra.suva.ch/suva/b2c/b2c/start.do;jsessionid=1SNHbj-0PppElAFvO7Ks0eUouc2-TQFykRoe_SAPdq5f-GW926vKwRXNGAkQrfkO;saplb_*=(J2EE505057620)505057650

SWEA, Swedish Work Environment Authority (2011). The Swedish Work Environment Authority's provisions and general recommendations on occupational exposure limit values, SWEA, Sweden, http://www.av.se/dokument/inenglish/legislations/eng1118.pdf

Tegeris JS, Balster RL (1994). A comparison of the acute behavioral effects of alkyl-benzenes using a functional observational battery in mice. Fundam Appl Toxicol 22:240-250.

Tschickardt M (2014). Solvent mixtures. Method number 6 (Lösemittelgemische; air monitoring methods in German language). In: Parlar H, Hartwig A (eds), Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe, Band 1, Luftanalysen, 18. Lieferung, Wiley-VCH, Weinheim. http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am0lmix006d0018/pdf

Turner FC (1962). NTIS [National Technical Information Service]/OTS 0206726; Doc ID 878214935, cited in ECB 2000.

Union Carbide Corporation (1985). NTI [National Technical Information Service]/OTS 0206745; Doc ID 878214980, cited in ECB 2000.

Valette G, Cavier R (1954). Percutaneous absorption and chemical composition of hydrocarbons, alcohols, and esters. Arch Int Pharmacodyn Ther 97:232-240, cited in ACGIH 2001.

Wakamatsu N, Collins JB, Parker JS, Tessema M, Clayton NP, Ton T-VT, Hong H-HL, Belinsky S, Devereux TR, Sills RC, Lahousse SA (2008). Gene expression studies demonstrate that the K-ras/Erk MAP kinase signal transduction pathway and other novel pathways contribute to the pathogenesis of cumene-induced lung tumors. Toxicol Pathol 36(5):743-752.

WHO, World Health Organization (1999). Cumene. Concise International Chemical Assessment Document (CICAD), Vol 18. International Program on Chemical Safety, Geneva, CH. http://www.who.int/ipcs/publications/cicad/cicad18_rev_1.pdf

Wolf MA, Rowe VK, McCollister DD, Hollingsworth RL, Oyen F (1956). Toxicological studies of certain alkylated benzenes and benzene. Arch Ind Health 14:387-398.

Yang LL (1987). NTIS [National Technical Information Service]/OTS 0522853, cited in ECB 2000.

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);

- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries
  (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm)
  or calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

Priced subscriptions:

- via one of the sales agents of the Publications Office of the European Union
  (http://publications.europa.eu/others/agents/index_en.htm).

KE-07-17-189-EN-N

Publications Office

doi: 10.2767/120149

ISBN 978-92-79-77248-1