Compound	LIMONENE	*Data collection sheet*
N°CAS: 7705-14-8 [(±)-Limonene]; 138-86-3 [Limonene, not specified]; 5989-27-5 [(*D*)-(+)-Limonene]; 5989-54-8 [(*S*)-(–)-Limonene]	CLP: Skin Irrit. 2, H315, Skin Sens. 1B, H317, Asp. Tox. 1, H304 Additional information: IARC not classifiable, Group 3	
1 ppm = 5.606 mg/m^3 (in air, 23 °C)		

Organisation Name	**EPA-DK**	**German IAQ**	**EPHECT**	**INDEX**	**NRC**	**Reach registrants ***
Risk Value Name		IAQG	Critical Exposure Limit (CEL)	Exposure Limit (EL)	SMAC	DNEL popul., chronic inhal.
Risk Value (mg/m^3)	4.5	Guide value I = 1 mg/m^3; Guide value II = 10 mg/m^3	9	0.45	115	8.33
Risk Value (ppm)			1.6		20	
Reference period					> 180 d	
Year	2013	2010				
Key Study		NTP (1990)	Falk-Filipsson et al. (1993)		NTP (1990)	
Study type	inhalation	oral chronic		inhalation	oral chronic	
Species	humans	F344/N-rats and B6C3F1-mice	human	human	mice (male)	
Duration of exposure in key study	2h			2h		
Critical effect	irritative symptoms in humans	histological lesions of liver tissue	subjective eye, nose, throat irritation	CNS related symptoms, irritation; endpoint: decline in vital capacity	liver toxicity	no information about DNEL derivation

Critical dose value	NOAEC 450 mg/m^3	LOAEL 500 mg/kg bw per day	NOAEL: 450 mg/m^3 (81 ppm)	450 mg/m^3	250mg/kg bw/d (mice) 300 mg/kg bw/d (rats)	long term inhalation DNEL (systemic effects) for the general population
Adjusted critical dose		LOEAL 357 mg/kg bw per day			70/kg / 20 m^3/ inh. Absorption 76 %	no information about DNEL derivation
		70/kg / 20 m^3/ inh. Absorption 63 %				
Single assessment factors (see table R.8.6)	10 x 10 x	intersp. 10, intrasp. 10, children factor 2	intrasp. 5, study duration 10	LOAEL→ NOAEL 10, sa → chr 10, UF_H 10	intersp.: 10	
Other effects						
Confidence						
UF_L used LOAEL; UF_H intraspecies variability; UF_A interspecies variability; UF_S used subchronic study; UF_D data deficiencies						

*DNELs derived based on key studies selected for risk characterisation.

EPHECT WP 7 (2013) / Paolo Carrer et al. – Exposure and health risk assessment – Report on the health risk associated with emissions from household use of selected consumer products

JRC. 2005. The INDEX project 2005. Critical appraisal of setting and implementation of indoor exposure limits in the EU. European Commission, Joint Research Centre JRC (Ed.). Ispra, Italy. Online: ec.europa.eu/health/ph_projects/2002/pollution/fp_pollution_2002_frep_02.pdf.

NRC (2008) Limonene. In: Committee on Spacecraft Exposure Guidelines, Committee on Toxicology Board on Environmental Studies and Toxicology Division on Earth and Life Studies National Research Council NRC (ed.): Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 5, Chapter 13 p. 250-274. The National Academic Press, Washington, D.C., USA

Elsa Nielsen, Ole Ladefoged, Inge Søborg. Evaluation of health hazards by exposure to d-Limonene and proposal of a health-based quality criterion for ambient air Editing: National Food Institute, Technical University of Denmark, 2013

Mölhave L, Kjaergaard SK, Hempel-Jorgensen A, Juto JE, Andersson K, Stridh G, Falk J (2000) The eye irritation and odor potencies of four Terpenes which are major constituents of the emissions of VOCs from Nordic soft woods. Indoor. Air 10: 315-318.

EFSA Scientific Opinion on Flavouring Group Evaluation 25, Revision 2 (FGE.25Rev2): Aliphatic and aromatic hydrocarbons from chemical group 311 EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. European Food Safety Authority (EFSA), Parma, Italy. EFSA Journal 2011; 9(6):2177
http://www.efsa.europa.eu/de/efsajournal/doc/2177.pdf

NTP (1990) NTP Toxicology and Carcinogenesis Studies of d-Limonene (CAS No. 5989-27-5) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP TR 347: 1-165.

ECHA database: (R)-p-mentha-1,8-diene CAS-Nr. 5989-27-5 and (S)-p-mentha-1,8-diene, CAS-Nr.- 5989-54-8 // last search – 12-2014
http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Compound	d +-Limonene		*Factsheet*
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	5000
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value was issued	2014
General information			
CLP Index No	4	INDEX	601-029-00-7
EC No	5	EINECS – ELINCS - NLP	227-813-5
CAS No	6	Chemical Abstracts Service number	7705-14-8 [(±)-Limonene]; 138-86-3 [Limonene, not specified]; 5989-27-5 [(D)-(+)-Limonene]; 5989-54-8 [(S)-(–)-Limonene]
Harmonised CLP classification	7	Human health risk-related classification	Skin Irrit. 2, H315 Skin Sens. 1B, H317 Asp. Tox. 1, H304 Additional information: IARC not classifiable, Group 3
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	136.23 1 ppm = 5.6 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	NTP (1990) EFSA (2011)
Read-across compound	10	Where applicable	
Species	11	Rat etc. / human	Fisher rats
Route/type of study	12	Inhalation, oral feed, etc.	Oral (gavage)
Study length	13	Days, subchronic, chronic	2 yrs
Exposure duration	14	Hours/day, days/week	5 days/week
Critical endpoint	15	Effect(s), site of	Liver histology
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	NOAEL
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	300 mg/kg bw/day
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hours/day, days/week (7/5)	1.4
Study Length	20	sa→ sc→ c *(R8-5)*	1
Route-to-route extrapolation factor	21a	70kg, 20 m^3/d ECHA R.8-2	1
Route-to-route extrapolation factor	21b	Differences in bioavailability between oral and inhalation exposure	See POD/TAF
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	11
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	4

	23 b	Dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10
AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26		1
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	140
background daily intake		mg/kg bw/day	0.6
Route-to-route extrapolation		(see note 21a)	3.5
POD/TAF	28	Calculated value (mg/kg bw)] - oral background (mg/kg bw/day) route-to-route (mg/m^3)#	300 / 140 = 2.14 2.14 - 0.6 =1.54 1.54 x 3.5 = 5.4 mg/m^3
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m^3]	5000
Additional comments	31		
Rationale section	32		

d-Limonene could be considered a chemical of low toxicity. In human volunteers, no irritative symptoms were recorded following inhalation of 450 mg/m^3 *d*-limonene for 2 hours (Falk-Filipsson 1993). This is supported by the RD50 (Larsen et al. 2000). Interaction with ozone leads to the formation of volatile compounds with irritant properties. At 1 mg/m^3 ozone, irritation was at the same level as that for the pure terpenes (Wilkins et al., 2003), indicating that at ambient ozone concentrations the combined irritant effect is negligible.

Renal tumours and nephrotoxicity induced in chronic studies in male rats are considered not relevant to humans [Hard].

From the NTP-study, the EFSA panel derived a NOAEL for d-limonene of 300 mg/kg bw/day: '*Based on the decreased body weights in female mice, a NOAEL of 500 mg/kg bw/day (5 days/week) could be derived, but considering the decrease in survival in the female rats exposed at 600 mg/kg bw/day (5 days/week) an overall NOAEL of 300 mg/kg bw/day (5 days/week) should be derived from these NTP studies.'* This latter value is taken as the point of departure for EU harmonisation reasons; it is understood that the value refers to a POD in rats.

Application of standard assessment factors for exposure duration, intra- and interspecies (rat) extrapolation gives a total adjustment factor of 140 and a human 'oral LCI' of 300/140 of 2.14 mg/day/kg bw. This value must be reduced because of considerable oral background exposure from flavouring in the population.

The total combined intake of 42 000 microgram/capita/day (EFSA 2011) corresponds to 600 microgram/kg bw/day for a person with a body weight of 70 kg. This value is considered more reliable than a previous estimated average daily intake via foods of about 0.3 mg/kg bw from the USA (Flavor and Extract Manufacturers Association 1991 — quoted from CICAD 1998). The calculation of the LCI is corrected accordingly by subtracting the oral background exposure (residual amount for inhalation 2.14– 0.6 = 1.54 mg/kg b.w.)

Only small differences between oral and pulmonary absorption were identified. The main route of elimination of d-limonene administered orally was via urine in animals and man, 75-95 % (mean 85 %) of the administered radioactivity being excreted in urine in 2-3 days (Kodama 1976). This is comparable to the relative pulmonary uptake of approximately 66 % of the amount supplied after inhalation exposure (Falk-Filipsson 1993). No absorption factor for the difference between starting route and end route is applied
Route-to-route extrapolation for 20 m^3/70 kg bw and the residual amount for uptake by inhalation gives an LCI rounded value of 5 mg/m^3.

d-Limonene has an absolute odour threshold of 38 ppb (Nagata, 2003).

References

EFSA (2011) Scientific Opinion on Flavouring Group Evaluation 25, Revision 2 (FGE.25Rev2): Aliphatic and aromatic hydrocarbons from chemical group 311 EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. European Food Safety Authority (EFSA), Parma, Italy EFSA Journal 2011; 9(6):2177. http://www.efsa.europa.eu/de/efsajournal/doc/2177.pdf

Falk-Filipsson A, Löf A, Hagberg M, Hjelm EW, Wang Z. d-limonene exposure to humans by inhalation: uptake, distribution, elimination, and effects on the pulmonary function. J Toxicol Environ Health. 1993 Jan;38(1):77-88.

Flavor and Extract Manufacturers' Association (1991) *d-Limonene Monograph*, Washington DC, pp. 1–4

Hard GC, Whysner J. Risk assessment of d-limonene: an example of male rat-specific renal tumorigens. Crit Rev Toxicol. 1994;24(3):231-54

Kodama, R., Yano, T., Furukawa, K., Noda, K. & Ide, H. (1976) Studies on the metabolism of dlimonene (p-mentha-1,8-diene). IV. Isolation and characterization of new metabolites and species differences in metabolism. Xenobiotica, 6, 377–389

Nagata Y. (2003): Measurement of odour threshold by triangle odour bag method. Odour Measurement Rev 118–127.

NTP (1990) NTP Toxicology and Carcinogenesis Studies of d-Limonene (CAS No. 5989-27-5) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP TR 347: 1-165.

Webb DR, Ridder GM, Alden CL (1989) Acute and subchronic nephrotoxicity of d-limonene in Fischer 344 rats. Food Chem. Toxicol. 27: 639-649.