Compound	α-PINENE	*Data collection sheet (1/2)*
N°CAS 80-56-8	**Classification GHS:** H332: Harmful if inhaled (cat. 4), H319: Causes serious eye irritation (cat. 2) **CLP:** not included	1 ppm (in air, 23 °C) = 5.61 mg/m3 1 ppm (in air, 20 °C) = 5.66 mg/m3 MW=136.23

Organization Name	**ACGIH**	**BAuA**	**German IAQ**	**AgBB**	**ANSES**	**AFS**
Risk Value Name	8-h TWA	Occup. target value	RWI (target value) RWII (adverse effects possible) for bicyclic monoterpenes, model substance = α-pinene	NIK (=LCI)	CLI (=LCI)	OEL
Risk Value (mg/m³)	**112.12 (calculated for 23°C)**	**56.06 (calculated for 23°C)**	**RWI=0.2** **RWII=2.0**	**1.5**	**0.45**	**150**
Risk Value (ppm)	20	10	RWI=0.036 RWII=0.357 (calculated for 23°C)	0.267 (calculated for 23°C)	0.0803 (calculated for 23°C)	25
Reference period		Subacute	Subacute			
Year	2008	2005	2003			1990
Key Study	No information available	Järvisalo J, Vainio H: Acta Pharmacologica et Toxicologica 1980;46(1):32–36	Johard U, Larsson K, Löf A, Eklund A: Controlled short-time terpene exposure induces an increase of the macrophages and the mastcells in bronchoalveolar lavage fluids. Am J Ind Med 1993;23:793–799	Value derived from AFS-OEL: × 0.01	Value taken from the EU-INDEX Project	No information available
Study type		Inhalation study	8 volunt. inhalating 450 mg/m³ mixture of α-pinene, beta-pinene, delta-3-carene (10:1:5). 4×3hrs,			

			in 2 weeks. Elevated cell-concentrations in BAL after exposition, interpreted as acute alveolar cellular reaction / inflammation marker.			
Species		Rat	Man			
Duration of exposure in key study		6h/d, 5d/w for 8 weeks	4 × 3 hrs in 2 weeks			
Critical effect		Study with turpentine (95% α-pinene). Enhanced activities of drug biotransformation enzymes of liver microsomes: NADPH cytochrome c reductase and 7-ethoxycoumarin deethylase, and microsomal content of cytochrome P-450 (increased 35–60% only during first weeks). Increase in liver microsomal epoxide hydratase and UDPglucuronosyltransferase tended to adapt less. Result describes not an adverse effect per se, but influence of biotransformation of drugs is possible.	20 hrs after exposure significant higher concentrations of alveolar cell concentrations (median pre-exposure 76 × $l0^6$ cells/L -> 126 × $l0^6$ cells/L), predominantly due to macrophages (72 × $l0^6$ cells/L -> 121 × $l0^6$ cells/L). Also mast cells increased: 1/10 -> 5/10 visual fields.			
Critical dose value		1,710 mg/m^3 (300 ppm)	LOAEL: 450 mg/m^3			

Adjusted critical dose		$ENAEL_{inhal}$: 128 mg/m³ (23 ppm)				
		Derived Exposition Target Value 56 mg/m³ (10 ppm)				
Single assessment factors (see table R.8.6)		No information given	UF_S 12 x UF_H 10 x $UF_{Children}$ 2 = 1.875 mg/m³ -> RWII = 2 mg/m³			
Other effects			Odour thresholds, different values published: α-pinene 3.9 mg/m³ (+)α-pinene 23 mg/m³ (−)α-pinene 107 mg/m³			
Confidence						
UF_L used LOAEL; UF_H intraspecies variability; UF_A interspecies variability; UF_S used subchronic study; UF_D data deficiencies						

Compound	**α-PINENE**		***Data collection sheet (2/2)***		
Organization Name	**EU-INDEX Project**	**Mersch-Sundermann review**	**Gminski et al.**	**Data from ECHA for not specified α-pinene, CAS 80-56-8**	**NTP study with not specified α-pinene, CAS 80-56-8**
Risk Value Name	IAQ	proposed LCI	Not appointed	Long term exposure systemic effects general population inhalation DNEL	NOAEL
Risk Value (mg/m³)	**0.45**	**4**	**Not appointed**	**1.06**	
Risk Value (ppm)	0.0803 (calculated for 23°C)	0.714 (calculated for 23°C)	Not appointed	0.187 (calculated for 23°C)	50
Reference period				Subchronic	Subchronic
Year	2005	2007	2011	2012 (status ECHA-Homepage)	2006

Key Study	Falk Filipsson A: Short term inha-lation exposure to turpentine: toxicokinetics and acute effects in men. Occup Environ Med 1996;53:100–105 Falk A, Hagberg M, Löf A, Wigaeus-Hjelm E, Wang Z: Uptake, distribution and elimination of a-pinene in man after exposure by inhalation. Scand J Work Environ Health 1990;16:372–8	Animal study: Kasanen JP, Pasanen AL, Pasanen P, Liesivuori J, Kosma VM, Alarie Y: Stereospecifity of the sensory irritation receptor for nonreactive chemicals illustrated by pinene enantiomers. Arch Toxicol 1998;72:514–523 Human exposition study: Falk Filipsson A: Short term inhalation exposure to turpentine: toxicokinetics and acute effects in men. Occup Environ Med 1996;53:100–105 Lowest OEL-value: Swedish OEL 150 mg/m^3 Odour threshold: lowest 4 mg/m^3	Human inhalation study: Gminski R. Marutzky R. Keve-kordes S. Fuhrmann F. Burger W. Hauschke D. Ebner W. Mersch-Sundermann V: Chemosensory irritations and pulmonary effects of acute exposure to emissions from oriented strand board. Human & Experimental Toxi-cology 2011;30(9):1204–21	NTP-Study 2005	NTP-Study TDMS Number 2030203 =TOX-81 Study
Study type	8 volunteers inhalated 450 mg/m^3 turpentene: alpha-pinene, beta-pinene, delta-3-carene, 5:1:3 (1st study) or alpha-pinene alone (2nd study). Irritation by alpha-pinene was reported at 450 mg/m^3	Animal study: Short (30') exposure (inhalation) and measure-ment of respiratory parameters. Concentrations of alpha-pinene 100–3,691 ppm.	24 volunteers were exposed for 2hrs to oriented strandboard (OSB) emissions in an emission chamber at 3 points of time (panels fresh, 2 and 8 weeks old). Chemosensory irritation, exhaled nitric oxide (NO) concentration,	Animal Study: Subchronic inhalation study exposition at 25 ppm / 50 ppm / 100 ppm / 200 ppm / 400 ppm. 10 Animals per sex and concentration used.	Animal Study: Subchronic inhalation study exposition at 25 ppm / 50 ppm / 100 ppm / 200 ppm / 400 ppm. 10 Animals per sex and concentration used.

	but not at 225 mg/m^3. Dis-comfort against turpentene was reported, also airway resistance was increased. Both studies: 1 Exposition for 2 hrs		eye blink frequency, lung function and subjective perception of irritation (eyes, nose, throat) and olfactory perception were investigated.		
Species	Man	Mouse / man		B6C3F1 Mice and F344 Rats	B6C3F1 Mice and F344 Rats
Duration of exposure in key study	1 Exposition for 2 hrs	Animal study: 30 min	3 × 2 hrs	(14 weeks according to ECHA) 90-day inhalation study	96 days for mice (14 weeks) =test-type "90 days"
Critical effect	Irritation / discomfort (self-reported) and airway resistance	Animal study: OF1 and NIH/S male mice, 4 of each used per experiment, expo-sure time 30', measurement of lung functions by body plethys-mograph. Endpoint RD50 = 50% depression of respiratory rate by sensory irritation of upper respiratory tract Human exposition study: 8 volunteers exposed to 450 mg/m^3 turpentene: α-pinene, beta-pinene, delta-3-carene, 5:1:3 (1st study) or α-pinene alone (2nd study). Irritation by α-pinene was reported at 450 mg/m^3 but not at 225 mg/m^3. Discomfort against turpentene was	No effects found except of odour perception.	From ECHA-Summary: Male and female mice at 100 ppm: minimal to moderate hyperplasia observed in the transitional epithelium of the urinary bladder. The NOAEL in male and female rats is 50 ppm based on minimal to moderate hyperplasia observed in the transitional epithelium of the urinary bladder in animals treated at 100 to 400 ppm	Significant effects (p<=0.05) Male rats, moderate effects: granular casts in kidney: accumulation of hyaline droplets starting at 25 ppm. Note: 9/10 animals showed nephropaty in control group (other effects). Female rats, minimal effects: chronic lung inflammation. Note: 4/10 in control group, 5/9 at 400 ppm. Mice in both sexes, minimal to moderate effects: hyperplasia of transitional epithelium of urinary bladder starting at 100 ppm (13/20 mice). The effect is concentration-dependent (200 ppm: 20/20 mice)

		reported, also airway resistance was increased. Both studies: 1 Exposition for 2 hrs			
Critical dose value	LOAEL: 450 mg/m^3 NOAEL: 225 mg/m^3	Animal study: RD50 1080 ppm (9 g /m^3) Human exposition study: LOAEL: 450 mg/m^3 OEL: 150 mg/m^3 Odour threshold: 4 mg/m^3	Concentration of α-pinene in the chamber: 1.1–2.2 mg/m^3. α-pinene was a leading component of the OSB-emission, TVOC was 4.9–8.9 mg/m^3. The results represent a NOAEL for OSB-emissions, including an α-pinene TVOC-proportion of 16–25%.		
Adjusted critical dose	IAQ exposure limit: 0.45 mg × m^{-3}	Animal study: 4.5 mg/m^3 Human exposition study: 4.5 mg/m^3 OEL:3.75 mg/m^3 Odour threshold:no adjustment, 4 mg/m^3			
Single assessment factors (see table R.8.6)	UF_L 10 x UF_S10 x UF_H 10 = 1000	Animal study: RD50 x 0.03 = reasonable OEL, then UF_S24/6 x UFH 10 = 40 Human exposition study: UFS10 x UFH 10 = 100 OEL: UFS24/6 x UFH 10 = 40			
Other effects	Odour thresholds: (+)α-pinene 12 mg/m^3 (2.1 ppm), (−)α-pinene 18 mg/m^3 (3.3 ppm) Reaction of (+)α-pinene with ozone amplifies irritative effect: Wolkoff P, Clausen PA, Wilkins	Odour thresholds, different values published: α-pinene range 4–25 mg/m^3			

	CK, Nielsen GD: Formation of strong airway irritants in terpene/ozone mixtures. Indoor Air 2000;10:82–91 (ASTM mouse bioassay: 56 ppm at 21°C= 316 mg/m^3 -> 30% lower respiration rate for mixture)				
Confidence					
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies					

Compound	**α-PINENE**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI Value and Status			
EU-LCI value	1	Mass/volume [µg/m^3]	2500
EU-LCI status	2	Draft / Final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2012
General Information			
CLP-INDEX-Nr.	4	INDEX	
EC-Nr.	5	EINECS – ELINCS - NLP	201-291-9
CAS-Nr.	6	Chemical Abstracts Service number	80-56-8
Harmonised CLP classification	7	Human Health Risk related classification	Not harmonised

Molar mass	8	[g/mol]	136.23
Key Data / Database			
Key study, Author(s), Year	9	Critical study with lowest relevant effect level	NTP 2006
Read across compound	10	Where applicable	
Species	11	Rat,… human	Mouse
Route/type of study	12	Inhalation, oral feed, …	Inhalation
Study length	13	Days, subchronic, chronic	SC
Exposure duration	14	Hrs/day, days/week	6h on 5 days/week
Critical endpoint	15	Effect(s), site of	Bladder epithelial changes
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, ….	NOAEC
POD Value	17	[mg/m^3] or [ppm]	50 ppm
Assessment Factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
AF Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		
AF Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	
	22 b	Severity of effect *(R 8-6d)*	
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	23 b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic Worker - General population	10

AF (sensitive population)	25	Children or other sensitive groups	
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	112
POD/TAF	28	Calculated value (µg/m³ and ppb)	…… 2502 µg/m³ …… 446.42 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	2500
Additional Comments	31		
Rationale Section	32		

Alpha pinene is a major component of turpentine and therefore typical for coniferous wood emissions, mainly scots pine and common spruce. To derive risk values (mainly occupational expositions like sawmills), often short term human inhalation studies were used, sometimes only with turpentine.

Examples for short term exposures are the study of Falk Filipsson (1996) and Falk et al. (1990). In both studies, 8 volunteers were exposed for 2 hrs. Effects were increased airway resistance and self reported irritation/discomfort. The study of Falk Filipsson used turpentine. Johard et al. (1993) describe the exposure of 8 volunteers to turpentine for 4x3 hrs in two weeks and found elevated cell-concentrations in bronchoalveolar lavage, interpreted as a cellular reaction showing acute inflammation (this study also used turpentine). A short-term animal study was the study of Kasanen et al. (1998), which identified the RD50 value due to sensory irritation of the upper respiratory tract after exposition of mice against alpha pinenes (D, L) for 30 minutes.

As described by the rationale, LCI-values represent a chronic exposition scenario, short-term studies require additional factors and are not preferred. Only one chronic animal inhalation study was identified by the data compilation sheet: Järvisalo and Vainio (1980), but again turpentine was used (95% alpha pinene) and the described enhanced activities of drug biotransformation enzymes of liver microsomes are not per se adverse. So the chosen POD was derived from the subchronic NTP-toxicity study (TOX-81) which used not enantiomer specified alpha pinene (CAS-No 80-56-8). This study was also chosen by ECHA to derive a DNEL (without explanation of the calculation). The NTP study is a subchronic inhalation animal

study (B6C3F1 Mice and F344 Rats) with expositions at 25 ppm / 50 ppm / 100 ppm / 200 ppm / 400 ppm. 10 Animals per sex and per concentration were used. The duration was up to 96 days (14 weeks) and therefore represents a subchronic 90 day study. Mice of both sexes showed minimal to moderate effects, i.e. hyperplasia of transitional epithelium of urinary bladder starting at 100 ppm. So, a NOAEL of 50 ppm was found for mice. The effect was concentration-dependent: 0/20 at 50 ppm, 13/20 at 100 ppm, 20/20 at 200 ppm and 400 ppm. It was decided not to use an additional factor for interspecies kinetic and dynamic differences (line 23b), because it is reasonable to assume that mice are more sensitive than humans because of faster metabolism, leading to higher exposition of bladder epithelium cells (in the NTP-study the effect was only found in mice, not in rats). Although NTP-data are not published in a scientific journal and some information is missing (e.g. methods, purity of chemicals) this study was chosen to be the best basis for deriving an LCI-value.

It should be noted, that D and L isomers of alpha-pinene cannot be separated with the analytical method normally applied for the emission chamber test standard method. So, the factsheet is prepared for not specified alpha pinene and the NTP complies with this. For the critical effect chosen (urinary bladder epithelium changes), the composition of inhaled isomers can presumably be neglected because bladder epithelium is mainly exposed to metabolites rather to alpha-pinene itself and Ishida et al. (1981) have shown, that in rabbits metabolism of D and L isomers of alpha-pinene leads to the excretion of the same compounds. Levin et al. (1992) confirmed in a human inhalation experiment, that (+) and (–)alpha-pinene both are metabolised to and excreted as verbenol in the same cis:trans ratio of 1:10. However, beta pinene and other terpenes showed a different metabolic pattern and may differently affect bladder epithelium, so simple transfer or read-across to other bicyclic monoterpenes seem to be inadequate. It should also be noted, that for irritation (not used as endpoint in this data sheet), D and L isomers of alpha-pinene behave different, only the D isomer of alpha-pinene was found to be irritative by Kasanen et al. (1998).

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