Compound	n-Hexane	*Data collection sheet*
N°CAS 110-54-3	**CLP:** Repr. 2 / Asp. Tox. 1 / STOT RE 2 / Skin Irrit. 2 / STOT SE 3 / Aquatic / Chronic 2	

Organisation Name	**ATSDR**	**US EPA (IRIS)**	**OEHHA**	**ANSES**
Risk Value Name	MRL	RfC	inhalation REL	TRV
Risk Value (µg/m³)	2100	700	7000	3000
Risk Value (ppm)	0.6	0.2	2	0.9
Reference period	chronic	chronic	chronic	chronic
Year	1999	2005	2000	2014
Key Study	Sanagi et al., 1980	Huang et al., 1989	Miyagaki, 1967	Huang et al., 1989
Study type	inhalation	subchronic inhalation	continuous inhalation	subchronic inhalation
Species	human	Wistar rats	male SM-A mice	Wistar rats
Duration of exposure in key study	6 h/d, 5 d/w, 104 w	12h/d, 7 d/w, 16 w	6 d/w, 52 w	12h/d, 7 d/w, 16 w
Critical effect	peripheral neuropathy (both sensory and motor)	peripheral neuropathy (decreased MCV at 12 w)	neurotoxicity, electrophysiological alterations in humans	liver and kidney effects
Critical dose value	LOAEC 204 mg/m³ (58 ppm)	BMCL = 430 mg/m³ (122 ppm)	NOAEL 100 ppm	BMCL = 430 mg/m³ (122 ppm)
	LOAEL 326 mg/m³ (75 ppm)			
Adjusted critical dose	no temporal adjustment	temporal and allometric adjustment	no temporal adjustment	temporal and allometric adjustment
		$BMCL_{ADJ}$ =215 mg/m³ (61 ppm)	adjustement for n-hexane purity (68%), NOAEL = 68 ppm	$BMCL_{ADJ}$ =215 mg/m³ (61 ppm)
Single assessment factors (see table R.8.6)	AF_H 10 x AF_L 10 =100	AF_A 3 x AF_H 10 x AF_S 3 x AF_D 3 = 300 (D=data base deficiencies: lack of developmental neurotoxicity study and a multigeneration reproductive and developmental toxicity study following inhalation exposure	AF_A 3 x AF_H 10 = 30	AF_A 2.5 x AF_H 10 x AF_S 3 = 75
Other effects				
Confidence		Medium		Medium/high

AF_L used LOAEL; AF_H intraspecies variability; AF_A interspecies variability; AF_S used subchronic study; AF_D data deficiencies

Compound	**n-Hexane**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	4300
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value was issued	2016
General information			
CLP Index No	4	INDEX	
EC No	5	EINECS – ELINCS - NLP	203-777-6
CAS No	6	Chemical Abstracts Service number	110-54-3
Harmonised CLP classification	7	Human health risk-related classification	Flam. Liq. 2 / Repr. 2 / Asp. Tox. 1 / STOT RE 2 / Skin Irrit. 2 / STOT SE 3 / Aquatic / Chronic 2
Molar mass and conversion factor	8	[g/mol] and [ppm - mg/m^3]	86.18 1 ppm = 3.5 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Huang et al., 1989
Read across compound	10	Where applicable	
Species	11	Rat etc. / human	Wistar rat
Route/type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic	Subchronic
Exposure duration	14	Hours/day, days/week	12h/d, 7 d/w during 16 weeks
Critical endpoint	15	Effect(s), site of	Motor nerve conduction velocity
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	BMCL
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	430 mg/m^3 / 122 ppm
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hours/day, days/week	2
Study Length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		1
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	1
	23 b	Kinetic + 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	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1

Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	100
POD/TAF	28	Calculated value (µg/m³ and ppb)	122/100 = 1220 ppb and 4270 µg/m³
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	4300
Additional comments	31		
Rationale section	32		

The available human and animal n-hexane inhalation exposure data suggest that the nervous system is the primary target organ of n-hexane toxicity [US EPA, 2005; OEHHA, 2000; ATSDR, 1999]. The US EPA, ATSDR, OEHHA and Anses have derived reference values for n-hexane inhalation based on this critical effect. Anses and the US EPA based their TRV and RfC on an experimental study by Huang et al. (1989), the OEHHA based its REL on a study of mice by Miyagaki (1967) and the ATSDR its MRL on an epidemiological study by Sanagi et al. (1980).

Despite the large number of human inhalation exposure studies for n-hexane, these studies are considered inappropriate for dose-response assessment. No human studies are available where exposure was to n-hexane alone; experimental studies can be used to derive the LCI. A number of studies identified a variety of effects on the nervous system, kidney, liver and developing foetus. The toxic effects in laboratory animals following inhalation exposure to n-hexane support the nervous system as the primary target of toxicity.

A study by Huang et al. (1989) was selected as the principal study with peripheral neuropathy in male rats as the critical effect. In this study, male Wistar rats were exposed by inhalation 12 hours/day, 7 days/week for 16 weeks to n-hexane (purity > 99 %) at 0, 500, 1200 or 3000 ppm (0, 1762, 4230, 10 574 mg/m³). A statistically significant reduction in motor nerve conduction velocity was observed at the doses of 1200 and 3000 ppm. Increased incidence of paranodal swellings, along with some evidence of demyelination and remyelination, was also reported at these 2 doses.

The literature shows clearly that reversibility depends on the dose. In the pivotal study by Huang et al. (1989), histopathological examination demonstrates degenerative effects on peripheral nerves in 1200 and 3000 ppm exposed rats. The significant decrease in the amount of S100 protein in peripheral nerves was observed not only in the high level exposure groups (1200 and 3000 ppm) but also in the lowest level group (500 ppm), although the motor nerve conduction velocity and morphological examination remained unchanged at this level.

This study supports a NOAEL of 500 ppm. A BMCL of 430 mg/m³ was calculated and adjusted to continuous human exposure (duration adjustment: 12 hours/day, 7 days/week). The BMR was defined as a change of one standard deviation (1SD) from the control mean for continuous endpoints. This BMR was selected because there was no clear biological rationale for selecting an alternative BMR level. The BMCL (1SD) of 121.6 ppm (430 mg/m³) for decreased MCV in rats exposed to n-hexane for 12 weeks was chosen as the point of departure based on the sensitivity of this neurological effect following n-hexane exposure and the confidence in the modelling results from this study at low doses. For the Huang et al. (1989) data set, the excess risk is equivalent to an approximately 6.8 % change in response.

A total assessment factor of 100 was applied to the point of departure of 122 ppm: 2 for adjustment for exposure duration, 10 for intraspecies variation, 2.5 for interspecies variation and 2 to extrapolate to chronic exposure from data in a less-than lifetime study. For allometric differences a default value of 1 according to US EPA guidelines was applied (ratio (Hb/g)rat / (Hb/g)Human higher than 1 (2.86)). An additional AF related to the irreversibility of the neurotoxic effects appears unnecessary. In fact, the lesions seem reversible if exposure is above the BMCL (122 ppm) but below 1200 ppm; the latter represents a high exposure dose. Moreover, the critical effect seems very sensitive (motor nerve conduction velocity) with a BMCL that is relatively protective.

n-Hexane has an absolute odour threshold of 1.5 ppm [Nagata, 2003].

References

ANSES (2014). Valeurs toxicologiques de référence (VTR) — Elaboration de VTR chronique par inhalation pour le n-hexane (CAS No 110-54-3) — rapport d'expertise collective, décembre 2013.

OEHHA (2000) Chronic toxicity summary. n-hexane (normal hexane). Appendix D.3 Chronic RELs and toxicity summaries using the previous version of the Hot Spots Risk Assessment guidelines (OEHHA 1999). Air Toxics Hot Spots. Risk Assessment Guidelines. Technical Support Document For the Derivation of Noncancer Reference Exposure Levels, p292-302 (OEHHA, Oakland).

Huang J, Kato K, Shibata E, et al. (1989). Effects of chronic n-hexane exposure on nervous system-specific and muscle-specific proteins. Arch Toxicol. 63(5):381-5.

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Sanagi S, Seki Y, Sugimoto K and Hirata M. (1980). Peripheral nervous system functions of workers exposed to n-hexane at a low level. Int Arch Occup Environ Health. 47(1):69-79.

United States Environmental Protection Agency (US EPA) (2005). Toxicological review of n-hexane (CAS No 110-54-3) in support of summary information on the Integrated Risk Information System (IRIS), EPA/635/R-03/012, November 2005 (US EPA, Washington DC.) 223 p.