Compound	N-Methyl-2-pyrrolidone (NMP) Data collection sheet			
N°CAS 872-50-2	**CLP:** Skin Irrit. 2 (H315), Eye Irrit. 2 (H319), STOT SE 3 (H335), Repr. 1B (H360)			
Organisation name	**DFG-MAK**	**SCOEL**	**REACH registrants**	**ECHA (RAC)**
Risk value name	MAK-value	SCOEL value	DNEL (workers)	DNEL
Risk value (µg/m³)	82000	40000	40000	20000 for workers, 10000 for pregnant workers
Risk value (ppb)	20000	10000	10000	
Reference period				
Year	2012	2007	2010	2007, 2007
Key study	NMP producers group 2005	weight of evidence	Saillenfait et al, 2001	weight of evidence; Saillenfait et al, 2001
Study type	Two-gen., inhalation (whole body)	subchronic	developmental (OECD414)	subchronic for workers, OECD414 for pregnant workers
Species	rat	rat	rat	rat
Duration of exposure in key study	6 h/d, 7x/wk	6 h/d, 5-7x/wk	6 h/d, GD 6-20	6 h/d, 5-7x/wk; 6 h/d, GD 6-20
Critical effect	reduced body weigh development in pups	respiratory irritation and chemosensory effects	reduced foetal body weight	respiratory irritation and chemosensory effects; reduced foetal body weight
Critical dose value	NOAEC: 206 mg/m^3 (50 ppm), LOAEC: 478 mg/ m^3 (116 ppm)	NOAELs in the range of 206-500 mg/m^3	LOAEC, foetotoxicity: 500 mg/m^3 (120 ppm); NOAEC 250 mg/m^3 (60 ppm); LOAEC maternal toxicity: 250 mg/m^3 (60 ppm) due to transient decrease in maternal body weight gain (NOAEC 125 mg/m^3, 30 ppm)	NOAEC 1000 mg/m^3 for workers; NOAEC 247 mg/m^3 for pregnant workers
		human volunteer study 8 hr exposure to 10, 40, 80 and 160 mg/m^3: No irritant potency even during peak exposures to 160 mg/m^3 (Bader et al., 2007)		
Adjusted critical dose	No modification	No modification	6 h/8 h; 6.7 m^3/10 m^3	
Single assessment factors (see table R.8.6)	2.5 (systemic toxicity), 1 (local effects)	5 (systemic toxicity), 4 (local effects)	ECETOC intraspecies (worker) 3	2.5 remaining differences (toxicodynamics), 5 intraspecies differences – workers, 10 intraspecies differences –general population, 5 for pregnant workers.
Other effects	Volunteer study with 8 hr exposure			

	to 80 mg/m^3: no signs of irritation, slight signs of eye and nasal irritation at 160 mg/m^3			

Compound	**N-Methyl-2-pyrrolidone (NMP)**		**Factsheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	1800
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2016
General information			
CLP Index No	4	INDEX	606-021-00-7
EC No	5	EINECS — ELINCS — NLP	212-828-1
CAS No	6	Chemical Abstracts Service number	872-50-4
Harmonised CLP classification	7	Human health risk-related classification	Skin Irrit. 2, Eye Irrit. 2, STOT SE 3, Repr. 1B
Molar mass and conversion factor	8	[g/mol] and [ppm — mg/m^3]	99.13 1 ppm = 4.12 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	BASF, 1994
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 (90 days)
Exposure duration	14	Hours/day, days/week	6 h/day, 5 days/week
Critical endpoint	15	Effect(s), site of	Decrease in body weight gain
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	NOAEC
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	500 mg/m^3
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hours/day, days/week	5.6
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)	280
POD/TAF	28	Calculated value (µg/m³ and ppb)	1785 µg/m³ and 433 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	1800
Additional comments	31		
Rationale section	32		

Toxicity data

NMP is an irritant to the skin and eyes. In a study with human volunteers whole body exposure to 80 mg/m³ for 8 h caused moderate odour nuisance, but no irritative effects. In this study only weak eye irritation or irritation of the nasal mucosa was reported in individual cases at exposure peaks of 160 mg/m³, at which no irritant effects were found for the physiological variables (eyelid closure, nasal rep. flow) (Bader, 2007).

Four hours of acute exposure of rats to an atmosphere of 5100 mg/m³ resulted in no mortality and no clinical signs of toxicity (BASF, 1988). The acute oral LD50 was identified to be 4150 mg/kg bw (Ansell et al. 1988).

The toxicological data base for repeated dose toxicity and reproductive toxicity of NMP is extensive, therefore in this context only the most relevant data on the inhalation route of exposure is summarised.

In the most relevant of 4 repeated dose inhalation studies subchronic head nose exposure of Wistar rats to atmospheres of 1000 mg/m³ and above for 6 hours/day, 5 times/week resulted in irritation of the respiratory tract (e.g. crust formation on nasal edges) and a statistically non-significant but dose-dependent decrease in bw gain in males (NOAEC 500 mg/m³). Changes in the haematopoietic system and testes were further detected at concentrations of 3000 mg/m³ and above (BASF SE, 1994).

Decrease in bw in males was also identified as the most sensitive health effect in a chronic whole-body inhalation study with rats at 400 mg/m³ (Lee et al., 1987). In this study excessive mortality was observed at 1000 mg/m³.

NMP was not found to be genotoxic in vitro and in vivo. In rats chronic inhalation (Lee et al., 1987) and oral exposure (Malley et al., 2001) did not result in carcinogenic effects. However, following chronic dietary uptake an increase in carcinogenic effects was observed in the livers of mice (preneoplatic lesions, adenomas, carcinomas). As the increase incidence was species specific and only observed in the high dose group >1000 mg/kg bw the relevance for human equivalent exposures is questionable.

A NOAEC of 247 mg/m³ was identified in an whole body inhalation developmental toxicity study in SD rats based on a statistically significant 5 % decrease of foetal bw at 494 mg/kg bw. Body weight gain of the dams was also affected with a 19 % decreased weight gain over the entire gestation period at 247 and 494 mg/m³ (Saillenfait, 2003).

Minimal effects on foetal body weight are supported by a NOAEC of 206 mg/m³ which was identified for foetal toxicity in a 2-generation study with rats. In this study whole body exposure to atmospheres of 478 mg/m³ resulted in delayed bw gains in pups. Maternal toxicity at this dose level included decreases in food consumption and body weight (DuPont, 1990).

In rabbits exposed to 1000 mg/m³ slight fetotoxicity in the absence of maternal toxicity was manifested as an increased occurrence of supernumerary 13th ribs (NOAEC developmental toxicity 500 mg/m³).

Derivation of EU-LCI

Decrease in body weight is the key feature of NMP toxicity in rats.
With subchronic head nose exposure this effect was detected at 1000 mg/m³ (NOAEC 500 mg/m³, BASF 1994).
In the most relevant developmental toxicity study with whole body exposure of SD rats this effect was observed in mated dams and progeny at 494 mg/m³ (NOAEC 294 mg/m³, Saillenfait 2001). It is noted that with whole

body exposure oral cross contamination via grooming may contribute to the internal dose. However this may only apply above the saturated vapour concentration (480-640 mg/m^3).

Both NOAECs (500 mg/m^3 — subchronic, 294 mg/m^3 maternal/developmental) was validated for the resulting most sensitive limit value:

1) Considering the systemic NOAEC of 500 mg/m^3 from the subchronic toxicity study in the rat (BASF 1994) as relevant dose descriptor and taking the appropriate starting point modification and assessment factors into account the EU-LCI is calculated as follows:
   Relevant dose descriptor (NOAEC): 500 mg/m^3
   Modification of the starting point factor (24 hour exposure): 6 h/24 h, 5/7 times a week
   Exposure duration factor (subchronic — chronic): 2
   Remaining differences interspecies toxicodynamics factor (rat-to-human): 2.5
   Intraspecies factor (general population): 10

   EU-LCI = 500 mg/m^3 × 0.25 × 0.7/(2 × 2.5 × 10) = 1.785 mg/m^3 = 1785 µg/m^3, rounded to 1800 µg/m^3

2) Considering the NOAEC of 294 mg/m^3 for maternal and foetal toxicity from the key prenatal developmental toxicity study in the rat (Saillenfait et al., 2001) as relevant dose descriptor and taking the appropriate starting point modification and assessment factors into account, the EU-LCI is calculated as follows:
   Relevant dose descriptor (NOAEC): 294 mg/m^3
   Modification of the starting point factor (24 -hour exposure): 6 h/24 h
   Allometry: 1 (external concentration)
   Exposure duration factor (no time extrapolation appropriate for developmental toxicity): 1
   Remaining differences interspecies toxicodynamics factor (rat-to-human): 2.5
   Intraspecies factor (general population): 10
   Quality of database factor: 1

   EU-LCI = 294 mg/m^3 × 0.25 × 1/(1 × 2.5 × 10 × 1) = 2.94 mg/m^3 = 2940 µg/m^3

An EU-LCI of 1800 µg/m^3 based on the subchronic toxicity study in rats is proposed. If this value is maintained local irritative effects at the respiratory tract are not to be expected (Bader, 2007).

References:

Bader et al., 2007. Human experimental exposure study on the uptake and urinary elimination of N-methyl 2-pyrrolidone (NMP) during simulated workplace conditions, Arch Toxicol 81:335-346.

BASF, 1988. Evaluation in rats of acute inhalation toxicity (LC50) of N-methyl-pyrrolidone as an aerosol liquid, Cited in ECHA disseminated dossier.

Ansell J.M. and Fowler J.A., 1988. The acute oral toxicity and primary ocular and dermal irritation of selected N-alkyl-2-pyrrolidones, Fd. Chem. Toxicol. 26: 475-479

BASF, 1994. Study on the inhalation toxicity of N-methyl-pyrrolidon as a liquid aerosol in rats — 90-day-test including an about 4-week post-exposure observation period, Cited in ECHA disseminated dossier.

Saillenfait et al., 2001. Developmental toxicity of N-methyl-2-pyrrolidone administered by gavage or inhalation to rats. Poster abstact, 29th Conference of the European Teratology Society, 2-5 Sep. 2001, Balatonfüred, Hungary.