SCOEL/REC/119
N-Methyl-2-Pyrrolidone

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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8-hour TWA:	10 ppm (40 mg/m^3)
STEL:	20 ppm (80 mg/m^3)
BLV:	20 mg/g creatinine 2-hydroxy-N-methylsuccinimide (2-HMSI) in urine, monitored morning-after-shift (18 h), *or* 70 mg/g creatinine 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP) in urine, monitored 2-4 h after exposure/shift
Additional categorisation:	-
Notation:	"skin"

The present Recommendation was adopted by SCOEL on 2015-09-23.

This evaluation is based on a previous evaluation by SCOEL (SCOEL/SUM/119; August 2007), further evaluations by Hartwig (2011) and by the Swedish Criteria Group for Occupational Standards (Montelius, 2014), the references cited in these reviews and a further literature search.

RECOMMENDATION EXECUTIVE SUMMARY

When reviewing the scientific data available for NMP, SCOEL recognised that NMP is a very well investigated substance, for which a relatively high number of reliable high-quality studies that is relevant for the occupational situation are available.

SCOEL has assessed the available information. NMP has a potential to cause adverse health effects and is a hazardous chemical agent. For NMP the available information is adequate for deriving a health-based OEL (8-hour TWA and STEL). The database is also adequate to derive a BLV and a 'skin' notation.

NMP shows intrinsic hazardous properties with respect to local and systemic effects. The following key effects were considered as being especially relevant for the protection of workers and in particular the OEL derivation:

(a) the potential of the substance to produce respiratory irritation and chemosensory effects, both in humans and animals, and

(b) the systemic toxicity of NMP, in particular reproductive toxicity in studies in experimental animals.

Outcome Considerations

A specification and discussion of these key effects is provided in chapter 7.9 of this document ("Mode of Action and Adverse Outcome Pathway Considerations"). Following SCOEL's Methodology for the Derivation of Occupational Exposure Limits (version 7, June 2013), the existing human data are considered highly relevant for OEL derivation.

(a) *Local irritancy/chemosensation:*

Subchronic studies in rats point to local nasal irritation by upon NMP exposure, with an NOAEL of 125 ppm (7.3.2.1.). There were no indications of respiratory irritation or other health effects of NMP in a study involving exposure of human volunteers to 10, 25 or 50 mg/m^3 [2.5, 6.2 or 12.5 ppm] over an 8 hour period (Åkesson and Paulsson, 1997). Workers exposed to levels of up to 280 mg/m^3 [70 ppm] reported severe eye irritation and headache, but no dose-response relationship could be established (Beaulieu and Schmerber, 1991). In a comprehensive experimental study (van Thriel et al., 2007) on 15 healthy young male volunteers exposed to 10 mg/m^3 [2.5 ppm], 40 mg/m^3 [10 ppm], 80 mg/m^3 [20 ppm] and 25/160 mg/m^3, the latter including peak exposures up to 160 mg/m^3 [40 ppm], NMP could be smelled by the subjects, and it was reported to be slightly annoying. For these olfactory symptoms a strong adaptation was observed, especially during the first 4 hours of exposure. SCOEL does not consider such symptoms as being adverse for workers (see 7.9). Symptoms indicative of an irritant potential, especially trigeminal sensations, were not elicited by NMP. The conclusion from this well executed and documented study was that NMP is an odorous substance, but without sensory irritation potency up to 80 mg/m^3 [20 ppm] and under conditions of 15-min peak exposures to 160 mg/m^3 [40 ppm]. Therefore, for local irritancy in humans a NOAEC of 20 ppm (highest concentration tested by van Thriel et al., 2007), is well established. The study of van Thriel et al. (2007) also considered possible influences of physical workload, which was simulated by six 10 min periods of exercise on a bicycle ergometer at 75 W.

(b) Systemic effects

Developmental toxicity and minor effects on fertility have been reported in reproductive toxicity studies in rats, rabbits and mice, following exposure to NMP by the inhalation or the oral route at maternally toxic doses. NOAELs for reproductive effects range from 206 to 500 mg/m^3 [51 – 125 ppm] in inhalation studies (see 7.8.2). As discussed in chapter 7.9, a NOAEC of 51 ppm (Solomon et al., 1995) is related to a borderline and transient and reversible effect on rat pup body weight gain. The degree of adversity of this effect for humans is considered to be borderline, as the effect seen at the next higher concentration of 116 ppm was borderline, fully reversible and of limited severity. In addition, in other inhalational developmental toxicity studies effects were seen not seen or were seen only in the presence of reduced food consumption and slight effects on maternal body weight. The consideration of this effect as being borderline is supported by oral studies, as even doses up to a level of 250 mg/kg did not show this effect.

In a 2-year chronic toxicity/carcinogenicity study by the inhalation route in rats minimal inflammation of the lung and slight systemic toxicity was reported in male rats at 18 months, but not at 24 months, at the highest exposure level of 400 mg/m^3 [100 ppm] (Lee et al., 1987). The dose level of 400 mg/m^3 [100 ppm] in this study can be considered to be a borderline chronic LOAEL/NOAEL. However, the observed lung effects are likely based on local irritancy. There was no indication of carcinogenicity in this 2-year study. An increased incidence of hepatocellular adenomas and carcinomas seen in a 18-months feeding study in mice (at the top dose of 7200 ppm NMP in the diet; Malley et al., 2001) is not regarded as relevant for the establishment of an OEL in humans, given the absence of genotoxic activity of NMP, both *in vitro* and *in vivo.* In addition, the over-sensitivity of the B6C3F1 mouse and other mouse strains to development of hepatocellular tumours has been recognised. Therefore, NMP is not regarded as a carcinogen for humans.

The derivation of an OEL considers both (a) acute local irritation effects, for which solid human data are available, and (b) the developmental effects (lower weight gain) upon repetitive dosing, as established in rats. For (a) local irritation, the conditions of the study of van Thriel et al. (2007) of 20 ppm provide a valid and well-defined point of NOAEC for the critical effect.

The study of van Thriel et al (2007) was a controlled human exposure study assessing especially sensitive and objectively verifiable effects. The study included experimental conditions of physical workload. It was performed in young male volunteers, which are considered as being highly susceptible to chemosensory effects (Brüning et al. 2014). Available data indicate that an intra-species uncertainty factor >1 may not be needed whenever good exposure studies with human volunteers are available (Brüning et al. 2014). Moreover, case studies have led to the conclusion that human acute experimental NOAECs for chemosensory effects are similar to NOAECs derived from exposures at the workplace (Brüning et al. 2014).

Therefore, the overall uncertainty factor applied by SCOEL considers possible differences due to gender and any possible remaining uncertainties. A factor of two appears adequate to account for the identified and remaining uncertainties.

Derived Limit Values

An *OEL (TWA) of 10 ppm and a STEL (15 min) of 20 ppm is therefore considered protective for workers*. The study by van Thriel et al. revealed that peak concentrations of 40 ppm were also without effect, thus supporting a STEL of 20 ppm.

For (b) reproductive toxicity, the reproductive and developmental toxicity study by inhalation in rats of Solomon et al (1995) provides for this critical effect a level of of 51 ppm as the NOAEC (for discussion/justification, see chapter 7.9). The critical effect was a slight exposure-related decrease in foetal body weight among the F1 offspring whose parents inhaled NMP at 116 ppm, which persisted until weaning and was then fully reversible. As explained in chapter 7.9, the degree of adversity of this effect for human health appears to be low, as (1) the magnitude of this experimental effect was borderline, (2) the effect was fully reversible, and (3) the effect as such was not supported by a third available inhalation study.

A further contribution to OEL derivation, when based on the body weight effects in the offspring described by Solomon et al (1995) and Saillenfait et al. (2003), is the quantitative risk analysis for NMP using PBPK and benchmark dose modelling by Poet et al. (2010; chapter 7.1.4). The modelling results suggest that the effective concentrations in humans would be higher as compared to rats. Although there are uncertainties related to the PBPK-modelling, these data further reduce the uncertainties related to species extrapolation. Therefore, no additional uncertainty factor for toxicokinetics is needed.

An OEL of 10 ppm (STEL of 20 ppm) as derived based on absence of local irritation in exposed humans (a), is challenged against the data on experimental reproductive toxicity (b) to answer the question whether the level could still be considered protective for this endpoint, despite the collected evidence does not support its consideration as such. The established OEL of 10 ppm (STEL of 20 ppm) would cover the potential hazard for this endpoint, too. The margin of 5 between the OEL and the experimental NOAEC (51 ppm) is considered adequate because of the low adversity of the body weight effect with limited relevance for human health (see above) and the low severity of the effects observed. This is further supported by the PBPK and benchmark analysis of Poet et al (see above), resulting in factors between an OEL of 10 ppm and the benchmarks BMC1SD (benchmark concentration corresponding to 1 SD) of 700 ppm and BMCL1SD (95% lower confidence limit) of 480 ppm, respectively.

Therefore, having evaluated all data and respective endpoints, SCOEL considers for NMP an OEL (8h TWA) of 10 ppm and a STEL (15 min) of 20 ppm as being protective for workers.

Skin notation

NMP is well absorbed through the skin, both in humans and in animal studies and some systemic toxicity (including developmental toxicity) is seen following dermal uptake. A *"skin" notation* is therefore considered necessary.

Biological Monitoring

Due to the significant dermal uptake of NMP, biological monitoring is recommended. 5-hydroxy-N-methyl-2-pyrrolidon (5-HNMP) and 2-hydroxy-N-methylsuccinimide (2-HMSI), two key metabolites of NMP, are appropriate biological indicators of exposure, and monitoring of either of these metabolites can be undertaken. The optimum sampling time for 5-HNMP is the first 2-4 h post-exposure, while in the case of the longer half-life metabolite 2-HMSI a urine collection 16 h post-exposure (on the morning after an 8 h work-shift) is advised. Both parameters should be corrected for urinary creatinine to compensate for diuretic variations. The delayed peak maximum at 16-24 h post-exposure and the long biological half-life makes urinary HMSI especially suitable for the surveillance of accumulative effects during a working week (Bader et al. 2007, 2008a). However either parameter may be chosen, depending on the available analytical methodology and the conditions pertaining to the particular workplace.

For the longer half-life metabolite 2-HMSI, an 8-h TWA of 10 ppm (40 mg/m^3) corresponds to a biological value of approximately 16 mg/g creatinine, 16 h post exposure for a work scenario without workload and approximately 22 mg/g creatinine for

a work scenario with moderate workload (75 Watt). *A Biological Limit Value (BLV) of 20 mg/g creatinine is recommended for 2-HMSI, measured on the morning after an 8 h work-shift.* This value is intermediate between the work scenario without workload and the work scenario with moderate workload, as assessed by Bader and co-workers (2007, 2008a), and is likely to be representative of a typical work scenario involving some physical activity.

For 5-HNMP, an 8-h TWA of 10 ppm (40 mg/m^3) corresponds to a biological value of approximately 60 mg/g creatinine, 2-4 h post exposure for a work scenario without workload and approximately 75 mg/g creatinine for a work scenario with moderate workload (75 Watt). *A Biological Limit Value (BLV) of 70 mg/g creatinine is recommended for 5-HNMP, measured 2-4 hours after the end of exposure.* This value is intermediate between the work scenario without workload and the work scenario with moderate workload, as assessed by Bader and co-workers (2007, 2008a), and is likely to be representative of a typical work scenario involving some physical activity.

Analytical measurement systems exist to determine the recommended levels with an appropriate level of precision and accuracy. This comprises both the measurement of NMP in air and the determination of 5-HNMP or 2-HMSI in urine as a matrix (chapter 6).

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RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

N-Methyl-2-pyrrolidone (NMP) is a water-miscible colourless liquid with a characteristic amine odour. The boiling point of NMP is 202°C at 101.3 Pa and its vapour pressure is 0.39 hPa at 20 °C and 0.45 hPa at 25 °C (IPCS, 2001). Log K_{ow} is – 0.38 and the density is 1.028 g/cm^3. NMP is not flammable [flash point, closed cup, 90°C, open cup 95°C (Åkesson, 1994)].

Name:	N-Methyl-2-pyrrolidone
Synonyms:	NMP, N-methylpyrrolidone, 1-methyl-2-pyrrolidone, 1-methyl-2-pyrrolidinone
Molecular formula:	C_5H_9NO
Structural formula:	

EC No.:	606-021-00-7
CAS No.:	872-50-4
Molecular weight:	99.13 g/mol
Conversion factors:	1 ppm = 4.12 mg/m^3
(20 °C, 101.3kPa)	1 mg/m^3 = 0.243 ppm

Note: Some studies, which are evaluated here, give NMP concentrations in mg/m^3, others in ppm. In this document, the respective original values are given. For information, the corresponding ppm or mg/m^3 figure may be calculated based on a rounded conversion factor of 4 or the exact factors indicated above.

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for NMP is provided by ECHA (2014b), as summarised in Tables 1 and 2.

Table 1: 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; (ECHA, 2014b).

Index no.	International Chemical Identification	EC no.	CAS no.	Classification		Labelling			Spec. Conc. Limits, M-factors
				Hazard Class & Category Code (s)	Hazard statement code (s)	Pictogram Signal Word Code (s)	Hazard statement code (s)	Suppl. Hazard statement code (s)	
606-021-00-7	N-methyl-2-pyrrolidone, 1-methyl-2-pyrrolidone	212828-1	872-50-4	Eye Irrit. 2 STOT SE 3 Skin Irrit. 2	H360D*** H319 H335 H315	GHS08 GHS07 Dgr	H360D*** H319 H335 H315		Repr. 1B H360D: C ≥ 5% STOT SE 3: H335: C ≥ 10%

*** *Repr. 1B, H360D May damage the unborn child.*
Eye Irrit. 2 H319 Causes serious eye irritation.
Skin Irrit. 2 H315 Causes skin irritation.
STOT Single Exp. 3 H335 May cause respiratory irritation.

Table 2: 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; (ECHA, 2014b).

Index no.	International Chemical Identification	EC no.	CAS no.	Classification	Labelling	Concentration limits
606-021-00-7	N-methyl-2-pyrrolidone, 1-methyl-2-pyrrolidone	212-828-1	872-50-4	Repr. Cat. 2; R61 Xi - R36/37/38	T R: 61-36/37/38 S: 53-45	Repr. Cat. 2; R61: C ≥ 5% Xi, R36/37/38: C ≥ 10%

Repr. Cat. 2; R61 May cause harm to the unborn child.
Xi - R36/37/38 Irritating to eyes, respiratory system and skin

Further to the above classification, the Netherlands submitted, in March 2013, a harmonised classification and labelling proposal to lower the specific concentration limit for reprotoxicity category 1B of NMP to 0.3% (generic value) (RIVM, 2013).

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

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

N-Methyl-2-pyrrolidone is not a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits for N-methyl-2-pyrrolidone exist in a number of countries, as shown in Table 3. An IOELV (indicative occupational exposure limit value) has been adopted at EU level (EU, 2009), and national limit values will exist in all Member States. The values presented below are presented as examples and are not an exhaustive listing of all limit values within the EU and other countries.

Table 3: Existing OELs for NMP; adapted from the GESTIS database (GESTIS, 2015).

	TWA (8 hrs)		STEL (15 min)		
EU countries	ppm	mg/m³	ppm	mg/m³	References
Austria	10	40	20	80	GKV (2011)
Belgium	10	40	20	80	Royal Decision (2014)
Denmark	5	20	10	40	BEK (2011)
European Union	10	40	20	80	SCOEL (2007, 2015)
Finland	10	40	20	80	MoSH (2012)
France	10	40	20	80	INRS (2012)
Germany (AGS)	20	82	40	164	BAUA (2006)
Germany (DFG)	20	82	40	164	DFG (2015)
Ireland	10	40	20	80	HSA (2011)
Italy	10	40	20	80	SSL (2008)
Latvia		100			GESTIS (2015)
Poland		40		80	MLSP (2002)
Spain	25	103	75	309	INSHT (2010)
Sweden	50	200	75	300	SWEA (2011)
The Netherlands		40		80	DLPLV (2007)
United Kingdom	25	103	75	309	HSE (2011)
Non-EU countries					
Switzerland	20	80	40	160	SUVA (2015)
Australia	25	103	75	309	Safe Work Australia (2011)
Canada (Ontario)		400			Ontario Ministry of Labour (2013)
New Zealand	25	103	75	309	HS (2013)
Japan	1				JSOH (2002)
USA	10				AIHA (2013)

In the USA, according to EPA (US EPA, 2015), the Occupational Safety and Health Administration (OSHA) has not established regulatory exposure limits for NMP. The only recommended exposure limit identified for NMP is a non-regulatory limit established by the American Industrial Hygiene Association (AIHA, 2013; see Table 3).

In addition to OELs, Biological Limit Values (BLVs) have been established/recommended by the following bodies:

a. SCOEL (2015), INSHT (2010): 20 mg/g creatinine 2-hydroxy-N-methylsuccinimide (2-HMSI) in urine, measured morning-after-shift (18 hours), and/or 70 mg/g creatinine 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP) in urine, measured 2-4 hours after the end of exposure/shift

b. Germany, DFG (2015): 5-HNMP, 150 mg/l (BAT)

c. Danish EPA (2014): A Biological Limit Value (BLV) of 20 mg/g creatinine is recommended for 2-HMSI, measured on the morning after an 8-hr work-shift. For 5-HNMP, a biological value of approximately 60 mg/g creatinine, 2-4 hrs post exposure for a work scenario without workload and approximately 75 mg/g creatinine for a work scenario with moderate workload (75 Watt).

d. USA, ACGIH (2012): 5-HNMP, 100 mg/l (BEI)

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence and use

NMP does not occur naturally in measurable amounts. There is only one study known to have isolated NMP from a marine fungus, *Clathria frondifera,* which shows that the substance can be produced naturally (Radhika et al., 2007). However, measured bio-concentration studies were not located and based on available environmental fate data, NMP is expected to have low bio-accumulation potential and low persistence (US EPA, 2015).

NMP is a synthetized organic substance. It has been manufactured on a commercial scale since the 1960s (RTI, 2001).

The primary use of NMP is as a solvent in a wide range of applications including the paints and petrochemical industries, for stripping and cleaning applications in the microelectronics industry, for the removal of graffiti, as a paint stripper and as a substitute for chlorinated solvents (IPCS, 2001). It is also used as an intermediate in the pharmaceutical, polymer and other chemical industries and as a formulating agent for plant protection and biocidal actives, and as a solvent for pigments, dyes and inks. Further uses include as a penetration enhancer for topically applied pharmaceuticals and as a vehicle in the cosmetics industry. It is increasingly used as a replacement for chlorinated solvents because of concern about the toxicological profile of some of the latter, e.g., it has been used to replace dichloromethane as a solvent in paint strippers.

5.2. Production and use information

Recent information on production and use of NMP has been compiled by several bodies (US EPA, 2015; ECHA, 2014a; Danish EPA, 2014; NICNAS, 2013; RIVM, 2013; SCCS, 2011; OECD, 2007).

According to OECD (2007) the annual world production capacity of NMP in 2003 was estimated at 100,000 to 150,000 tons, subdivided into 30,000 – 50,000 tons/a for Europe (3 production sites), 60,000 – 80,000 tons/a for USA (3 production sites), and 10,000 – 20,000 tons/a for Asia/Pacific (4 production sites). During 2005, the European production capacity was reduced to about 20,000 – 30,000 tons.

The main uses of NMP products are summarized in Table 4. The quantification in "% of the total" refers to the distribution of NMP across these product uses. This quantification has been presented by OECD (2007) and is representative at world scale; however it is not EU-specific. Further NMP uses identified by NICNAS (2013) and SCCS (2011) are in cosmetics as a solvent, fragrance and surfactant. Uses of NMP in road construction applications, battery industries, membrane manufacturing, in functional fluids, and in laboratories were reported by ECHA (2014a) and RIVM (2013). According to the US EPA (2015), the National Institutes of Health (NIH) Household Products Database lists 47 products containing NMP, in concentrations ranging from 1-100 percent. In contrast, in the EU there is only one consumer use as a printing ink registered in REACH (Danish EPA, 2014).

According to the SCCS (2011) final concentrations in cosmetic products are not known. A survey by the Danish EPA revealed that concentrations of NMP in finished products vary from a few percentages up to 85% (Danish EPA, 2014). Home maintenance products may even consist of 100% NMP (US EPA, 2015).

Table 4: Main uses of NMP containing products according to Harreus et al. (2011), OECD (2007), and Jouyban et al. (2010)

Industry	Application	Percent of Total
Electronics	Cleaning agent for silicon wafers, de-fluxing, edge bead removal, photoresist stripping, auxiliary in printed circuit board technology	20
Agricultural chemicals	Solvent for herbicide, pesticide and fungicide formulations	15
Pharmaceuticals	Solvent or co-solvent; chemical penetration enhancer for enhancement of transdermal delivery of hydrophilic and hydrophobic drugs from an aqueous phase	15
Coatings	Solvent for acrylic and epoxy resins, polyurethane paints, waterborne paints or finishes, printing inks, synthesis/diluent of wire enamels, coalescing agent	20
Petrochemical processing	Lube oil processing, natural and synthetic gas purification	10
Industrial and consumer cleaners	Paint removers, floor strippers, graffiti remover, industrial degreasing, injection head and cast-molding equipment cleaning	20

Further sources of information are Product Registers and the Nordic SPIN Database. Product Registers in Sweden, Denmark and Switzerland were interrogated on NMP-containing-product information by OECD (2007). The Nordic SPIN Database was interrogated by the Danish EPA (2014). The registers include the numbers of products marketed in these countries, the total amount of NMP contained in the products and the corresponding NMP concentrations.

5.3. Occupational exposure

Although NMP does not have a high vapour pressure, the pattern and wide range of uses results in some potential for occupational exposure by inhalation. Exposure may be to NMP as a vapour, as an aerosol or as a mixture of both, the relative proportions being dependent on temperature and relative humidity (DFG, 1998).

At normal room temperature and humidity (60% relative humidity) and concentrations of NMP below 80 mg/m^3, aerosol formation is unlikely, however aerosol formation is potentiated at higher humidity and with increasing concentrations of NMP (DFG, 1998). Levels of up to 10 mg/m^3 NMP have been measured in the breathing zone of workers involved in the removal of graffiti (Anundi et al., 1993, 2000), while workers in the microelectronics industry have been exposed to up to 6 mg/m^3 (Beaulieu and Schmerber, 1991). Much higher exposures (up to 280 mg/m^3) were reported in the microelectronics

industry when NMP was used at a temperature of 80°C (Beaulieu and Schmerber, 1991). Exposures of up to 64 mg/m^3 have been measured in the breathing zone of paint-strippers, with peak exposures of up to 280 mg/m^3 (Åkesson and Jönsson, 2000a).

Dermal exposure to NMP in occupational settings is also likely, given the pattern and wide range of uses. NMP is readily absorbed through the skin, and dermal exposure thus is considered to contribute significantly to the internal NMP dose. There are several older reports in the literature of toxic effects resulting from skin contamination through spills, inhalation of fumes may however have contributed to the toxicity seen (DFG, 1998). Additionally, Bader and co-workers have reported dermal absorption of NMP from the vapour phase, equivalent to approximately 30 % of the total inhalation dose in an experimental study in human volunteers, the design of which included a phase in which inhalational uptake was prevented by face shields (Bader et al., 2008a).

5.4. Routes of exposure and uptake

As explained above, there is the possibility of occupational exposure by both inhalation and dermal uptake. In view of potential high dermal exposure biological monitoring is recommended (Greim, 1998).

6. MONITORING EXPOSURE

NMP can be monitored in the air at the workplace by applying the following methods:

- OSHA (1991), OSHA Stopgap method nr. PV2043
- NIOSH (1998), NIOSH method 1302
- Breuer et al., (2014), MAK method 1
- Rosenberger et al., (2014), MAK method 2

In all these methods NMP in air is adsorbed onto a solid sorbent (activated charcoal or silica gel) followed by extraction of the NMP with an organic solvent (either a methylene chloride solution in methanol, pure methanol or a potassium hydroxide solution in methanol). The NMP-containing extract can be then be analysed by gas chromatography (GC), using either flame ionisation (FID), nitrogen-phosphorus (NPD) or mass spectrometry (MS) detection, each technique with its limit of quantification (LOQ) and characteristics (see Table 5).

Table 5: Overview of sampling and analytical methods for monitoring NMP at the workplace

Method	Sorbent	Desorption solution	Analysis	Recovery (%)	LOQ	Relative standard deviation	Concentration range	References
NIOSH method 1302	Activated charcoal	methylene chloride solution in methanol (95:5)	GC-NPD	98.8	0.02 µg/ sample	5 %	0.063-25.8 µg/sample	NIOSH, 1998
	Activated charcoal	methylene chloride solution in methanol (95:5)	GC-FID	98.8	0.3 µg/ sample	1%	0.662-2066 µg/sample	
MAK method 1*	Silica gel	potassium hydroxide solution in methanol	GC-NPD	99	Absolute: 1.6 ng Relative: 0.1 mg/m^3	2.3-5.8%	9-130 mg/m^3	Breuer et al., 2014
MAK method 2*	Silica gel	methanol	GC-MS	92	Absolute: 0.3 ng Relative: 0.15mg/ m^3	4%	2.5-15 mg/m^3	Rosenberger et al., 2014

** This method can be used to detect 0.1 times up to 2 times the limit value for workplace air (MAK value) proposed by the Deutsche Forschungsgemeinschaft (DFG).*

The proposed method 1302 by NIOSH (1998) is considered to be an improvement of the OSHA in-house method from 1991, because of their higher sensitivity and recovery at lower sample levels.

Alternatively to the above discontinuous methods, airborne NMP can be analysed on a continuous basis by photoacoustic IR spectrometry (INNOVA, 1412 Photo Acoustic Field Gas-Monitor) with a detection limit of 0.16-1.24 mg/m^3 depending on the optical filter used (calculated based on the equation and list of detection limits mentioned in Lumasense, Denmark (2015) (Åkesson and Paulsson 1997; Jönsson and Åkesson, 2003; Bader et al., 2007). There appears to be no appropriate methodological approach for NMP at the moment using passive air sampling.

Regarding biomonitoring of NMP, Bader et al. (2008b) describes a method for measurement of 5-HNMP and 2-HMSI in urine using GC/MS. The method is based on work by Jönsson and Åkesson (1997a). The method involves addition of deuterium-labeled 5-HNMP and 2-HMSI to the samples, as internal standards. Solid phase extraction (SPE) is then applied to separate the metabolites from the matrix, which is followed by elution with an ethyl acetate-methanol solution. The method has been evaluated by the MAK Commission, and the evaluation results are summarized in Table 6.

Table 6: Evaluation of the MAK method for the determination of 5-HNMP and 2-HMSI in urine

5-Hydroxy-N-methyl-2-pyrrolidon (5-HNMP)	
Precision (series)	Standard deviation (rel): *s* = 0.9% - 1.2% Confidence interval: *u* = 2.0%- 2.7% in the concentration range from 7.5-75 mg 5-HNMP per liter urine where *n*=10 determinations
Precision (day to day)	Standard deviation (rel): *s* = 1.3% - 2.3% Confidence interval: *u* = 2.9% - 5.1% in the concentration range from 7.5-75 mg 5-HNMP per liter urine where *n*=10 determinations
Recovery	*r* =97% at 150 mg/l
Detection limit	1 mg 5-HNMP per liter urine
2-Hydroxy-N-methylsuccinimide (2-HMSI)	
Precision (series)	Standard deviation (rel): *s* = 1.4% - 1.7% Confidence interval: *u* = 3.1%- 3.8% in the concentration range from 7.5-75 mg 2-HMSI per liter urine where *n*=10 determinations
Precision (day to day)	Standard deviation (rel): *s* = 3.7% - 4.1% Confidence interval: *u* = 8.3% - 9.1% in the concentration range from 5-75 mg 2-HMSI per liter urine where *n*=10 determinations
Recovery	*r* =101% at 75 mg/l
Detection limit	1 mg 2-HMSI per liter urine

Åkesson and Jönsson (2000c) and Carnerup et al. (2006) proposed, as an alternative to the MAK method, a concept using liquid chromatography-electrospray tandem mass spectrometry. Also several concepts involving minor modifications of the basic approaches by Jönsson and Åkesson (1997a) and Bader et al. (2008b), such as replacement of solid phase extraction (SPE) by liquid-liquid extraction (LLE) are applied by different authors. An overview of such concepts is provided in Table 7.

Table 7: Overview of NMP bio-monitoring concepts applied

Reference	Compound measured	Method description
Åkesson and Paulsson (1997)	NMP (p + u)	To 2 ml of plasma or urine, 2 ml toluene and 4 ml 12 M potassium hydroxide (KOH), containing 0-25% ammonia were added. After shaking for 10 minutes the toluene phase was transferred into glass vials with PFTE screw caps. The analyses of NMP were performed by gas liquid chromatography (GLC) (Varian 3700; autosampler 8035) with a nitrogen phosphorus detector (NPD; Varian TSD).
Jönsson and Åkesson (1997a)	5-HNMP and 2-HMSI (u)	Simultaneous determination of 5-hydroxy-N-methylpyrrolidone (5-HNMP) and 2-hydroxy-N-methylsuccinimide (2-HMSI) in urine involving purification from urine by adsorption to a C8 solid-phase extraction column and then elution by ethyl acetate-methanol (80:20). After evaporation, the samples were derivatised at 100 degrees C for 1 h by bis(trimethylsilyl)trifluoroacet- amide. Ethyl acetate was then added and the samples were analysed by gas chromatography-mass spectrometry in the electron impact mode.
Jönsson and Åkesson (1997b)	MSI and 2-HMSI (u+p)	A method for determination of N-methylsuccinimide (MSI) and 2-hydroxy-N-methylsuccinimide (2-HMSI) in human urine and of MSI in human plasma was developed involving purification from urine and plasma by C8 solid-phase extraction and analysed by gas chromatography-mass spectrometry in the negative-ion chemical ionisation mode
Åkesson and Jönsson (2000c)	5-HNMP (u+p)	Blood and urine were sampled before, during, and up to 40 hours after exposure were purified, derivatised, and analysed for 5-HNMP on a gas chromatograph/mass spectrometer in the electron impact mode.
Carnerup et al. (2001)	5-HNMP and 2-HMSI (u+p)	Simultaneous determination of 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP) and 2-hydroxy-N-methylsuccinimide (2-HMSI) was developed involving purification from plasma and urine by solid-phase extraction using Isolute ENV+ columns, and analysis by liquid chromatography coupled to a mass spectrometer fitted with an atmospheric pressure turbo ion spray ionisation interface in the positive ion mode.
Ligocka et al. (2002)	5-HNMP (u)	Different solvents and alternative methods of extraction including liquid-liquid extraction (LLE) on Chem Elut and solid-phase extraction (SPE) on Oasis HLB columns were tested.

Åkesson et al. (2004)	NMP (u+p) MSI (u+p)	NMP was measured in plasma and urine using the method described by Åkesson and Paulsson (1997). MSI in plasma and urine was measured using the measured described by Jönsson and Akesson (1997).
Carnerup et al. (2006)	NMP,5-HNMP, 2-HMSI, MSI and 2-Pyrrolidone (2-P) (u+p)	Liquid chromatography with tandem mass spectrometry (LC-MS/MS).
Bader et al. (2007)	NMP, 5-HNMP and 2-HMSI (u)	Urinary NMP and its metabolites 5-HNMP and 2-HMSI were measured according to Åkesson and Paulsson (1997).
Kubota et al. (2007)	NMP, MSI and 2-HMSI (u)	Combination of solid-phase extraction (SPE) and gas chromatography with a flame thermionic detector (GC/FTD) was developed for determination of N-methyl-2-pyrrolidone (NMP), N-methylsuccinimide (MSI), and 2-hydroxy-N-methylsuccinimide (2-HMSI) in human urine.
Suzuki et al. (2009)	NMP, 5-HNMP, MSI and 2-HMSI (u)	Urinary concentrations of NMP and its metabolites 5-hydoxy-N-methyl-2-pyrrolidone (5-HNMP), N-methyl-succinimide (MSI), and 2-hydroxy-N-methylsuccinimide (2-HMSI) were determined. Development of a HPLC-ESI-MS/MS method that excluded using SPE, but included the use of deuterium-labeled compounds to directly correct the remaining matrix effect for electrospray ionization (ESI) detection.
Meier et al. (2013)	5-HNMP and 2-HMSI (u)	5-Hydroxy-N-methyl-2-pyrrolidone (5-HNMP) and 2-hydroxy-N-methyl-succinimide (2-HMSI were analyzed in urine based on Bader et al. (2008b)
Haufroid et al. (2014)	5-HNMP and 2-HMSI (u)	Urinary 5-HNMP and 2-HMSI were determined using liquid chromatography with tandem mass spectrometry.

p: plasma, u: urine

7. HEALTH EFFECTS

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

7.1.1. Human data

Human volunteer studies have shown that NMP is rapidly absorbed following exposure by the inhalation, dermal or oral route (Ursin et al., 1995; Åkesson and Paulsson, 1997; Åkesson and Jönsson, 1997; Åkesson and Jönsson, 2000b,c; Akrill et al., 2002; Jönsson and Åkesson, 2003; Åkesson et al., 2004; Bader et al., 2008a). A study involving exposure of six healthy male volunteers to NMP in an exposure chamber for 8 h at concentrations of 10, 25 and 50 mg/m^3 showed rapid uptake following inhalation, with metabolism to the mono-hydroxy metabolite 5-hydroxy-N-methyl-2-pyrrolidone (5-HNMP), which was further metabolised to N-methylsuccinimide (MSI) and then to 2-hydroxy-N-methylsuccinimide (2-HMSI) (Åkesson and Paulsson, 1997; Åkesson and Jönsson, 2000c, Jönsson and Åkesson, 2003). The half-lives of NMP, HNMP, MSI and 2-HMSI following inhalation of NMP were 4, 6, 8 and 16 h, respectively, with 100% urinary excretion, and the relative proportions of NMP and its metabolites in urine were 2% NMP, 60% 5-HNMP, 0.1% MSI and 37% 2-HMSI (Åkesson and Paulsson, 1997). Carnerup and co-workers have identified 2-pyrrolidone (2-P) as a minor metabolite in both humans and in rats (Carnerup et al., 2005, 2006). 2-P has been reported to be a developmental toxicant and may possibly be responsible for the reproductive effects seen in animal studies with NMP (Carnerup et al., 2005, 2006).

Bader and co-workers have confirmed 5-HNMP, 2-HMSI and free NMP as the major urinary metabolites following inhalation exposure of 16 male volunteers to concentrations of 10, 40, 80 and 25/160 mg/m^3 NMP (Bader et al., 2008a). The relative proportions of these urinary metabolites were approximately 68:31:1 at the exposure level of 40 mg/m^3 NMP under resting conditions. Half-lives of 3.9, 7.5 and 28 hours for NMP, 5-HNMP and 2-HMSI respectively at the exposure level of 40 mg/m^3 NMP under resting conditions were reported by Bader et al. (2008a). Bader and co-workers also reported delayed elimination of NMP following dermal-only exposure to NMP vapour, with peak times for free NMP, 5-HNMP and 2-HMSI being delayed by approximately 4 hours (Bader et al., 2007, 2008a).

Xiaofei and co-workers studied the pharmacokinetics of NMP in four workers exposed to 0.46 – 2.84 mg/m^3 for 12 hours per day for a 5 day working week and five volunteers who observed the work processes for a single 8 hour day and were exposed to a mean concentration of 1.15 mg/m^3 (Xiaofei et al., 2000). NMP levels in plasma and urine were monitored in both workers and volunteers and the data used to derive a pharmacokinetic model for NMP. Metabolic saturation was not predicted at concentrations below approximately 40 mg/m^3. The predictability of the model was demonstrated by monitoring of NMP levels in plasma and urine in a second set of workers.

After oral administration of 100 mg NMP to three healthy male volunteers, 65% of the administered dose was recovered in urine, comprising 2% NMP, 67% 5-HNMP, 0.1% MSI and 31% 2-HMSI (Åkesson and Jönsson, 1997). One third of the oral dose of NMP was not found as any of these metabolites, the lack of mass balance possibly indicating incomplete absorption from the gastrointestinal tract or the presence of unidentified metabolites (Åkesson and Jönsson, 1997).

A 6-h topical study in male and female volunteers using a single dose of 300 mg undiluted NMP showed peak plasma concentrations of NMP three hours after application. A fraction of 22 to 24% of the total dose was recovered in the urine for females and males respectively (Åkesson and Jönsson, 2000b). Mean peak plasma levels of 5-HNMP were observed after 4 hours in females and after 6 in males, while plasma MSI and 2-HMSI peaked after 8 hours and 24 hours respectively (Åkesson et al., 2004). The authors compared the pharmacokinetics of 50% aqueous dermally applied NMP in a group of 6 male volunteers with the results obtained with undiluted NMP and showed peak levels of NMP 8 hours after application, MSI after 12 hours and 2-HMSI after 24 – 30 hours

(Åkesson et al., 2004). The results indicated delayed absorption of NMP in aqueous formulations, a result also found in animal studies.

Akrill and co-workers examined the excretion of 5-HNMP in 2 volunteers exposed for 15 minutes to aqueous NMP solutions (5 – 25%: one hand) followed by urine collection for 48 hours (Akrill et al., 2002). They found that urinary levels of 5-HNMP were at a maximum after about 10 h and excretion continued for 48 h after exposure. The half-life of 5-HNMP was approximately 11 h, confirming the delayed absorption of NMP and prolonged half life of NMP and its metabolites observed by Åkesson and co-workers following dermal exposure compared with inhalation, particularly for aqueous solutions of NMP. It can be estimated from these data that 15 minutes exposure to 15% aqueous NMP is equivalent to inhalation of 10 mg/m^3 NMP with respect to absorption and elimination profile (Akrill et al., 2002).

A permeability rate through human skin of 171 + 59 g/m^3 has been derived for NMP (Ursin et al., 1995). Ligocka and co-workers demonstrated a mean 67.9% absorption of NMP through the skin in 12 human volunteers exposed to 300 mg NMP via a skin patch (Ligocka et al., 2003). Of the total dose 12.6% was excreted as 5-HNMP, 6-12 hours after exposure, while 2-HMSI peaked at 2 time periods, 12-24 hours after exposure (3.3% of dose) and 36-48 hours after exposure (3.2% of dose). The authors also demonstrated a significant relationship between CYP2E1 mRNA content in peripheral blood lymphocytes and levels of 5-HNMP and 2-HMSI excreted in urine within 24 hours and suggested that the activity of this enzyme in an individual should be taken into account when interpreting the results of biological monitoring of exposure to NMP (Ligocka et al., 2003).

7.1.2. Animal data

Toxicokinetic studies have been carried out in rats using the dermal, inhalation, oral or intravenous routes, with similar results. As in humans, NMP was rapidly absorbed and distributed, with 80 - 90% excretion in urine within 24 h (Wells and Digenis, 1988; RTI, 1990, cited in IPCS, 2001); Midgley et al., 1992; Ravn-Jonsen et al., 1992; Payan et al., 2003). Faecal excretion was 2 – 4% of total dose, and there was very limited excretion as CO_2 (0.9 – 1.7%) or volatile organic compounds. A distribution study following intravenous administration of radio-labelled NMP showed distribution to all tissues, with highest levels of radioactivity being observed in the liver, bile and small intestine, kidneys, stomach and testis (Wells and Digenis, 1988).

Following topical administration of NMP radio-labelled with ^{14}C on the C_2 atom to rat skin at doses of 0.2, 2 and 20 mg/cm^2, applied to an area of 12 cm^2, there was 50% absorption of the 2 lower doses while 75% of the 20 mg/cm^2 dose was absorbed, suggesting that NMP promotes its own absorption. Maximum blood levels were observed approximately 8 hours after application (RTI, 1990, cited in IPCS, 2001). A percutaneous absorption study applying NMP as the pure substance, as a 30% solution in water and as a 30% solution in limonene, showed uptakes of 31%, 3.5% and 72% respectively, suggesting that the use and nature of the vehicle also influences uptake (Huntingdon Life Sciences, 1998, cited in IPCS, 2001). Payan and co-workers demonstrated that percutaneous absorption flux in rats was proportional to the concentration of NMP applied and was dependent on skin thickness, suggesting a passive diffusion process (Payan et al., 2003). Maximum absorption fluxes of 10 and 20 mg/cm^2 NMP were determined for 20 µl/cm^2 and 40 µl/cm^2 respectively. Absorption decreased when neat NMP was diluted.

In a study in which rats were exposed to 618 mg/m^3 NMP (whole body) for 6 h, NMP crossed the placental barrier, with an equilibrium being reached between foetal and maternal blood. Elimination of NMP was slower in pregnant than non-pregnant rats (Ravn-Jonsen et al., 1992).

As also observed in the human volunteer studies reported by Åkesson and co-workers, the main urinary metabolite in rats was 5-HNMP, amounting to 70 – 75% of administered dose following intravenous administration (Wells et al., 1992) and 60% after an oral dose of 500 mg/kg (RTI, 1990 cited in IPCS, 2001). In the latter study, a further 10 – 15% was a metabolite of 5-HNMP and 5% was unchanged NMP. At the lower oral dose of 5 mg/kg, NMP was completely metabolised and at least 4 urinary metabolites were detected, indicating that metabolic pathways may become saturated at higher dose levels. The study did not identify the 2-HMSI metabolite demonstrated in humans (Åkesson and Paulsson, 1997). Ligocka and co-workers also demonstrated that the main metabolite in rats following dermal administration of NMP was 5-HNMP (Ligocka et al. 2003). Excretion of this metabolite was significantly reduced in rats pre-treated with the CYP2E1 inhibitor diethyldithiocarbamate, confirming that CYP2E1 is involved in the metabolism of NMP (Ligocka et al. 2003; see also 7.1.1.).

7.1.3. In vitro data

A study by Dick et al (2001) has been assessed by the Swedish Criteria Group for Occupational Standards (Johanson and Rauma 2008, Montelius 2014) as being suitable for an estimation of dermal absorption of NMP by human skin i*n vitro*. The rate of absorption of undiluted NMP was calculated as 10 mg/cm^2 per hour. Extrapolation of data to 2000 cm^2 skin (equivalent to both hands and forearms) and 1 hour of exposure gave a dermal absorption of 20,000 mg (20 g). This uptake was estimated to be about 10 times higher than the uptake within 8 h of inhalation at the Swedish OEL of 50 ppm [200 mg/m^3].

7.1.4. Toxicokinetic modelling

Poet and coworkers (2010) applied PBPK- and benchmark dose modelling to calculate the point of departure (POD) as the area under the blood concentration-time curve (AUC) for NMP in blood. The application focussed on two experimental inhalation studies on developmental toxicity in rats (Saillenfait et al 2003, Solomon et al 1995; see 7.8.2). Since *in utero* exposures were of concern, the models considered major physiological changes occurring in the dam or mother over the course of gestation. The rat PBPK model was used to determine the relationship between NMP concentrations in maternal blood and decrements in foetal/pup body weights following exposures to NMP vapour. Body weight decrements seen after vapour exposures occurred at lower NMP blood levels than those observed after oral and dermal exposures. Benchmark dose modelling was used to define a point of departure (POD) for foetal/pup body weight changes based on dose-response information from two inhalation studies in rats. In this analysis, dose-response models were used to predict from the experimental data of both Solomon et al. and Saillenfait et al. the benchmark concentrations (BMC) resulting in a decrease in mean body weight (foetal/pup) corresponding to 1 SD (BMC1SD) and its 95% lower confidence limit (BMCL1SD). The calculated human equivalent concentration (HEC, for 8h/d and 5d/wk) for BMC1SD was 700 ppm and for BMCL1SD 480 ppm. Although there are uncertainties related to these PBPK modelling, these modelling results basically suggest that the effective concentrations in humans would be higher as compared to rats.

For the U.S. Environmental Protection Agency (EPA), this PBPK model was further optimised by Poet (2013, as cited in Lumpkin and Gentry 2013; Schlosser 2013). In the following evaluation by EPA, it was noted that the model generally produced very similar simulations (compared to the originally published version) following *i.v.* and dermal exposures in rats and for inhalation and dermal exposures in humans. Also, the modified model code was considered to be capable of predicting parent compound and metabolite profiles from multiple data sets, providing blood and urine measurements in rodents and humans exposed to NMP by multiple routes of exposure (*i.v.,* dermal and inhalation).

EPA especially recognised that the model described well the urinary clearance of 5-HNMP after a range of *i.v.* and inhalation exposures (Lumpkin and Gentry 2013; Schlosser 2013).

7.1.5. Biological monitoring

Studies in both humans and animals show that NMP is readily absorbed through the skin (RTI, 1990, cited in IPCS, 2001; Midgely et al, 1992; Åkesson and Jönsson, 2000b). Bader and co-workers have measured dermal absorption of NMP from the vapour phase, equivalent to approximately ~ 30 % of the total inhalation dose in an experimental study in human volunteers, the design of which included a phase, in which uptake through inhalation was prevented by face shields and absorption of NMP vapour was likely to have occurred mainly through the exposed skin areas of the hands, arms and lower neck (Bader et al., 2008a). Dermal absorption can therefore contribute significantly to body burden. Measurement of non-metabolised NMP in plasma or urine has been proposed as a biological monitor, reflecting exposure from both the inhalation and dermal routes (Åkesson and Paulsson, 1997; Xiaofei et al., 2000), but has several disadvantages, including the comparatively short half-life of NMP and the low concentrations in urine.

The metabolites of NMP are more appropriate biological indicators of exposure, and measurement of the major metabolite 5-HNMP, with a half-life of 6-7 hours, in urine or plasma has been proposed as a suitable method for biological monitoring (Åkesson and Jönsson, 2000c; Jönsson and Åkesson, 2003). The same group has also suggested measurement of MSI, given the readily available analytical method for this metabolite (Jönsson and Åkesson, 2001). However MSI has a somewhat larger volume of distribution and levels in urine are low.

In an 8-hour inhalation study in male volunteers exposed to NMP at concentrations of 10, 25 and 50 mg/m^3, Åkesson and Jönsson reported an excellent correlation between NMP air levels and plasma or urinary 5-HNMP (Åkesson and Jönsson, 2000c). An 8-hour exposure to an air concentration of 10 mg/m^3 NMP resulted in a level of 22 mmol 5-HNMP/mol creatinine in urinary samples collected during the last 2 hours of exposure, while exposure to 50 mg/m^3 NMP resulted in a level of 110 mmol/mol creatinine. The same group also proposed 2-HMSI in urine as an appropriate biological marker for NMP exposure, as sensitive analytical methods were available (Carnerup et al, 2001; Jönsson and Åkesson, 2003; Carnerup et al., 2005, 2006). Given the long half-life of 2-HMSI, this metabolite may be advantageous over 5-HNMP as a biological marker, particularly in situations where workers may be exposed topically to aqueous solutions of NMP. In such situations, dermal absorption of NMP is delayed (Åkesson et al., 2004), but the impact of this on peak levels of 2-HMSI is much less marked than for 5-HNMP.

A comprehensive study in 16 human volunteers (see section 7.1.1 for methodological details of this study), Bader and co-workers have confirmed that levels of urinary NMP, 5-HNMP and 2-HMSI show close correlations to airborne NMP. In this study, the authors considered that 5-HNMP and 2-HMSI were preferable biomarkers for workplace surveillance (Bader et al., 2008a). The delayed peak maximum of 16-24 h post-exposure and the long biological half-life makes urinary HMSI especially suitable for the surveillance of accumulative effects during a working week (Bader et al. 2008a). The results of Bader and co-workers indicate that the optimum sampling time for 5-HNMP is 2-4 h post-exposure, while in the case of 2-HMSI, a urine collection 16 h post-exposure (i.e. on the morning after an 8 h work-shift) is indicated. Although Åkesson and co-workers have proposed that results of biological monitoring should be expressed as absolute urinary concentrations of 2-HMSI or 5-HNMP, adjusted for urine density, rather than relative to urinary creatinine levels (Åkesson et al., 2004), Bader and co-workers corrected both parameters for urinary creatinine to compensate for diuretic variations (Bader et al., 2007, 2008a).

Linear regression analysis of NMP in air and of post-exposure 5-HNMP in urine in the above study indicated an average concentration of approximately 60 mg/g creatinine (post exposure) for an exposure of 40 mg/m^3 NMP without workload and approximately 75 mg/g creatinine in a work scenario with moderate workload [six 10 minute periods of exercise during the 8-hour exposure period, on a bicycle ergometer (75 Watt)] (Bader et al., 2008a). The regression curve reported by Åkesson and Jönsson (2000c) for a series of 8 h exposures to 10, 25 and 50 mg/m^3 NMP was considerably steeper than the curve calculated in the Bader and co-workers study, and provided an estimate of 90 mg/g creatinine for urinary 5-HNMP after an 8 h exposure to 40 mg/m^3 NMP. Similarly, regression analyses between NMP in air and urinary 2-HMSI peak values (16 – 24 h post-exposure) in the Bader et al. study pointed to an average concentration of 16 mg/g creatinine (without workload) and to 22 mg/g creatinine (moderate workload) for a whole-body exposure at 20 mg/m^3 NMP. Comparable to the situation with 5-HNMP, the results from an inhalation study by Jönsson and Åkesson (2003) point to higher urinary 2-HMSI concentrations than in the Bader and co-workers study, with an estimated level of 40 mg 2-HMSI/g creatinine at 40 mg/m^3 NMP. These differences may be due to methodological differences between the two studies although Bader and co-workers also suggest that differences in the dermal absorption of NMP are likely to have contributed to the discrepancies between the studies (Bader et al., 2007, 2008a).

Meier et al (2013) reported on a study investigating current exposures to NMP in the spraying department of an automobile plant using biological monitoring. 5-HNMP and 2-HMSI were analysed in 69 urine samples of 14 workers exposed to NMP and of 9 non-exposed controls. Measurements of airborne exposure levels were not included. Three different working tasks ('loading' and 'cleaning' of the sprayer system and 'wiping/packing' of the sprayed materials) and three sampling times (pre-shift, post-shift, and pre-shift of the following day) were studied in exposed workers. Median levels of 5-HNMP and 2-HMSI in post-shift urine of exposed workers were 0.91 and 0.52 mg/g creatinine, respectively, whereas median levels in controls were below the limit of detection. Decreased levels of 5-HNMP were observed in pre-shift urine samples on the following day (0.39 mg/g creatinine) in exposed workers, while the concentration of 2-HMSI did not change (0.49 mg/g creatinine). Highest exposures occurred during sprayer cleaning with a maximum level of 8.31 mg/g creatinine of 5-HNMP in post-shift urine. In contrast to 'wipers/packers', no decrease in 5-HNMP could be observed in pre-shift urine samples on day 2 of the 'loaders' and 'cleaners'. Overall, exposure in terms of 5-HNMP post-shift and 2-HMSI pre-shift of the following day were well below existing biological limit values of the European Union (70 and 20 mg/g creatinine, respectively). The authors suggested that the analysis of 5-HNMP in pre-shift samples also provided essential information, particularly in situations involving direct handling of liquid NMP-containing formulations.

Haufroid et al (2014) conducted a field study to examine the value of urinary 5-HNMP and 2-HMSI in workers exposed to N-methyl-2-pyrrolidone (NMP) and to look for health effects of exposure. Airborne NMP was determined according to the NIOSH method. Urinary 5-HNMP and 2-HMSI (after and before next shift) were determined by liquid chromatography with tandem mass spectrometry. Outcomes were effects on lung, kidney, skin and mucous membranes, nervous system, haematopoiesis and liver determined by clinical examination and laboratory measurements. Univariate statistical methods and multiple regressions were used to analyse results. Skin absorption, smoking and other potential confounders were taken into account. Three-hundred-twenty-seven workers were eligible out of which 207 workers (63%) participated. Ninety-one of these worked with NMP. Occupational exposure to NMP did often not occur daily and ranged from non-detectable to 25.8 mg/m^3 (median = 0.18). Urinary 2-HMSI (mg/l; before next shift) was the best biomarker of exposure to NMP, explaining about 70% of the variance, but most likelihood ratios did not allow for ruling exposure in or out, at these low levels of exposure. Creatinine adjustment did not improve the results clearly. No clear and consistent health effects could be associated with NMP exposure. No indication for a bias due to non-participation was found. It was concluded by the authors that biological monitoring, primarily urinary 2-HMSI (before next shift), is of value to estimate exposure to NMP, even when exposure is irregular and low. No irritant or other health effects were found.

7.2. Acute toxicity

7.2.1. Human data

No information is available on the acute toxicity of NMP in humans, but the substance is of low acute toxicity in animals.

7.2.2. Animal data

Oral LD50 values in rats, mice, rabbits and guinea pigs are reported to lie in the range 3500 – 7900 mg/kg bw (Bartsch et al., 1976; Ansell and Fowler, 1988) while dermal LD50 in rats and rabbits are in the range 4000 – 10,000 mg/kg bw (Bartsch et al., 1976; Weisbrod, 1981; Clark, 1984, cited in Greim, 1998). No deaths occurred in an acute inhalation study in rats exposed nose-only to a 5100 mg/m^3 vapour/ aerosol mixture with a mass median aerodynamic diameter (MMAD) of 4.6 µm (respirable fraction 87%), the LC50 was >5100 mg/m^3 (BASF, 1988, cited in IPCS, 2001). LC50s in the range of 3100 – 8800 mg/m^3 were determined in another study also involving exposure to an aerosol (du Pont, 1988, cited in Greim, 1998). Effects seen following oral or inhalational exposure included mucosal irritancy, narcosis and non-specific symptoms of toxicity (BASF, 1988, cited in IPCS, 2001; Ansell and Fowler, 1988).

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

In a human volunteer study, involving six subjects exposed to 10, 25, or 50 mg/m^3 [2.5, 6.25 or 12.5 ppm] NMP over an 8 hour period, there were no acute changes in the nasal cavity as assessed by continuous acoustic rhinometry, and no significant differences were observed in FEV1 (forced expiratory volume in 1 s), vital capacity or forced expiratory capacity, measured by spirometry (Åkesson and Paulsson, 1997). Two volunteers reported detecting an odour at 50 mg/m^3 [12.5 ppm]. The subjects did not experience any symptoms of eye or respiratory tract irritation, or other symptoms such as headache, dizziness, and nausea.

Workers exposed to up to 280 mg/m^3 [70 ppm] NMP in working areas in the microelectronics fabrication industry where warm NMP (80 °C) was being handled reported severe eye irritation and headache (Beaulieu and Schmerber, 1991). Due to methodological deficiencies, an exposure – response relationship could not be established in this study.

In a study of 38 graffiti removers, working 8 hour shifts in the Stockholm underground system and exposed to a mixture of solvents including NMP, there was a significantly higher prevalence of tiredness, headaches and symptoms affecting airways, eyes and skin than population controls (Langworth et al., 2001). Eight-hour exposures (TWA) were below 20% of the Swedish Permissible Exposure Limit for all solvents measured, but short-term exposures occasionally exceeded the short-term exposure limits. Mean short-term exposure to NMP over 15 minutes was 4.71 + 6.17 mg/m^3 (AM), with a range of 0.01 – 24.61. The relationship between the different exposure measurements and reported symptoms were generally weak, and no specific relationship with NMP exposure could be identified.

A comprehensive study in 15 healthy young male volunteers has been undertaken, in order to investigate possible chemosensory effects of NMP under workplace conditions (van Thriel et al., 2007). One subject, out of 16 subjects initially, dropped out of the

study at an early stage for reasons unrelated to NMP exposure. Exposure scenarios used in the study were 10 mg/m^3, 40 mg/m^3, 80 mg/m^3 and 25/160 mg/m^3, the latter including peak exposures up to 160 mg/m^3. The 10 mg/m^3 condition was defined as a non-irritating odorous control condition. The subjects were exposed for an 8-hour (typical shift) period once a week over an 8 week period, with an exposure-free period of 1 week between two subsequent sessions, i.e. a total of 4 exposures during the experimental period. All four inhalational conditions were investigated with and without additional physical workload. The physical workload consisted of six 10 minute periods of exercise during the 8-hour exposure period on a bicycle ergometer (75 Watt). [The toxicokinetic aspects of this study are discussed in 7.1.1, the biomonitoring aspects in 7.1.5.] Chemosensory effects of NMP were assessed using the following measures: (1) eye blink rates, based on EMG recordings, (2) nasal air flow, assessed by anterior rhinomanometry, (3) breathing rates, based on electrophysiological measurements, (4) neurobehavioral/psychological tests of attentional functions (chemosensory mediated distraction), (5) subjective acute symptoms (including acute symptoms of odour and trigeminally mediated health effects) according to the Swedish Performance Evaluation System (SPES), (6) intensity of chemosensory sensations (e.g. odour intensity, intensity of eye irritations) based on ratings assessed with the labelled magnitude scale (LMS) and (7) odour threshold shifts measured by flow-olfactometry (self- and cross-adaptation). The study included a dermal-only exposure phase in which inhalational uptake was prevented by face shields, in order to measure dermal uptake of NMP from the vapour phase, and urine samples were taken in order to investigate the absorption and elimination of NMP in humans under workplace-oriented conditions. The results showed that NMP could be smelled by the subjects (odour intensity, showing some adaption over the 8 hour exposure period) and it was reported to be slightly annoying. However other symptomology indicative of an irritant potential, especially trigeminal sensations, were not elicited by NMP. Median intensity ratings of annoyance only reached "moderate" intensities. The odour intensity was rated slightly higher than annoyance, but the ratings exceeded "moderate" only during exposure peaks. The peak concentrations were mirrored by the ratings of odour intensity and annoyance. However, neither nasal flow values (AAR), nor eye blink rates, and breathing rates showed any dose-related response, even at the peak exposure of 160 mg/m^3. None of the neuropsychological tests revealed any NMP-related effect with respect to cognitive abilities of the subjects during the exposures. The authors of the study concluded that NMP can be characterised as an odorous substance without irritant potency even during peak exposures of 160 mg/m^3 (van Thriel et al., 2007).

A Japanese study of 15 workers, who cleaned components with an NMP solution (>90%), examined clinical effects (urine and blood status) and effects on motor and cognitive functions. Exposure, which was mainly by inhalation, was measured at about 0.13 – 0.25 ppm [0.6 – 1 mg/m^3] (8 h TWA, 5 days). The authors reported no effects when compared with a control group (Nishimura et al 2009).

7.3.2. Animal data

7.3.2.1. Inhalation

A series of subacute, subchronic and chronic inhalation toxicity studies have been carried out in rats involving exposure to NMF as an aerosol or as a vapour. Of these, the studies of Lee and co-workers (Lee et al., 1987) and the 1992–1995 studies carried out by BASF are considered to be the most reliable for determining a No-Adverse-Effect-Level (NOAEL).

Lee and co-workers exposed rats to 100, 500, or 1000 mg/m^3 NMP for 6 h/day, 5 days/week, for 4 weeks, using whole-body exposure (Lee et al., 1987). Exposure was predominantly to an aerosol, with >95% of droplets <10 µm. Deaths were seen at 1000 mg/m^3 NMP, accompanied by bone marrow hypoplasia and evidence of toxicity in lymphoid tissue (thymus, spleen, and lymph nodes) Concentration-related lethargy and

irregular respiration were observed at all dose levels, reversible within 30 – 45 min of exposure at the 100 and 500 mg/m^3 exposure levels. No treatment-related histopathological changes were reported at these dose levels.

Irritation of the nasal passages at levels of 1000 mg/m^3 and above was observed in inhalational toxicity studies carried out using exposure levels of between 10 and 10,000 mg/m^3 NMP as a liquid aerosol, head-only exposure, 6 h/day, 5 days/week for 2, 4 or 13 weeks (BASF, 1992, 1993b, 1993c, 1994, cited in Greim, 1998). Deaths were seen at 7000 mg/m^3 NMP and above, with female rats being more sensitive than males, while exposure to 3000 mg/m^3 for 13 weeks or to 4000 mg/m^3 and above for 14 days caused respiratory tract, decreased testis weights associated with histopathological changes including cell loss in the germinal cell epithelium and evidence of mild systemic toxicity, comprising body weight loss, mild hepatotoxicity and treatment-related changes in haematological parameters. In the 13-week study, 3000 mg/m^3 NMP aerosol (6h/working day) caused clinical symptoms of upper respiratory tract irritation, general unspecific systemic toxicity, and in some male animals cellular depletion of the germinal epithelium of the testes. Whereas the symptoms of general toxicity were mostly reversible during a 4-week recovery period, the testes damage persisted. The NOAEC for systemic toxicity was 1000 mg/m^3, but there were slight signs of local nasal irritation at 1000 mg/m^3 without histopathological correlate. Therefore, the NOAEC for local effects to the upper respiratory tract was judged to be 500 mg/m^3 [125 ppm] (BASF 1994). Yellow discoloration of the urine noted at levels of 100 mg/m^3 and higher may be due to a coloured unidentified metabolite or to hepatic dysfunction (IPCS, 2001). In a series of whole-body inhalation studies in rats, comparing fine aerosols with coarse aerosols and varying humidity conditions, toxicity was more marked when exposure was to coarse droplets and high relative humidity (BASF, 1995a , b, c, d, e, f, g, cited in IPCS, 2001).

Exposure of rats to NMP vapour at a level of 1750 mg/m^3 for 6 h/day, 5 days/week for 6 weeks caused only slight irritation of nasal passages (BASF, 1983, cited in Greim, 1998), while repeated exposure to 6600 mg/m^3 was lethal to mice but without effect on rats, guinea pigs, rabbits or cats (BASF, 1964a, cited in Greim, 1998).

In a 2-year inhalation study, CD-1 rats (120 per sex per dose level) were exposed to NMP as a vapour at levels of 0, 40, or 400 mg/m^3 for 6 h/day, 5 days/week, whole body exposure (Lee et al., 1987). Ten rats per sex were subjected to haematology and blood and urine chemistry analysis after 1, 3, 6, 12, and 18 months of exposure and ten rats per sex were sacrificed after 3, 12, and 18 months. All surviving rats were killed at the end of 24 months of exposure. Lee et al noted "alveolitis, acute, focal" in 2/84 male and in 13/84 female controls, and in 10/85 and 12/85 male and female 400 mg/m3 rats. There was "alveolar cell hyperplasia/aggregated macrophages" in 0/84 male and 4/85 female controls and in 4/84 and 9/84 male and female 400 mg/m3 rats. Other histological lung effects were not observed. Male rats exposed to 400 mg/m^3 for 18 months showed slight body weight loss, higher haematocrit and higher alkaline phosphatase levels in serum than were observed in the control group. There was no such difference after 24 months of exposure. At the 400 mg/m^3 exposure level, male rats excreted larger urine volumes, and both males and females excreted dark yellow urine.

7.3.2.2. Oral exposure

Repeat-dose oral toxicity studies have been carried out in rats, mice, rabbits, guinea pigs, dogs, and cats (BASF 1964b, 1978a, cited in Greim, 1998; Meleschtschenko, 1970; Becci et al., 1983; GAF, 1990, cited in Greim, 1998; Malek et al., 1997); Malley et al., 1999, 2001). Of these, only the BASF (1978a) gavage study in rats and the 28-day, 90-day and 18-month/2 year dietary studies of Malek, Malley and co-workers provide adequate detail about methodology and results obtained.

In a 28-day study in rats administered 0, 257, 514, 1028, or 2060 mg/kg bw/day NMP for 5 days/week by oral gavage (BASF, 1978a, cited in Greim, 1998), dose-related

changes included tremor, restlessness, ruffled fur, and defensive reactions, decreases in body weight gain and increases in relative liver and kidney weights. Relative and absolute testis weights were decreased in males receiving 2060 mg/kg bw/day, accompanied by histological changes in the testis. The NOAEL in this study was 514 mg NMP/kg bw (BASF, 1978a, cited in Greim, 1998).

The feeding studies in rats carried out more recently by the NMP Producers Group (Malek et al.,1997; Malley et al., 1999, 2001) at dietary dose levels up to 30,000 mg NMP/kg for 28 days, 18,000 mg NMP/kg for 90 days and 15,000 mg NMP/kg for 2 years showed sedative effects and consistent decreases in body weight and body weight gain at higher dose levels, accompanied by lower food consumption. Centrilobular hypertrophy accompanied by increases in liver weight was reported in high dose females in the 90-day study, while increases in kidney weight in both sexes were not associated with histopathological changes. At 2 years, male rats at the highest dose level showed a significantly increased incidence of severe progressive nephropathy, accompanied by decreased survival. In addition, top dose males showed increased incidences of polyarteritis in the caecum, mesenteric lymph node and testis and accumulation of pigment-containing macrophages in the spleen. While the kidney was concluded to be the main target organ in male rats, testicular degeneration and atrophy in top dose males was also a consistent finding. Top dose females showed lymphoid depletion of the mesenteric lymph node and accumulation of pigment-containing macrophages in the spleen at 2 years. Although there were dose-related trends in the incidence of a number of these changes in lower dose groups, none were statistically significant. The NOAEL in the 90-day study was 3000 mg/kg diet, equivalent to 169 mg/kg bw/day in male rats and 217 mg/kg bw/day in female rats, and in the 2-year study was reported to be 5000 mg/kg, equivalent to 207 mg/kg bw/day in male rats and 283 mg/kg bw/day in female rats (Malley et al., 1999, 2001).

In 28-day, 90-day and 18-month studies in mice (Malek et al., 1997; Malley et al., 1999, 2001), effects on body weight change and food consumption were less marked than those seen in rats. Centrilobular hypertrophy accompanied by increases in liver weight were seen in male and female B6C3F1 mice administered NMP at levels of 7500 mg/kg in the diet for 90 days or 2 years (equivalent to 1931 mg/kg bw/day) and at 1200 mg/kg in the diet (males only) for 2 years, while histological changes were reported in the kidneys of mice receiving 2030 mg/kg diet and above for 28 days. The NOAEL in the 90-day study was 1000 mg/kg diet, equivalent to 277 mg/kg bw/day, and in the 18-month study was 600 mg/kg in male mice (equivalent to 89 mg/kg bw/day) and 1200 mg/kg in female mice (equivalent to 115 mg/kg bw/day) (Malley et al., 1999, 2001).

7.3.2.3. Dermal exposure

Summary details only of a repeat-dose dermal toxicity study in rabbits are provided in the 1990 report of GAF (GAF, 1990, cited in Greim, 1998). Undiluted NMF applied to the intact or abraded skin of rabbits at levels of 0, 411, 822 or 1645 mg/kg/day for 20 days produced local irritancy but there were no signs of systemic toxicity although one animal treated with 1645 mg/kg/day (abraded skin) died.

7.3.3. In vitro data

There are no in vitro toxicity data, which are relevant for the current evaluation.

7.4. Irritancy and corrosivity

7.4.1. Human data

Leira and co-workers reported development of skin irritancy and contact dermatitis in 10/12 workers exposed to NMP 8 hours a day for 2 days (Leira et al., 1992). Åkesson & Jönsson observed redness, swelling and thickening and vesiculation of the skin in

workers in the paint-stripping industry coming into contact with NMP (Åkesson & Jönsson, 2000a), while irritant contact dermatitis was seen in three workers newly exposed to NMP; this was attributed to a hygroscopic effect of the solvent on the *stratum corneum* (Jungbauer et al. 2001).

7.4.2. Animal data

7.4.2.1. Skin

Several skin irritation studies in rabbits involving a single application of 0.5 ml NMP under an occlusive dressing have shown a low potential for irritancy (Draize et al., 1944; Ansell & Fowler, 1988). In contrast, severe erythema and subsequent scaling at the application site was reported in a study in rabbits carried out by BASF (BASF, 1963, cited in Greim, 1998). Repeated daily dermal administration of 450 mg/kg body weight to rabbits caused painful and severe haemorrhage and eschar formation after four doses; the reaction to a dose of 150 mg/kg body weight per day was less marked (BASF, 1993a, cited in IPCS (2001). Application of 20 daily doses of undiluted NMF at dose levels up to 1645 mg/kg bw/day to the intact or abraded skin of rabbits caused only mild irritation (GAF, 1990, cited in Greim, 1998).

7.4.2.2. Eyes

Following instillation of 0.1 ml NMP into the eyes of New Zealand White marked conjunctival irritancy including corneal opacity, iritis, and conjunctivitis was observed (Draize et al., 1944). The effects were reversible within the 21 day observation period of the study. Moderate to marked eye irritancy was also reported in studies carried out in rabbits by BASF (1951, 1963, cited in Greim, 1998), Ansell and Fowler (1988) and GAF (GAF, 1990, cited in Greim, 1998).

7.4.3. In vitro data

No data found.

7.5. Sensitisation

7.5.1. Human data

There are no reports of sensitisation in workers following dermal contact with NMP. NMP produced no signs of contact sensitisation in a repeated-insult patch test in human subjects, although minor to moderate transient irritation was observed (Lee et al., 1987).

7.5.2. Animal data

In a modified Draize test in guinea pigs, repeated application of a 5% NMP solution did not produce any signs of sensitisation (Lee et al., 1987). No further details were provided. Similarly, no evidence of sensitisation was observed in an intradermal sensitisation potential test involving 4 intradermal injections of 0.1 ml of 1% NMP in saline in Guinea pigs, followed by application of a 5% or a 50% aqueous solution of NMP and examination after 24 and 48 h (du Pont, 1976a, cited in IARC, 2001). The 50% solution produced slight irritancy at the application site.

7.5.3. In vitro data

Shortt et al (2014) described antineoplastic and immune-modulatory activity in a cMYC driven myeloma model in vitro. The authors challenged the use of NMP as an "inert" drug-delivery vehicle.

7.6. Genotoxicity

7.6.1. Human data

There are no human studies known on genotoxicity of NMP.

7.6.2. Animal data

No evidence of clastogenicity or aneugenicity was seen in a micronucleus test in which male and female NMRI mice were administered single oral doses (by gavage) of 950, 1900, or 3800 mg NMP/kg body weight. The animals showed signs of systemic toxicity as evidenced by irregular respiration, coloured urine, and general poor health (Engelhardt and Fleig, 1993). Similarly, no evidence of clastogenicity or aneugenicity was seen in a bone marrow chromosomal aberration study in which male and female Chinese hamsters were administered single oral doses of 1900 or 3800 mg NMP/kg body weight, dose levels which produced signs of systemic toxicity (Engelhardt and Fleig, 1993).

Significantly increased post-implantation losses were observed compared with controls in a dominant lethal test in male NMRI mice given 391 mg NMP/kg body weight intraperitoneally once per week for 8 consecutive weeks (BASF, 1976a, cited in Greim, 1998). In a micronucleus test in male and female Chinese hamsters exposed for 6 weeks (6 h/day, 5 days/week) to 3300 mg NMP/m^3 a slight but non-significant increase in structural chromosomal aberrations in the bone marrow was reported (BASF, 1976b, cited in Greim, 1998). None of the studies was performed according to current regulatory standards, and therefore they are not adequate for the purposes of evaluation of the mutagenicity of NMP.

7.6.3. In vitro

A number of bacterial mutagenicity studies have been carried out, using tester strains TA 97, 98, 100, 102, 104, 1535, 1537 and NMP dose levels in the range of 0.01–1000 µmol/plate, equivalent to 0.99 µg/plate to 99 mg/plate, with cytotoxicity being evident at the highest dose levels (BASF, 1978b, cited in Greim, 1998; Maron et al., 1981; Mortelmans et al., 1986; Wells et al., 1988). All tests gave negative results with and without metabolic activation. Negative results were also obtained in mammalian cells, in the L5178Y mouse lymphoma test (du Pont, 1976b, cited in IPCS, 2001), in the HPRT (hypoxanthine guanine phosphoribosyl transferase) test in CHO cells and in the UDS (unscheduled DNA synthesis) assay in rat primary hepatocyte cultures (GAF, 1990, cited in Greim, 1998). NMP at high concentrations of 77 230 mmol/l, equivalent to 7.6–23 g/l, has however been reported to induce aneuploidy in Saccharomyces cerevisiae strain D61 (Mayer et al., 1986, 1988; Mayer and Goin, 1988; Zimmermann et al., 1988).

7.7. Carcinogenicity

7.7.1. Human data

There are no epidemiological studies known on carcinogenicity of NMP.

7.7.2. Animal data

In a 2-year inhalation study, groups of 120 male and 120 female Charles River CD rats were exposed to NMP as a vapour at levels of 0, 40, or 400 mg/m^3 for 6 h/day, 5 days/week, whole body exposure, as already detailed in section 7.3.2 (Lee et al., 1987). Male rats exposed to 400 mg/m^3 showed slight body weight loss, higher haematocrit and higher alkaline phosphatase levels in serum and they excreted larger

urine volumes than did the control group. Both males and females excreted dark yellow urine. Minimal inflammation in the lung was observed at the highest exposure level of 400 mg/m^3. There were no significant differences in morbidity or mortality and no evidence of carcinogenic effects of NMP in this study.

Carcinogenicity studies in rats and mice commissioned by the NMP Producers Group showed no evidence of a carcinogenic effect in rats at dietary concentrations of 15000 mg/kg and below (Malley et al., 2001). Male B6C3F1 mice receiving NMP at levels of 7200 mg/kg in the diet (equivalent to 1089 mg/kg bw/day) showed a significant increase in hepatocellular carcinoma (13/50 compared with 4/50 in the control group) (Malley et al., 2001). Female mice in this dose group also showed a significant increase in hepatocellular carcinoma (3/50 compared with 0/50 in the control group), however the incidence fell within the historical control. Hepatocellular adenomas were also increased in both male and female mice. The authors considered that these tumours were produced by a non-genotoxic mechanism, due to enhanced cell proliferation in the liver (Parod et al., 2001).

7.8. Reproductive toxicity

7.8.1. Human data

A 23-year old laboratory technician was occupationally exposed to NMP during her first 20 weeks of pregnancy, in particular due to an NMP spill in week 16 of pregnancy. She experienced malaise, headache, and nausea during the 4 days following the spill, and at week 25, signs of delayed foetal development were observed. A stillborn foetus was delivered at week 31. No information on the mother's level of exposure to NMP is available, and it was concluded that it was impossible to establish if exposure to NMP was the causative factor (Solomon et al., 1996; Bower, 1997).

7.8.2. Animal data

7.7.2.1. Fertility

The repeat dose toxicity studies summarised in section 7.3.2 indicate that exposure of male rats to high levels of NMP is associated with decreased testicular weight and histopathological changes including cell loss in the germinal cell epithelium (BASF, 1978a, cited in Greim, 1998, 1992, cited in IPCS, 2001, 1993b, 1993c, 1994, cited in Greim, 1998; Malek et al., 1997). A toxicokinetic study in rats with radio-labelled NMP showed highest levels of radioactivity in the testis, liver, bile, small intestine, kidneys and stomach, with 0.9% of the administered dose being recovered in the testis (Wells and Digenis, 1988).

However, Fries and co-workers reported no effect on testis or sperm morphology and sperm count in 24 male Wistar rats exposed to NMP vapour at a level of 618 mg/m^3 (150 ml/ m3) for 90 days (Fries et al. 1992, cited in Greim, 1998).

7.7.2.2. Developmental toxicity

NMP has been shown to cross the placental barrier, with an equilibrium between foetal and maternal blood (Ravn-Jonsen et al., 1992).

7.7.2.3. Inhalation

In a two-generation reproduction study in rats 10 males and 20 females per dose level were exposed whole body to 0, 10, 51 or 116 ppm [0, 41, 206, or 478 mg/m^3] of NMP vapour (relative humidity 40–60%) for 6 h/day, 7 days/week, for a minimum of 14 weeks (Solomon et al., 1995). Animals were mated after a 12-week exposure period and both parents and offspring were examined for adverse effects on reproduction. No effects on reproductive ability were recorded. However, a very slight but statistically significant reduced body weight gain was evident in the F1 pups whose parents had been exposed to 116 ppm [478 mg/m^3]. P0 dams showed reduced sensitivity to noise. The NOAEL for both reproductive and maternal toxicity was reported to be 51 ppm [206 mg/m^3] (Solomon et al., 1995).

A developmental toxicity study by the inhalation route, at exposure levels of 0, 10, 51 or 116 ppm [0, 41, 206, or 478 mg/m^3] of NMP vapour, was carried out in rats by Solomon and co-workers as part of the two-generation reproductive toxicity study reported above (Solomon et al., 1995). No effects on pregnancy rate, numbers of viable litters, corpora lutea, implantations, foetal deaths, resorptions, litter size, or incidence of foetal malformations or variations were reported, although the mean foetal weight was slightly, but statistically significantly decreased in the highest dose group.

NMP was reported to have no embryotoxic, foetotoxic or teratogenic effects in pregnant rats exposed whole body to 0, 100, or 360 mg /m^3 [0, 25 or 90 ppm] for 6 h/day on days 6–15 of gestation (Lee et al., 1987). Maternal toxicity was not observed in this study.

Whole body exposure of pregnant rats to 680 mg/m^3 [170 ppm] NMP vapour for 6 h/day on days 4–20 of gestation resulted in increased pre-implantation loss compared with the control group, there was no significant effect on the number of implantations per dam or on number of live foetuses (Fries et al., 1992, cited in Greim, 1998; Hass et al., 1995). Delayed ossification of the skull, cervical vertebrae, sternebrae, and metatarsal and digital bones was also observed, in the absence of clinical signs of maternal toxicity, malformations were not increased.

In a study conducted by Saillenfait and co-workers, pregnant rats were exposed whole body to NMP vapour at concentrations of 0, 30, 60 and 120 ppm [0, 125, 250, 500 mg/m^3] for 6 h/day, on days 6 – 20 of gestation (Saillenfait et al., 2003). Significant decreases in maternal body weight gain and food consumption were seen at 120 ppm, with some slight decrease in body weight gain also being evident at 60 ppm. There were no adverse effects on embryo/foetal viability or evidence of teratogenicity at any concentration tested. A marginal foetal toxicity was indicated by reduced foetal weight at 120 ppm (5.52 ± 0.4 g vs. 5.81 ± 0.39 g in controls). No maternal or developmental toxicity was recorded at 30 and 60 ppm [125 and 250 mg/m^3], respectively.

In a neurobehavioural teratology study in pregnant rats exposed whole body to 622 mg/m^3 [156 ppm] NMP vapour for 6 h/day on days 7–20 of gestation, most of the behavioural tests gave similar results for the exposed and control animals (Hass et al., 1994). An occasionally increased latency in Morris swimming maze and a statistically borderline impairment in operant behaviour with delayed spatial alternation were however noted among the exposed offspring. Pups had a somewhat lower body weight and slight delay in achieving some developmental milestones in the pre-weaning period.

Pregnant rabbits were exposed head only for 6 h/day to 0, 200, 500, or 1000 mg/m^3 [50, 125 or 250 ppm] NMP (vapour/aerosol; MMAD 2.7–3.5 µm) on days 7–19 post-insemination. Slight developmental toxicity in the absence of maternal toxicity was manifest as an increased occurrence of supernumerary 13th ribs in the 1000 mg/m^3 [250 ppm] group (BASF, 1993d, cited in IPCS, 2001). No malformations were observed. The NOAEL for developmental and maternal toxicity was 500 mg/m^3 [125 ppm].

7.7.2.4. Oral

In a multi-generation reproduction study by the oral route, in which rats were exposed in the diet to NMP at doses of 50, 160, or 500 mg/kg bw/day, the highest dose level caused an increased incidence of stillbirths, decreased parental body weight and food consumption, slightly lower male fertility and female fecundity (Exxon, 1991, cited in IPCS, 2001). Because of pup toxicity at the 500 mg/kg bw level, the dose was decreased to 350 mg/kg bw. for the remainder of the study. There was a concomitant reduction in survival and growth rates in the F1 generation and testis weights were reduced in the male pups. No effect was seen in the 50 and 160 mg/kg bw per day groups. When the dose was reduced to 350 mg/kg bw/day, NMP did not cause maternal toxicity or reduced pup survival. The NOEL for parental and reproductive effects was 350 mg/kg bw/day and that for growth and development of the offspring was 160 mg/kg bw/day.

Pregnant rats were given daily NMP doses of 0, 40, 125, or 400 mg/kg bw/day by oral gavage on days 6–15 of gestation. Maternal and foetotoxicity were observed at the highest dose level compared with control, as evidenced by decreases in maternal body weight gain decrement, reduced foetal body weights and increased incidence of foetal stunting (EXXON, 1992, cited in IPCS, 2001). Oral gavage administration of 997 mg/kg bw/day to rats on days 6–15 of gestation caused increased resorptions (95%) and malformations in 8 out of 15 surviving foetuses, accompanied by foetal mortality, reduced placental and foetal weights, and reduced foetal lengths (BASF, 1971, cited in Greim, 1998). Insufficient detail was provided on maternal toxicity in this study. In an oral developmental toxicity study in Sprague Dawley rats, using dose levels of 0, 125, 250, 500 and 750 mg/kg body weight by gavage, significant impairments in maternal body weight gain and food consumption were noted at doses of 500 mg/kg body weight and above (Saillenfait et al. 2002). At the 250 mg/kg dose, effects on body weight gain (day 6 – 21) and absolute weight gain were about 10% below control and associated with a reduction in foetal weight at this dose level. Only the latter gained statistical significance. Foetal body weight was dose dependently decreased at 250 mg/kg (10%) and 500 (30%) or 750 mg/kg (47% less than control) as was maternal body weight gain. A significant increase (p 0.01 or 0.05) in malformations was observed at 500 and 750 mg/kg and consisted of external (anasarca, anal atresia, the latter considered not to be dose-related), soft tissue (persistent truncus arteriosus) and skeletal findings (fusion or absence of cervical arches were most prominent).

In rabbits, gavage administration of 55, 175 or 540 mg/kg bw/day NMP on days 6–18 of gestation caused developmental toxicity as evidenced by post-implantation loss, altered foetal morphology, and increased incidences of cardiovascular and skull malformations at 540 mg/kg body weight per day (GAF, 1991). The NOAEL for developmental toxicity was 175 mg/kg bw/day. Maternal toxicity as evidenced by decreased body weight gain was apparent at 175 and 540 mg/kg bw/day.

In mice, oral doses of 0, 1055, or 2637 mg/kg bw/day on days 11–15 of gestation caused an increase in resorptions, increased incidence of runts, diminished foetal weight and length, and an increased rate of malformations including as cleft palate at the highest dose level (BASF, 1970, cited in Greim, 1998). The lower dose level caused no apparent foetotoxicity, however insufficient detail was provided on maternal toxicity in this study.

7.7.2.5. Dermal

Pregnant rats were administered daily dermal doses of 0, 75, 237, or 750 mg/kg bw/day NMP on days 6-15 of gestation (Becci et al., 1982). Maternal and developmental toxicity were evident at the highest dose level, evidenced by decreased maternal body weight gain, increased resorptions and decreased foetal body weight, skeletal abnormalities

including missing sternebrae and fused/split/extra ribs, incomplete closing of the skull, incomplete ossification of vertebrae, fused atlas and occipital bones, and reduced or incomplete hyoid bone on day 20 of gestation. There was no increase in the incidence of soft tissue anomalies. The NOAEL for maternal and developmental toxicity was 237 mg/kg body weight per day.

In rabbits dermally exposed to 0, 100, 300, or 1000 mg/kg bw/day NMP as a 40% aqueous solution for 6 h/day on days 7–19 post-insemination, slight foetal toxicity as evidenced by an increased occurrence of supernumerary 13th ribs was apparent at 1000 mg/kg bw/day (BASF, 1993a, cited in IPCS, 2001). There were no signs of maternal toxicity. The NOAEL for maternal and developmental toxicity was 300 mg/kg body weight per day.

7.7.2.6. Other routes

Intraperitoneal studies in mice have shown evidence of developmental toxicity of NMP, evidenced by exencephaly, open eyelids, microphthalmia, cleft palate, oligodactyly, shortened or kinked tails, fusions and curvature of neck and chest vertebrae, and fusion of sternebrae and ribs (BASF, 1970, cited in Greim, 1998; Schmidt, 1976). Conclusions cannot be drawn from these studies, due to the inappropriate method of exposure and lack of detail on maternal toxicity.

7.8.3. In vitro data

Flick and coworkers (Flick et al., 2009) studied the toxicity of NMP and 3 metabolites (5-HNMP, MSI, 2-HMSI) in an *in vitro* culture system comprising whole rat embryos. The embryos were exposed to up to 0.06% NMP, equivalent to 0.006 mol/l in the medium, and up to 0.44% 5-HNMP, MSI or 2-HMSI on days 9.5-11.5 of pregnancy. The results showed that exposure to NMP (≥0.03% or 0.003 mol/l) and 5-HNMP (≥0.10%) cause foetal injuries comprising abnormalities of the cranium, abnormal development of the second visceral arch and delayed anterior neuropore closure. On this basis the authors concluded that NMP and 5-HNMP could be classified as weak teratogens, and that 2-HMSI and MSI have no teratogenic effects. [*Note:* The extremely high NMP concentrations used in this study should be recognised, 0.003 mol/l equalling 300 mg/l. In the human biomonitoring study of Xiaofei et al. (2000), an 8 h TWA exposure to 0.5 ppm resulted in a plasma concentration of 0.1 mg NMP per litre. Upon linear extrapolation, a human exposure (8 h TWA) to the proposed OEL of 10 ppm would therefore result in a plasma NMP concentration of only 2 mg/l. Therefore, the findings of this study cannot be related to any human exposure condition.]

7.9. Mode of action and adverse outcome pathway considerations

NMP is an aprotic solvent miscible with both water and lipophilic solvents. Owing to these properties, it has a high potential to penetrate the human skin barrier and to act systemically.

NMP has a characteristic amine-like ”fishy” odour. In terms of criteria of the current SCOEL “Methodology for the Derivation of Occupational Exposure Limits” (version 7, June 2013; chapter 3.1) this effect in humans is very slight, leading to an awareness of exposure. Such an effect is not considered as being adverse for workers.

The key toxicity observed in humans is local irritation, based on data both in humans (upper airways) and in experimental animals (lung). Workers exposed to up to 280 mg/m^3 NMP at 80 °C reported severe eye irritation and headache (Beaulieu and Schmerber, 1991), although an exposure–response relationship could not be established.

A carefully designed human volunteer study (van Thriel et al., 2007) has indicated the absence of irritation at mean airborne concentrations up to 80 mg/m^3 [20 ppm] (with 15 min peaks of 160 mg/m^3 [40 ppm]).

Experimentally, there are a number of animal studies by the inhalation route, which is the generally preferred exposure route to derive an OEL (SCOEL Methodology, chapter 3.3.2). A common effect across most of these studies is slight retardation in body weight gain. Considering this effect (among others), in a 90-day rat inhalation study (BASF 1994, cited in Greim, 1998; 7.3.2) the NOAEC was assessed to be 500 mg/m^3 [125 ppm].

Upon a 2 years inhalation study in rats (Lee et al., 1987) there was minimal inflammation in the lung at the highest exposure level of 400 mg/m^3 (100 ppm). This effect appears generally compatible with the local irritating properties of NMP. Also, at this highest concentration male rats showed slight reduction in mean body weight. It must be noted that there was a wide dose-spacing in the study of the 2-years study of Lee et al, with the next lower concentration (with no such effect) at 40 mg/m^3 [10 ppm].

The central studies are three rat developmental toxicity studies upon inhalation. Slight retardation in foetal and pup weight gain was reported in two studies (Solomon et al., 1995; Saillenfait et al., 2003; 7.8.2), but not in a third study (Lee et al., 1987):

(1) Saillenfait et al. (2003) reported on reduced food consumption, reduced maternal body weight gain, and reduced foetal weight at 120 ppm [480 mg/m^3]. At 60 ppm [240 mg/m^3] there was only a slight reduction in maternal body weight gain on days 6-13 of gestation, but no significant later reduction on days 13-21.

(2) Solomon et al. (1995) reported a very slight decrease in foetal weight in the F1 offspring at 116 ppm [464 mg/m^3], with NOAEC being 51 ppm [204 mg/m^3]. This slight effect also appeared at birth among the pups of the reproductive phase where it persisted for 21 days after birth, when NMP inhalation of the mother ceased. Thereafter, the body weight of the offspring was within the range of the control values. [A low palatability of the mother's milk might be a factor contributing to this effect.] Again, no developmental effects appeared in the 10 ppm [41 mg/m^3] or 51 ppm [210 mg/m^3] groups.

(3) In the rat developmental toxicity study by Lee et al. (1987) exposure to 100 [24 ppm] or 360 mg/m^3 [87 ppm] (6 h/d on days 6 through 15 of gestation) did not affect either the outcome of pregnancy or the embryonal growth rate.

Thus, the results of all these three developmental toxicity studies show only very slight or no effects at doses up to 120 ppm. Considering the overall weight of evidence, there might be a tentative, borderline and transient and reversible effect on the pup weight, with a NOAEC of 51 ppm, based on the study of Solomon et al. (1995). However, if such an effect would be assumed to exist, the degree of adversity for humans appears to be very low, as the effect is slight/borderline and fully reversible. It is not supported by all inhalation studies performed. In the study by Saillenfait et al, there was some decrease in foetal BW at 120 ppm, but in the presence of reduced maternal food consumption and small reductions in maternal body weight. As the studies by Lee et al (1987) and by Solomon et al (1995) were performed at the same laboratory, one would expect no relevant methodological differences between these studies.

In summary, for local irritancy in humans a NOAEC of 20 ppm (highest concentration tested, with peak concentrations of 40 ppm, van Thriel et al., 2007) is well established. Experimentally, a NOAEC of 51 ppm is only related to a borderline, transient and reversible effect on pup weight, with a very low toxicological significance for workers and humans in general.

7.10. Lack of specific scientific information

Overall, for NMP, a very well investigated chemical substance. The specific scientific information currently available is considered to be adequate for the recommendation of an OEL.

8. GROUPS AT EXTRA RISK

NMP is largely metabolised *via* CYP2E1 (7.1.1; 7.1.2), an isoform that displays some metabolic variability in humans (Bolt et al., 2003). However, the biological relevance of this phenomenon for solvent metabolism in workers, if any, is controversial (Lucas et al., 2001; Haufroid et al., 2002). Therefore, no practical conclusions can be drawn, as far as specific individual situations of a potential metabolic hyper-susceptibility to NMP are concerned.

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