The MAK Collection for Occupational Health and Safety

N-Methyl-2-pyrrolidone (vapour)

MAK Value Documentation, addendum – Translation of the German version from 2019

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N-Methyl-2-pyrrolidone (vapour)[1)] / 1-Methylpyrrolidin-2-one (vapour)

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of *N*-methyl-2-pyrrolidone [872-50-4].
The critical effects in rats are irritation of the upper respiratory tract, foetotoxicity and neurotoxicity. Male volunteers did not show adverse irritant or cognitive effects after 8-hour exposure to *N*-methyl-2-pyrrolidone at a concentration of 20 ml/m³ with and without exposure peaks of 40 ml/m³ and with physical workload.
A MAK value of 20 ml/m³ had been set for *N*-methyl-2-pyrrolidone vapour. This value has now been confirmed even considering the increased respiratory volume at the workplace (see List of MAK and BAT Values, Sections I b and I c).
Exposure to *N*-methyl-2-pyrrolidone aerosols increases the intake by dermal absorption but there is no information indicating by how much. Therefore, the MAK value is only valid for the vapour of *N*-methyl-2-pyrrolidone and exposure to aerosols or vapour/aerosol mixtures must be controlled by biomonitoring methods.
As the critical effect of *N*-methyl-2-pyrrolidone is assumed to be local, Peak Limitation Category I has been designated. The excursion factor of 2 is retained.

Keywords

N-methyl-2-pyrrolidone; 1-methylazacyclopentan-2-one; *N*-methyl-2-ketopyrrolidine; *N*-methyl-2-oxypyrrolidine; *N*-methylpyrrolidinone; *N*-methyl-2-pyrrolidinone; 1-methyl-5-pyrrolidinone; *N*-methylpyrrolidone; 1-methyl-2-pyrrolidone; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; reproductive toxicity; fertility; developmental toxicity; peak limitation; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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1) The substance can occur simultaneously as vapour and aerosol.

N-Methyl-2-pyrrolidone (vapour)[1)]

[872-50-4]

Supplement 2019

MAK value (1994)	**20 ml/m³ (ppm) ≙ 82 mg/m³**
Peak limitation (2018)	**Category I, excursion factor 2**
Absorption through the skin (1992)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1994)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (2007)	**150 mg 5-hydroxy-*N*-methyl-2-pyrrolidone/l urine**
1 ml/m³ (ppm) ≙ 4.11 mg/m³	**1 mg/m³ ≙ 0.243 ml/m³ (ppm)**

Documentation for *N*-methyl-2-pyrrolidone was published in 1994 (documentation "*N*-Methyl-2-pyrrolidone" 1998), followed by a supplement on peak limitation in 2002 (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010a), a re-evaluation in 2006 (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b) and a supplement on prenatal toxicity in 2012 (supplement "N-Methyl-2-pyrrolidon" 2012, available in German only).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. This does not apply to gases and vapours with a blood:air partition coefficient < 5 (see List of MAK and BAT Values, Sections I b and I c). The blood:air partition coefficient of *N*-methyl-2-pyrrolidone is calculated to be about 88 600 using the formula of Buist et al. (2012). This supplement evaluates whether the MAK value of *N*-methyl-2-pyrrolidone needs to be re-assessed as a result of the higher respiratory volume at the workplace.

The vapour pressure of *N*-methyl-2-pyrrolidone and the vapour-to-aerosol ratio are dependent upon the level of relative humidity in the air and the temperature. For

1) The substance can occur simultaneously as vapour and aerosol.

example, at room temperature and 60% relative humidity, *N*-methyl-2-pyrrolidone forms an aerosol at concentrations of about 412 mg/m³ (100 ml/m³) and above. At 100% relative humidity, *N*-methyl-2-pyrrolidone occurs only in aerosol form. At 0% relative humidity, the vapour becomes saturated only at about 1318 mg/m³ (320 ml/m³). Therefore, aerosols are not expected to form when exposure at the workplace does not exceed the MAK value of 82 mg/m³ (20 ml/m³) and the humidity remains within the usual range. However, it needs to be taken into account that aerosols always occur when *N*-methyl-2-pyrrolidone is sprayed. As a result of the low vapour pressure of *N*-methyl-2-pyrrolidone, the highest technically achievable concentrations of *N*-methyl-2-pyrrolidone vapour are in the range from 120 to 140 ml/m³ (documentation "*N*-Methyl-2-pyrrolidone" 1998; supplement "N-Methyl-2-pyrrolidon" 2012, available in German only).

Toxicokinetics and Metabolism

Absorption, distribution, elimination

A series of studies have shown that *N*-methyl-2-pyrrolidone is readily absorbed after inhalation, oral and dermal exposure. This was described in detail in the 2006 supplement (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b) and has been confirmed by other studies; these are discussed below.

In a random sample of 56 persons taken from the general population, metabolites of *N*-methyl-2-pyrrolidone were found in more than 96% of the urine samples. The median, 95th percentile and maximum values of the metabolite 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP) were 69.5 µg/l, 337.0 µg/l and 620.0 µg/l, respectively; the corresponding values of the metabolite 2-hydroxy-*N*-methylsuccinimide (2-HMSI) were 63.5 µg/l, 200.4 µg/l and 256.2 µg/l, respectively. According to the authors, the high incidence of *N*-methyl-2-pyrrolidone in the urine of the general population, at low overall concentrations, reflects the pervasiveness of this substance in the environment (Schindler et al. 2012). It was estimated that the daily intake level for *N*-methyl-2-pyrrolidone of the general population is almost 3 µg/kg body weight and day (Ulrich et al. 2018).

An inhalation study determined that 90% of the substance was absorbed by inhalation (88%–93%) after 8-hour exposure of volunteers to an *N*-methyl-2-pyrrolidone concentration of 50 mg/m³ (about 12 ml/m³) (Åkesson and Jönsson 2000).

After 6-hour exposure of rats to *N*-methyl-2-pyrrolidone vapour concentrations of 10 or 100 ml/m³, absorption of the substance via inhalation amounted to 7.3% and 9.5%, respectively (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b). These values refer to the percentage of the total amount administered that was absorbed by the animals. However, the total amount administered includes also the fraction remaining in the inhalation apparatus and in the syringe (about 30%, respectively). The actual fraction absorbed by inhalation, i.e. the difference between the concentrations in the inhaled and exhaled air, was not measured.

To identify potential differences in absorption after exposure to *N*-methyl-2-pyrrolidone in dry (24%–33% humidity) or humid air (68%–88% humidity), 6 male volunteers were exposed to *N*-methyl-2-pyrrolidone concentrations of 0 or 20 mg/m³ (about 5 ml/m³) for 8 hours at rest. Blood samples were taken before exposure and

2, 4, 6, 8, 10, 12, 24, 32, 48 and 72 hours after the beginning of exposure. Total urine was collected up to 120 hours after the beginning of exposure. The amount of *N*-methyl-2-pyrrolidone and its metabolites 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP), 2-hydroxy-*N*-methylsuccinimide (2-HMSI), *N*-methylsuccinimide (MSI) and 2-pyrrolidone excreted with the urine was 7% higher after exposure to *N*-methyl-2-pyrrolidone in humid air than after exposure in dry air; however, the difference was not statistically significant. There were large individual differences, particularly after exposure to *N*-methyl-2-pyrrolidone in humid air (excretion 5.0–17 µmol *N*-methyl-2-pyrrolidone (about 0.5–1.7 mg), AUC (area under the curve) 58–313 µmol *N*-methyl-2-pyrrolidone × hour/l urine (about 5.75–31.03 mg × hour/l)). Peak concentrations of *N*-methyl-2-pyrrolidone in plasma were 10 (9.2–12) and 9.7 (5.2–32) µmol/l in dry or humid air, respectively. Under both conditions, the peak urinary concentrations were 15 µmol/l (about 1.73 mg/l) for 5-HNMP and 5.0 µmol/l (0.57 mg/l) for MSI. The values determined for 2-HMSI revealed slight differences (dry: 4.8; humid: 4.4 µmol 2-HMSI/l (about 0.62 or 0.57 mg/l, respectively)) (Carnerup et al. 2006). The fact that significant differences were not found under the two exposure conditions indicates that the higher level of humidity prevented the formation of aerosol at the concentrations tested (Umweltbundesamt 2015), as this would have increased uptake as a result of the additional amounts absorbed through the skin. An *N*-methyl-2-pyrrolidone concentration in plasma of 10 µmol/l is equivalent to about 1 mg/l plasma.

Exposure of 6 male volunteers to *N*-methyl-2-pyrrolidone concentrations of 10, 25 or 50 mg/m^3 (about 2.5, 6, 13 ml/m^3) for 8 hours at rest resulted in *N*-methyl-2-pyrrolidone levels in plasma of 0.33 mg/l (0.20–4.3 mg/l), 0.99 mg/l (0.44–2.2 mg/l) and 1.6 mg/l (1.2–2.4 mg/l), respectively, at the end of exposure (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b; Åkesson and Paulsson 1997). Exposure was probably to vapour only; aerosols are not expected to occur at these concentrations and with the procedure used.

Data for 8 male volunteers demonstrated that exposure to 20 ml/m^3 (2 × 4 hours) leads to an average plasma concentration of *N*-methyl-2-pyrrolidone of 1.6 mg/l. The respective concentrations were 0.2 and 0.8 mg/l after exposure to 2.5 and 10 ml/m^3 (Poet et al. 2016).

By interpolating these data, exposure to an *N*-methyl-2-pyrrolidone concentration of 5 ml/m^3 would lead to an *N*-methyl-2-pyrrolidone concentration in plasma of 0.4 mg/l. The concentrations in plasma determined by Carnerup et al. (2006) after exposure to about 5 ml/m^3 (20 mg/m^3) were more than twice as high at 1 mg/l plasma. This is confirmed by the data of Åkesson and Paulsson (1997). The reason why the results differ remains unclear. There are greater interindividual variations in the data from Carnerup et al. (2006) and Åkesson and Paulsson (1997) than in the data for the 8 male volunteers compiled by Poet et al. (2016) in Table 3.

The metabolite levels in the urine of 14 workers of an automobile company with exposure to *N*-methyl-2-pyrrolidone and 9 workers without exposure were analysed. The median values for the metabolites 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP) and 2-hydroxy-*N*-methylsuccinimide (2-HMSI) in the post-shift urine of exposed workers were 0.91 and 0.52 mg/g creatinine, respectively, while the metabolite levels in the urine of the controls were below the limit of detection of 0.023 mg/l urine for 5-HNMP and 0.015 mg/l for 2-HMSI. The maximum urinary level of 5-HNMP of 8.31 mg/g creatinine was determined after the cleaning of the spray booth. The exposure concentrations were not determined (Meier et al. 2013).

In another study with 207 male workers from 21 companies in Switzerland, 91 of the workers were exposed to *N*-methyl-2-pyrrolidone during graffiti removal or while performing other activities that were not described in more detail. Determinations of individual exposure levels yielded a median *N*-methyl-2-pyrrolidone concentration of 0.18 mg/m³ (0.002–6.99 mg/m³). At the end of the shift, urinary levels of 0.6 mg/l (0.1–29.0 mg/l) were determined for the metabolite 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP) and 0.8 mg/l (0.2–23.3 mg/l) for the metabolite 2-hydroxy-*N*-methylsuccinimide (2-HMSI) (unexposed workers: 0.1 mg/l (0.1–0.8 mg/l) for 5-HNMP and 0.3 mg/l (0.1–1.5 mg/l) for 2-HMSI). Determinations made pre-shift yielded concentrations of 0.45 mg/l (0.1–22.90 mg/l) for the metabolite 5-HNMP and 1.55 mg/l (0.1–58.0 mg/l) for the metabolite 2-HMSI (unexposed workers: 0.1 mg/l (0.1–0.6 mg/l) for 5-HNMP and 0.3 mg/l (0.1–2.4 mg/l) for 2-HMSI). The metabolite levels in the urine adjusted to creatinine did not significantly correlate with exposure. The authors concluded from the findings that, at low levels of exposure, the 2-HMSI level per litre of urine is a more reliable indicator of exposure to *N*-methyl-2-pyrrolidone (Haufroid et al. 2014).

After groups of 42 female rats were given a single gavage dose of 125 or 500 mg/kg body weight, the levels of *N*-methyl-2-pyrrolidone, 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP), *N*-methylsuccinimide (MSI) and 2-hydroxy-*N*-methylsuccinimide (2-HMSI) in plasma and urine were quantified up to 72 hours after exposure. Of the dose administered, 48% was excreted with the urine as 5-HNMP and 2%–5% as 2-HMSI; overall 53%–59% was recovered in the urine. The highest concentrations obtained in plasma were 1.2 and 6.9 mmol/l (about 119 and 683 mg/l, after 1 and 2 hours, respectively) for *N*-methyl-2-pyrrolidone, 0.42 and 0.76 mmol/l (about 48.4 and 87.5 mg/l, after 4 and 12 hours, respectively) for 5-HNMP, 0.07 and 0.31 mmol/l (about 7.9 and 35.1 mg/l, after 4 and 12 hours, respectively) for MSI and 0.02 and 0.05 mmol/l (about 2.6 and 6.5 mg/l, each after 12 hours) for 2-HMSI. Depending upon the metabolite, these maximum concentrations occurred at different time points. In groups of 10 female rats given 3 gavage doses of 125 or 500 mg/kg body weight at 24-hour intervals, 48%–58% was excreted with the urine as 5-HNMP and 1.5%–4.2% as 2-HMSI after 5 days; overall, 62% and 50%, respectively, of the dose administered was recovered in the urine (Carnerup et al. 2005).

The highest concentrations in the tissues and organs of 26 male and 20 female Wistar rats given a single dose of ^{14}C-*N*-methyl-2-pyrrolidone of 250 mg/kg body weight by intraperitoneal injection were reached after 4 hours; the greatest accumulations were observed in the muscles, the adipose tissue, the liver and the testes. About 80% of the radioactivity was recovered in the urine and about 5% in the faeces 72 hours after administration. No differences were found between the male and female animals (Sitarek and Kilanowicz 2006).

In rats, 50 mg/l plasma was determined 6 hours after nose-only exposure to 100 ml/m³ (about 400 mg/m³) (Poet et al. 2016). Assuming linear extrapolation, exposure to 20 ml/m³ would lead to an *N*-methyl-2-pyrrolidone concentration in the plasma of rats of 10 mg/l; in contrast, the *N*-methyl-2-pyrrolidone concentration in the plasma of volunteers was 1.6 mg/l plasma (Poet et al. 2016). Exposure to the same external concentration thus results in a significantly lower burden in humans than in rats.

PBPK model

On the basis of the findings from developmental toxicity studies in rats with inhalation exposure, a point of departure for decreased body weights in foetuses and offspring was defined using a benchmark calculation. A human equivalent concentration of 480 ml/m³ was calculated for exposure at the workplace using PBPK modelling. The authors concluded that an adequate level of protection is provided by the internationally recognized exposure limits for *N*-methyl-2-pyrrolidone vapour of 10 to 20 ml/m³ (supplement "N-Methyl-2-pyrrolidon" 2012, available in German only; Poet et al. 2010).

An improved PBPK model for *N*-methyl-2-pyrrolidone in humans was used to calculate a human equivalent concentration that corresponds to the internal dose point of departure value of rats. For this, a benchmark dose for the decrease in the body weights of the offspring of rats observed in the study of Solomon et al. (1995) was calculated and an AUC of 470 mg/l × hour was derived for *N*-methyl-2-pyrrolidone in plasma. This is approximately equivalent to exposure to 75 ml/m³ by inhalation for 6 hours a day. In humans, this AUC value is reached after inhalation and dermal exposure to the vapour at a concentration of 490 ml/m³ (Poet et al. 2016). This indicates that the body burden of humans from *N*-methyl-2-pyrrolidone in the blood is less than that of rats after exposure to the same external concentration and the same AUC is reached in humans only after exposure to markedly higher concentrations.

Effects in Humans

Single exposures

To study uptake and elimination, 15 healthy male non-smokers were exposed 8 hours to *N*-methyl-2-pyrrolidone vapour at constant concentrations of 10, 40 or 80 mg/m³ (2.4, 9.6, 19.2 ml/m³) or to a concentration of 25 mg/m³ with 4 exposure peaks of 160 mg/m³ (about 6–40 ml/m³, 15-minute exposure peaks, time-weighted average of 72 mg/m³ (about 17.5 ml/m³)). The volunteers were exposed whole-body in an exposure chamber. All exposures were carried out both without and with temporary physical activity on a bicycle ergometer (6 × 10 minutes at 75 watts). A marked increase in the amount of the metabolites 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP) and 2-hydroxy-*N*-methylsuccinimide (2-HMSI) excreted was observed with increasing exposure concentrations of *N*-methyl-2-pyrrolidone. Exposure to 82 mg/m³ (= MAK value) resulted in urinary concentrations of 2.4 mg/l of *N*-methyl-2-pyrrolidone, 117 mg/g creatinine of 5-HNMP and 32 mg/g creatinine of 2-HMSI. Additional physical activity increased the burden by about one third to 3.4 mg/l urine of *N*-methyl-2-pyrrolidone, 150 mg/g creatinine of 5-HNMP and 44 mg/g creatinine of 2-HMSI. Concentrations of up to 160 mg/m³ (about 40 ml/m³) caused olfactory effects and minimal trigeminal sensations (for example nasal irritation). Volunteers carried out neuropsychological tests to simulate mental workload (MWL). Minimal nasal irritation, which increased with the concentration, was reported by volunteers under mental workload conditions, but not during physical activity. Acute effects on the central nervous system (CNS) can therefore be ruled out. The data do not

indicate that exposure to *N*-methyl-2-pyrrolidone leads to cognitive impairment (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b; Bader et al. 2007; van Thriel et al. 2007).

In an additional experiment to determine the purely dermal uptake of *N*-methyl-2-pyrrolidone from the gas phase, 16 male volunteers were exposed to *N*-methyl-2-pyrrolidone vapour at a constant concentration of 80 mg/m³ (about 20 ml/m³) in an exposure chamber while the uptake of *N*-methyl-2-pyrrolidone by inhalation was prevented by a face mask that provided filtered fresh air. After 8 hours, it was determined that 71 ± 8 mg *N*-methyl-2-pyrrolidone equivalents were absorbed percutaneously, while 169 ± 15 mg *N*-methyl-2-pyrrolidone equivalents were absorbed after whole-body exposure without a face mask. After physical activity (75 watts/1 hour), the concentration of *N*-methyl-2-pyrrolidone equivalents in the urine was 79 ± 8 mg (only percutaneous exposure) and 238 ± 18 mg (whole-body exposure) of *N*-methyl-2-pyrrolidone. Uptake exclusively through the skin did not significantly differ after respiration at rest or during physical activity. Therefore, the contribution of dermal absorption to the total uptake was up to 42% at rest and up to 33% with a moderate workload (Bader et al. 2008). Under MAK conditions (respiratory volume of 10 m³/8 hours ≙ 50 watts), 420 mg *N*-methyl-2-pyrrolidone equivalents would be absorbed by inhalation (difference of the *N*-methyl-2-pyrrolidone equivalents absorbed by inhalation only (= 61 mg) × 50/75 watts × 8 hours and addition of 98 mg *N*-methyl-2-pyrrolidone equivalents absorbed by inhalation only during respiration at rest). Assuming that absorption through the skin does in fact increase during physical activity, even though no significant difference was observed under experimental conditions, then the amount absorbed only through the skin during exposure at the level of the MAK value would be 27% of the amount absorbed via inhalation and 21% of the total uptake (8 mg *N*-methyl-2-pyrrolidone equivalents × 50/75 watts × 8 hours + 71 mg *N*-methyl-2-pyrrolidone equivalents).

Repeated exposure

Irritation was not observed in volunteers after exposure to *N*-methyl-2-pyrrolidone concentrations of 0, 10, 25 or 50 mg/m³ (about 2.4, 6.1 or 12.2 ml/m³) for 8 hours on 4 days. Blood tests did not reveal unusual findings. Only 2% was excreted via the urine as unchanged *N*-methyl-2-pyrrolidone (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b; Åkesson and Paulsson 1997). The urinary concentrations of the metabolites of *N*-methyl-2-pyrrolidone were not reported.

In two microelectronics companies, an unpleasant smell, headaches and chronic eye irritation were reported after exposure to *N*-methyl-2-pyrrolidone (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b; Beaulieu and Schmerber 1991). However, the methods used to determine the exposure levels were inadequately described. Therefore, a NOAEC (no observed adverse effect concentration) or LOAEC (lowest observed adverse effect concentration) cannot be derived from this study. The study is not used for the derivation of the MAK value; however, its findings are regarded as evidence of potential irritation.

Personal air monitoring and stationary determinations of the exposure levels for 5 workers of an adhesive-producing company yielded *N*-methyl-2-pyrrolidone concentrations of 0.2–3 mg/m³ (about 0.05–0.75 ml/m³). The 8-hour time-weighted

average increased to 6.6 mg/m³ (about 1.6 ml/m³) with peaks of 18.7 mg/m³ (about 4.5 ml/m³) and 15.5 mg/m³ (about 3.8 ml/m³) with peaks (5 minutes) of 85 mg/m³ (about 20.7 ml/m³) in 2 other workers carrying out manual cleaning activities. The post-shift urinary data for the 5 workers were < 0.125 mg/g creatinine of *N*-methyl-2-pyrrolidone and < 15 mg/g creatinine of 5-hydroxy-*N*-methyl-2-pyrrolidone and < 2.3 mg/g creatinine of 2-hydroxy-*N*-methylsuccinimide. The post-shift urinary concentrations of the 2 workers who carried out cleaning activities increased to 0.472 and 0.711 mg/g creatinine of *N*-methyl-2-pyrrolidone and 33.5 and 124 mg/g creatinine of 5-hydroxy-*N*-methyl-2-pyrrolidone and 1.6 and 14.7 mg/g creatinine of 2-hydroxy-*N*-methylsuccinimide. The cleaning worker with the highest levels reported irritation of the eyes and upper respiratory tract and a sore throat, stomach ache and a headache. His level of body burden was significantly higher than would be expected based on the concentrations in the air. The authors attributed this to increased absorption through the skin resulting from the manual cleaning of the mixing vessel using a resin solvent containing *N*-methyl-2-pyrrolidone and inadequate occupational safety measures. In addition, the *N*-methyl-2-pyrrolidone concentration in the vessel may have been higher than the maximum levels determined directly outside of the vessel, which would have led to higher levels of inhalation exposure. The post-shift urinary levels of the 3 inspectors who were on site were below the limit of detection after 4 hours and were 9.0 and 14.6 mg/g creatinine of 5-hydroxy-*N*-methyl-2-pyrrolidone and 2.3 mg/g creatinine of 2-hydroxy-*N*-methylsuccinimide after 6 or 8 hours (Bader 2017; Bader et al. 2006).

The exposure of 15 workers in a Japanese company to *N*-methyl-2-pyrrolidone concentrations of 0.14–0.26 ml/m³ resulted in *N*-methyl-2-pyrrolidone concentrations of 0.17–0.22 mg/l in the urine. *N*-Methyl-2-pyrrolidone was not detected in the urine of 15 unexposed workers (controls). No differences were determined between the exposed workers and the controls as regards clinical data, motor and sensory abilities and neurological effects (Nishimura et al. 2009).

In another study with 207 male workers from 21 companies in Switzerland, 91 of the workers were exposed to *N*-methyl-2-pyrrolidone during graffiti removal or other activities that were not described in more detail. Personal air monitoring yielded a median concentration of *N*-methyl-2-pyrrolidone (airborne *N*-methyl-2-pyrrolidone) of 0.18 mg/m³ (0.002–6.99 mg/m³). No adverse health effects were found in the lungs, kidneys, skin, mucosa, nervous system, liver or haematopoietic system of exposed workers after clinical examination (semi-structured clinical examination) (see also Section "Absorption, distribution, elimination"; Haufroid et al. 2014).

Reproductive toxicity

A 23-year-old laboratory worker was occupationally exposed to *N*-methyl-2-pyrrolidone during the first 20 weeks of pregnancy. A spill during week 16 of pregnancy resulted in contamination of her clothing and skin. In the following 4 days, the affected woman experienced nausea, headaches and malaise. There are no data for the level of exposure. Delayed embryonic development was diagnosed in gestation week 25 and the child was stillborn in week 31. The authors ruled out any other risk factors (pre-existing conditions, exposure to other reproductive toxins, chromosomal abnormalities of the foetus, organ abnormalities of the foetus) (Solomon et al. 1996).

Perinatal mortality in the general population in the United States was reported to be 9.1/1000 (Bower 1997).

Local effects on skin and mucous membranes

In 50 test persons treated repeatedly with *N*-methyl-2-pyrrolidone in a patch test, neither irritation nor signs of sensitization were determined after 24-hour dermal exposure (no other details). In another publication, skin irritation and contact dermatitis were described in electronics industry workers who were dermally exposed to liquid *N*-methyl-2-pyrrolidone for 2 days (8 hours/day) (documentation "*N*-Methyl-2-pyrrolidone" 1998; Lee et al. 1987; Leira et al. 1992).

After using *N*-methyl-2-pyrrolidone for cleaning activities, irritative contact dermatitis was reported in 3 workers of a company which manufactured child car seats (Jungbauer et al. 2001).

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

The LC_{50} in rats was 3100–8800 mg/m³ (aerosol) (documentation "*N*-Methyl-2-pyrrolidone" 1998).

Oral administration

Depending upon the species, the LD_{50} values were in the range of 3–7 g/kg body weight. Narcotic effects and unspecific symptoms were observed (documentation "*N*-Methyl-2-pyrrolidone" 1998).

Subacute, subchronic and chronic toxicity

Inhalation

There are no new data available.

In a teratogenicity study with whole-body exposure of groups of 25 female Crl:CD rats to *N*-methyl-2-pyrrolidone aerosols at concentrations of 0, 100 or 360 mg/m³ (about 0, 24 or 88 ml/m³) for 6 hours a day for 10 days, sporadic lethargy and irregular breathing were observed during the first 3 days of exposure at concentrations as low as 100 mg/m³. These effects were no longer observed after additional days of exposure and during the 10-day observation period. In groups of 15 female and 15 male Crl:CD rats exposed whole-body to an aerosol/vapour mixture at concentrations of 0, 100, 500 or 1000 mg/m³ (about 0, 24, 122 or 240 ml/m³) for 6 hours a day for 4 weeks, lethargy and irregular breathing were observed after 3–4 hours of exposure even at the lowest concentration of 100 mg/m³; these effects lasted until the end of exposure. The effects were reversible 30–45 minutes after the end of exposure in all

animals of the 100 and 500 mg/m³ concentration groups, but only in a few animals of the high exposure group. In addition, after exposure to the *N*-methyl-2-pyrrolidone concentration of 1000 mg/m³, mortality was increased (8/30 died, 5/30 sacrificed in extremis) within 10 days and damage to the lungs, bone marrow and lymphatic organs and changes to the blood count were reported. In a 2-year carcinogenicity study with whole-body exposure via inhalation, 120 male and 120 female Crl:CD rats were exposed to *N*-methyl-2-pyrrolidone vapour concentrations of 0, 40 or 400 mg/m³ (about 0, 10 or 100 ml/m³) 5 times a week, for 6 hours a day. The authors did not find any significant histopathological effects. The incidence of acute focal alveolitis (lowest severity grade) was increased in the males (controls: 2/82; 400 mg/m³: 10/85); no increased incidence was observed in the females (controls: 13/83; 400 mg/m³: 12/82). In addition, a slight increase in hyperplasia of the alveolar cells with aggregated macrophages was observed (controls: 0/84, 400 mg/m³: 4/84 males; controls: 0/85, 400 mg/m³: 9/84 females). After 18 months, an increase in the haematocrit level, alkaline phosphatase and the urine volume and a slight, 6% reduction in body weight in comparison with that of the control animals was found in the male rats of the high concentration group. CNS effects were not described (documentation "*N*-Methyl-2-pyrrolidone" 1998; Lee et al. 1987).

In a developmental toxicity study, groups of 10 male and 20 female Crl:CD(SD)BR rats were exposed whole-body to *N*-methyl-2-pyrrolidone vapour concentrations of 0, 10, 51 or 116 ml/m³. The animals were exposed on 7 days a week, for 6 hours a day, for at least 100 days. In the rats of the F0 generation, a diminished reaction to tapping on the cage was observed after exposure to the high concentration of 116 ml/m³. The effect was significant in comparison with the behaviour of the controls ($p \leq 0.05$). The NOAEC of this study was 51 ml/m³ (documentation "*N*-Methyl-2-pyrrolidone" 1998; DuPont 1990; Solomon et al. 1995).

Whole-body exposure of rats to *N*-methyl-2-pyrrolidone vapour at a concentration of 1750 mg/m³ (about 425 ml/m³) for 6 weeks resulted merely in slight nasal secretions (documentation "*N*-Methyl-2-pyrrolidone" 1998; BASF AG 1983). In view of the high concentration level, it can be assumed that exposure was to an aerosol/vapour mixture.

After 2-week exposures of rats to an *N*-methyl-2-pyrrolidone aerosol of 1000 mg/m³ (about 243 ml/m³), it was found that whole-body exposure was more potent than head–nose exposure. Depending upon humidity levels and thus the aerosol fraction as well as the size of the droplets, mortality was observed after whole-body exposure, but not after head–nose exposure (WHO 2001). It is to be assumed that whole-body exposure led to additional dermal and oral exposure in this study.

A comparison of the potency of *N*-methyl-2-pyrrolidone in vapour form or in the form of a vapour/aerosol mixture after whole-body exposure of rats is shown in Table 1. While exposure to the aerosol induced CNS effects at concentrations as low as 24 ml/m³ (about 100 mg/m³), CNS effects were found only at concentrations of 116 ml/m³ (about 477 mg/m³) and above after exposure to the vapour. Effects were not induced at a vapour concentration of 51 ml/m³ (about 210 mg/m³). Therefore, the aerosol appears to have a much higher potency. However, it needs to be taken into account that the aerosol studies used whole-body exposure and thus resulted in additional dermal and oral exposure.

Table 1 Comparison of the potency of *N*-methyl-2-pyrrolidone as a vapour or vapour/aerosol mixture after whole-body exposure of rats

Exposure to vapour	References	Exposure to vapour/aerosol	References
10 days NOAEC 51 ml/m³, LOAEC 116 ml/m³ aerosol formation was not investigated, foetotoxicity (body weights of F1 animals ↓), CNS effects F0 animals (slightly decreased reaction to tapping on cage)	DuPont 1990; Solomon et al. 1995	**10 days** LOAEC 100 mg/m³ (24 ml/m³) lethargy and irregular breathing (days 1–3)	Lee et al. 1987
		4 weeks LOAEC 100 mg/m³ (24 ml/m³) lethargy and irregular breathing (days 1–28) 1000 mg/m³ (240 ml/m³) lethargy and severe breathing difficulties, mortality: 8/30, morbidity: 5/30, body weights ↓, congestive oedematous lung changes, interstitial pneumonia, bone marrow hyperplasia and haemorrhage, atrophy and necrosis of thymus, spleen and lymph nodes, no effects in other tissues, neutrophils ↑, lymphocytes ↓, no changes to other haematological parameters, some of the effects reversible	Lee et al. 1987
2 years NOAEC 10 ml/m³, LOAEC 100 ml/m³ haematocrit value ↑, alkaline phosphatase ↑, urine volume ↑, body weights ↓ (6%) ♂: acute focal alveolitis* (slight) no CNS effects described	DuPont 1982; Lee et al. 1987		

* $p < 0.05$

CNS: central nervous system; LOAEC: lowest observed adverse effect concentration; NOAEC: no observed adverse effect concentration

Oral administration

Three feeding studies in rats with exposure periods of 4 weeks, 3 months or 2 years determined NOAELs (no observed adverse effect levels) of 3000–6000 mg/kg feed in the males and 3000–5000 mg/kg feed in the females. At higher doses of 7500 mg/kg feed and above, reduced body weight gains, increased relative organ weights, increased relative testis weights and atrophy and degeneration of the seminiferous tubules of the testes, liver cell hypertrophy, increased foot splay and reduced excitability (slight sedation) were observed. In addition, chronic progressive nephropathy was observed in the males, which is not considered relevant to the assessment because it is a species and sex-specific effect (supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b).

Reproductive and developmental toxicity

Fertility

Effects on the testes were described after exposure to high doses. After 13-week head–nose exposure to *N*-methyl-2-pyrrolidone at a concentration of 3000 mg/m^3, a reduction in the absolute testis weights and cell loss in the germinal epithelium of the testes were observed (documentation "*N*-Methyl-2-pyrrolidone" 1998; supplement "*N*-Methyl-2-pyrrolidone (vapour)" 2010b).

Developmental toxicity

With the exception of one study with head–nose exposure (BASF AG 1993), all other inhalation studies of developmental toxicity used whole-body exposure.

Inhalation studies of prenatal developmental toxicity found that *N*-methyl-2-pyrrolidone causes developmental delays in the offspring of rats at the maternally toxic concentration of 120 ml/m^3 and in the offspring of rabbits at the maternally non-toxic concentration of 1000 mg/m^3 (about 243 ml/m^3). An increase in malformations was not observed in any of the inhalation studies. The NOAEC for prenatal developmental toxicity was 87 ml/m^3 for rats and 122 ml/m^3 for rabbits (supplement "N-Methyl-2-pyrrolidon" 2012, available in German only; BASF AG 1993; Lee et al. 1987; Saillenfait et al. 2003).

In a multi-generation study with rats, inhalation exposure of both sexes to *N*-methyl-2-pyrrolidone at a concentration of 478 mg/m^3 (about 116 ml/m^3) resulted in reduced body weight gains in the F1 generation. The pups were not exposed together with the dams up to postnatal day 21. After weaning, the body weights of the F1 animals were at the same levels as those of the controls. In addition, signs of foetotoxicity were observed in the F2 generation. No effects were observed after exposure to a concentration of 206 mg/m^3 (about 51 ml/m^3) (documentation "*N*-Methyl-2-pyrrolidone" 1998; DuPont 1990; Solomon et al. 1995).

Other studies also observed reduced body weight gains (7%–8%) in the F1 generation after inhalation exposure of the dams to *N*-methyl-2-pyrrolidone at a concentration of 150 ml/m^3 from gestation days 7 to 20 and exposure of the dams to 165 ml/m^3 from gestation days 4 to 20 (6 hours a day, 7 days a week) (no other details; Fries et al. 1992; Hass 1990; Jakobsen and Hass 1990).

No foetotoxic effects were observed in rats exposed by inhalation to *N*-methyl-2-pyrrolidone at a concentration of 360 mg/m³ (aerosol, about 87 ml/m³) from gestation days 6 to 15 (Lee et al. 1987).

Developmental delays were found also after oral exposure to doses that were not or were only slightly maternally toxic. Maternally toxic doses induced an increased incidence of malformations after oral or dermal exposure (supplement "N-Methyl-2-pyrrolidon" 2012, available in German only).

In groups of 26 male Imp:WIST rats given gavage doses of *N*-methyl-2-pyrrolidone of 0, 100, 300 or 1000 mg/kg body weight and day, on 5 days a week, for 10 weeks, infertility and severe damage to the epithelium in the seminiferous tubules of the testes were observed at the high dose of 1000 mg/kg body weight and day. Mating with untreated female rats after exposure for 10 weeks to doses of 300 mg/kg body weight and day and above resulted in the decreased viability of the offspring in the first 4 days of life. At 80.9%, the survival index was significantly ($p < 0.05$) lower than that of the controls (94%) (Sitarek and Stetkiewicz 2008).

Female Wistar rats were given gavage doses of *N*-methyl-2-pyrrolidone of 0, 150, 450 or 1000 mg/kg body weight and day on 5 days a week beginning 2 weeks before mating and during mating, gestation and lactation. At the lowest dose of 150 mg/kg body weight and day and above, the viability of the offspring was significantly ($p < 0.05$) reduced (survival index 86.4%) 3 weeks after birth in comparison with that of the controls (94%). At the dose of 450 mg/kg body weight and day (and doses above this), the fertility index was significantly reduced at 71.4 (controls 91.7). In the high dose group of 1000 mg/kg body weight and day, the number of living offspring was significantly lower and the number of stillbirths was increased (Sitarek et al. 2012).

Other effects

N-Methyl-2-pyrrolidone is an enhancer of the bone morphogenetic protein (BMP) and is therefore investigated as a substance that regenerates bone tissue (Miguel et al. 2009).

It was demonstrated in vitro that inflammatory processes induced by lipopolysaccharides, such as cytokine production, are inhibited in macrophages by *N*-methyl-2-pyrrolidone via the down-regulation of the NF-κB pathway (Ghayor et al. 2015).

Manifesto (MAK value/classification)

The critical effects are irritation, foetotoxic effects and CNS effects.

MAK value. The MAK value for *N*-methyl-2-pyrrolidone of 20 ml/m³ (vapour only) was established in 1994 based on a multi-generation study in rats in which no effects were induced by daily exposure to *N*-methyl-2-pyrrolidone vapour at a concentration of 51 ml/m³ (200 mg/m³) from postnatal day 34 up to weaning of the litter. Exposure to a concentration of 116 ml/m³ caused delayed weight gains in the pups that were reversible after weaning and CNS effects in F0 animals, which exhibited a significantly decreased reaction to tapping on the cage (DuPont 1990; Solomon et al. 1995).

In a 10-day and a 4-week study in rats with whole-body exposure to an *N*-methyl-2-pyrrolidone aerosol/vapour mixture at a concentration of 100 mg/m³ (about 24.3 ml/m³), lethargy (probably a CNS effect) and irregular breathing were observed after 3–4 hours (Lee et al. 1987). In the multi-generation study with whole-body exposure to *N*-methyl-2-pyrrolidone vapour, no CNS effects were observed at a concentration that was twice as high (51 ml/m³, 200 mg/m³). Also in this study, CNS effects were observed in the F0 generation at a concentration of 116 ml/m³ (Solomon et al. 1995). With respect to CNS effects, an aerosol seems to be more potent than vapour. As CNS effects require systemic absorption, one possible explanation for this difference is that the animals of the aerosol study with whole-body exposure were exposed to higher levels of the substance because liquid *N*-methyl-2-pyrrolidone was additionally absorbed through the skin and, above all, orally during grooming. In humans, about 90% of *N*-methyl-2-pyrrolidone vapour is absorbed by inhalation. Therefore, exposure to an aerosol will not result in a much higher level of uptake in humans. *N*-Methyl-2-pyrrolidone is readily absorbed through the skin. However, the amount of liquid *N*-methyl-2-pyrrolidone that is additionally absorbed through the skin after aerosol exposure cannot be determined.

The effects observed in workers after exposure to *N*-methyl-2-pyrrolidone (Beaulieu and Schmerber 1991) were regarded as evidence of sensory irritation induced by *N*-methyl-2-pyrrolidone.

In a study with 8-hour exposure of volunteers to *N*-methyl-2-pyrrolidone vapour at a constant concentration of 80 mg/m³ (about 20 ml/m³) or at peak exposure levels of up to 160 mg/m³ (about 40 ml/m³) with and without physical activity, only olfactory effects were observed, but no notable irritation. Fewer symptoms of nasal irritation were reported after exposure during physical activity than at rest. A test carried out during exposure did not yield evidence of adverse effects on cognitive performance (Bader et al. 2007; van Thriel et al. 2007).

As there are no data available for aerosol exposure in humans that are relevant for assessment and not enough data are available to compare irritation induced in rats after exposure to vapour or an aerosol, the MAK value is derived on the basis of the volunteer study that found no signs of irritation after exposure to *N*-methyl-2-pyrrolidone vapour at a concentration of 20 ml/m³. As CNS effects were not observed, it can be assumed that this value provides protection against neurotoxic effects. The MAK value of 20 ml/m³ for *N*-methyl-2-pyrrolidone only in vapour form has thus been retained. For *N*-methyl-2-pyrrolidone in aerosol form, no conclusions can be drawn as there are no data available for additional absorption through the skin.

Biomonitoring can be used to monitor exposure to *N*-methyl-2-pyrrolidone in the form of a vapour/aerosol mixture. The BAT value for 5-hydroxy-*N*-methyl-2-pyrrolidone of 150 mg/l urine, which was derived in correlation with the MAK value of 20 ml/m³, must not be exceeded (Bader et al. 2016).

Peak limitation. As a systemic and local LOAEC has not been established for humans, it has yet to be determined whether the initial effects are systemic or local. A conclusion cannot be drawn with confidence on the basis of animal studies whether systemic effects such as the effects on the CNS are the primary effects at 120 ml/m³. In a 2-year study, very slight alveolitis was observed only in male rats after exposure to 100 ml/m³.

As neither irritation nor CNS effects were induced in the volunteer study with physical activity and peak exposures of up to 40 ml/m³, *N*-methyl-2-pyrrolidone has been classified in Peak Limitation Category I with an excursion factor of 2.

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