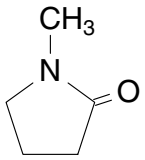
N-Methyl-2-pyrrolidone (vapour) H

Classification/MAK value:	**20 ml/m^3 (ppm)** **80 mg/m^3** **peak limitation category II,2** **pregnancy risk group C**
Classification dates from:	**1994**
Synonyms:	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
Chemical name (CAS):	1-methyl-2-pyrrolidinone
CAS number:	872-50-4
Structural formula:	
Molecular formula:	C_5H_9NO
Molecular weight:	99.13
Melting point:	–24°C
Boiling point:	204.3°C
Density at 25°C:	1.028 g/cm^3
Vapour pressure at 40°C:	1.33 hPa
Vapour pressure at 20°C:	0.32 hPa
1 ml/m^3 (ppm) = 4.12 mg/m^3	**1 mg/m^3 = 0.243 ml/m^3 (ppm)**

Note

During inhalation exposure to *N*-methyl-2-pyrrolidone and depending on the concentration, temperature and humidity, the proportions of the substance present in the air as vapour and as aerosol can vary. The vapour pressure of *N*-methyl-2-pyrrolidone and the ratio of vapour to aerosol are functions of the relative humidity and the temperature. For example, at room temperature and 60 % relative humidity, aerosol formation takes place at concentrations of about 412 mg/m^3 (100 ml/m^3) and more. At 100 % relative humidity *N*-methyl-2-pyrrolidone is found only in the aerosol form. At 0 % relative humidity vapour saturation is not achieved until the concentration reaches about 1318 mg/m^3 (320 ml/m^3). Therefore, during workplace exposures when the MAK value of 80 mg/m^3 (20 ml/m^3) is not exceeded, aerosol formation is not to be expected at normal humidities. However, during inhalation studies with exposure to low concentrations of *N*-methyl-2-pyrrolidone aerosols, part of the aerosol can become vapour and conversely, during exposure to high concentrations of *N*-methyl-2-pyrrolidone vapour, condensation can lead to the formation of aerosol-vapour mixtures. Characterization of the exposure atmosphere has, however, not been carried out in many of the inhalation studies. In studies in which the substance is inhaled in animal exposure chambers, the effective dose is affected by the aerosol fraction because *N*-methyl-2-pyrrolidone is readily absorbed through the skin and oral uptake can also not be excluded. In some of the inhalation studies this problem was avoided by the use of head-only exposure systems.

1 Toxic Effects and Modes of Action

N-Methyl-2-pyrrolidone is a water-miscible organic solvent which is readily absorbed through the skin. In animals exposed to *N*-methyl-2-pyrrolidone, a characteristic yellow discoloration of the urine develops and can serve as an indicator for the systemic availability of the substance. Uptake of single oral, dermal or inhaled acutely toxic doses of the substance results in functional central nervous disorders and central nervous depression. *N*-Methyl-2-pyrrolidone is an irritant of skin and mucous membranes.

In most studies the effects of repeated doses of *N*-methyl-2-pyrrolidone are not characteristic. In addition to the irritant effects, changes in the haematopoietic system and in the liver and kidneys are observed. High oral doses and head-only exposure to high aerosol concentrations result in testis atrophy.

Prenatal toxic effects are observed in rats and rabbits after inhalation of high concentrations of *N*-methyl-2-pyrrolidone and after oral or dermal application of high doses, even in the absence of maternal toxicity.

The available genotoxicity studies have yielded mainly negative results both *in vitro* and *in vivo*. In a dominant lethal study, however, post implantation losses were increased. In a long-term inhalation study in the rat, *N*-methyl-2-pyrrolidone did not have carcinogenic effects.

Studies of the mechanism of action of *N*-methyl-2-pyrrolidone are not available.

2 Toxicokinetics

Studies of the toxicokinetics of *N*-methyl-2-pyrrolidone in rats yielded similar results independent of whether the substance was administered by intravenous injection (Wells and Digenis 1988) or by the dermal or oral routes (Research Triangle Institute 1991). *N*-Methyl-2-pyrrolidone is absorbed rapidly and distributed in the organism; 80 % to 90 % of the dose is excreted within 24 hours, mostly as metabolites. *N*-Methyl-2-pyrrolidone doses of 45 mg/kg body weight were administered intravenously mixed with *N*-methyl-2-pyrrolidone radioisomers labelled either with ^{14}C on the ring or the methyl group, or with ^{3}H on the ring, or with ^{14}C and ^{3}H in double label studies (^{14}C:^{3}H = 1:2). No significant differences between the toxicokinetics of the various radioisomers were found.

N-Methyl-2-pyrrolidone labelled with ^{14}C on the C2 atom was administered orally in doses of 5 and 500 mg/kg body weight and dermally in doses of 0.2, 2 and 20 mg/cm^2, each on a skin area of 12 cm^2. After dermal application of 0.2 and 2 mg/cm^2, 50 % of the dose was absorbed; of the 20 mg/cm^2 dose, about 75 % was absorbed. In animals given the high dose, the maximum blood levels were achieved after about 8 hours. It is conceivable that with high doses of *N*-methyl-2-pyrrolidone the substance promotes its own absorption (Research Triangle Institute 1991). This is also suggested by the fact that *N*-methyl-2-pyrrolidone applied to the skin of the rat and mouse increases the skin penetration of hydrophilic substances *in vitro* and *in vivo* (Sasaki *et al.* 1990a, Sodicoff *et al.* 1990).

Intravenously administered *N*-methyl-2-pyrrolidone (45 mg/kg body weight) was rapidly distributed in all tissues and then, after the distribution phase, eliminated from the blood plasma with a half-life of 7 hours. Six hours after administration the largest amounts of the substance were found in the liver, bile and small intestine (2 % of the dose in each case) and in kidneys, stomach and testes (0.6 % to 0.9 %) (Wells and Digenis 1988).

The total amount excreted in the urine 12 hours after intravenous injection was 70 % of the dose; after 24 hours it had increased only slightly to 80 % (Wells and Digenis 1988). After oral administration of *N*-methyl-2-pyrrolidone doses of 5 or 500 mg/kg body weight, 84 % and 75 % of the dose, respectively, was excreted in the urine. Excretion of the higher dose was delayed during the first 8 hours (Research Triangle Institute 1991). For both studies the faecal elimination was given as 2 % to 4 % and the exhalation of $^{14}CO_2$ as 0.9 % to 1.7 % of the dose. Less than 0.1 % of the dose was exhaled as volatile organic substances.

After intravenous injection of *N*-methyl-2-pyrrolidone, the main urinary metabolite (70 % to 75 % of the dose) was identified as 5-hydroxy-*N*-methylpyrrolidone (Wells *et al.* 1992). After the high oral dose of 500 mg/kg body weight, it was deduced from the course of the excretion pattern that 60 % of the dose was excreted as 5-hydroxy-*N*-methylpyrrolidone, 10 % to 15 % as a metabolite formed from 5-hydroxy-*N*-methylpyrrolidone and 5 % as unchanged *N*-methyl-2-pyrrolidone. After the low dose of 5 mg/kg body weight, the urine contained at least four metabolites and no unchanged *N*-methyl-2-pyrrolidone. There was evidence for the production of conjugates with glu-

curonic or sulfuric acid or of metabolites in which the lactam ring had been opened. It seems likely that saturation of metabolism takes place in the dose range between 5 and 500 mg/kg body weight (Research Triangle Institute 1991).

Therefore, if the hydrolysis of *N*-methyl-2-pyrrolidone to yield *N*-methyl-γ-aminobutyric acid takes place at all, as has been postulated by other authors (Ansell and Fowler 1988), it is only to a limited extent. These authors had suggested that the central nervous effects of *N*-methyl-2-pyrrolidone seen after high doses are associated with the production of *N*-methyl-γ-aminobutyric acid.

Comparative studies of the toxicokinetics of *N*-methyl-2-pyrrolidone inhaled by pregnant (day 19 or 20 of pregnancy) and non-pregnant rats at a concentration of 150 ml/m^3 (618 mg/m^3) for 6 hours were described in an abstract. The maximum levels in the blood of the non-pregnant rats were achieved 4 hours after the end of exposure, in the pregnant rats 8 hours after the end of exposure. The *N*-methyl-2-pyrrolidone concentrations in the foetal blood were similar to those in the dams. Elimination from the blood followed zero order kinetics, whereby the elimination rate in the non-pregnant animals was twice that in the dams and foetuses (Ravn-Jonsen *et al.* 1992).

3 Effects in Man

In 50 test persons treated repeatedly with *N*-methyl-2-pyrrolidone in a patch test, neither irritation nor signs of sensitization were seen after 24-hour dermal exposures (no other details) (Lee *et al.* 1987).

On the other hand, in another publication skin irritation and contact dermatitis were described in employees from the electronic industry who were exposed dermally for 2 days (8 hours/day) to liquid *N*-methyl-2-pyrrolidone (Leira *et al.* 1992).

4 Animal Experiments and *in vitro* Studies

4.1 Acute toxicity

The average lethal doses of *N*-methyl-2-pyrrolidone (LD_{50} values) after oral and parenteral administration to a variety of animal species were of the order of several g/kg body weight, independent of the administration route (Table 1). In most cases unspecific symptoms or narcotic effects were observed.

Determination of the acute inhalation toxicity of *N*-methyl-2-pyrrolidone aerosol yielded a 4-hour LC_{50} value of more than 5100 mg/m^3 for the rat (BASF 1988). In another study which can also be assumed to have involved exposure to an aerosol, the LC_{50} values were in the range between 3100 and 8800 mg/m^3 (DuPont 1988).

Table 1. Acute toxicity of *N*-methyl-2-pyrrolidone

Administration route	Species	LD_{50} [mg/kg body weight]	References
oral	rat	3500	BASF 1963
		3600	BASF 1951
		3800	Bartsch *et al.* 1976
		4150	Ansell and Fowler 1988
		4850	BASF 1971
		7900	Meleschtschenko 1970
	mouse	4000	Weisbrod 1981
		5100	BASF 1970
		5300	Meleschtschenko 1970
		7500	Bartsch *et al.* 1976
	guinea pig	4400	Meleschtschenko 1970
	rabbit	3500	Meleschtschenko 1970
dermal	rat	7000	Weisbrod 1981
	rabbit	6000	Clark 1984
s.c.	mouse	3000	BASF 1951
i.p.	rat	2400	Bartsch *et al.* 1976
	mouse	1900	BASF 1963
		3100	BASF 1970
		4300	Bartsch *et al.* 1976
i.v.	rat	2200	Bartsch *et al.* 1976

Exposure of 30 mice for 2 hours to an atmosphere enriched with *N*-methyl-2-pyrrolidone vapour at 100 to 120°C (180–200 mg/m^3) caused irritation of the eyes and upper airways (Stasenkowa and Kotschekov 1965). Exposure of 12 rats for 8 hours to an atmosphere saturated with *N*-methyl-2-pyrrolidone at 20°C also resulted in mild mucosal irritation (BASF 1963).

4.2 Subacute, subchronic and chronic toxicity

4.2.1 Inhalation

Aerosol

The studies in which rats were exposed to *N*-methyl-2-pyrrolidone aerosols for periods up to 13 weeks are shown in Table 2. Exposure of rats in animal exposure chambers to *N*-methyl-2-pyrrolidone concentrations in the range between 100 and 500 mg/m^3 for a period of 4 weeks resulted in lethargy and irregular breathing. At 1000 mg/m^3, however, deaths, damage to the lungs, bone marrow and lymphatic organs, and blood count changes developed within as little as 10 days (Lee *et al.* 1987).

In several inhalation studies in which animals were exposed by head-only exposure (BASF 1989a, 1993a, 1993b, 1994) to *N*-methyl-2-pyrrolidone concentrations between 10 and 10000 mg/m^3 for periods up to 13 weeks, effects in the form of irritation of the nasal mucosa were first seen at concentrations of 1000 mg/m^3 or more and not until towards the end of the 13-week exposure period (BASF 1994). The yellow discoloration of the urine seen after exposure to 100 mg/m^3 or more may be considered as an indication that absorption has taken place. After exposure to 3000 mg/m^3 for 13 weeks (BASF 1994) and at concentrations of 4000 mg/m^3 or more for 2 weeks (BASF 1993a) unspecific signs of mild intoxication developed in the form of body weight loss, respiratory tract irritation, and changes in the blood count and in haematological parameters. Reduction in testis weights correlated with the histopathological finding of cell loss in the germinal epithelium of the testis in at least 40 % of the animals; this alteration still persisted 4 weeks after the end of exposure. In addition there was evidence for toxic effects on the lungs and liver. Exposure to *N*-methyl-2-pyrrolidone concentrations of 7000 mg/m^3 resulted in high mortality within a few days; the female animals were more sensitive (BASF 1993a).

Vapour

The results of inhalation studies with *N*-methyl-2-pyrrolidone vapour are shown in Table 3.

With the exception of two studies with rats (BASF 1983, Lee *et al.* 1987) the reports available (BASF 1964b, GAF 1990, Stasenkowa and Kotschekov 1965) are inadequately documented or are from early studies which do not meet present day requirements.

Exposure of rats for a period of 6 weeks to *N*-methyl-2-pyrrolidone vapour concentrations of 1750 mg/m^3 caused merely slight secretion from the nose (BASF 1983). Repeated exposure to 6600 mg/m^3 was lethal for mice but had no effects on rats, guinea pigs, rabbits or cats (BASF 1964b). In an inadequately documented study it is reported that autopsy of mice and rats after exposure for 5 months to the conspicuously low concentrations of 100 to 200 mg/m^3 revealed changes in the spleen, liver, lungs and kidneys (Stasenkowa and Kotschekov 1965). These findings must be considered to be questionable.

In a long-term inhalation study, groups of 120 male and 120 female CD-1 rats were exposed to N-methyl-2-pyrrolidone vapour concentrations in air of 41.2 or 412 mg/m^3, 6 hours daily, 5 times per week. From each study group 10 males and 10 females were subjected to haematological and clinical chemical examination after 1, 3, 6, 12 and 18 months. Groups of 10 male and 10 female animals were killed after 3, 12 and 18 months for gross pathological and histopathological examination. All survivors were killed after a 2-year study period (see Section 5.7). After 18 months the haematocrit value, the alkaline phosphatase activity and the urine volume were increased in the males of the high dose group. In the males of the 40 mg/m^3 group there was a slight increase in the incidence of chronic progressive nephropathy after 12 months. In the animals of the 400 mg/m^3 group which died before the 18-month sampling date or were killed *in extremis,* chronic progressive nephropathy was diagnosed in 8 of 23 animals compared with 4 of 19 control rats. However, there were no differences in either incidence or severity of this finding in the groups killed after 18 and 24 months (Lee *et al.* 1987).

Table 2. Inhalation studies with repeated exposure of animals to *N*-methyl-2-pyrrolidone aerosols

Species, strain, number per dose, sex	Exposure route, characterization of the aerosol	Exposure duration	Concentration [mg/m^3]	Findings	References
rat CD-1 15 ♂ 15 ♀	exposure chamber, > 95 % of the droplets < 10 µm	4 weeks, 6 h/day, 5 days/week	100 500	*from 100 mg/m^3:* after 3–4 h exposure lethargy, irregular breathing; effects regressed 45 min after end of exposure; no effects on histopathology, body weights, blood, urine	Lee *et al.* 1987
		10 days, 6 h/day, 5 days/week	1000	lethargy and severe respiratory difficulties hardly regressed 18 h after end of exposure, mortality: 8/30, morbidity: 5/30, body weights decreased, congestive oedematous lung changes, interstitial pneumonia, bone marrow hypoplasia and haemorrhage, atrophy and necrosis of thymus, spleen and lymph nodes, no effects in other tissues, neutrophils increased, lymphocytes decreased, no effects on other haematological parameters; some of the effects regressed 2 weeks after end of exposure	
rat Wistar 10 ♀	head-only exposure, aerosol: 24 %–29.4 %; MMAD: 3.8–4.4 µm	2 weeks, 6 h/day, 5 days/week	1000	yellow discoloration of the urine; no effects on mortality, body weights, haematological parameters, blood count, pathology, NOAEL 1000 mg/m^3	BASF 1989a, 1992
rat Wistar 5 ♂ 5 ♀	head-only exposure, MMAD: 2.9–3.7 µm	2 weeks, 6 h/day, 5 days/week	4000 7000 10000	*from 4000 mg/m^3:* yellow discoloration of the urine, unspecific clinical symptoms, body weights decreased, neutrophils increased, lymphocytes decreased; ♂: absolute testis weights decreased, cell loss in the germinal epithelium of the testis in 3/5, ALT increased; ♀: ulceration of the glandular stomach, adrenal and lung weights increased, clotting time increased, ALT increased;	BASF 1993a

Table 2. continued

Species, strain, number per dose, sex	Exposure route, characterization of the aerosol	Exposure duration	Concentration [mg/m^3]	Findings	References
				from 7000 mg/m^3: mortality: ♀ 5/5, therefore exposure of ♂ discontinued after 4 days and animals observed for 9 days, lung changes; ♂: body weights decreased reversibly, testis weights decreased irreversibly, cell loss in the testis germinal epithelium in 4/5, liver weights increased; *10000 mg/m^3:* study ended after 4 days, mortality: ♀ 5/5, ♂ 2/5, morbidity ♂ 3/5, ♂: ulceration of the glandular stomach	
rat Wistar 5 ♂, 5 ♀	head-only exposure	4 weeks, 6 h/day, 5 days/week	10 30 100	*100 mg/m^3:* intensive yellow discoloration of the urine; NOAEL 100 mg/m^3	BASF 1993b
rat Wistar 10 ♂, 10 ♀	head-only exposure, MMAD: 1.6–3.5 µm rel. humidity: 52 %–61 %	13 weeks, 6 h/day, 5 days/week	500 1000 3000	*from 500 mg/m^3:* yellow discoloration of the urine; *from 1000 mg/m^3:* irritation of the nasal mucosa towards the end of the exposure; *3000 mg/m^3:* unspecific clinical symptoms, irritation of the respiratory tract, ALT increased; ♂: body weights decreased, erythrocytes, Hb, haematocrit and MCV increased, absolute testis weights decreased; cell loss in the germinal epithelium of the testis in 4/10, no effects in other tissues; ♀: neutrophils increased, lymphocytes decreased; NOAEL 500 mg/m^3	BASF 1994
rat Wistar 10 ♂, 10 ♀	head-only exposure, MMAD: 1.6–3.5 µm rel. humidity: 52 %–61 %	13 weeks, 6 h/day, 5 days/week, observation period 4 weeks	3000	♂: body weight gain decreased, Hb and haematocrit increased, testis damage (see above) irreversible in 7/10	BASF 1994

ALT: alanine aminotransferase, MCV: mean corpuscular volume, MMAD: “mass median aerodynamic diameter”, Hb: haemoglobin, NOAEL: no observed adverse effect level

Table 3. Inhalation studies with repeated exposure to *N*-methyl-2-pyrrolidone vapour

Species, strain[1], number per dose group, sex[1]	Exposure duration	Exposure concentration [mg/m^3]	Findings	References
rat 12	10 days, 6 h/day	1500 [4]	no symptoms, no pathological changes; study inadequately documented	GAF 1990
rat 4	17 exposures, 6 h/day, 5 days/week	6600 [2]	no symptoms; autopsy did not reveal substance-related effects	BASF 1964b
rat Sprague-Dawley 10 ♂, 10 ♀	6 weeks, 6 h/day, 5 days/week	1750 [3]	yellow discoloration of the urine, slight nasal secretion from 8th exposure; clinical-chemical and haematological parameters unaffected, no pathological findings	BASF 1983
rat 20	5 months, 4 h/day, 6 days/week	100–150	nerve and muscle excitability initially decreased, no effect on body weights; lung and kidney changes	Stasenkowa and Kotschekov 1965
rat Sprague-Dawley 10 ♂, 10 ♀	1, 3, 6, 12, 18 months, 2 years, 6 h/day, 5 days/week	41.2 412	*41.2 mg/m^3:* nephropathy from month 13; *from 412 mg/m^3:* yellow discoloration of the urine, nephropathy; ♂: body weights decreased; from month 18: alkaline phosphatase, urine volume and haematocrit increased	Lee *et al.* 1987
mouse 10	17 exposures, 6 h/day, 5 days/week	6600 [2]	mortality 9/10 after 3–14 exposures without clinical symptoms, autopsy revealed no substance-related findings	BASF 1964b
mouse 30	1 month, 2 h/day, 6 days/week	180–200	general condition unaffected, body weights decreased, nerve and muscle excitability increased, no effect on blood count; spleen, liver, lung changes	Stasenkowa and Kotschekov 1965
guinea pig 4	17 exposures, 6 h/day, 5 days/week	6600 [2]	no symptoms, autopsy revealed no substance-related findings	BASF 1964b
rabbit 2	17 exposures, 6 h/day, 5 days/week	6600 [2]	no symptoms, clinical-chemical parameters unaffected	BASF 1964b
cat 2	17 exposures, 6 h/day, 5 days/week	6600 [2]	no symptoms, clinical-chemical parameters unaffected	BASF 1964b

[1] strain and sex generally not specified, [2] saturation concentration of *N*-methyl-2-pyrrolidone vapour at 50°C, [3] saturation concentration of *N*-methyl-2-pyrrolidone vapour at 25°C, [4] saturation concentration of *N*-methyl-2-pyrrolidone vapour at room temperature

4.2.2 Ingestion

The studies in which *N*-methyl-2-pyrrolidone was administered repeatedly *per os* are shown in Table 4.

The findings of most of the studies (BASF 1964a, GAF 1976, 1977, Meleschtschenko 1970) do not provide a coherent toxicity profile and cannot be assessed because they are inadequately documented or the methods were inadequate (e.g. numbers of animals too small).

Administration of *N*-methyl-2-pyrrolidone by gavage for 4 weeks to rats resulted in body weight reductions in male animals given 514 mg/kg body weight and day. Doses of 1028 mg/kg body weight caused increased liver and kidney weights and reduced lymphocyte counts. In the group given *N*-methyl-2-pyrrolidone doses of 2056 mg/kg body weight, testis weights were decreased by about 50 % and histological examination revealed testis alterations (BASF 1978a).

4.2.3 Dermal absorption

Application of undiluted *N*-methyl-2-pyrrolidone to the intact or scarified skin of rabbits in doses of 411, 822 or 1645 mg/kg body weight and day for 20 days produced merely local irritation and no systemic effects. In the highest dose group one animal given the substance on the scarified skin died. More details are not available (GAF 1990).

4.3 Effects on skin and mucous membranes

Application of undiluted *N*-methyl-2-pyrrolidone to the shaved dorsal skin of rabbits for 5 to 15 minutes causes severe erythema and subsequent scaling of the skin. After contact with the substance for 20 hours severe oedema of the dorsal skin was observed as well; on the ears necrosis developed (BASF 1963). On the other hand, after occlusive application of 0.5 ml *N*-methyl-2-pyrrolidone or the diluted substance to the shaved dorsal skin of rabbits for 24 hours, only mild irritation was reported (Ansell and Fowler 1988, Sasaki *et al.* 1990b).

Application of up to 20 doses of *N*-methyl-2-pyrrolidone to the intact or scarified skin of rabbits (see Section 4.2.3) and to the skin of mice resulted only in mild irritation (GAF 1990, Stasenkowa and Kotschekov 1965).

In the rabbit eye, *N*-methyl-2-pyrrolidone caused moderate to marked irritation (Ansell and Fowler 1988, BASF 1951, 1963, GAF 1990). Applied into the conjunctival sac, 50 µl *N*-methyl-2-pyrrolidone caused redness, swelling and corneal clouding which persisted in a milder form even after 8 days (BASF 1963).

Table 4. Studies in which oral doses of *N*-methyl-2-pyrrolidone were administered repeatedly to experimental animals

Species, strain, number per dose, sex	Administration period, route	Dose (mg/kg body weight)	Findings	References
rat Sprague-Dawley 10 ♂, 10 ♀	4 weeks, 5 days/week gavage	257 514 1028 2056	*from 257 mg/kg:* yellow discoloration of the urine; *from 514 mg/kg:* ♂ body weights decreased; *from 1028 mg/kg:* liver and kidney weights increased, lymphocyte count decreased; *2056 mg/kg:* tremor, restlessness, ruffled fur, defensive reactions, testis weights about 48% decreased, histological changes in the testes	BASF 1978a
rat 10 n.s.	6 weeks	790 1580	inadequate documentation; *1580 mg/kg:* liver glycogen, serum cholesterol and total bilirubin increased	Meleschtschenko 1970
rat Wistar 25 ♂, 25 ♀	13 weeks 800, 2000, 5000 ppm in the diet	60 150 375	inadequate documentation; *from 60 mg/kg:* ♂ thyroid weights increased, ♀ body weights decreased; *375 mg/kg:* ♂ ALT increased	GAF 1976, 1990
mouse CD-1 30 ♂, 30 ♀	13 weeks 400, 1000, 2500 ppm in the diet	60 150 375	inadequate documentation *from 60 mg/kg:* ♂: body weights decreased, liver weights increased in a dose-dependent manner, weights of adrenals, thyroid, pituitary increased, clinical-chemical parameters unaffected, pathology unaffected	GAF 1977, 1990
guinea pig 3 n.s.	2, 3 or 4 days gavage	2056	mortality 3/3, leukocytosis, granulocytosis, blood urea increased, pulmonary congestion and oedema, fatty degeneration of liver and kidneys	BASF 1964a
rabbit 3 n.s.	25 doses, 5 days/week gavage	411	pathology unaffected	BASF 1964a
rabbit 3 n.s.	5, 9 or 30 doses, 5 days/week, gavage	1028	premature mortality 2/3, with fatty degeneration of the heart and liver necrosis	BASF 1964a

Table 4. continued

Species, strain, number per dose, sex	Administration period, route	Dose (mg/kg body weight)	Findings	References
rabbit 2 n.s.	3 or 6 doses gavage	2056	mortality 2/2, with fatty degeneration of the heart and liver necrosis	BASF 1964a
rabbit 6 n.s.	6 weeks	790 1580	inadequate documentation; dose-dependent changes in the heart, liver, kidneys, gastrointestinal tract	Meleschtschenko 1970
cat 2 n.s.	once and then after 13 days for another 20 days	1028 514	mortality: 1/2, body weights decreased, anorexia, salivation, emesis, atonia, coordination disorders, leukocytosis, lymphocytosis, neutrophilic granulocytosis, urine: protein, erythrocytes, leukocytes, urethral epithelial cells	BASF 1964a
dog beagle 6 ♂, 6 ♀	13 weeks in the diet	25 79 250	*from 79 mg/kg:* body weights decreased, ♂: serum cholesterol levels decreased, serum albumin increased, thrombocyte and megakaryocyte counts increased, all values in the range of the historical controls	Becci *et al.* 1983

n.s.: not specified

4.4 Allergenic effects

In a modified Draize test, a 5 % *N*-methyl-2-pyrrolidone solution applied repeatedly to guinea pigs did not produce sensitization (no other details) (Lee *et al.* 1987).

4.5 Reproductive and developmental toxicity

4.5.1 Fertility

The proportion of a dose of *N*-methyl-2-pyrrolidone which was recovered in the testes was large (0.9 %) relative to that in other organs (see Section 2, Wells and Digenis 1988). Fertility parameters were studied in 24 male Wistar rats exposed for 90 days in animal exposure chambers to an *N*-methyl-2-pyrrolidone vapour concentration of 618 mg/m^3 (150 ml/m^3) for 6 hours daily on 7 days per week. Half of the animals were killed at the end of the exposure period, the other half after 90 exposure-free days. In both groups testis weights, the results of pathological examination of the testes, sperm morphology, sperm count and body weight development of the animals were unaffected by the exposure (Fries *et al.* 1992).

However, after exposure of animals to higher concentrations of *N*-methyl-2-pyrrolidone, effects on the testes were described. Thus in Wistar rats exposed in head-only exposure systems to *N*-methyl-2-pyrrolidone aerosols, reduced absolute testis weights and, in the histopathological examination, cell loss in the germinal epithelium of the testis in 40 % to 70 % of the animals were seen after 2 weeks exposure to concentrations of 4000 mg/m^3 or more and after 13 weeks exposure to 3000 mg/m^3 or more. The effects were not reversible within the 4-week recovery period. At an aerosol concentration of 7000 mg/m^3 these effects were seen after as little as 4 days exposure and 9 days observation (BASF 1993a, 1994, Table 2). Likewise, administration of *N*-methyl-2-pyrrolidone to Sprague-Dawley rats by gavage of doses of 2056 mg/kg body weight, daily for 4 weeks, resulted in reduction of the testis weights by one half and in histologically detectable testis changes (BASF 1978a, Table 4).

In a dominant lethal test in the mouse an increase in post-implantation losses was demonstrated (BASF 1976c, Section 4.6.2).

4.5.2 Developmental toxicity

Studies of the distribution of *N*-methyl-2-pyrrolidone in the organism (Section 2) have demonstrated that *N*-methyl-2-pyrrolidone is transferred to the foetus and achieves the same concentrations in the foetal tissue as in the dam (Ravn-Jonsen *et al.* 1992).

Prenatal toxic effects of *N*-methyl-2-pyrrolidone have been demonstrated in rats, mice and rabbits after inhalation, ingestion and dermal absorption of the substance. The data available for developmental toxicity of *N*-methyl-2-pyrrolidone are shown in Table 5.

Exposure of pregnant rats in animal exposure chambers to an *N*-methyl-2-pyrrolidone concentration of 680 mg/m^3 caused an increased incidence of resorptions, reduced foetal weights and delayed ossification. Development was delayed in the progeny of rats exposed to 622 mg/m^3 (Fries *et al.* 1992). After head-only exposure of pregnant rabbits to *N*-methyl-2-pyrrolidone concentrations of 1000 mg/m^3 or more, the incidence of foetuses with 13 ribs was significantly increased (BASF 1993d). The maternal toxicity was not increased in either study. No embryotoxic, foetotoxic or teratogenic effects were seen in rats exposed to 360 mg/m^3 (Lee *et al.* 1987) or in rabbits at 500 mg/m^3 (BASF 1993d).

Administration of oral *N*-methyl-2-pyrrolidone doses of 997 mg/kg body weight to pregnant rats by gavage did not cause maternal toxicity but an increased incidence of resorptions, foetal mortality, reduced placental and foetal weights, reduced foetal lengths, delayed ossification and an increased incidence of malformations (BASF 1971). In mice, doses of 2637 mg/kg body weight caused reductions in foetal weight and length, delayed ossification and an increased incidence of malformations including cleft palate, in the absence of maternal toxicity (BASF 1970). At a dose of 1055 mg/kg body weight the incidence of resorptions was still slightly increased. In rabbits similar effects were seen at doses of 540 mg/kg body weight, which also produced maternal toxicity (GAF 1991a). The NOEL (no observed effect level) for prenatal toxicity was below 332 mg/kg body weight in the rat, below 1055 mg/kg body weight in the mouse and was 175 mg/kg body weight in the rabbit.

After dermal exposure of rats, prenatal toxicity was observed at doses similar to the effective oral doses; 750 mg/kg body weight was maternally toxic and caused an increased incidence of resorptions, a reduction in the number of live foetuses, reduced foetal weights and an increased incidence of malformations (Becci *et al.* 1982). Dermal application of 1000 mg/kg body weight to pregnant rabbits did not cause maternal toxicity but skeletal variations were seen in the foetuses (BASF 1993c). The NOEL for rats was 237 mg/kg body weight, for rabbits 300 mg/kg body weight.

4.5.3 Multi-generation studies

In a multi-generation study with rats (see Table 6), inhalation of an *N*-methyl-2-pyrrolidone concentration of 478 mg/m^3 resulted in reduced body weight gain in the F_1 generation and reduced sensitivity to noise after weaning and in signs of foetotoxicity in the F_2 generation. Exposure to 206 mg/m^3 had no effects (DuPont 1990).

Oral administration of *N*-methyl-2-pyrrolidone doses of 500 mg/kg body weight and day led to fertility disorders, increased incidence of still births, reduced survival and growth of the progeny and reduced testis weights in the F_1 generation. Doses of 160 mg/kg body weight were without effect (GAF 1991b).

Table 5. Developmental toxicity of *N*-methyl-2-pyrrolidone

Species strain number of animals[1]	Exposure conditions	Exposure: day of gestation	Dose or concentration	Findings	References
rat Wistar 28	inhalation, animal exposure chamber, vapour	4–20 6 h/day	680 mg/m^3 (165 ml/m^3)	F_0: no maternal toxicity; F_1: preimplantation losses increased (20/23), resorptions slightly increased, foetal weights decreased, malformations not increased, delayed ossification	Fries *et al.* 1992
rat Wistar 19	inhalation, animal exposure chamber, vapour	7–20 6 h/day, post-exposure observation of the progeny: ♀ 80 days *pp* ♂ 100 days *pp*	622 mg/m^3 (151 ml/m^3)	F_0: systemically available (discoloration of the urine), no maternal toxicity; F_1: *prenatal*: no embryotoxicity; *postnatal*: survival unaffected, body weights during lactation decreased, *behavioural studies*: physiological development and development of the righting reflex delayed, other reflexes unaffected, results of "Rotarod", "open field activity" unaffected, results of learning in the swimming test unclear	Fries *et al.* 1992
rat Sprague-Dawley 25	inhalation, animal exposure chamber, aerosol	6–15 6 h/day	100 mg/m^3 360 mg/m^3	F_0: no maternal toxicity; F_1: no foetal toxicity, malformations not increased	Lee *et al.* 1987
rat Sprague-Dawley 20	inhalation, animal exposure chamber, vapour	4–8 or 11–15 6 h/day	3300 mg/m^3 (800 ml/m^3)	F_0: no maternal toxicity; F_1: no foetal toxicity, malformations not increased	BASF 1976b
rabbit 4–5	inhalation, head-only, at 300 mg/m^3 vapour, at higher concentrations aerosol-vapour mixture, aerosol particles 3.8–4.0 µm, relative humidity 54 %	7–19	300, 1000, 2000 mg/m^3	*300 mg/m^3:* F_0: systemically available (discoloration of the urine), no maternal toxicity; *1000 mg/m^3:* F_0: slight maternal toxicity: clotting time increased, liver weights slightly increased, serum proteins slightly decreased; F_1: no foetal toxicity; *2000 mg/m^3:* F_0: slight maternal toxicity: discoloration of the fur, γ-GT in serum slightly increased; F_1: resorptions increased, number of live foetuses decreased	BASF 1991

Table 5. continued

Species strain number of animals[1]	Exposure conditions	Exposure: day of gestation	Dose or concentration	Findings	References
rabbit Himalayan 15	inhalation, head-only, at 200 mg/m^3 vapour; at higher concentrations aerosol-vapour mixture, aerosol particles MMAD 2.7–3.5 µm, relative humidity 53 %–56 %	7–19 6 h/day	200, 500, 1000 mg/m^3	*from 200 mg/m^3:* F_0: systemically available (discoloration of the urine); *1000 mg/m^3:* F_0: no maternal toxicity, F_1: foetotoxicity: incidence of skeletal variations increased (13 ribs in 32 %, historical controls 2 %), malformations not increased	BASF 1993d
rat Sprague-Dawley 29–32	oral, gavage	6–15	332, 997 mg/kg body weight (0.323, 0.970 ml/kg body weight)	*332 mg/kg:* F_1: placental and foetal weights slightly decreased; *997 mg/kg:* F_0: no maternal toxicity; F_1: number of implantations and *corpora lutea* unaffected, resorptions 95 %, number of live foetuses markedly decreased, placental and foetal weights markedly decreased, foetal lengths decreased, delayed ossification, malformations increased (9/15): skeletal and visceral, undescended testes (3/6)	BASF 1971
mouse NMRI 20 and 22	oral, gavage	11–15	1055, 2637 mg/kg body weight (1.026; 2.565 ml/kg body weight)	*1055 mg/kg:* F_0: no maternal toxicity; F_1: resorptions slightly increased, litter size decreased; *2637 mg/kg:* F_0: no maternal toxicity, mortality 1/22 on day 14, (no other details); F_1: resorptions increased, litter size, foetal weights and lengths decreased, delayed ossification, malformations increased (19.2 %, control 0 %), of those 18.1 % cleft palate	BASF 1970

Table 5. continued

Species strain number of animals[1]	Exposure conditions	Exposure: day of gestation	Dose or concentration	Findings	References
rabbit New Zealand White 20	oral, gavage	6–18	55, 175, 540 mg/kg body weight	*55 mg/kg:* F_0: no maternal toxicity; *175 mg/kg:* F_0: signs of mild maternal toxicity: body weights and food consumption decreased; F_1: no foetal toxicity; *540 mg/kg:* F_0: maternal toxicity: body weights and food consumption decreased; F_1: abortion 1/20, postimplantation losses and resorptions increased, number of live foetuses decreased, uterus weights decreased, malformations increased (heart, skull), variations increased (skull, spine)	GAF 1991a
rat Sprague-Dawley 4–5	dermal, shaved skin, (oral uptake prevented) (dose-finding study)	6–15	500, 1100, 2500 mg/kg body weight	*500 mg/kg:* F_0: systemically available (discoloration of the urine), no maternal toxicity; F_1: no foetal toxicity; *from 1100 mg/kg:* F_0: maternal toxicity: body weights decreased; F_1: resorptions increased (65/66); *2500 mg/kg:* F_0: mortality of the dams; F_1: abortions (4/4)	Becci *et al.* 1982
rat Sprague-Dawley 22–24	dermal, shaved skin, (oral uptake prevented)	6–15	75, 237, 750 mg/kg body weight	*237 mg/kg:* F_0: systemically available (discoloration of the urine), no maternal toxicity; F_1: no foetal toxicity *750 mg/kg:* F_0: maternal toxicity: body weights decreased; F_1: resorptions increased, number of live foetuses decreased, foetal weights decreased, malformations increased (ribs, skull), variations increased	Becci *et al.* 1982
rabbit Himalyan 15	dermal, shaved skin, semiocclusive	7–19	100, 300, 100 mg/kg body weight	*from 300 mg/kg:* F_0: systemically available (discoloration of the urine), no maternal toxicity; F_1: no foetal toxicity; *1000 mg/kg:* F_0: no maternal toxicity; F_1: incidence of skeletal variations (ribs) increased	BASF 1993c

Table 5. continued

Species strain number of animals[1]	Exposure conditions	Exposure: day of gestation	Dose or concentration	Findings	References
mouse NMRI 21–23	i.p.	11–15	627, 1568 mg/kg body weight (0.610, 1.525 ml/kg body weight)	*1568 mg/kg:* F_0: dams without symptoms (no other details); F_1: resorptions increased, litter size, foetal weights and lengths decreased, delayed ossification, malformations increased (15.7 %, control 2.3 %), of those 14.7 % cleft palate	BASF 1970
mouse AB-Jena 25–32	i.p.	once on day 3, 7 or 11; once on day 9	166 mg/kg body weight; 129, 166 mg/kg body weight	F_0: maternal toxicity not mentioned; F_1: resorptions increased; F_1: malformations increased in a dose-dependent manner (11 and 19 %, control 0 %)	Schmidt 1976
mouse AB-Jena 22–36	i.p.	7–11	74, 92, 129 mg/kg body weight	F_0: maternal toxicity not mentioned *from 74 mg/kg:* F_1: resorptions increased, *from 92 mg/kg:* F_1: malformations increased in a dose-dependent manner (12 and 19 %, control 0 %)	Schmidt 1976
		1–14	14, 37, 74 mg/kg body weight	F_0: maternal toxicity not mentioned *from 37 mg/kg:* F_1: resorptions increased, delayed ossification	
mouse C57B1 19–25	i.p.	7–11	37, 74, 130 mg/kg body weight	F_0: maternal toxicity not mentioned from 37 mg/kg: F_1: preimplantation losses increased, resorptions increased, foetal weights decreased *from 74 mg/kg:* F_1: number of live foetuses decreased *130 mg/kg:* F_1: malformations increased, (26.5 %, control 1.7 %)	Schmidt 1976
		1–14	74 mg/kg body weight	F_0: maternal toxicity not mentioned; F_1: dead implants, only 1 dam could be evaluated, no other details	

[a] animals per group (dose or study), MMAD: mass median aerodynamic diameter, γ-GT: γ-glutamyltransferase, *pp*: *post partum*

Table 6. Multi-generation studies with *N*-methyl-2-pyrrolidone

Species	Administration route, dose	Exposure duration	Findings	References
rat Sprague-Dawley	inhalation 10, 50, 116 ml/m^3 (41, 206, 478 mg/m^3), 6 h/day, 7 days/week	F_0: from age 34 days, during mating and gestation until weaning of the litter	478 mg/m^3: F_1: body weights on day 21 decreased, reduced sensitivity of adult animals to noise; F_2: foetal weights decreased	DuPont 1990
rat Sprague-Dawley Crl:CDBR 30 ♂, 30 ♀	diet 50, 160, 500 mg/kg body weight	F_0: from 10 weeks before mating, ♂ until end of 2nd mating F_{1b}, ♀ until weaning of the second litter (F_{1b}); F_{1b}: from weaning, during mating, ♂ until end of 2nd mating (F_{2b}), ♀ during gestation, until end of lactation of the F_{2b} litter	500 mg/kg: F_0: ♀: body weights decreased, food consumption during gestation and lactation (F_{1a} and F_{1b}) decreased, F_{1a}: still births increased, F_{1a}, F_{1b}: survival to day 4 *pp* decreased, F_{1b}: body weights decreased; ♂: mating index decreased, fertility index decreased, testis size reduced (10/30); ♀: fertility index decreased, gestation index slightly decreased, number of pigmented macrophages in the uterus decreased, ovary size reduced, number and size of *corpora lutea* decreased; F_{2a} and F_{2b}: still births increased, survival until day 4 *pp* decreased	GAF 1991b

pp: post partum

4.6 Genotoxicity

4.6.1 in vitro

N-Methyl-2-pyrrolidone has been tested in the *Salmonella* mutagenicity test with and without metabolic activation in the strains TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538, TA2638, UTH8413 and UTH8414 in the plate incorporation test and in the strains TA98 and TA104 in the preincubation test. The doses tested were in the range between 0.01 and 1000 µmole/plate (0.9913 µg to 99.13 mg/plate) whereby the highest dose had cytotoxic effects. In all the tests, negative results were obtained with *N*-methyl-2-pyrrolidone (BASF 1978b, GAF 1990, Maron *et al.* 1981, Mortelmans *et al.* 1986, Wells *et al.* 1988).

In *Saccharomyces cerevisiae* strain D61.M, *N*-methyl-2-pyrrolidone concentrations of 150 to 230 mM induced aneuploidy (Mayer and Goin 1988, Mayer *et al.* 1986, 1988, Zimmermann *et al.* 1989).

Negative results were also obtained in the mouse lymphoma test (DuPont 1976), in the HPRT (hypoxanthine guanine phosphoribosyl transferase) test in CHO cells (a cell line derived from Chinese hamster ovary cells) and in the UDS test (for unscheduled DNA synthesis) in primary rat hepatocyte cultures (GAF *et al.* 1990).

4.6.2 *in vivo*

In a micronucleus test in which NMRI mice were given single oral doses of *N*-methyl-2-pyrrolidone of 950, 1900 or 3800 mg/kg body weight, no evidence of clastogenic effects or aneuploidy was seen (BASF 1989b, Engelhardt and Fleig 1993).

In a dominant lethal test in which male NMRI mice were given single intraperitoneal *N*-methyl-2-pyrrolidone doses of 391 mg/kg body weight, the percentage of postimplantation losses (13.62 %) was significantly increased relative to the control values (6.72 % in untreated animals, 8.75 % in animals treated with double distilled water) when conception took place two weeks after the injection. The authors were of the opinion that the value was within the normal biological range of this parameter (BASF 1976c). Calculation of the mutagenicity index suggests that the substance could have mutagenic effects.

When Chinese hamster were exposed for 6 weeks (6 hours/day, 5 days/week) to *N*-methyl-2-pyrrolidone vapour at a concentration of 800 ml/m^3 (3296 mg/m^3), a slight but not significant increase in structural chromosomal aberrations could be demonstrated in the bone marrow (BASF 1976a). However, as no positive control was included in the study, the results cannot be used in the present evaluation.

In another study in which male and female Chinese hamsters were treated once with oral *N*-methyl-2-pyrrolidone doses of 1900 or 3800 mg/kg body weight, neither structural nor numerical chromosomal aberrations could be detected (Engelhardt and Fleig 1993).

4.7 Carcinogenicity

Groups of 90 male and 90 female CD-1 rats were exposed 5 times per week for 6 hours daily to *N*-methyl-2-pyrrolidone vapour concentrations in air of 41.2 or 412 mg/m^3 (10 and 100 ml/m^3) (DuPont 1980, Lee *et al.* 1987, see Section 4.1.2). At the end of the 2 years of exposure, the body weight gain of the male rats of the 412 mg/m^3 group was seen to be significantly reduced (by about 6 %). There were no significant differences in morbidity or mortality. In the 412 mg/m^3 group in both sexes and in the female rats of the 41.2 mg/m^3 group the perineal region was more frequently discoloured and wet than in the controls. The male and female animals of the 412 mg/m^3 group had dark yellow urine and in the males the urine volume was increased. Other significant differences in haematological, clinical-chemical or urinary parameters were not found.

In the female rats of the 412 mg/m^3 group the incidence of mammary tumours was decreased and the incidence of mammary hyperplasia increased. The incidence of pituitary tumours was slightly increased in the lower dose group in both sexes but not in the higher dose group (Lee *et al.* 1987).

5 Manifesto (MAK value, classification)

In 1993 the reassessment of the MAK value for *N*-methyl-2-pyrrolidone was considered to be necessary because new data had become available since the 1988 review and the substance had acquired increased importance as a replacement for chlorinated hydrocarbons. The new data concerned especially the effects of inhaled *N*-methyl-2-pyrrolidone. It is important to remember that the tendency of gaseous *N*-methyl-2-pyrrolidone to form aerosols and to condense onto skin is affected by the concentration, humidity and temperature. *N*-Methyl-2-pyrrolidone is readily absorbed through the skin.

If rats inhale *N*-methyl-2-pyrrolidone aerosols during head-only exposure, concentrations of 7000 mg/m^3 and more are lethal within a few days; within 14 days, 4000 mg/m^3 causes reductions in testis weights and histological changes in the germinal epithelium of the testes. This effect was also seen after a 13-week exposure to 3000 mg/m^3. After exposure to 500 mg/m^3 no effects were seen. However, exposure of rats to 478 mg/m^3 (116 ml/m^3) in a multi-generation study caused delayed body weight gain in the pups and reduced sensitivity to noise after weaning. At 206 mg/m^3 (50 ml/m^3) no effects were recorded.

The MAK value for *N*-methyl-2-pyrrolidone vapour was therefore established at 80 mg/m^3 (20 ml/m^3).

In 1989 *N*-methyl-2-pyrrolidone, with the MAK value of 400 mg/m^3 (100 ml/m^3), was classified in pregnancy risk group D mainly because the lack of appropriate inhalation studies prevented a classification in pregnancy risk group C. Such studies are now available with both rats and rabbits. They demonstrate that at an *N*-methyl-2-pyrrolidone concentration of 360 mg/m^3 for rats exposed in animal exposure chambers and 500 mg/m^3 for rabbits exposed via the head only (90 % aerosol), no prenatal toxic effects

are found. Prenatal toxic effects were seen in rabbits exposed to 1000 mg/m^3 and in rats at 680 mg/m^3. In the progeny of rats exposed to 622 mg/m^3 development was delayed. During exposure in animal exposure chambers the possibility that dermal absorption takes place in addition to inhalation cannot be ruled out. Taken as a whole, the results of the reproductive toxicity studies with *N*-methyl-2-pyrrolidone administered to rats and rabbits orally, dermally and especially by inhalation indicate that the substance, with its new MAK value of 80 mg/m^3 (20 ml/m^3), is to be classified in Pregnancy risk group C; the possibility of dermal absorption must, however, be ruled out.

Because of the danger associated with absorption of *N*-methyl-2-pyrrolidone through the skin, the designation "H" is necessary.

Since the MAK value was based on systemic toxic effects and the elimination half time is more than 2 hours, *N*-methyl-2-pyrrolidone is classified in Peak limitation category II,2.

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