Nordic Expert Group for Criteria Documentation
of Health Risks from Chemicals

115. N-Methyl-2-pyrrolidone (NMP)

Bengt Åkesson

Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following member:

Helgi Gudbergsson	Municipal Institute of Public Health, Iceland
Petter Kristensen	National Institute of Occupational Health, Norway
Per Lundberg (chairman)	National Institute of Occupational Health, Sweden
Vesa Riihimäki	Institute of Occupational Health, Finland
Adolf Schaich Fries	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxline, Medline, Cancerlit and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access are used. The draft document is discussed within the Expert Group and is finally accepted as the Group's document.

An editorial work is performed by the Group's Scientific Secretary, Brita Beije, at the National Institute of Occupational Health in Sweden.

Only literature judged as reliable and relevant for the discussion is referred to in this document. Concentrations in air are given in mg/m^3 and in biological media in mol/l. In case they are otherwise given in the original papers they are if possible recalculated and the original values are given within brackets.

The documents aim at establishing a dose-response / dose-effect relationship and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on N-Methyl-2-pyrrolidone was made by Bengt Åkesson M.D., Department of Occupational and Environmental Medicine, University Hospital, S-221 85 Lund, Sweden. The final version was accepted by the Nordic Expert Group, June 13-15, 1994 as its document.
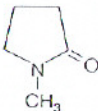
Brita Beije
Scientific Secretary

Per Lundberg
Chairman

Contents

1. Physical and Chemical Data

Systematic name	N-methyl-2-pyrrolidone (NMP)
Synonyms	N-methylpyrrolidone methylpyrrolidone N-methyl-α-pyrrolidone N-methyl-2-pyrrolidinone 1-methyl-2-pyrrolidinone N-methylpyrrolidinone 1-methyl-5-pyrrolidinone N-methyl-2-oxypyrrolidine N-methyl-2-ketopyrrolidine Butyrolactam
Trade name	M-pyrol
CAS number	872-50-4
Formula	C_5H_9NO
Structural formula	

Molecular weight	99.13
Vapour pressure	0.039 kPa (0.29 mm Hg) at 20°C 0.045 kPa (0.33 mm Hg) at 25°C
Boiling point	202°C at 101.3 kPa (760 mm Hg)
Melting point	-23 to -24.4°C
Flash point	95°C (204°F; open cup) 90°C (194°F; closed cup)
Explosivity	1.3-9.5 % (v/v) in air
Density	1.028 g/cm^3

Partition octanol/water coefficient (K_{ow})   0.42

Conversion factors   1 ppm = 4.12 mg/m^3; 1 mg/m^3 = 0.24 ppm

NMP is a colourless liquid with a mild amine odour. It is a basic and polar compound with high stability. It is only slowly oxidized by air and is easily purified by fractional distillation. NMP is hygroscopic. NMP is completely miscible with water. It is highly soluble in lower alcohols, lower ketones, ether, ethyl acetate, chloroform and benzene and moderately soluble in aliphatic hydrocarbons (23, 36).

NMP is not corrosive to carbon steels. Normal sewage treatment biodegrades NMP into a stable carbonyl compound (10). The dissipation of NMP showed half-lives of about 4 days in clay, 8 days in loam, and 12 days in sand (21).

2. Occurrence, Uses

2.1. Uses

The large number of applications of the commercial use of NMP is due to its strong and selective solvent power. One of the major uses of NMP is in the petrochemical industry as a solvent for extractions for aliphatic and aromatic hydrocarbons, natural and manufactured gases, lubricating oils, coal and tars and compounds containg oxygen, nitrogen and/or halogens (23).

NMP dissolves most mono- and polymers and catalyzes many polymerization reactions. Thus, NMP is an advantageous reaction medium for the manufacturing of polymers, e.g., aromatic polyamides, polyimides, polysulfides, polyvinyl chlorides, polyvinyl acetat, fluorinated resins, and natural polymers. The catalytic effect of NMP is also used in a variety of non-polymer chemical reactions, e.g. in alkylation, acylation, ethynylation, vinylation, disproportionation, pyrolysis, chlorination, and sulfation reactions.

NMP is used for stripping and cleaning applications in the microelectronics fabrication industry. The high electrical conductivity makes NMP useful in electrolytic capacitors and in batteries. In agricultural applications NMP is used as a formulating agent for insecticides, herbicides, and fungicides. Other applications are as a formulating agent in pigments, dyes and inks. NMP is further used as an intermediate in the pharmaceutical industry, as a penetration enhancer for topically applied drugs and as a vehicle in the cosmetic industry.

An important new use of NMP is as a substitute for other solvents of poorer stability, greater volatility, and higher inherent toxicity, e.g., for chlorinated hydrocarbons such as methylene chloride in paint strippers. The use of NMP as a remover of graffiti has increased enormously (23).

2.2. Occupational exposure

Only two studies of the air concentration levels of NMP in the occupational setting have been reported. Workers in a microelectronics fabrication industry were exposed to NMP air concentrations (time-weighted averages (TWA) for 8 h in their personal breathing zone) ranging from <0.1 to 6 mg/m^3. The highest TWA concentrations, 3-6 mg/m^3, were connected with work tasks with warm NMP. Samples collected in the work area revealed full-shift NMP air concentrations from <0.1 to 280 mg/m^3 (6). Peak NMP exposure of 10 mg/m^3 was reported in a study of the exposure to organic solvents among graffiti removers (3).

2.2.1. Measurement of NMP in the air
Sampling of NMP in the air may be performed on solid sorbents, such as silica gel (9), Amberlite XAD-7 (1) or charcoal, or in acidic absorption solution. NMP is desorbed from the solid adsorbents and extracted from the absorption solution by an organic solvent (e.g. ethyl acetate, dichloromethane, toluene). Efficient desorption was obtained when sampling on Amberlite XAD-7 and desorption with toluene or ethyl acetate. Analysis of NMP in air samples is performed, by gas chromatographic methods, employing flame ionisation or nitrogen-phosphorus detectors. The detection limits of these methods correspond to a NMP air concentration of ≤ 0.1 mg/m^3 (15 min, 0.200 l/min).

2.2.2. Measurement of NMP in biological samples
Plasma and urine concentrations of NMP, may after matrice modulating steps, be determined by HPLC. The chromatography is performed in the reversed phase mode with an UV-absorbance detector (12, 33, 42, 44). NMP in blood and urine samples may also be performed by extracting the NMP by an organic solvent (e.g. toluene or ethyl acetate). The solvent phase is analysed with a gas chromatographic method, using a nitrogen-phosphorus or mass spectrometric detector. The detection limits for NMP in blood and urine samples are 0.04 and 0.1 µmol/l, respectively.

3. Kinetics

3.1. Uptake

NMP was, in rat, readily absorbed through the skin (33) and the respiratory (35) and gastrointestinal (33) tracts. Rats exposed, by inhalation, to 620 mg/m^3 NMP for 6 h showed an increase in the NMP concentration in blood from 0 to 4 h after termination of the exposure. For pregnant rats the increase was seen from 0 to 8 h (35). The peak plasma concentration for both males and females occurred 2 h after administration by gastric intubation. After application of NMP to the skin, the peak concentration in plasma occurred at 1 h for males and at 2 h for females. The percutaneous absorption of a single dose was constant during the period 1-6 h after the skin application as measured by plasma concentrations. The urinary excretion suggests a percutaneous uptake of about 70%. The percutaneous absorption in rat tended to be more extensive in females than in males. The uptake through human

skin, in vitro, is about 4 times lower than through rat skin (34). The metabolic pattern of NMP and its metabolites indicates an important reabsorption of NMP in the kidneys (33).

3.2. Distribution

In rat there is a rapid distribution to all major organs after intravenous administration of radiolabeled NMP. The plasma NMP level declined significantly during 5 to 30 min after the administration and was thereafter only slightly decreased up to 2 h. The apparent volume of distribution was 0.3-0.5 l/kg body weight. Six h after administered radiolabeled NMP, the highest accumulation of radioactivity occurred in the liver, small and large intestine, testes, stomach, and kidneys although the thymus and bladder had the largest concentrations when expressed as per gram of tissue. After 24 h the radioactivity was still measurable in the liver and intestines (42). NMP passes the placenta and after exposure for 6 h foetal blood concentrations are similar to maternal blood concentrations (35).

3.3. Biotransformation

The main pathway for biotransformation of NMP in rat is hydroxylation to 5-hydroxy-N-methyl-2-pyrrolidone (44). The excretion in urine revealed the formation to 5-hydroxy-N-methyl-2-pyrrolidone, corresponding to 70-75% of the dose, and two other minor polar metabolites (15 and 9 %; 42). There is no formation of the isomer 3-hydroxy-N-methyl-2-pyrrolidone (44). Formation of CO_2 by metabolic degradation of the pyrrolidone-ring is of minor importance. The almost identical metabolism for dermal and oral administration routes indicates little first-pass metabolism (33).

3.4. Elimination

The elimination of NMP in rat is predominately through biotransformation to polar metabolites. Only a minor part is excreted in the urine as the mother compound (<1%). There is a minor biliary excretion of about 2%. The elimination of NMP in the expired air is also minimal (1-2%). The metabolites are excreted via the kidneys. No conjugated metabolites were found in the urine (42).

The rapid distribution phase of intravenously administered NMP is followed by a slow terminal elimination phase. In rats, the half-life of NMP in plasma is 7-10 h. Metabolites were not detected in plasma in any appreciable quantities until 4 h after administration and unmetabolized NMP still accounted for more than 80 % of the radioactivity in plasma after 6 h. The urinary excretion accounted for about 70% of the dose within 12 h and 80% within 24 h (42). The half-life for urinary excretion, expressed as the radioactivity level in urine, was 2.3 h (23).

NMP administered either orally or percutaneously showed, after the uptake and distribution phases, identical elimination patterns as compared with intravenously administered NMP. An oral dose reached peak concentration in plasma after 2 h.

Table 1. N-methyl-2-pyrrolidone (NMP): LD_{50} values for some animal species.

Species	Route of administration	LD_{50} (mg/kg body weight)	Ref
Rat[1]	intravenous	2300	5
Mouse[2]	intravenous	3600	5
Rat[1]	intraperitoneal	2500	5
Mouse[2]	intraperitoneal	4400	5
Rat[1]	peroral	3900	5
Rat[1]	peroral	4200	2
Rat[3]	peroral[5]	7900	32
Mouse[4]	peroral	4100	41
Mouse[4]	peroral[5]	5300	32
Mouse[2]	peroral	7700	5
Rabbit[4]	peroral[5]	3500	32
Guinea pig[4]	peroral[5]	4400	32
Rat[4]	dermal	7000	41
Rat[1]	dermal	2500-10000	11
Rabbit[3]	dermal	4000-8000	23
Rabbit[3]	dermal[6]	2000-4000	23

1. Sprague-Dawley rats; 2. NMRI mice; 3. Albino rabbits; 4. Strain not reported; 5. Middle lethal dose; 6. Abraded skin.

From 2 h until 8 h, the plasma concentration declined with a half-life of 9-12 h. At this time point more than 80% of the dose was still unmetabolized. Thereafter the biotransformation rapidly became more evident and by 12 h virtually all of the NMP dose was in the form of the polar metabolites (33).

There was a difference in the elimination of NMP from the blood between non-pregnant and pregnant rats. Non-pregnant rats eliminated 0.21 mM/kg body weight/h and pregnant rats only 0.11 mM/kg body weight/h. The elimination followed a 0-order function (35).

3.5. Biological exposure indicators

There is no information available on biological exposure indicators.

4. General Toxicology

4.1. Acute toxicity

Most of the studies are performed on rats and mice after intravenous, intraperitoneal or oral administration. The LD_{50} values are shown in Table 1. Inhalation studies

(Table 3) have been performed, with the exception of the 4-week study of Lee et al (1987), with no or only a slight mortality in the studied animals. In the studies with both males and females no sex differences were observed.

In an acute oral toxicity study (2) with Sprague-Dawley rats, non-survivors showed irritation of the pyloric and gastrointestinal tracts and darkening of kidneys, liver, and lungs. At sub-lethal doses, 1/8 of the LD_{50} value (LD_{50} = 4200 mg/kg body weight) ataxia and diuresis were recorded in survivors.

4.2. Factors that affect toxicity

NMP increases the ability of other compounds to penetrate skin and, thus, may increase the uptake of these compounds. A 500-fold increase of the skin permeability has been reported (25). The enhancing effect of NMP is transient. The penetration of a compound, accelerated by NMP, may be negligible after NMP itself has penetrated (38).

5. Effects on Organs

5.1. Effects on skin and mucous membranes

Several workers in an electrotechnical company experienced skin irritation after a few days work with NMP. Ten out of 12 exposed workers displayed acute irritant contact dermatitis of the hands. The severity of the reactions seemed to reflect the degree and duration of contact with NMP and the effects cleared within 3 weeks after termination of exposure (29).

A total of fifteen 24 h exposures of NMP to the skin every other day in 50 human subjects caused various minor to moderate transient irritations. No signs of contact sensitization were observed (23).

The dermal toxicity of NMP is reported to be low to moderate (2,11). Skin irritation tests in rabbits using a modified Draize procedure showed a primary irritation index of 0.5, indicating a low potential for skin irritation. Aqueous solutions of NMP caused skin irritation in guinea pigs at 50% but not at 5% (23). In a teratogenicity study dry skin was found at the application site of pregnant Sprague-Dawley rats exposed to dermal doses of 500-2500 mg/kg body weight and per 25 cm^2 (7).

In a primary ocular irritation test on New Zealand white rabbits, 0.1 ml of undiluted NMP was dosed into the conjunctival sac of one eye, the other eye served as control. A subgroup of the exposed rabbits had their eyes washed out 30 sec after the application. The conjunctival effects [ocular irrition, e.g. corneal opacity, iritis, and conjunctivitis, scored according to the Draize method (13)] faded within 21 days. For the washed out eyes these conjunctival effects faded within 14 days (2).

A study in a microelectronics fabrication industry (8-h TWA exposures to <0.1 to 6 mg/m^3 NMP) indicates that severe eye irritation and headache can be expected at air concentrations as low as 3 mg/m^3 even for short periods of time (30 min). Measurements in the work areas, in which the workers occasionally worked, revealed full-shift NMP air concentrations up to 280 mg/m^3. Thus, periods with high peak exposures should be taken into account when calculating the dose-effect relationship (6).

5.2. Effects on respiratory organs

In an inhalation study, Charles River CD rats (15 of each sex at each concentration) were exposed to NMP concentrations of 0, 100, 500, and 1000 mg/m^3 for 6 h/day, 5 days/week for 4 weeks using whole body exposure (28). The test atmosphere was generated as a respirable aerosol with >95% of the droplets below 10 μm. At all NMP exposure levels, signs of lethargy and irregular respiration started after 3-4 h of exposure. At the 1000 mg/m^3 levels an increased mortality was found. Out of 30 rats, 8 died during the first 9 days and the exposure was stopped after 10 days. The examination of the rats at this level showed marked pulmonary edema and congestion in the dead animals. Focal interstitial pneumonitis and increased number of neutrophils in the alveolar capillaries were observed in the rats killed after termination of the exposure. These effects were reversible in surviving rats within 2 weeks after end of exposure. No adverse effects on the respiratory system were observed at the exposure levels of 100 or 500 mg/m^3.

When the same investigators exposed rats (Charles River CD; 120 males and 120 females at each concentration) for two years in an exposure chamber to NMP concentrations of 0, 40, and 400 mg/m^3 for 6 h/day, 5 days/week, they could not observe any effects on the respiratory system. The particle size distribution was not analyzed but the amount of aerosol detected was reported to be low (28).

Inhalation of 210 mg/m^3 NMP (mice; 2 h per day, 6 days/week, 1 month) caused respiratory irritation (39).

5.3. Effects on liver

Male rats exposed to a NMP level of 400 mg/m^3 (see 5.2) showed after 18 months higher alkaline phosphatase levels in plasma than observed in the rat control group. However, there was no such difference after 24 months of exposure (28).

Dietary administration of NMP to male and female Wistar-derived rats at dose levels of 40, 100, and 250 mg/kg body weight/day for 90 days caused increased SGPT enzyme values at the highest exposure level (23).

Sublethal oral doses of NMP (1/5 of the LD_{50} values; 1.58 g/kg body weight to rats and 0.7 g/kg body weight to rabbits) for 1.5 month caused, in the rats, increased concentrations of glycogen in the liver, bilirubin in serum, and cholesterol in the blood. In the rabbits, dystrophy was observed in the liver. Administration of 1/10 of the LD_{50} values did not cause these effects (27).

Orally administered NMP doses of 0.025, 0.25, or 2.5 mg/kg body weight/day for 6 months caused increased concentration of glycogen in the liver at the highest dose level, but no effects in the rabbits (32).

Dietary administration of NMP to male and female beagle dogs at dose levels of 25, 79, and 250 mg/kg body weight/day for 90 days exhibited, in males, a decrease of the serum cholesterol level with increasing NMP dose level (8). An intravenous dose of 200 mg/kg body weight to rats induced hyperglycemia (4).

5.4. Effects on kidneys

Inhalation of NMP concentrations of 40 and 400 mg/m^3 for 12 months (see 5.2) caused, in male rats, a slightly increased incidence of chronic progressive nephropathy at 40 mg/m^3 but notably not at the higher exposure level, 400 mg/m^3. Furthermore, rats exposed at the same concentrations, and examined before 18 months exhibited chronic progressive nephropathy in 8 out of 23 rats at 400 mg/m^3 and in 4 out of 19 control rats. There were no significant differences in incidence or severity of chronic progressive nephropathy between control and exposed groups after 18 or 24 months of exposure. At the 400 mg/m^3 level, male rats excreted larger urine volumes and both males and females excreted dark yellow urine (28).

A dose-related frequency of dams excreting bright yellow coloured urine was also found at dermal NMP administration of Sprague-Dawley rats (7).

Sublethal oral doses of NMP (rabbits; 1/5 of the LD$_{50}$ value; 0.7 g/kg body weight) for 1.5 month caused dystrophy of the kidneys. Oral administration of 0.35 g/kg body weight (1/10 of the LD$_{50}$ value) did not cause this effect (27).

5.5. Effects on gastrointestinal tract

Sublethal oral doses of NMP (rabbits; 1/5 of the LD$_{50}$ values; 0.7 g/kg body weight) during 1.5 month caused dystrophy in the gastrointestinal tract. Oral administration of 0.35 g/kg body weight (1/10 of the LD$_{50}$ value) did not cause this effect on the gastrointestinal tract (27).

5.6. Effects on heart and circulatory system

An intravenous dose of 500 mg/kg body weight to rats caused hypotension and severe disturbances of the cardiac rhythm. A dose of 200 mg/kg body weight had no effect on the electrocardiogram or arterial blood pressure (4).

Sublethal oral doses of NMP (rabbits; 1/5 of the LD$_{50}$ value; 0.7 g/kg body weight) for 1.5 month caused dystrophy of the heart. Oral administration of 0.35 g/kg body weight (1/10 of the LD$_{50}$ value) did not cause this effect (27).

5.7. Effects on blood and blood forming organs

Exposure to an air concentration of 1000 mg/m^3 NMP (see 5.2) caused, after 10 days of exposure, bone marrow hypoplasia, atrophy of all lymphoid tissue in spleen and thymus, and increased relative and absolute numbers of neutrophils as well as a decreased relative number of lymphocytes. The effect was reversible in surviving rats within 2 weeks after end of exposure (28).

Increased numbers of reticulocytes and neutrophils in the blood was reported in a 6 months study of rats given an oral NMP dose of 2.5 mg/kg body weight/day. The effect was not observed at dose levels of 0.025 or 0.25 mg/kg body weight/day, or in rabbits at any of the three dose levels tested (32).

In the two-year NMP inhalation study (see 5.2), male rats, exposed to 400 mg/m^3 exhibited higher haematocrits than controls after 18 months. However, there was no such effect after 24 months (28). Inhalation of 210 mg NMP/m^3 (mice; 2 h per day , 6 days/week, 1 month) caused increased spleen weight (39).

Dietary administration of NMP to male and female Charles River CD-1 mice at dose levels of 48, 120, and 300 mg/kg body weight/day for 90 days caused depressed spleen weights in females at the highest exposure level and in males at the two highest levels (23).

Dietary administration of NMP to male and female beagle dogs at dose levels of 25, 79, and 250 mg/kg body weight/day for 90 days caused an increase in mean platelet counts that correlated with an increased number of megakaryocytes in the sternal marrow (8).

5.8. Effects on central and peripheral nervous system

Rats exposed to NMP levels of 100, 500, and 1000 mg/m^3 for 6 h/day (see 5.2) showed signs of lethargy and irregular respiration at all exposure levels. The effects were observed 3-4 h after the start of exposure. At 100 and 500 mg/m^3, the effects faded within 18 h and no other significant clinical signs or pathological lesions were recorded. At 1000 mg/m^3 there was no recovery within 18 h. Two years of exposure to 400 mg/m^3 for 6 h/day caused no signs of lethargy and irregular respiration (28).

Mice (NMRI strain), administered an oral NMP dose of 0, 950, 1900, or 3800 mg/kg body weight, exhibited dose related irregular respiration (14).

Effects of NMP on the central nervous system was studied in rats (Mol: WIST) after NMP exposure to 620 mg/m^3 for 90 days (6 h/day, 7 days/week). Examination of evoked potentials in the brain at the termination of exposure showed no indications of neurotoxic effects in the central nervous system (20).

In vitro NMP showed a weak inhibitive activity of acetylcholinesterase (AChE) with an IC$_{50}$ (the concentration of the inhibitor giving 50% inhibition) of 12.1 mM at 0.5 mM AChE (24).

5.9. Other effects

Inhalation of 400 mg NMP/m^3 for 2 years (se 5.2) caused, in male rats, reduced mean body weight compared with controls (28). Decreased body weights could also be observed when mice were exposed by inhalation to 210 mg NMP/m^3 for 2 h/day, 6 days/week for 1 month (39).

A dose-dependent decrease in body weight gain was observed when Beagle dogs were exposed in the diet, to NMP at 25, 79, and 250 mg/kg body weight/day for 90 days (8).

Dietary administration of NMP to male and female Wistar-derived rats at dose levels of 40, 100, and 250 mg/kg body weight/day for 90 days caused, in females, increased thyroid weights at the highest dose level (23).

6. Immunotoxicity and Allergy

There is no information available on immunotoxicity and allergy.

7. Mutagenicity and Genotoxicity

The mutagenicity of NMP was examined in the Salmonella/microsome assay (8 different Salmonella strains, with and without metabolic activation by Arochlor-induced rat liver S9 mix) at six log-linear doses ranging from 0.01 to 1000 μmol/plate (43). The revertant numbers in the base-repair substitution strains TA102 without S9 (at all NMP doses) and TA104 without S9 (at 0.01, 1, and 10 μmol/plate doses) were significantly greater than those of controls. The increase in revertant numbers exhibited no linear dose-response relationships and was less than two-fold greater than the background. NMP was cytotoxic at the highest dose in the preincubation tests.

NMP, in combination with a mixture of ethyl acetate and propionitrile, induced marked mitotic chromosome loss in the D61.M strain of the yeast Saccharomyces cerevisiae (45). Pure NMP induced chromosome loss only in combination with cold shock (31), but not with continuous incubation at 20°C (46).

There was no increase in micronucleated erythrocytes in mouse nor in structural or numerical chromosomal aberrations in Chinese hamster bone marrow after exposure to single oral doses up to 3800 mg/kg body weight (14).

8. Carcinogenicity

In the two-year inhalation study (Charles River CD rats; 120 males and 120 females at each concentration; 0, 40, and 400 mg/m^3; 6 h/day, 5 days/week; whole body exposure) Lee et al (1987) reported that NMP had no oncogenic potential. However, a slightly greater incidence of pituitary tumours was found in both male and female at the low exposure level, but not at the high exposure level. Also,

female rats exhibited, at the low exposure level, a decreased incidence of mammary gland tumours and an increased incidence of mammary gland hyperplasia (28). However, since no detailed carcinogenicity data were reported in the study, the oncogenic potential of NMP may not be evaluated.

9. Reproduction Toxicology

In two different studies, rats (Mol:WIST) were exposed by inhalation to 620 mg/m^3 NMP vapour for 6 h/day (20, 22). In the teratology study (20) the rats were exposed on days 4-20 of gestation. Significantly higher preimplantation loss and lower foetal weight were found in the exposed group than in the controls. Further recordings were delayed ossification of the skull, cervical vertibrae, sternebrae, and metatarsal and digital bones in the exposed animals. No increase in malformations was found.

In the neurobehavioural teratology study (22) the rats were exposed on days 7-20 of gestation. No clinical signs of maternal toxicity was found, i.e. weight gain during gestation, pregnancy length, number of pups and sex distribution in the litter, neonatal death and number of implants per dam were normal. However, there was a neurobehavioural effect of NMP exposure during pregnancy. Tests after weaning revealed impairment of higher cognitive functions related to solving complex tasks. The effects may be permanent as they were observed in adulthood.

The same inhalation exposure profile (620 mg/m^3; 6 h/day, 7 days/week, for 90 days), was performed in the Mol: WIST rats for studies on toxic effects of NMP on testes and semen. Examinations at the termination of exposure and 90 days later showed no abnormal histopathological changes or differences in testes weights between the control and exposure groups. Neither were there any abnormalities of semen, sperm cell morphology or cell concentration (20).

Charles River CD female rats were exposed to either 100 or 360 mg/m^3 airborne NMP for 6 h per day on day 6 through 15 of gestation. The exposure consisted of a mixture of aerosol/vapour of unknown particle size distribution. No effects of the NMP exposure on the outcome of pregnancy, embryonal growth rate or development of vital organs and skeletons of the foetuses were found. Neither were there any abnormal clinical signs or pathological lesions in the maternal rats (28).

Dermal NMP doses to Sprague-Dawley rats (750 mg/kg body weight/day during days 6 through 15 of gestation) caused developmental toxicity. Examination on day 20 of gestation showed reduced dam body weight gain during gestation. The resorption of foetuses was increased and the foetal body weight decreased. In addition, skeletal anomalies including missing sternebrae, fused/split/extra ribs, incomplete closing of the skull, incomplete ossification of vertebrae, fused atlas and occipital bones, and reduced or incomplete hyoid bone were observed at this dose. Maternal toxicity was also reported. However, the increased number of resorptions as well as the general decrease in foetal body weight may explain the lower maternal weight. Therefore the maternal toxicity is

questionable. No effects in dams or foetuses were seen at doses of 37 or 237 mg/kg body weight/day (7).

In a preceding dose range-finding study, a dermal dose of 1100 mg/kg body weight/day during days 6 through 15 of gestation was embryolethal (65 out of 66 foetuses were resorbed), and caused a depression in dam body weight gain. A dose of 500 mg/kg body weight/day had no adverse effect on pregnancy, dam body weights, implantations or gestation (7).

Various intraperitoneally administered NMP doses (14-166 mg/kg body weight; single or repeatedly) to two strains of mice (AB Jena and C57B1), during various phases of pregnancy, caused increased post-implantation loss and a reduced body weight of the foetuses. Morphological defects such as 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 were observed. The most severe embryotoxic effect after a single administration (166 mg/kg body weight) in the Jena strain was observed on the seventh day of gestation when 23% of the implanted embryos died and on the ninth day of gestation when a rate of 19% of foetal malformations was observed. The Lowest Observed Adverse Effect Level (LOAEL) for repeated administrations through day 7 to 11 of gestation was 92 mg/kg body weight in the AB Jena mice strain and 74 mg/kg body weight in C57B1. However, since no information on maternal toxicity is given in this study, evaluation of the results is difficult (37).

Repeated intraperitoneal (1570 mg/kg body weight) and oral (2640 mg/kg body weight) doses to NMRI-mice through days 11 to 15 of gestation caused increased resorption rate, increased incidence of runts and diminished foetal weight and length and an increased rate of malformations such as cleft palate. No maternal toxicity was observed. Repeated intraperitoneal or oral doses of 630 mg/kg body weight and 1060 mg/kg body weight, respectively, caused no observable embryotoxicity (15).

Repeated oral NMP doses of 1000 mg/kg body weight/day to Sprague-Dawley rats through days 6 to 15 of gestation killed 95% of the embryos and caused malformations in 8 out of 15 surviving developed foetuses as well as reduction in body weight of the dams. No adverse effects were observed at repeated doses of 330 mg/kg body weight/day (15, 16).

Oral (40, 125, or 400 mg/kg body weight/day) NMP doses to Sprague-Dawley rats through days 6 to 15 of gestation caused, at the highest dose, maternal toxicity consisting of weight gain decrement during exposure and, compared to the control rats, reduced foetal body weights and increased incidence of foetal stunting. The No Observable Adverse Effect Level (NOAEL) was 125 mg/kg body weight/day for maternal and foetal toxicity (18).

New Zealand White SPF female rabbits (20 rabbits at each dose level) were orally administered NMP doses of 55, 175, and 540 mg/kg body weight/day on day 6 to 18 of gestation. Maternal toxicity, decreased body weight gain, was observed at 175 and 540 mg/kg body weight/day. Developmental toxicity, such as post-implantation loss, altered foetal morphology and increased incidences of

Table 2. N-methyl-2-pyrrolidone (NMP) exposure and accompanying effects (6).

NMP air concentration (mg/m^3)	Observed and/or recorded effects
200-340	Unbearable for even a minimal time period.
62-70	Immediate perception. Immediately uncomfortable. Acceptable only for about 30 seconds. Eye irritation reported for this short-time exposure.
3-6	Immediate perception. Uncomfortable after about 30 min. Eye irritation. Headaches.
<0.1	No effect.

cardiovascular and skull malformations, were observed at 540 mg/kg body weight/day (23).

In a multi-generation reproduction study (23), rats were exposed in the diet to NMP doses of 50, 160, and 500 mg/kg body weight/day (Spraque-Dawley CDBR rats; 30 males and 30 females at each dose level and generation). The first parental generation (P1) was exposed at least 10 weeks prior to mating (mating continued for about 3 weeks), during gestation, lactation and through weaning of the litter (F1a), at least 2 weeks prior to a second mating, and during gestation, lactation and through weaning of the litter (F1b). The second parental generation (P2=F1b) was, from Day 21 postpartum, exposed at least 10 weeks prior to mating, during gestation, lactation and through weaning of the litter (F2a), at least 2 weeks prior to a second mating, and during gestation, lactation and through weaning of the litter (F2b). The highest dose level (500 mg/kg body weight/day) caused reproductive and developmental toxicity, shown by decreased parental body weight, food consumption, and reproductive parameters, with a concomitant reduction in survival and growth rates in the offspring. The data from the 50 and 160 mg/kg body weight/day experiments do not clearly demonstrate a NOAEL (19).

10. Exposure, Effect and Response Relationships

10.1. Effects of short-term exposure

The short-term NMP exposure-effect relationships from a microeletronics industry (Table 2) are based on data from time-weighed full-shift average (6). Thus, these averages may comprise high peak exposure periods.

Table 3. Experimental inhalation toxicity of N-methyl-2-pyrrolidone.

Dose (mg/m^3)	Species	Duration	Effects	Ref
5100	Rat	6h	No lethal effect observed.	23
1500	Rat	6h/d, 10d	No lethal effect observed.	23
1400	Several	6-8h	No lethal effect observed.	23
1000	Rat	6h/d, 5d/w, 10d	8/30 died. Focal pneumonia, bone marrow hypoplasia, atrophy of spleen and thymos. Increased relative and absolute number of neutrophils. Decreased relative number of lymphocytes. Lethargy and irregular respiration.	28
500	Rat	6h/d, 5d/w, 4w	Lethargy and irregular respiration.	28
400	Rat	6h/d, 5d/w, 2y	Dark urine. In males: Increased haematocrit, alkaline phosphatase activities and urine volumes and reduced body weight.	28
180-200	Mouse	2h/d, 6d/1w, 1m	Decreased body weight gain, increased spleen weight and a mild respiratory irritation.	39
100-150	Rat	4h/d, 5m	Mild respiratory irritation.	39
100	Rat	6h/d, 5d/w, 4w	Lethargy and irregular respiration.	28
40	Rat	6h/d, 5d/w, 2y	Dark urine.	28

Several=rats, mice, cats, guinea pigs, and rabbits.
d=day, w=week, m=month, and y=year

10.2. Effects of long-term exposure

No information on humans is available. Effects on animals are shown in Table 3. For the high NMP air concentrations reported it must be taken into account, that air saturated with NMP at 20°C has a NMP concentration of 1400 mg/m^3. Thus higher airborne exposure levels consist of mixtures of vapour and aerosol.

10.3. Developmental

The reproductive toxicity have been studied in rabbits (23), rats (7,15,16,18, 20,22,28), and mice (15,37) after various routes of NMP administration during the gestation period (Table 4).

Table 4. Reported studies of maternal and developmental toxicity of N-methyl-2-pyrrolidone in some different species after various routes of administration.

Administration			Observed effects	
Route (Ref.)	Treatment	Day/s in the gestation period	Maternal	Embryo/Foetus
RABBIT				
Oral[1] (23)	540 mg/kg/d	6-18	Effects.	Postimplant.loss. Malform.
	175 mg/kg/d	"	Effects.	N.o.
	55 mg/kg/d	"	N.o.	N.o.
RAT				
Inhalation[2] (20)	620 mg/m^3	4-20 (6h/d)	N.o.	Preimplant.loss. Decr.b.w. Delayed ossification.
Inhalation[2] (22)	620 mg/m^3	7-20 (6h/d)	N.o.	Neurobehavioural effects.
Inhalation[3] (28)	360 mg/m^3 100	6-15 (6h/d) "	N.o. N.o.	N.o. N.o.
Oral[4] (16)	1000 mg/kg/d 330	6-15 "	Decr. b.w. gain N.o.	Embryomort.(95%). Malform. N.o.
Oral[4] (18)	400 mg/kg/d 125 40	6-15 " "	Decr. b.w. gain N.o. N.o.	Decreased. b.w. Incr. stunting. N.o. N.o.
Dermal[4] (7)	750 mg/kg/d 237 75	6-15 " "	Decr. b.w. gain[a] N.o. N.o.	Incr. resorp. Decr.b.w. Malform. N.o. N.o.
MOUSE				
Oral[5] (15)	2640 mg/kg/d 1060	11-15 "	N.o. N.o.	Incr. resorpt .Decr. b.w. Malform. N.o.
I. p.[5] (15)	1570 mg/kg/d 630	11-15 "	N.o. N.o.	Incr. resorpt. Decr. b.w. Malform. N.o.
I.p.[6] (37)	166 mg/kg 166 129 129 mg/kg/d 92 74 74 37 14	3, 7, or 11 9 " 7-11 " " 1-14 " "	N.r. " " " " " " " "	Postimplantation loss. Postimplantation loss. Malform. Postimplantation loss. Malform. Postimplantation loss. Postimplantation loss. Postimplantation loss. Postimplantation loss. Postimplantation loss. N.o.
I. p.[7] (37)	130 mg/kg/d 74 37 74	7-11 " " 1-14	N.r. " " "	Postimplantation loss. Malform. Embryomortality. Postimplantation loss. Embryomortality.

N.o.=No effects observed; N.r.=Not reported; Incr.=Increased; Decr.=Decreased; I.p.=intraperitoneal; b.w.=body weight; [a] Uncertain observation; [1] New Zealand White SPF; [2] Mol:WIST rats; [3] Charles River CD rats; [4] Spraque Dawley rats ; [5] NMRI-mice; [6] AB Jena; mice; [7] C57B1 mice

In rabbits, the LOAEL and the NOAEL for maternal toxicity at oral administration are 175 and 55 mg/kg body weight/day, respectively, and for developmental toxicity 540 and 175 mg/kg body weight/day, respectively.

In rats, the LOAEL and the NOAEL for both maternal and developmental toxicity after oral administration are 400 and 330 mg/kg body weight/day, respectively. Dermal administration causes both maternal and developmental toxicity at 750 and 237 mg/kg body weight/day, respectively. Data for LOAEL are not avaible for inhalation exposure, whereas the NOAEL for maternal toxicity is 620 mg/m^3 for 6h/day. The concentrations causing developmental toxicity are 620 and 360 mg/m^3, respectively.

The reported data of reproduction toxicity in mice are defective and may not be evaluated.

11. Research Needs

The knowlegde of the effects of NMP exposure in humans is minimal, and furthermore, the few reported studies give contradicting results. The industrial exposure pattern needs mapping. Human studies involving experimental inhalation are needed for evaluation of the effects of short-term exposure. The metabolism in humans needs to be evaluated for assessing the risk of exposure and for studies of the possibility of biological monitoring. Studies of dermal uptake in humans are very much needed, especially considering concomitant exposure to other toxic compounds in industry.

There are further needs for skilful reproductive toxicity studies in different species. It is important to assess the dose-response relationship and to estimate the NOAEL for the central nervous system of the foetus. Further, studies of exposure to NMP before and round the time of implantation are needed for assessing the preimplantation loss.

The carcinogenic effect of subchronic and chronic exposure to NMP and the immunological or allergic effects of NMP should be further investigated.

12. Discussion and Evaluation

NMP, a widely used solvent, is involved in a variety of chemical reactions. NMP is increasingly used as a substitute for other solvents of higher inherent toxicity in the occupational and environmental settings, e.g. chlorinated hydrocarbons (23).

There is minimal attention in the published literature regarding occupational exposure levels of NMP. This may be due to low NMP air concentrations in workshops with normal hygienic standard as compared to the level of occupational exposure limits (OEL; 200-400 mg/m^3). Thus, the evaluation of the effects of exposure to NMP is almost exclusively based on animal data. The

toxicity of NMP has earlier been evaluated by Lundberg in 1987 (30), US Environmental Protection Agency (EPA) in 1990 (17), and Wallén in 1991 (40).

The pharmacokinetics of NMP in rats after various routes of administration, intravenous (42), oral (33), percutaneous (33) and inhalation (35), are similar. NMP is efficiently absorbed from the respiratory and gastrointestinal tracts as well as through the skin and rapidly distributed to all organs. Data indicate a greater percutaneous uptake in female rats than in males (33). NMP passes the placenta and may be accumulated in the foetus (35). NMP is eliminated by biotransformation, mainly to 5-hydroxy-2-methyl-N-pyrrolidone which is excreted in the urine (44). The urinary excretion of radio-labeled NMP accounted for 80% within 24 h (33, 42). NMP is probably reabsorbed in the kidneys (33).

The acute toxicity studies in rodents exhibit NMP as moderately toxic (26). No LD_{50} values after inhalation of NMP are reported. In various studies, however, rats have been exposed to 1500-6000 mg NMP/m^3 without an increase in mortality. This indicates the same level of acute toxicity due to NMP exposure by inhalation as for other routes of administration.

There is, however, a discrepancy in the results of the reported inhalation toxicity studies. Inhalation of 1000 mg NMP/m^3 for 10 days caused a marked increase in the mortality of rats, as well as lethargy and irregular respiration (28). Furthermore, inhalation of 100 or 500 mg/m^3 for 4 weeks caused lethargy and irregular respiration, although to a minor extent. However, 400 mg/m^3 for two years did not cause any of these effects (28). The discrepancy may be due to shortcomings in the reported studies. However, the methods used to generate NMP exposure levels may have been of vital importance. Due to the low volatility and the hygroscopicity of NMP, the air-borne NMP may consist of a mixture of vapour and aerosol. The toxicity studied in inhalation experiments may be determined by the place of deposition. Thus, the discrepancy in the results of the reported inhalation tests may be due to different vapour/aerosol ratio as well as particle size distribution.

In sum, the animal studies show that exposure to NMP may cause degenerative changes in the respiratory system, the hemopoietic, and lymphoid tissues. Some studies show that NMP exposure affect males and females differently. These differences are probably random and not caused by sex differences. Excretion of dark coloured (yellow) urine is reported in most studies but has not been further investigated. These findings of adverse effects show that exposure to NMP may present a risk of injury to human health due to its potential to cause subchronic toxicity.

Lee et al (1987) reported that NMP exhibited no carcinogenic effects in rats in their two-year study. The slightly greater incidence of pituitary tumours, the decreased incidence of mammary gland tumours and the increased incidence of mammary gland hyperplasia reported is not adherent with detailed data, and may thus not be evaluated. No other studies of the carcinogenic effects of NMP are available. For adequate evaluation of the carcinogenicity of NMP further studies are needed.

The mutagenic potential of NMP is weak. Only a slight increase in the number of revertants was observed when tested in the Salmonella assay with base-pair substitution strains (43). NMP has been shown to induce aneuploidy in yeast (Saccharomyces cerevisiae) cells (31).

There are some shortcomings in the reported studies of the reproductive toxicity of NMP. A dose-response relationship could not be established because an insufficient number of doses were used. No, or incomplete, data on the maternal toxicity have been reported, the major organogenesis period has not been completely covered, and in each study only one species has been studied. However, despite these limitations, the studies on reproductive toxicity show that NMP may cause developmental toxicity at doses causing no or mild maternal toxicity.

The dermal toxicity of NMP in animals is considered to be low to moderate (2,11). Attempts to sensitize guinea pigs have been unsuccessful (23). In humans, experimental skin exposure to NMP may cause transient irritation (23). Furthermore, reversible dermatitis has been reported in workers after a few days work with NMP (29). Although the experimental study did not indicate skin sensitization, NMP exposure to the skin may be associated with a considerable risk in the occupational setting. Due to the low vapour pressure, skin penetration ability, and penetration enhancing power of NMP, an additional risk of NMP skin exposure in the industrial setting may be percutaneous absorption of NMP (33) as well as together with other toxic compounds (25).

NMP is regarded as a moderate to severe eye irritant having produced corneal opacity and conjunctivitis in rabbit. Permanent eye damage has not been reported (2). Data on human exposure in a microelectronics industry (6) exhibited severe eye irritation and headaches after 30 min exposure to NMP levels of 3-6 mg/m^3. In the evaluation of the risk of NMP exposure it must be taken into account that the 8-h TWA of 3 mg/m^3 may contain peak exposure periods and the influence of peak amine exposures on occular effects has earlier been reported (47). Exposures to NMP levels of 280 mg/m^3 or higher were unbearable even for a few seconds.

The critical effect of NMP during occupational exposure is irritation of the eye and the skin. Additionally, another critical effect of NMP may be its enhancing skin penetration effect of other compounds. The evaluation of the critical effect which should be considered when establishing an occupational exposure limit for NMP is, however, based on a very limited amount of data.

13. Summary

A critical survey and evaluation of the relevant literature, to be used as a basis for establishing an occupational exposure limit for N-methyl-2-pyrrolidone (NMP), is presented.

NMP is a widely and increasingly used solvent. The toxicity of NMP is, however, not well known. The observed irritative effects on skin and eyes predict that NMP may be a moderate to severe irritant. Subchronic exposure to NMP may cause degenerative tissue changes and affect the respiratory, hemopoietic, and lymphoid system. Lethargy and irregular respiration observed after both inhalation and oral administration may be due to a neurotoxic effect. NMP seems to possess a weak mutagenic effect. For evaluation of the carcinogenic potential further data are needed.

Reproductive toxicity studies show developmental toxicity at doses causing no or mild maternal toxicity. After different routes of administration of NMP in rabbits, rats, and mice, effects such as decreased dam body weight gain, increased resorption rate, decreased body weights, delayed ossification, and an increased rate of malformation were observed. Prenatal exposure to NMP may in rats cause postnatal neurobehavioural effects.

The critical effect of NMP in the occupational exposure is irritation on eye and skin. Additionally, another critical effect of NMP may be its enhancing skin penetration effect on other compounds.

Key words: developmpental toxicity, exposure, eye irritation, maternal toxicity, metabolism, N-methyl-2-pyrrolidone, skin irritation, subchronic effects.

14. Summary in Swedish

Åkesson B. 115. N-metyl-2-pyrrolidon. Nordiska expertgruppen för
kriteriedokumentation av kemiska hälsorisker. *Arbete och Hälsa* 1994;40:1-24.

Kritisk genomgång och värdering av den litteratur, som funnits relevant för
fastställande av ett yrkeshygieniskt gränsvärde för N-metyl-2-pyrrolidon.

Trots att NMP är ett vanligt förekommande lösningsmedel, med allmän och
ökande användning, är kunskapen om dess toxicitet liten. Den irritation som på
människa observerats på hud och ögon tyder på att NMP är ett irriterande/kraftigt
irriterande ämne.

Subkronisk NMP exponering kan orsaka vävnadskada och påverka andning,
blodbildning och lymfsystem. Apati och oregelbunden andning, som observerats
både efter inandning och oral administration, kan vara en neurotoxisk effekt. Den
mutagena effekten hos NMP är liten. NMP's cancerogena effekt kan ej utvärderas
då data saknas. Exponeringsdoser, som har ingen eller endast mild toxisk effekt
på modern, har i reproduktionsstudier visat utvecklingsskadande toxicitet. När
dräktiga gnagare på olika vägar administrerats NMP, har man observerat minskad
viktökning hos modern, ökad fosteravstötning, minskad fostervikt, försenad
skelettbildning och en ökad grad av missbildningar. NMP exponering före födseln
kan orsaka effekter på det neurologiska beteendet.

Den kritiska effekten av yrkesmässig NMP exponering är irritation på hud och
ögon. En annan effekt, som kan ha stor betydelse, är NMP's förmåga att öka
upptaget genom huden av andra ämnen.

Nyckelord: exponering, hud irritation, metabolism, N-metyl-2-pyrrolidon,
reproduktionstoxicitet, subkroniska effekter, ögon irritation.

15. References

1. Andersson B, Andersson K. Determination of heterocyclic tertiary amines in air. *Appl Occup Environ Hyg* 1991;6:40-43.

2. Ansell JM, Fowler JA. The acute oral toxicity and primary ocular and dermal irritation of selected N-alkyl-2-pyrrolidones. *Fd Chem Toxic* 1988;26:475-479.

3. Anundi H, Lind M-L, Friis L, Itkes N, Langworth S, Edling C. High exposures to organic solvents among graffiti removers. *Int Arch Occup Environ Health* 1993;65:247-251.

4. Baggio G, Ferrari F, Ferrari P. Adrenaline release caused by N-methylpyrrolidone injected into the adrenal gland. Farmaco, Ed. *Prat* 1976;31:275-282.

5. Bartsch W, Sponer G, Dietmann K, Fuchs G. Acute toxicity of various solvents in the mouse and rat. *Arzneim.-Forsch (Drug Res)* 1976;26:1581-1583.

6. Beaulieu HJ, Schmerber KR. M-Pyrol (NMP) use in the microelectronics industry. *Appl Occup Environ Hyg* 1991;6:874-880.

7. Becci PJ, Knickerbocker MJ, Reagan EL, Parent RA, Burnette LW. Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats. *Fundam Appl Toxicol* 1982;2:73-76.

8. Becci PJ, Gephart LA, Koschier FJ, Johnson WD, Burnette LW. Subchronic feeding study in beagle dogs of N-methylpyrrolidone. *J Appl Toxicol* 1983;3:83-86.

9. Blome H, Hennig M. Messung ausgewählter aliphatischer und aromatischer Amine in der Luft von Arbeitsbereichen. *Staub-Reinhalt Luft* 1984;44:27-32.

10. Chow ST, Ng TL. The biodegradation of N-methyl-2-pyrrolidone in water by sewage bacteria. *Water Res* 1983;17:117-118.

11. Clark B, Furlong JW, Ladner A, Slovak AJM. Dermal toxicity of dimethyl acetylenedicarboxylate, N-methylpyrrolidone, triethylene glycol dimethyl ether, dioxane and tetralin in the rat. *IRCS Med Sci* 1984;12:296-297.

12. Dell UD, Fiedler J, Jacobi H, Kamp R. Beitrag zur Bestimmung von 2-Oxo-pyrrolidin-Derivaten aus biologischem Material. *Fresenius Z Anal Chem* 1980;304:407-411.

13. Draize JH, Woodward G, Calvery HO. Methods for the study of irrition and toxicity of substances applied topically to the skin and mucous membranes. *J Pharmacol Exp Ther* 1944;82:377.

14. Engelhardt G, Fleig H. 1-Methyl-2-pyrrolidinone (NMP) does not induce structural and numerical chromosomal aberrations i vivo. *Mutation Res* 1993;298:145-155.

15. Environmental Protection Agency. *Letter from Ciba-Geigy Corp to USEPA regarding initial information on studies demonstrating embryolethality in both the mouse and rat with N-methylpyrrolidone.* NITS: OTS0513411. (EPA Doc I.D. 88-880000001).

16. Environmental Protection Agency. *Evaluation of development toxicity on N-methylpyrrolidone with attachment and cover letter dated 052588.* NITS: OTS0513411-1. (EPA Doc I.D. 89-880000180).

17. Environmental Protection Agency. N-Methylpyrrolidone; Proposed test rule. OPTS 42114. *Federal Register* 1990;55:11398-11407.

18. Environmental Protection Agency. *Developmental toxicity study in rats with N-methylpyrrolidone.* NITS: OTS0539109. (EPA Doc I.D. 88-920001848).

19. Environmental Protection Agency. EPA to study paint stripping chemicals, expedite NMP review. *Pesticide Toxic Chem News* 1992;20(50):22-23.

20. Fries AS, Hass U, Jakobsen BM, Jelnes JE, Lund SP, Simonsen L. *Toxic effects of N-methylpyrrolidone on fetal development, the central nervous system, and semen in rats.* Copenhagen: Arbejdsmiljøfonden, 1992. (In Danish; summary and conclusion in English). ISBN 87-7359-543-8.

21. Gordon A, Gordon M. Analysis of volatile organic compounds in a textile finishing plant effluent.*Trans Ky Acad Sciences* 1981;42(3-4):149.

22. Hass U. *Neurobehavioural teratology of industrial chemicals. Effects of prenatal exposure to organic solvents on postnatal development and behaviour - validation and use of a screening test battery in laboratory rats.* Copenhagen: National Institute of Occupational Health, 1992. (Ph.D thesis).

23. International Specialty Products (ISP), Chemical Division: M-Pyrol; N-Methyl-2-Pyrrolidone Handbook with Toxicity Overview suppl. New York.

24. Karadsheh N, Kussie P, Linthicum DS. Inhibition of acetylcholinesterase by caffeine, anabasine, methyl pyrrolidine and their derivatives. *Toxicol Lett* (Amst) 1991;55:335-342.

25. Kawaguchi T, Seki T, Juni K. Percutaneous absorption of zidovudine through rat and human skin. *Chemotherapy* (Tokyo) 1990;38:897-901. (In Japanese)

26. Klaassen CD. Principles of toxicology. In: Klaassen CD, Amdur MO, Doull J, eds. *Toxicology.* MacMillan Publ Co, 1986:11-32. ISBN 0-02-36450-0.

27. Kommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe der Deutschen Forschungsgemeinschaft. *Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinsche Begründung von MAK-Werten* .16 ed. Weinheim: Verlag Chemie, 1990.

28. Lee KP, Chromey NC, Culik R, Barnes JR, Schneider PW. Toxicity of N-methyl-2-pyrrolidone (NMP): Teratogenic, subchronic, and two-year inhalation studies. *Fundam Appl Toxicol* 1987;9:222-235.

29. Leira HL, Tiltnes A, Svendsen K, Vetlesen L. Irritant cutaneous reactions to N-methyl-2-pyrrolidone (NMP). *Contact Dermatitis* 1992;27:148-150.

30. Lundberg P. N-methyl-2-pyrrolidone. Scientific basis for Swedish occupational standard. *Arbete och Hälsa* 1987;39:173-177.

31. Mayer VW, Goin CJ, Taylor-Mayer RE. Aneuploidy induction in Saccharomyces cerevisiae by two solvent compounds, 1-methyl-2-pyrrolidinone and 2-pyrrolidinone. *Environ Mutagen* 1988;11:31-40.

32. Meleschenko KF. Sanitary hygienic characterizing of methylpyrrolidone as water pollution. *Gig Sanit* 1970;36:84-85. (In Russian)

33. Midgley I, Hood AJ, Chasseaud LF, Brindley CJ, Baughman S, Allan G. Percutaneous absorption of co-administered N-methyl-2-[^{14}C]pyrrolidinone and 2-[^{14}C]pyrrolidinone(^{14}C) in the rat. *Fd Chem Toxic* 1992;30:57-64.

34. Priborsky J, Mühlbachova E. Evaluation of in vitro percutaneous absorption across human skin and in animal models. *J Pharm Pharmacol* 1990;42:468-472.

35. Ravn-Jonsen A, Edelfors S, Hass U, Lund SP. The kinetic of N-methyl-2-pyrrolidinone in pregnant rats and their foetuses compared with non-pregnant rats. *Toxicol Letters* 1992; suppl. 136 (Abstract).

36. Sasaki H, Kojima M, Mori Y, Nakamura J, Shibasaki J. Enhancing effect of pyrrolidone derivatives on transdermal drug delivery. I. *Int J Pharmac* 1988;44:15-24.

37. Schmidt R. Tierexperimentelle Untersuchungen zur embryotoxischen und teratogenen Wirkung von N-Methyl-Pyrrolidon (NMP). *Biologische Rundschau* 1976;14:38-41.

38. Southwell D, Barry BW, Evans R, Fildes FJT. The accelerant effect on N-methylpyrrolidone of the model compound mannitol into cadaver human skin, a transient effect. *J Pharm Pharmacol* 1981;33: Suppl. 3P.

39. Stasenkova KP, Kochetkova TA. Toxicological characteristics of methyl- pyrrolidone. *Teksikol Novykh Prom Khim Veshchestv* 1965;7:27-28.

40. Wallén M. *Methylpyrrolidinone.* Stockholm: National Chemicals Inspectorate, 1991. (Scientific Documentation and Research)

41. Weisbrod D, Seyring B. Comparative studies on acute toxicity to warm-blooded animals and fish of technical solvent N-methylpyrrolidin-2-one and N-methyl-ε-caprolactam. *Toxikol Anal Probl Lösungsmittel Expo Fortr Minisymp* 1979:55-59.

42. Wells DA, Digenis GA. Disposition and metabolism of double-labeled [^{3}H and ^{14}C] N-methyl-2-pyrrolidinone in the rat. *Drug Metab Dispos* 1988;16:243-249.

43. Wells DA, Thomas HF, Digenis GA. Mutagenicity and cytotoxicity of N-methyl-2-pyrrolidinone and 4-(methylamino)butanoic acid in the Salmonella/microsome assay. *J Appl Toxicol* 1988;8:135-139.

44. Wells DA, Hawi AA, Digenis GA. Isolation and identification of the major urinary metabolite of NMP in the rat. *Drug Metab Dispos* 1992;20:124-126.

45. Zimmermann FK, Holzwarth ULI, Scheel I, Resnick MA. Aprotic polar solvents that affect porcine brain tubulin aggregation in vitro induce aneuploidy in yeast cells growing at low temperature. *Mutation Res* 1988;201:431-442.

46. Zimmermann FK, Scheel I, Resnick MA. Induction of chromosome loss by mixtures of organic solvents including neurotoxins. *Mutation Res* 1989;224:287-303.

47. Åkesson B, Bengtssson M, Florén I. Visual disturbances after industrial triethylamine exposure. *Int Arch Occup Environ Health* 1986;57:297-302.

Acknowledgements.

Submitted for publication , December 21, 1994

Appendix 1.

Permitted or recommended maximum levels of N-methyl-2-pyrrolidone (NMP) in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	100	400		1988	1
Finland	25	-		1993	2
Iceland	-	-		1989	3
Netherlands	100	400		1994	4
Norway	50	200		1989	5
Sweden	50	200		1993	6
	75	300	15 min		
USA (ACGIH)	-	-		1994-95	7
(NIOSH)	-	-		1990-91	8

References

1. *Grænsværdier for stoffer og materialer*. København: Arbejdstilsynet,1988 (Anvisning Nr.3.1.0.2) .

2. *HTP-värden 1993*. Tammerfors: Arbetsministeriet, 1993 (Säkerhetsmeddelande 25).
   ISBN 951-47-8343-3.

3. *Mengunarmörk og adgerdir til ad draga úr mengun*. Skrá yfir mengunarmörk. Reykjavik: Vinnueftirlit Rikisins,1989.

4. *De Nationale MAC-lijst 1994*. Den Haag: 1994 (Arbeidsinspectie P 145).
   ISBN 90-399-0600-9.

5. *Administrative normer for forurensinger i arbeitsatmosfaere*. Veiledning til arbeidsmiljøloven. Oslo: Direktoratet for arbeidstilsynet, 1989 (Bestillingsnr. 361).

6. *Hygieniska gränsvärden.*. Stockholm: Arbetarskyddsstyrelsen, 1993 (AFS 1993:9).
   ISBN 91-7930-046-4.

7. *Threshold Limit Values and biological exposure indices for 1994-95*. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists,1994. ISBN 1-882417-06-2.

8. Rules and Regulations. *Federal Register Vol.54*. Washington: US Government, 1990:2329-2984.

CRITERIA DOCUMENTS FROM THE NORDIC EXPERT GROUP

The Criteria Documents are in a Scandinavian language, with summary in English. Those marked with * are in English. Those marked with D are published in collaboration with the Dutch Expert Committee for Occupational Standards (DECOS). Those marked with N are published in collaboration with NIOSH, USA.

Acetaldehyde	Arbete och Hälsa 1986:25
Acetone	Arbete och Hälsa 1986:39
Acetonitrile	Arbete och Hälsa 1989:22, 1989:37*
Acrolein	Arbete och Hälsa 1991:45
Acrylates	Arbete och Hälsa 1983:21
Acrylonitrile	Arbete och Hälsa 1985:4
Allyl alcohol	Arbete och Hälsa 1986:8
Aluminium	Arbete och Hälsa 1992:45, 1993:1*
Ammonia	Arbete och Hälsa 1986:31
Arsenic, inorganic	Arbete och Hälsa 1981:22, 1991:9, 1991:50*
Arsine	Arbete och Hälsa 1986:41
Asbestos	Arbete och Hälsa 1982:29
Benomyl	Arbete och Hälsa 1984:28
Benzene	Arbete och Hälsa 1981:11
Boric acid, Borax	Arbete och Hälsa 1980:13
1,3-Butadiene	Arbete och Hälsa 1994:36*
1-Butanol	Arbete och Hälsa 1980:20
Cadmium	Arbete och Hälsa 1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	Arbete och Hälsa 1990:2*D
Carbon monoxide	Arbete och Hälsa 1980:8
Chlorine, Chlorine dioxide	Arbete och Hälsa 1980:6
Chloromequat chloride	Arbete och Hälsa 1984:36
4-Chloro-2-methylphenoxy acetic acid	Arbete och Hälsa 1981:14
Chlorophenols	Arbete och Hälsa 1984:46
Chromium	Arbete och Hälsa 1979:33
Cobalt	Arbete och Hälsa 1982:16
Cobalt and cobalt compounds	Arbete och Hälsa 1994:39*
Copper	Arbete och Hälsa 1980:21
Creosote	Arbete och Hälsa 1988:13, 1988:33*
Cyclohexanone, Cyclopentanone	Arbete och Hälsa 1985:42
n-Decane	Arbete och Hälsa 1987:25, 1987:40*
Deodorized kerosene	Arbete och Hälsa 1985:24
Diacetone alcohol	Arbete och Hälsa 1989:4, 1989:37*
Diesel exhaust	Arbete och Hälsa 1993:34, 1993:35*
2-Diethylaminoethanol	Arbete och Hälsa 1994:25*N
Diethylamine, Diethylenetriamine, Dimethylamine & Ethylenediamine	Arbete och Hälsa 1994:23*
Diisocyanates	Arbete och Hälsa 1979:34, 1985:19
Dimethyldithiocarbamates	Arbete och Hälsa 1990:26, 1991:2*
Dimethylethylamine	Arbete och Hälsa 1991:26, 1991:50*
Dimethylformamide	Arbete och Hälsa 1982:28
Dimethylsulfoxide	Arbete och Hälsa 1991:37, 1991:50*
Dioxane	Arbete och Hälsa 1982:6
Epichlorohydrin	Arbete och Hälsa 1981:10
Ethyl acetate	Arbete och Hälsa 1990:35*D
Ethylbenzene	Arbete och Hälsa 1986:19
Ethylene bisdithiocarbamates	Arbete och Hälsa 1993:24, 1993:35*