Concise International Chemical Assessment Document 35

N-METHYL-2-PYRROLIDONE

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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TABLE OF CONTENTS

FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, the appropriate form of the document (i.e., EHC or CICAD), and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents to ensure that it meets the specified criteria for CICADs.

The draft is then sent to an international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

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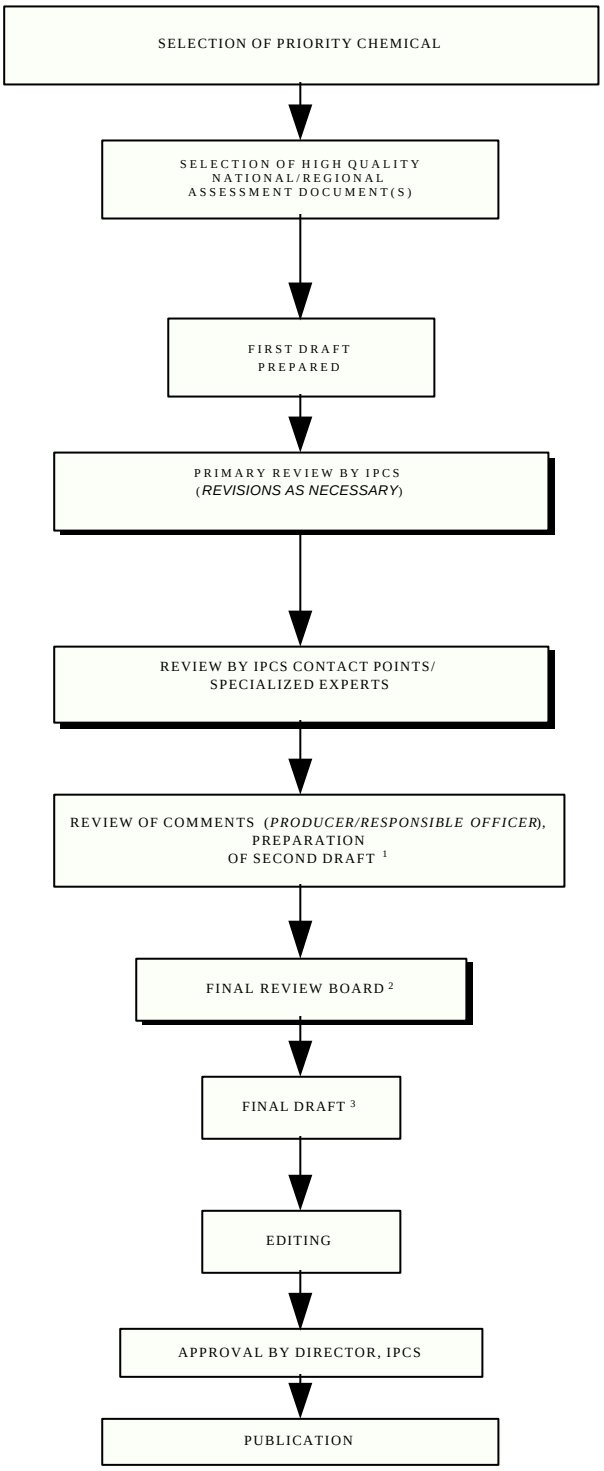
[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

A consultative group may be necessary to advise on specific issues in the risk assessment document.

The CICAD Final Review Board has several important functions:

– to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
– to verify that the peer reviewers' comments have been addressed appropriately;
– to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
– to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on *N*-methyl-2-pyrrolidone was based primarily on a review prepared for the Nordic Expert Group (Åkesson, 1994) and on a review of human health concerns prepared by the United Kingdom's Health and Safety Executive (HSE, 1997). For data on environmental fate and behaviour, no comprehensive document of the same status was identified. Instead, HSDB (1997) was used as an additional source document. Supplementary unvalidated data, mainly ecotoxicological, were found in IUCLID (1995), and some additional articles were identified in the open literature (searched through July 1998). Information concerning the nature and availability of the source documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was considered at a meeting of the Final Review Board, held in Stockholm, Sweden, on 25–28 May 1999. Participants at the Final Review Board meeting are listed in Appendix 3. After the Final Review Board meeting, advice was sought from a consultative group, consisting of Dr B. Heinrich-Hirsch, BgVV, Germany, Mr Frank Sullivan, Consultant, United Kingdom, Dr Robert Chapin, National Institute of Environmental Health Sciences, USA, Dr Gary Kimmel, US Environmental Protection Agency, USA, and Professor Rolf Hertel, BgVV, Germany (Chair), regarding the interpretation of data on the reproductive toxicity of *N*-methyl-2-pyrrolidone. Based on the advice from this group, the author, in collaboration with the Secretariat, revised the relevant sections of the document. The revised CICAD was approved as an international assessment by the members of the Final Review Board in a mail ballot. The International Chemical Safety Card for *N*-methyl-2-pyrrolidone (ICSC 0513), produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

N-Methyl-2-pyrrolidone (NMP) (CAS No. 872-50-4) is a water-miscible organic solvent. It is a hygroscopic colourless liquid with a mild amine odour. NMP is used in the petrochemical industry, in the microelectronics fabrication industry, and in the manufacture of various compounds, including pigments, cosmetics, drugs, insecticides, herbicides, and fungicides. An increasing use of NMP is as a substitute for chlorinated hydrocarbons.

NMP may enter the environment as emissions to the atmosphere, as the substance is volatile and widely used as a solvent, or it may be released to water as a component of municipal and industrial wastewaters. The substance is mobile in soil, and leaching from landfills is thus a possible route of contamination of groundwater.

In air, NMP is expected to be removed by wet deposition or by photochemical reactions with hydroxyl radicals. As the substance is completely miscible in water, it is not expected to adsorb to soil, sediments, or suspended organic matter or to bioconcentrate. NMP is not degraded by chemical hydrolysis. Data from screening tests on the biodegradability of NMP show that the substance is rapidly biodegraded.

In rats, NMP is absorbed rapidly after inhalation, oral, and dermal administration, distributed throughout the organism, and eliminated mainly by hydroxylation to polar compounds, which are excreted via urine. About 80% of the administered dose is excreted as NMP and NMP metabolites within 24 h. A probably dose-dependent yellow coloration of the urine in rodents is observed. The major metabolite is 5-hydroxy-*N*-methyl-2-pyrrolidone.

Studies in humans show comparable results. Dermal penetration through human skin has been shown to be very rapid. NMP is rapidly biotransformed by hydroxylation to 5-hydroxy-*N*-methyl-2-pyrrolidone, which is further oxidized to *N*-methylsuccinimide; this intermediate is further hydroxylated to 2-hydroxy-*N*-methylsuccinimide. These metabolites are all colourless. The excreted amounts of NMP metabolites in the urine after inhalation or oral intake represented about 100% and 65% of the administered doses, respectively.

NMP has a low potential for skin irritation and a moderate potential for eye irritation in rabbits. Repeated daily doses of 450 mg/kg body weight administered to the skin caused painful and severe haemorrhage and eschar formation in rabbits. These adverse effects have not been seen in workers occupationally exposed to pure NMP, but they have been observed after dermal exposure to NMP used in cleaning processes. No sensitization potential has been observed.

In acute toxicity studies in rodents, NMP showed low toxicity. Uptake of oral, dermal, or inhaled acutely toxic doses causes functional disturbances and depressions in the central nervous system. Local irritation effects were observed in the respiratory tract when NMP was inhaled and in the pyloric and gastrointestinal tracts after oral administration. In humans, there was no irritative effect in the respiratory system after an 8-h exposure to 50 mg/m^3.

There is no clear toxicity profile of NMP after multiple administration. In a 28-day dietary study in rats, a compound-related decrease in body weight gain was observed in males at 1234 mg/kg body weight and in females at 2268 mg/kg body weight. Testicular degeneration and atrophy in males and thymic atrophy in

females were observed at these dose levels. The no-observed-adverse-effect level (NOAEL) was 429 mg/kg body weight in males and 1548 mg/kg body weight in females. In a 28-day intubation study in rats, a dose-dependent increase in relative liver and kidney weights and a decrease in lymphocyte count in both sexes were observed at 1028 mg/kg body weight. The NOAEL in this study was 514 mg/kg body weight. In another rat study, daily dietary intake for 90 days caused decreased body weights at doses of 433 and 565 mg/kg body weight in males and females, respectively. There were also neurobehavioural effects at these dose levels. The NOAELs in males and females were 169 and 217 mg/kg body weight, respectively.

The toxicity profile after exposure to airborne NMP depends strongly on the ratio of vapour to aerosol and on the area of exposure (i.e., head-only or whole-body exposure). Because of higher skin absorption for the aerosol, uptake is higher in animals exposed to aerosol than in those exposed to vapour at similar concentrations. Studies in female rats exposed head only to 1000 mg/m^3 showed only minor nasal irritation, but massive mortality and severe effects on major organs were observed when the females were whole-body exposed to the same concentration of coarse droplets at high relative humidity. Several studies in rats following repeated exposure to NMP at concentrations between 100 and 1000 mg/m^3 have shown systemic toxicity effects at the lower dose levels. In most of the studies, the effects were not observed after a 4-week observation period.

In rats, exposure to 3000 mg NMP/m^3 (head only) for 6 h/day, 5 days/week, for 13 weeks caused a decrease in body weight gain, an increase in erythrocytes, haemoglobin, haematocrit, and mean corpuscular volume, decreased absolute testis weight, and cell loss in the germinal epithelium of the testes. The NOAEL was 500 mg/m^3.

There are no data in humans after repeated-dose exposure.

NMP did not show any clear evidence for carcinogenicity in rats exposed to concentrations up to 400 mg/m^3 in a long-term inhalation study.

The mutagenic potential of NMP is weak. Only a slight increase in the number of revertants was observed when tested in a *Salmonella* assay with base-pair substitution strains. NMP has been shown to induce aneuploidy in yeast *Saccharomyces cerevisiae* cells. No investigations regarding mutagenicity in humans were available.

In a two-generation reproduction study in rats, whole-body exposure of both males and females to 478 mg/m^3 of NMP vapour for 6 h/day, 7 days/week, for a minimum of 100 days (pre-mating, mating, gestation, and lactation periods) resulted in a 7% decrease in fetal weight in the F_1 offspring. A 4–11% transient, non-dose-dependent decrease was observed in the average pup weight at all exposure levels tested (41, 206, and 478 mg/m^3).

When NMP was administered dermally, developmental toxicity was registered in rats at 750 mg/kg body weight. The observed effects were increased preimplantation losses, decreased fetal weights, and delayed ossification. The NOAEL for both developmental effects and maternal toxicity (decreased body weight gain) was 237 mg/kg body weight.

Inhalation studies in rats (whole-body exposure) demonstrated developmental toxicity as increased preimplantation loss without significant effect on implantation rate or number of live fetuses at 680 mg/m^3 and behavioural developmental toxicity at 622 mg/m^3. In an inhalation study (whole-body exposure), the NOAEL for maternal effects was 100 mg/m^3, and the NOAEL for developmental effects was 360 mg/m^3.

Several further studies on the reproductive effects of NMP have been performed, but these have not been published and are not generally available. For the information of the reader, a short synopsis of these studies is presented in section 8.7.3 of this document. However, the studies are not used in the evaluation of the health effects of NMP.

A tolerable inhalation concentration, 0.3 mg/m^3, based on mortality and organ damage, is expected to be protective against any possible reproductive toxicity. Similarly, an oral tolerable intake of 0.6 mg/kg body weight per day, based on a 90-day study, is expected to provide adequate protection against possible reproductive effects. Because of non-existent data on the exposure of the general population and very limited information on occupational exposure, no meaningful risk characterization can be performed.

It is not possible to perform a quantitative ecotoxicological risk assessment on the basis of the present data. However, based on the biodegradability shown, the lack of expected bioconcentration (based on a log octanol–water partition coefficient of ! 0.38), and the indicated low acute toxicity to aquatic organisms as well as birds, it is tentatively concluded that NMP should not pose a significant environmental risk.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

N-Methyl-2-pyrrolidone (CAS No. 872-50-4) is also known as NMP, 1-methyl-2-pyrrolidone, *N*-methyl-pyrrolidone, and 1-methyl-2-pyrrolidinone. 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. The substance 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.

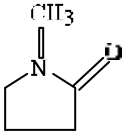
Additional physical/chemical properties are presented in Table 1 as well as in the International Chemical Safety Card (ICSC 0513) reproduced in this document.

Table 1: Some physical/chemical properties of NMD.[a]

Property	Value
Relative molecular mass	99.13
Density	1.028 g/cm^3
Melting point	!23 to !24.4 °C
Boiling point	202°C at 101.3 Pa
Vapour pressure	39 Pa at 20 °C 45 Pa at 25 °C
Henry's law constant	1.6 × 10^{-3} Pa•m^3/mol at 25 °C[b]
log K_{ow}	!0.38
Conversion factors (20 °C, 101.3 kPa)	1 ppm = 4.12 mg/m^3 1 mg/m^3 = 0.24 ppm

[a] From Åkesson (1994), except where otherwise noted.
[b] Hine & Mookerjee (1975).

The chemical structure of NMP is illustrated below:



3. ANALYTICAL METHODS

3.1 Measurement of NMP

Sampling of NMP in air may be performed on solid sorbent or in absorption solution. NMP is desorbed from the solid adsorbent and extracted from the absorption solution by an organic solvent. Analysis of NMP in a liquid phase is performed by gas chromatographic methods, employing flame ionization detection (FID) or nitrogen–phosphorus detection (NPD). The detection limits of these methods (15 min, 0.2 litres/min) correspond to NMP air concentrations of 0.1 mg/m^3 (FID) and 0.01 mg/m^3 (NPD) (Blome & Hennig, 1984; Andersson & Andersson, 1991; Åkesson & Paulsson, 1997).

NMP in biological samples may, after matrix modulating steps, be determined by high-performance liquid chromatographic methods (Wells & Digenis, 1988; Midgley et al., 1992; Wells et al., 1992). Alternatively, NMP in blood and urine may be extracted by an organic solvent and analysed with gas chromatographic methods, 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/litre (0.004 and 0.01 mg/litre), respectively (Åkesson & Paulsson, 1997).

No evaluated analytical method for NMP in water samples is reported.

3.2 Measurement of NMP metabolites

Analysis of 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP), *N*-methylsuccinimide (MSI), and 2-hydroxy-*N*-methylsuccinimide (2-HMSI) may be performed, with or without derivatization steps, with gas chromatographic methods, using mass spectrometric detection in electron impact or chemical ionization mode. The detection limits in blood are 0.05, 0.01, and 0.03 µmol/litre (0.005, 0.001, and 0.003 mg/litre), respectively, and in urine, 2, 0.03, and 2 µmol/litre (0.2, 0.003, and 0.2 mg/litre), respectively (Jönsson & Åkesson, 1997a,b,c).

The NMP metabolites in plasma or urine, summed or separately, may be used as biological NMP exposure indicators. The plasma concentration of 5-HNMP at termination of exposure is preferred, as 5-HNMP is the major metabolite with a suitable half-life (Åkesson & Jönsson, 2000a).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

NMP is mainly used as a solvent for extraction in the petrochemical industry, as a reactive medium in polymeric and non-polymeric chemical reactions, as a remover of graffiti, as a paint stripper in the occupational setting, and for stripping and cleaning applications in the microelectronics fabrication industry. It is also used as a formulating agent in pigments, dyes, and inks and in insecticides, herbicides, and fungicides. 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 cosmetics industry.

There are no known natural sources of NMP.

NMP may enter the environment as a fugitive emission during its production or use (ISP, undated; Barry, 1987; Priborsky & Mühlbachova, 1990; HSDB, 1997). It may also be released to the environment as a component of municipal and industrial wastewaters.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

The vapour pressure of NMP (39–45 Pa; see Table 1) suggests that the substance will volatilize from dry surfaces. Its Henry's law constant has been calculated to be 1.6×10^{-3} Pa·m^3/mol (Hine & Mookerjee, 1975). Based on this value, substantial volatilization from water is not expected. According to a simple fugacity calculation (corresponding to Mackay's Level I fugacity model: Mackay, 1979; Mackay & Paterson, 1981, 1982), more than 99% of NMP released into the environment will partition to water (assuming equilibrium distribution).

In the atmosphere, NMP is expected to undergo a rapid gas-phase reaction with hydroxyl radicals, with an estimated half-life of 5.2 h (Atkinson, 1987). Reaction with (tropospheric) ozone is expected to be an insignificant route of removal from the atmosphere (Levy, 1973; Farley, 1977). Because of its high solubility in water, NMP may undergo atmospheric removal by wet deposition (HSDB, 1997).

A calculated adsorption coefficient (K_{oc}) of 9.6 indicates that NMP is highly mobile in soil (Swann et al., 1983). Soil thin-layer chromatography also indicates a high mobility in soil, R_f values being 0.65–1.0 in four different soils (Shaver, 1984). The calculated adsorption coefficient further indicates that adsorption to sediments or suspended organic matter in aquatic environments should be insignificant (HSDB, 1997). The dissipation of NMP showed half-lives of about 4 days in clay, 8 days in loam, and 12 days in sand (Shaver, 1984).

Unvalidated data on hydrolytic half-lives (IUCLID, 1995) suggest that NMP is not degraded by chemical hydrolysis. According to Åkesson (1994), NMP is a highly stable compound.

Screening studies using activated sludge indicate that NMP is biodegraded aerobically after a lag phase of a few days. A 95% degradation after 2 weeks was shown in a static die-away system, and an average 7-day biodegradability of 95% was shown in a semicontinuous activated sludge (SCAS) system. A stable carbonyl compound was identified as a biodegradation product (Chow & Ng, 1983).

In a test conducted according to Guideline 301C of the Organisation for Economic Co-operation and Development (modified MITI-I test), 73% of an initial concentration of 100 mg NMP/litre was degraded within 28 days of incubation by the non-adapted activated sludge (MITI, 1992). From this result, NMP has been classified as readily biodegradable under aerobic conditions.

After 24 h, NMP underwent 94% removal by 1-day acclimatized sludge, measured by chemical oxygen demand (COD) (Matsui et al., 1988). In a flow-through biological treatment system with a retention time of 18 h, NMP underwent >98% removal (Rowe & Tullos, 1980). In an inherent biodegradability study (SCAS test), NMP was removed to >98% as measured by COD after 24 h (Matsui et al., 1975). In another inherent biodegradability study, removal of COD was >90% after 8 days, with a 3- to 5-day acclimation period (Zahn & Wellens, 1980).

From NMP's calculated bioconcentration factor of 0.16 (HSDB, 1997) and its low log octanol–water partition coefficient (K_{ow}) of !0.38 (see Table 1), only a minor potential for bioaccumulation is to be expected.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

NMP has been qualitatively detected in US drinking-water supplies (Lucas, 1984). The substance

was identified in leachate from a municipal landfill in Ontario (Lesage, 1991).

In a survey of 46 US industrial effluent samples, NMP was detected in 1 of the samples (Bursey & Pellizzari, 1982). In shale retort water, NMP was found at concentrations of 3 mg/litre (Dobson et al., 1985) and up to 10.1 mg/litre (Syamsiah et al., 1993). The substance was identified in wastewater from the petrochemical industry in Japan (Matsui et al., 1988). It was also detected in the raw effluent from a textile finishing plant in the USA (Gordon & Gordon, 1981).

In a German investigation of three different biologically treated wastewaters (domestic wastewater, wastewater from a lubricating oil refinery, and wastewater from an oil reclaiming facility), NMP was qualitatively identified in the domestic wastewater (Gulyas et al., 1993).

No information was found on levels in ambient air, in soil, or in biota.

6.2 Occupational exposure

NMP concentrations in air in the personal breathing zones of graffiti removers are reported to be up to 10 mg/m^3, both short peak exposure (Anundi et al., 1993) and 8-h time-weighted average (TWA) (Anundi et al., 2000). Workers in the microelectronics fabrication industry are exposed to up to 6 mg/m^3 (personal breathing zones; 8-h TWA), and samples collected in the work area revealed full-shift NMP air concentrations up to 280 mg/m^3 when warm NMP (80 °C) was being handled (Beaulieu & Schmerber, 1991). In the paint stripping industry, workers are exposed to NMP concentrations up to 64 mg/m^3 (personal breathing zones; 8-h TWA), and 1-h peak samples revealed concentrations up to 280 mg/m^3 (Åkesson & Jönsson, 2000c).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

In rats, NMP is rapidly absorbed via inhalation, ingestion, and dermal administration and widely distributed throughout the body (Midgley et al., 1992; Ravn-Jonsen et al., 1992). The peak plasma concentration after administration of a mixture of [2-^{14}C]-NMP and [5-^{14}C]-2-pyrrolidone by gastric intubation (112/75 mg/kg body weight in 0.6 ml distilled water) occurred after 2 h; after application to the skin (2.5/1.67 mg/cm^2 skin on 9 cm^2 in 150 µl isopropanol), the peak plasma concentration occurred after 1 h for males and 2 h for females. Following dermal application of the two compounds, the plasma concentrations showed little variation 1–6 h after administration, indicating that the absorption through the skin during this period was relatively constant (Midgley et al., 1992). The percutaneous absorption, expressed as the total excretion in urine, faeces, and expired air, was 69% in males and 78% in females. The levels of total radioactivity in plasma were markedly higher in female rats than in male rats for 12 h after the application, reflecting a greater percutaneous absorption in females (Midgley et al., 1992). The percutaneous absorption of NMP may differ when NMP is applied as pure NMP or as an NMP solution. In a dermal absorption study in the rat, the absorbed amounts of applications of pure NMP, 30% NMP in water, and 30% NMP in (R)-(+)-limonene were 31%, 3.5%, and 72%, respectively (Huntingdon Life Sciences, 1998). In rats exposed whole body by inhalation to 618 mg NMP/m^3 for 6 h, the NMP concentration in the blood increased from 0 to 4 h after termination of the exposure (Ravn-Jonsen et al., 1992). Such an increase is due to a percutaneous uptake of adsorbed NMP on fur and skin when the animals are whole-body exposed to aerosol NMP. When a solution of 10% NMP as a penetration enhancer was studied for 24 h *in vitro*, the skin permeability of NMP was 4 times higher in rats than in humans (Bartek et al., 1972; Priborsky & Mühlbachova, 1990).

After intravenous administration to rats, there is a rapid distribution to all major organs. The plasma NMP level declined 5–30 min after administration and was only slightly decreased from then on up to 2 h. Six hours after administration of radiolabelled NMP, the highest accumulation of radioactivity occurred in the liver, small and large intestines, testes, stomach, and kidneys, although the thymus and bladder had the highest concentrations when expressed per gram of tissue. After 24 h, the radioactivity was still measurable in the liver and intestines. The rapid distribution phase is followed by a slow terminal elimination phase (Wells & Digenis, 1988).

In rats whole-body exposed to 618 mg NMP/m^3 by inhalation for 6 h, NMP passed through the placenta, and the concentrations in fetal and maternal blood were similar 6 h after the start of exposure. The elimination of NMP from the blood was faster in non-pregnant than in pregnant rats (0.21 versus 0.11 mg/kg body weight per hour, respectively) (Ravn-Jonsen et al., 1992).

Following intravenous administration in rats, the main pathway for biotransformation of NMP is by hydroxylation. The major metabolite excreted in urine, 70–75% of the dose, is identified as 5-HNMP. Two other minor polar metabolites (15% and 9%) were not identified

(Wells & Digenis, 1988; Wells et al., 1992). Formation of carbon dioxide is of minor importance. The almost identical metabolism for NMP administered by dermal and oral routes indicates that little first-pass metabolism occurs (Midgley et al., 1992). Twelve hours after an orally or percutaneously administered dose, all of the NMP in plasma was in the form of the polar metabolites (Midgley et al., 1992).

All studies of NMP exposure of rats report discoloration (yellow-orange-brownish) of urine. The coloration, noted at 100 mg/m^3 and higher concentrations, was probably dose related, but has not been studied further. It may be due to a coloured unidentified metabolite or to an effect in the body (e.g., in the liver).

The half-life of NMP in plasma is 7–10 h. The urinary excretion of NMP and NMP metabolites accounted for about 70% of the dose within 12 h and 80% within 24 h (RTI, 1990; E.I. du Pont de Nemours and Company, 1995a). Only a minor part is excreted into the urine as the mother compound (<1%). There is minor biliary excretion of about 2%. The elimination of NMP in expired air is also minimal (1–2%). No conjugated metabolites were found in the urine (Wells & Digenis, 1988).

In humans, as in rats, NMP is rapidly absorbed via inhalation (Åkesson & Paulsson, 1997), ingestion (Åkesson & Jönsson, 1997), and dermal administration (Ursin et al., 1995; Åkesson & Jönsson, 2000b). An uptake of about 90% by the inhalation route was found when the difference between inhaled and exhaled NMP concentrations was calculated. NMP is rapidly biotransformed by hydroxylation to 5-HNMP, which is then further oxidized to MSI; MSI is in turn hydroxylated to 2-HMSI. The peak plasma concentrations after an 8-h exposure to NMP occurred at the termination of exposure for NMP, at 2 h post-exposure for 5-HNMP, at 4 h post-exposure for MSI, and at 16 h post-exposure for 2-HMSI. The half-lives in plasma after a short period of distribution were 4 h, 6 h, 8 h, and 16 h, respectively. The detected amounts in urine after inhalation were as follows: NMP (2%), 5-HNMP (60%), MSI (0.1%), and 2-HMSI (37%). The recovery was about 100%. After oral administration, the amounts detected in urine were as follows: NMP (1%), 5-HNMP (67%), MSI (0.1%), and 2-HMSI (31%), corresponding to 65% of the administered dose. There was no tendency for coloration in any of the urine samples collected, and none of the synthesized metabolites was coloured (Åkesson & Jönsson, 1997, 2000a,b). In a 6-h topical single-application study with administration of 300 mg NMP in volunteers (six per sex), the NMP concentration in plasma reached a maximum 3 h after application in both males and females. Twenty-four per cent and 22% of the dose in males and females, respectively, were recovered in urine as NMP and NMP metabolites (Åkesson & Jönsson, 2000b). The permeability rate of NMP through living human skin, adjusted for the permeability rate of ^{3}H-labelled water, was 171 ± 59 g/m^3 per hour (Ursin et al., 1995).

The NMP metabolites in plasma or urine, summed or each metabolite separately, may be used as biological NMP exposure indicators. The plasma concentration of 5-HNMP at termination of exposure is preferred, as 5-HNMP is the major metabolite with a suitable half-life (Åkesson & Jönsson, 2000a).

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

Studies in rodents indicate that NMP has low acute toxicity. No deaths occurred in rats (five per sex) when head-only exposed by inhalation for 4 h to 5100 mg/m^3 of a vapour/aerosol mixture with mass median aerodynamic diameter (MMAD) of 4.6 µm (respirable fraction 87%) (LC_{50} >5100 mg/m^3). During the exposure, symptoms such as rapid, irregular respiration, shortness of breath, decreased pain reflex, and slight bloody nasal secretion were observed. Post-exposure, rapid respiration, slightly bloody fur around the nose, and yellow urine excretion were registered. From 4 days post-exposure, no symptoms were observed. Examination of the lungs 14 days post-exposure showed darkening of lungs, indicating irritation (BASF, 1988). Three separate 4-h whole-body exposures (aerosol, thermal vaporization, and saturated vapour) displayed an approximate lethal concentration of 1700 mg/m^3 in rats (E.I. du Pont de Nemours and Company, 1977).

Oral LD_{50}s for rats, mice, guinea-pigs, and rabbits ranged from 3900 to 7900 mg/kg body weight (Ansell & Fowler, 1988), and dermal LD_{50}s for rats and rabbits ranged from 4000 to 10 000 mg/kg body weight (Bartsch et al., 1976). Non-surviving rats in an acute oral toxicity study showed irritation of the pyloric and gastrointestinal tracts and darkening of kidneys, liver, and lungs (LD_{50} 4150 mg/kg body weight) (Ansell & Fowler, 1988). At sublethal doses (one-eighth of the LD_{50}), ataxia and diuresis were recorded in survivors (Clark et al., 1984).

8.2 Irritation and sensitization

Skin irritation tests in New Zealand White rabbits (n = 6) exposed to 0.5 ml NMP were performed (Draize et

al., 1944). The test sites were occluded for 24 h and then examined for skin reactions. Only slight erythema was observed. When the examination was repeated 72 h and 7 days after the start of exposure, no effects were observed. The tests showed a low potential for skin irritation and resulted (for both intact and abraded skin and averaged reading from 24 and 72 h) in a primary irritation index of 0.5 (out of a maximum 8) (BASF, 1963; Ansell & Fowler, 1988). Repeated daily dermal administration of 450 mg/kg body weight to rabbits caused painful and severe haemorrhage and eschar formation after four doses; the reaction to a dose of 150 mg/kg body weight per day was less marked (BASF, 1993a). Aqueous solutions of NMP were tested for primary skin irritation in 10 male albino guinea-pigs. Twenty-four hours after application, slight erythema was observed in two guinea-pigs with the 50% solution and in 0 with the 5% solution. After 48 h, no effects were registered (E.I. du Pont de Nemours and Company, 1976b). Dry skin at the application site was found in rats at dermal doses of 500–2500 mg/kg body weight and per 25 cm^2 of skin (Becci et al., 1982).

Sensitization potential tests, defined as the increase of response at challenge after a series of four intradermal injections (0.1 ml of 1% NMP in 0.9% saline solution; one injection per week), were performed in 10 male albino guinea-pigs. Two weeks after the intradermal injections, the animals were exposed to aqueous solutions of NMP. About 0.05 ml each of a 5% and a 50% (vol/vol) solution were applied and lightly rubbed in to the shaved intact shoulder skin. Nine guinea-pigs that did not have intradermal injections of NMP were used as control animals. No sensitization was found when the animals were examined after 24 and 48 h. After 24 h, there was slight erythema at the 50% solution test sites in 6 out of 10 challenged guinea-pigs and in 4 out of 9 controls. No effects were observed when animals were examined after 48 h. The 5% NMP solution caused no irritation (E.I. du Pont de Nemours and Company, 1976b).

Primary eye irritation tests (Draize et al., 1944) were performed in New Zealand White rabbits (n = 9). Intraocular applications of 0.1 ml NMP into one eye (the other eye served as untreated control) caused conjunctival effects, such as corneal opacity, iritis, and conjunctivitis. The effects faded within 21 days after the application. When the exposed eye was washed out 30 s after the application (performed in three of the nine exposed rabbits), the effects faded within 14 days. The primary irritation index scores for unwashed/washed eye were 41/35, 40/26, 34/18, 8/1, 4/0, and 0/! after 1, 2, 3, 7, 14, and 21 days post-exposure, respectively. The tests in the rabbits indicated a moderate potential for eye irritation (Ansell & Fowler, 1988).

8.3 Short-term exposure

8.3.1 Inhalation

Concentration-related signs of lethargy and irregular respiration were observed at all dose levels in rats exposed to 100, 500, or 1000 mg NMP/m^3 (mainly aerosol; >95% of the droplets <10 µm) for 6 h/day, 5 days/week, for 4 weeks using whole-body exposure. At the two lowest exposure levels, these signs were reversible within 30–45 min post-exposure. No signs of pathological lesions were observed at these dose levels. At 1000 mg/m^3, there was excessive mortality. In dead animals, myelotoxic effects in terms of bone marrow hypoplasia and atrophy and/or necrosis of the lymphoid tissue in thymus, spleen, and lymph nodes were found. In surviving animals, these findings were not observed at 14 days post-exposure (Lee et al., 1987).

In a series of inhalation toxicity studies, female rats were exposed to 1000 mg NMP/m^3, 6 h/day, 5 days/week, for 2 weeks (Table 2). The head-only exposure, independent of aerosol fraction and humidity, caused no effects other than slight nasal irritation and coloured urine (BASF, 1992, 1995g). Whole-body exposure (coarse droplets and high relative humidity) caused massive mortality, apathy, decreased body weight and body weight gain, irritation in the nasal region, and severe effects on organs and tissues (BASF, 1995d,f,g). Whole-body exposure (fine droplets and low or high relative humidity) caused no deaths and less severe effects (BASF, 1995a,c,e). It should be noted that NMP may exist in various proportions of vapour and aerosol depending on the concentration, temperature, and atmospheric humidity. The maximum vapour phase at room temperature is 1318 mg/m^3 in dry air (0% relative humidity), 412 mg/m^3 at normal humidity (60% relative humidity), and 0 mg/m^3 in wet air (100% relative humidity).

Ten female rats per dose level were exposed whole body to 0 or 1000 mg NMP/m^3 (coarse/dry; MMAD 4.7–6.1 µm; 10% relative humidity) for 6 h/day, 5 days/week, for 4 weeks. There were no deaths. The body weights were decreased, and apathy, ruffled fur, and respiratory irritation were observed (BASF, 1995b).

8.3.2 Oral

Rats (10 per sex) were intubated 5 days/week for 4 weeks with 0, 257, 514, 1028, or 2060 mg NMP/kg body weight per day. In males, a dose-dependent decrease was observed in body weight at 1028 and 2060 mg/kg body weight (11% and 16%, respectively), and a decrease in relative and absolute testes weight was

Table 2: Inhalation toxicity in female rats exposed to 1000 mg NMP/m³ for 2 weeks.[a]

Exposure characterization[b]	Area	Effects observed	Reference
Fine/dry (<3 µm 10% RH)	Whole body	No deaths. Slight decrease in body weight gain ($P < 0.05$). Slight decrease in lymphocytes. Slight increase in neutrophils.	BASF, 1995c
Fine/dry (3.8–4.4 µm; 35% RH)	Nose only	No deaths.	BASF, 1992
Coarse/wet (4.8 µm; 70% RH)	Whole body	Nine deaths. Congestion in nearly all organs, lesions in spleen and lungs. Surviving rat recovered in 2 weeks.	BASF, 1995f
Coarse/wet (4.4–4.5 µm; 70% RH)	Head only	No deaths. Nasal irritation.	BASF, 1995g
Coarse/wet (4.4–4.5 µm; 70% RH)	Whole body	Nine deaths. Serious lesions in spleen (depletion and necrosis of lymphocytes) and bone marrow (panmyelophthisis and gelatinous bone marrow). In the surviving rat: Body weight and absolute organ weight different from means of the control group.	BASF, 1995g
Coarse/wet (5.1–5.2 µm; 70% RH)	Whole body	Eight deaths. Apathy, irregular respiration, convulsions, tremor, and poor general health state. Pulmonary oedema and multifocal purulent pneumonia. Necrotic alterations in liver. Cell depletion in bone marrow and necrosis in spleen. Ulceration in the glandular stomach. Increased adrenal weight. In the surviving rats: No significant gross or microscopic findings.	BASF, 1995d
Fine/dry (<3 µm; 10% RH)	Whole body	No deaths. Sensory irritation (significant changes: respiratory rate decreased, minute volume lower, inspiration time longer).	BASF, 1995a
Fine/wet (>3 µm; 70% RH)	Whole body	No deaths. Slight ($P = 0.05$) decrease in white cells and lymphocytes and increase in liver weight. Increased relative lung weight. Nasal irritation symptoms.	BASF, 1995e

[a] Female rats ($n = 10$) were exposed to 1000 mg NMP/m³ with an exposure schedule of five 6-h exposures per week for 2 weeks. A control group of 10 female rats was exposed to air.
[b] RH = relative humidity.

observed in nine animals at 2060 mg/kg body weight. The histological examination showed adverse effects on seminiferous tubule epithelium and formation of multi-nucleate giant cells and clumping of sloughed-off cells. In both sexes, a dose-dependent increase in relative liver and kidney weights and a decrease in body weight gain were observed at 1028 and 2060 mg/kg body weight, and lymphocyte count decreased following exposure to 1028 and 2060 mg/kg body weight. At 2060 mg/kg body weight, testes weights decreased in nine males, and histological changes in the testes were observed. At 2060 mg/kg body weight, symptoms of general toxicity, such as tremor, restlessness, ruffled fur, and defensive reactions, were registered (BASF, 1978a). The NOAEL and lowest-observed-adverse-effect level (LOAEL) in this study were 514 and 1028 mg NMP/kg body weight, respectively.

In a repeated-dose toxicity study (Malek et al., 1997), rats (five per sex) were given 0, 2000, 6000, 18 000, or 30 000 mg NMP/kg diet for 28 days. The mean daily NMP doses were 0, 149, 429, 1234, and 2019 mg/kg body weight in males and 0, 161, 493, 1548, and 2268 mg/kg body weight in females. Compound-related decreases in body weight and body weight gain were observed in male rats at 18 000 and 30 000 mg/kg diet and in female rats at 30 000 mg/kg diet. In males at 18 000 and 30 000 mg/kg diet, the mean body weight on test day 28 was reduced by 17% and 33%, respectively, compared with the control value, and the body weight gain was reduced by 40% and 72%, respectively. In females at 30 000 mg/kg diet, the mean body weight on test day 28 was reduced by 14% compared with the control value, and the body weight gain was reduced by 52%. The decreases in body weight and body weight gain were correlated with lower food consumption. In males at 18 000 and 30 000 mg/kg diet, food consumption was

reduced by 19% and 31%, respectively, and food efficiency was reduced by 26% and 59%, respectively. In females at 30 000 mg/kg diet, food consumption was reduced by 23%, and food efficiency was reduced by 36%. Microscopic lesions associated with decreased food consumption and depressed body weights were present in male rats at 18 000 and 30 000 mg/kg diet and in female rats at 30 000 mg/kg diet. These histological alterations included hypocellular bone marrow in both sexes, testicular degeneration and atrophy in males, and thymic atrophy in females. Based on this study, the NOAEL was found to be 6000 mg/kg diet (429 mg/kg body weight) in male rats and 18 000 mg/kg diet (1548 mg/kg body weight) in female rats.

In a repeated-dose toxicity study (Malek et al., 1997), mice (five per sex) were given 0, 500, 2500, 7500, or 10 000 mg NMP/kg diet for 28 days. The mean daily NMP dose was 0, 130, 720, 2130, and 2670 mg/kg body weight in males and 0, 180, 920, 2970, and 4060 mg/kg body weight in females. Swelling of epithelium of distal renal tubuli was observed in two out of five males at 7500 mg/kg diet, in four out of five males at 10 000 mg/kg diet, and in three out of five females at 10 000 mg/kg diet. There were no compound-related effects on body weight or food consumption at any dose level. Based on this study, the NOAEL was found to be 2500 mg/kg diet (720 mg/kg body weight) in male mice and 7500 mg/kg diet (2970 mg/kg body weight) in female mice.

8.4 Medium-term exposure

8.4.1 Inhalation

In a medium-term exposure study, rats (10 per sex per dose level) were exposed (head only) to 0, 500, 1000, or 3000 mg NMP/m^3 for 6 h/day, 5 days/week, for 13 weeks. These groups were sacrificed and examined at the end of exposure. An additional two satellite groups (10 rats per sex per dose level) were identically exposed to 0 or 3000 mg/m^3 and sacrificed after 13 weeks of exposure and a 4-week post-exposure period to obtain information on the reversibility of possible effects. The generated NMP atmospheres consisted of a large proportion (82–92%) of respirable aerosol particles (MMAD 2.1–3.5 µm; relative humidity 52–61%). Dark yellow discoloration of the urine was found at all levels, and nasal irritation as shown by crust formation on nasal edges at 1000 mg/m^3 was observed at the end of the exposure period. At 3000 mg/m^3, non-specific clinical symptoms and irritation of the respiratory tract were registered. In male rats, body weight was significantly decreased (34%) and absolute testes weight was decreased. Cell loss in germinal epithelium of testes in 4 out of 10 male rats was noted. Slight increases in erythrocytes, haemoglobin, haematocrit, and mean corpuscular volume were observed. In female rats, the number of polymorphonuclear neutrophils increased and the number of lymphocytes decreased. Examination of the satellite group at the end of the 4-week post-exposure observation period showed a significant lower body weight gain in males compared with the controls. The testes effects registered in the 3000 mg/m^3 group sacrificed at the end of exposure were also registered in the satellite group at the end of the 4-week post-exposure observation period. The NOAEL was 500 mg NMP/m^3 for both male and female rats (BASF, 1994).

8.4.2 Oral

Rats (10 per sex) were administered 0, 3000, 7500, or 18 000 mg NMP/kg diet for 90 days. The mean daily NMP dose was 0, 169, 433, and 1057 mg/kg body weight in males and 0, 217, 565, and 1344 mg/kg body weight in females. A decrease in body weight and body weight gain was correlated with lower food consumption and food efficiency and was observed in both males and females at dose levels of 7500 mg/kg diet (6% and 15% in males and females, respectively) and 18 000 mg/kg diet (28% and 25% in males and females, respectively). Compound-related adverse effects were observed in males in 3 out of 36 neurobehavioural parameters. Increased foot splay was observed at 7500 and 18 000 mg/kg diet. This effect was not reversed in the recovery group. A higher incidence of low arousal and slight palpebral closure was observed in males at 18 000 mg/kg diet, suggesting a sedative effect of NMP. The NOAEL for this study was 3000 mg NMP/kg diet (equivalent to mean doses of 169 mg/kg body weight in males and 217 mg/kg body weight in females) (E.I. du Pont de Nemours and Company, 1995b).

Dogs (six per sex per dose level) administered NMP at doses of 0, 25, 79, or 250 mg/kg body weight per day in the diet for 90 days showed no statistically significant adverse effects. A dose-dependent decrease in body weight gain and an increase in platelet count and megakaryocytes within a normal range were observed. At the exposure termination, no significant differences between high-dose and control groups were reported (Becci et al., 1983). The NOAEL for dietary exposure in dogs in this study is 250 mg/kg body weight per day.

8.5 Long-term exposure and carcinogenicity

In a 2-year inhalation study, Charles River CD rats (120 per sex per dose level) were exposed (whole body) to NMP vapour concentrations of 0, 40, or 400 mg/m^3 for 6 h/day, 5 days/week. Ten rats per sex were subjected to haematology and blood and urine chemistry analysis after 1, 3, 6, 12, and 18 months of exposure. Ten rats per sex were sacrificed after 3, 12, and 18 months. All

surviving rats were killed at the end of 24 months of exposure and subjected to a gross examination. All vital organs and tissues were subjected to microscopic examination. Respiratory tract toxicity was observed at 400 mg/m^3 as a minimal inflammation in the lung. Male rats exposed to 400 mg/m^3 for 18 months showed higher haematocrit and higher alkaline phosphatase levels in serum than were observed in the control group. There was no such difference after 24 months of exposure. At the 400 mg/m^3 dose level, male rats excreted larger urine volumes, and both males and females excreted dark yellow urine. The 2-year study showed a 6% reduction in the mean body weight in male rats at the 400 mg NMP/m^3 dose level (statistical significance not reported). NMP was reported to have no oncogenic potential (Lee et al., 1987).

8.6 Genotoxicity and related end-points

8.6.1 In vitro

NMP has been tested in bacterial mutagenicity assays in the dose range of 0.01–1000 µmol/plate (0.99 µg/plate to 99 mg/plate) with and without metabolic activation by Aroclor-induced rat liver S9. In the direct plate incorporation in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, and TA104 at highest dose, signs of cytotoxicity (decreased number of revertants or bacterial lawn thinning) were observed. In strains TA102 and TA104 without activation, a minor and no dose-related increase in the number of revertants were observed. When using a preincubation method in strains TA98 and TA104, no effects were registered (Wells et al., 1988). Also, in another preincubation test in strains TA98, TA100, TA1535, and TA1537 (NMP dose levels up to 10 mg/plate) with and without Aroclor-induced rat or hamster liver S9, no mutagenic activity was observed (Mortelmans et al., 1986). Other studies, also using *Salmonella typhimurium* strains for testing the mutagenicity of NMP, reported no mutagenic activity (BASF, 1978b; Maron et al., 1981).

Two assays in yeast show that NMP may induce aneuploidy. Incubation of *Saccharomyces cerevisiae* strain D61.M with NMP in the dose range of 77–230 mmol/litre (7.6–23 g/litre) caused a dose-related effect. Concentrations of 179 mmol/litre (18 g/litre) and higher were toxic and decreased the level of survival by more than 50% (Mayer et al., 1988). The decrease in survival was shown to be the same when NMP was used at a concentration of 2.44% for incubation of the same yeast strain (Zimmermann et al., 1988).

Negative results were obtained in a study of the ability of NMP to induce unscheduled DNA synthesis in rat primary hepatocyte cultures (GAF, 1988) and in a study of the mutagenic activity of NMP in L5178Y mouse lymphoma cells (E.I. du Pont de Nemours and Company, 1976a).

8.6.2 In vivo

In a micronucleus test, NMRI mice (both sexes) were orally administered a single dose of 950, 1900, or 3800 mg NMP/kg body weight. Irregular respiration, colored urine, and general poor health were observed. No clastogenic effects or aneuploidy were observed when mice were examined at 24, 48, and 72 h after dose administration. Positive controls displayed clastogenic and aneugenic activity. Thus, no mutagenic activity with NMP was found (Engelhardt & Fleig, 1993).

In a bone marrow chromosomal aberration study, Chinese hamsters (both sexes) were exposed to a single oral dose of 1900 or 3800 mg NMP/kg body weight. Irregular respiration, coloured urine, and general poor health were observed. At 16 (only high dose level) and 24 h after administration, bone marrow samples were taken. Structural and numerical chromosomal alterations were found in positive control animals but not in NMP-exposed animals, indicating no mutagenic activity with NMP (Engelhardt & Fleig, 1993).

Signs of toxicity were reported in two older studies: a micronucleus test in Chinese hamsters (both sexes) (BASF, 1976) exposed for 6 weeks (6 h/day, 5 days/week) to 3300 mg NMP/m^3 and a germ cell genotoxic activity test (a dominant lethal test) in male NMRI mice (BASF, 1976) with intraperitoneal administration of 391 mg NMP/kg body weight (once per week for 8 consecutive weeks). The inhalation study displayed a slight but non-significant increase in structural chromosomal aberrations in the bone marrow. In the intraperitoneal study, a significantly increased post-implantation loss was observed (relative to the control animals). The studies were not performed to current regulatory standards and could not be fully evaluated for NMP mutagenic activity.

8.7 Reproductive toxicity

The reproductive toxicity of NMP in rats is summarized in Table 3.

8.7.1 Effects on fertility

8.7.1.1 Inhalation

In a two-generation reproduction study, rats (10 males and 20 females per dose level) were exposed whole body to 0, 41, 206, or 478 mg/m^3 of NMP vapour (relative humidity 40–60%) for 6 h/day, 7 days/week, for a minimum of 14 weeks (P_0 generation). The P_0 generation was 34 days old at exposure onset. At 119 days of age, one male and two females from the same exposure

Table 3: Reproductive toxicity of NMP in rats.

Species; type of study	Exposure	Toxicity		NOAEL/LOAEL	Reference
		Fetal	Maternal		
Rat; two-generation; inhalation (whole body), 6 h/day, 7 days/week	0 mg/m³ 41 mg/m³ 206 mg/m³ 478 mg/m³	None None None Pup body weight decrease (4–11%)	None None None Decrease in response to sound	Reproductive toxicity: NOAEL = 206 mg/m³; LOAEL = 478 mg/m³ Maternal toxicity: NOAEL = 206 mg/m³; LOAEL = 478 mg/m³	Solomon et al., 1995
Rat; testes and semen toxicity study; inhalation (whole body); 6 h/day, 7 days/week; <90 days	0 mg/m³ 618 mg/m³	None None	None None	Reproductive toxicity: NOAEL = 618 mg/m³	Fries et al., 1992
Rat; two-generation study; inhalation (whole body)	0 mg/m³ 478 mg/m³	None Fetal body weight decrease (mean 7%)	None None	Developmental toxicity: LOAEL = 478 mg/m³	Solomon et al., 1995
Rat; developmental toxicity; inhalation (whole body); days 4–20, 6 h/day	0 mg/m³ 680 mg/m³	None Increased preimplantation loss but no effect on number of implantations per dam or number of live fetuses; delayed ossification	None None	Developmental toxicity: LOAEL = 680 mg/m³ Maternal toxicity: NOAEL = 680 mg/m³	Hass et al., 1995
Rat; developmental toxicity; inhalation (whole body); days 7–20, 6 h/day	0 mg/m³ 622 mg/m³	None Decreased body weight; neuro-behavioural effects	None None	Developmental toxicity: LOAEL = 622 mg/m³ Maternal toxicity: NOAEL = 622 mg/m³	Hass et al., 1994
Rat; developmental toxicity; inhalation (whole body); days 6–15, 6 h/day	0 mg/m³ 100 mg/m³ 360 mg/m³	None None None	None None Lethargy and irregular respiration during the first 3 days of exposure	Developmental toxicity: NOAEL = 360 mg/m³ Maternal toxicity: NOAEL = 100 mg/m³; LOAEL = 360 mg/m³	Lee et al., 1987
Rat; range-finding developmental toxicity study; dermal; days 6–15	0 mg/kg body weight per day 500 mg/kg body weight per day 1100 mg/kg body weight per day 2500 mg/kg body weight per day	– – – –	None None Massive resorption; decreased body weight gain Lethal	Maternal toxicity: NOAEL = 500 mg/kg body weight per day; LOAEL = 1100 mg/kg body weight per day	Becci et al., 1982
Rat; developmental toxicity study; dermal; days 6–15	0 mg/kg body weight per day 75 mg/kg body weight per day 237 mg/kg body weight per day 750 mg/kg body weight per day	None None None Increased resorption, delayed ossification	None None None Decreased body weight gain	Developmental toxicity: NOAEL = 237 mg/kg body weight per day; LOAEL = 750 mg/kg body weight per day Maternal toxicity: NOAEL = 237 mg/kg body weight per day; LOAEL = 750 mg/kg body weight per day	Becci et al., 1982

group were allowed to mate. The P_0 males were exposed for >100 days (pre-mating and mating periods), and the females were exposed for >106 days (pre-mating, mating, gestation, and lactation periods). At the end of the mating period, 50% of the P_0 males were sacrificed and examined for adverse reproductive effects. The other 50% of the P_0 males were examined 21 days later (recovery period). From the delivered offspring, exposed from day 4 postpartum, one male and one female per litter were examined for adverse reproductive effects on day 21 postpartum. The remaining offspring were designated as the F_1 generation. At the end of the weaning period, the P_0 dams were sacrificed and examined for adverse effects on reproduction. In parallel, the sex-specific effects of exposure to 0 and 478 mg/m^3 vapour for 6 h/day, 7 days/week, for a minimum of 14 weeks were studied by cross-mating of exposed and unexposed males and females from the F_1 generation for production of an F_2 generation. No effects on body, testes, or ovarian weights or on reproductive ability were recorded. A 4–11% decrease in pup weight of the F_1 offspring whose parents both inhaled NMP was observed from day 1 to day 21 postpartum, but not at day 28 postpartum. This effect was not clearly dose related and reached statistical significance for the low and high, but not for the intermediate, exposure groups (Solomon et al., 1995).

In a reproduction study, male rats (12 per dose level) were exposed whole body to 0 or 618 mg NMP/m^3 (vapour; <50% relative humidity) for 6 h/day, 7 days/week, for 90 days. There were no abnormal histopathological changes or differences in testis weights when rats were examined at the termination of exposure and 90 days later. Nor were there any abnormalities of the semen, sperm cell morphology, or cell concentration (Fries et al., 1992).

8.7.2 Developmental toxicity

8.7.2.1 Inhalation

In the two-generation reproductive toxicity study of Solomon et al. (1995), a developmental toxicity study was performed in rats. Groups of 10 males and 20 females were whole-body exposed to 0 or 478 mg NMP/m^3 for 6 h/day, 7 days/week, for a minimum of 14 weeks. Exposed males were then mated with exposed females, and non-exposed males were mated with non-exposed females (controls). For the developmental toxicity evaluation, the pregnant females were sacrificed on day 21. No effects on pregnancy rate, numbers of viable litters, corpora lutea, implantations, fetal deaths, resorptions, litter size, or incidence of fetal malformations or variations were found. A 7% decrease ($P \# 0.05$) in mean fetal weight in the exposed group was observed.

In a developmental study, pregnant rats (27 in the control group and 28 in the exposed group) were exposed whole body to 0 or 680 mg NMP/m^3 (vapour; <50% relative humidity) for 6 h/day on days 4–20 of gestation. The dose was chosen to correspond to the "worst-case" level of human exposure. No clinical signs of maternal toxicity were seen. The number of dams with preimplantation loss was increased in the exposed group. Preimplantation loss was observed in 20 out of 23 litters compared with 11 out of 20 litters in the control group ($P < 0.05$); no significant effect on the number of implantations per dam or the number of live fetuses was observed. Compared with the control group ($P < 0.05$), there was also an increase in the incidence of delayed ossification of the skull, cervical vertebrae 4 and 5, sternebrae, and metatarsal and digital bones in the exposed animals. No increased incidence of malformations was found (Hass et al., 1995).

In a neurobehavioural teratology study, pregnant rats were exposed whole body to 0 or 622 mg NMP/m^3 (vapour; <50% relative humidity) for 6 h/day on days 7–20 of gestation. The dose was chosen to minimize maternal toxicity and offspring mortality, based on earlier experience in the laboratory. Maternal weight development during days 7–20 was 15% slower among the exposed dams (no statistical analysis reported). In the exposed group, a lower body weight of the pups and slight delay in achieving some developmental milestones in the preweaning period were observed. While most of the behavioural tests gave similar results for the exposed and control animals, an occasionally increased latency in Morris swimming maze and a statistically borderline impairment in operant behaviour with delayed spatial alternation were noted among the exposed offspring (Hass et al., 1994).

In a developmental toxicity study, pregnant rats (25 per dose level) were exposed whole body to 0, 100, or 360 mg NMP/m^3 for 6 h/day on days 6–15 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 in vital organs and skeletons of the fetuses were found. Nor were there abnormal clinical signs or pathological lesions in the maternal rats. During the first 3 days, lethargy and irregular respiration were observed in the dams exposed to 100 mg/m^3 (Lee et al., 1987).

8.7.2.2 Dermal

In a range-finding study of developmental toxicity, pregnant rats (3–5 per exposure level) were exposed to daily dermal doses of 0, 500, 1100, or 2500 mg NMP/kg body weight during days 6 through 15 of gestation. At the highest dose level, all dams died or aborted before day 20 of gestation. The dose level of 1100 mg/kg body weight caused a depression in dam body weight gain

and was embryolethal; 65 out of 66 fetuses were resorbed. A daily dermal dose of 500 mg/kg body weight had no adverse effect on pregnancy, dam body weights, implantations, or gestation (Becci et al., 1982).

In a developmental toxicity study, pregnant rats (about 22 per dose level) were administered daily dermal NMP doses of 0, 75, 237, or 750 mg/kg body weight during days 6 through 15 of gestation. At the highest dose, maternal and developmental toxicity were shown: on day 20 of gestation, decreased dam body weight gain, increased resorption of fetuses, and decreased fetal body weight, as well as skeletal abnormalities, 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. No increase was observed in the incidence of soft tissue anomalies. The NOAEL in dams and fetuses was 237 mg/kg body weight per day. The lower maternal body weight observed may be explained by increased resorption rate and decreased fetal body weight (Becci et al., 1982).

8.7.3 Additional studies

A number of studies that are not available in the open literature and therefore are not usable as a basis for risk assessment in this CICAD are reported in this section as supporting data for the developmental effects of NMP.

In a multigeneration reproduction study, rats were exposed in the diet to NMP at doses of 50, 160, or 500 mg/kg body weight per day. The first parental generation (P_1) was exposed during a period prior to mating, gestation, lactation, and weaning of the litter (F_{1a}) and during a period prior to a second mating, gestation, lactation, and weaning of the litter (F_{1b}). The second parental generation ($P_2 = F_{1b}$) was exposed from day 21 postpartum as the P_1 generation until the first litter (F_{2a}) and the second litter (F_{2b}) were delivered. The highest dose level caused decreased parental body weight and food consumption and a concomitant reduction in survival and growth rates in the offspring. The data from the 50 and 160 mg/kg body weight per day experiments with slightly lower male fertility and female fecundity indices do not clearly demonstrate a NOAEL (EXXON, 1991).

In a pre-test of developmental toxicity, five pregnant rabbits per dose level were exposed to 0, 300, 1000, or 2000 mg NMP/m^3 (vapour/aerosol; MMAD 3.8–4.0 µm) for 6 h/day on days 7–19 post-insemination. Maternal toxicity was expressed as prolonged clotting time, decreased plasma protein content, and increased liver weight at both 1000 and 2000 mg/m^3. In the main study, pregnant rabbits (15 per dose level) exposed head only for 6 h/day to 0, 200, 500, or 1000 mg NMP/m^3 (vapour/aerosol; MMAD 2.7–3.5 µm) on days 7–19 post-insemination showed no signs of maternal toxicity. At 1000 mg/m^3, a slight fetal toxicity was seen as increased occurrence of skeletal variations (accessory 13th ribs) (BASF, 1993b). The two studies show NOAELs for developmental and maternal toxicity of 500 mg/m^3 (BASF, 1991).

In a developmental study, pregnant rats (25 per dose level) were given daily NMP doses of 0, 40, 125, or 400 mg/kg body weight by oral gavage on days 6–15 of gestation. Maternal and fetal toxicity were observed at the highest dose level compared with controls. The toxicity was indicated as maternal body weight gain decrement, reduced fetal body weights, and increased incidence of fetal stunting at 400 mg/kg body weight (EXXON, 1992).

In another developmental toxicity study (GAF, 1992), orally administered doses of 55, 175, or 540 mg NMP/kg body weight per day in pregnant rabbits (20 per dose level) on days 6–18 of gestation caused maternally decreased body weight gain at 175 and 540 mg/kg body weight per day. Developmental toxicity was shown as post-implantation loss, altered fetal morphology, and increased incidences of cardiovascular and skull malformations at 540 mg/kg body weight per day.

An oral daily dose of 997 mg NMP/kg body weight administered to rats by gavage on days 6–15 of gestation showed no maternal toxicity but increased the incidence of resorptions (95%) and caused malformations in 8 out of 15 surviving fetuses. Other adverse effects observed were fetal mortality, reduced placental and fetal weights, and reduced fetal lengths. No adverse effect was observed at 332 mg NMP/kg body weight, but a minor decrease in placental weight was observed. Reported maternal toxicity data were unsatisfactory (US EPA, 1988).

Oral daily doses of 0, 1055, or 2637 mg/kg body weight on days 11–15 of gestation in mice caused an increase in resorption rate, increased incidence of runts, diminished fetal weight and length, and an increased rate of malformations such as cleft palate at the higher dose level. The lower dose level caused no observable embryotoxicity. Both developmental and maternal toxicity are insufficiently reported, and the exposure covers only a part of organogenesis (US EPA, 1988).

The maternal toxicity in rabbits after dermal application was studied in a range-finding study. Pregnant rabbits (15 per dose level) were exposed daily to dermal doses of 0, 400, 600, or 800 mg/kg body weight (as 40% aqueous solution). There was maternal toxicity, expressed as prolonged clotting time at 800 mg/kg body weight (BASF, 1993a).

In a developmental toxicity study, 15 pregnant rabbits per dose level were exposed daily by dermal application to 0, 100, 300, or 1000 mg NMP/kg body weight for 6 h/day on days 7–19 post-insemination. The application doses were made as 40% aqueous solution. There were no signs of maternal toxicity. At 1000 mg/kg body weight per day, a slight fetal toxicity was seen as increased occurrence of skeletal variation (accessory 13th ribs) (BASF, 1993a).

An intraperitoneal daily dose to mice of 0, 630, or 1570 mg/kg body weight on days 11–15 of gestation caused increased resorption rate, increased incidence of runts, diminished fetal weight and length, and an increased rate of malformations such as cleft palate at the high level. No maternal toxicity was observed. The low dose level caused no observable embryotoxicity. No information on maternal toxicity is given in this study; thus, evaluation of the results is difficult (US EPA, 1988).

NMP doses of 14–166 mg/kg body weight singly or repeatedly intraperitoneally administered to mice during various phases of pregnancy caused increased post-implantation loss and a reduced body weight of the fetuses. 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 LOAEL for repeated doses was 74 mg/kg body weight administered on days 7–11 of gestation. No information on maternal toxicity is given in this study; thus, evaluation of the results is difficult (Schmidt, 1976).

8.8 Immunological and neurological effects

Effects on the immune system (thymic atrophy in female rats, decreased leukocyte count in both sexes) have been described in studies performed in rats after a 28-day oral administration at high dose levels (see section 8.3).

9. EFFECTS ON HUMANS

A 23-year-old laboratory technician was occupationally exposed to NMP during her first 20 weeks of pregnancy. The uptake via the lungs was probably of minor importance, as the NMP was handled at room temperature. Hand rinsing of glassware with NMP and cleaning up of an NMP spill in week 16 of pregnancy may have brought about a much larger uptake through the skin. During the 4 days following the spill, malaise, headache, and nausea were experienced. Examination of the pregnancy at week 14 showed no signs of delayed development; however, at week 25, signs of delayed fetal development were observed, and at week 31, a stillborn fetus was delivered. Stillbirth in this period of pregnancy is unusual. However, as the level of exposure is unknown, it is impossible to establish if exposure to NMP is the causative factor (Solomon et al., 1996; Bower, 1997).

A total of 15 24-h exposures in a repeated-insult patch test in human subjects (n = 50) caused minor to moderate transient irritations. No signs of contact sensitization were observed. Direct contact of skin with NMP caused redness, swelling, thickening, and painful vesicles when NMP was used as a cleaner (Leira et al., 1992) or as a paint stripper (Åkesson & Jönsson, 2000c).

Workers exposed to NMP in working areas with air concentrations up to 280 mg/m^3 reported severe eye irritation and headache. With the methods of assessing the exposure level (sampling on charcoal and tracer gas method) and the response (observation and informal interview), it is impossible to develop a concentration–response relationship (Beaulieu & Schmerber, 1991). Six volunteers exposed to 10, 25, or 50 mg/m^3 during 8 h in a chamber study registered their symptoms, before the start of exposure and then every 2 h for 16 h, in a questionnaire on a scale from 0 to 10 (0 = no symptoms and 10 = not tolerated). The volunteers displayed none of the following symptoms: eye or respiratory tract irritation; hacking cough, nose secretion, or blockage, sneezing, itching, or dryness in the mouth and throat, or other symptoms in upper airways; itching, secretion, smarting pain, visual disturbances, or other symptoms such as headache, dizziness, and nausea; and other symptoms. Two volunteers reported detecting an odour at 50 mg/m^3. There were no significant differences in the spirometric data displayed by the forced expiratory volume in 1 s, vital capacity, and the highest forced expiratory capacity measured before or after any level of exposure. There were no acute changes in the nasal cavity assessed by continuous acoustic rhinometry. Even though the effects observed in this study were not very pronounced, the possibility of undetected effects still remains (the number of volunteers was only six) (Åkesson & Paulsson, 1997).

No epidemiological studies were located.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

In a static test on the acute toxicity of NMP to the freshwater guppy (*Poecilia reticulata*), a 96-h LC_{50} value of 2670 mg/litre was determined, based on the nominal concentration (Weisbrod & Seyring, 1980).

Unvalidated study results reported in IUCLID (1995) indicate that NMP has low acute toxicity to fish, crustaceans, algae, and bacteria (short-term LC_{50} or EC_{50} values >500 mg/litre). No data on the long-term toxicity of NMP to aquatic organisms have been identified.

10.2 Terrestrial environment

No recent and evaluated data on the toxicity of NMP to terrestrial species were found. However, some older results from short-term studies on birds were found in IUCLID (1995). According to these data, the acute toxicity following a single oral dose as well as the subacute toxicity following dietary exposure are low (LD_{50} >2000 mg/kg body weight and LC_{50} >5000 mg NMP/kg diet, respectively).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

Data on the effects of exposure to NMP in humans are scanty. The toxicity evaluation is therefore based on animal data.

NMP is efficiently absorbed from the respiratory and gastrointestinal tracts as well as through the skin and is rapidly distributed to all organs. A relatively large proportion of the administered NMP dose was recovered in the testis after intravenous administration.

The acute toxicity of NMP is low. The air concentration of NMP causing acute toxicity in whole-body-exposed rats was less than one-third of that causing acute toxicity in head-only-exposed rats.

In a chamber study, a single exposure of volunteers did not cause irritation-related symptoms in eyes or the respiratory tract at exposures up to 50 mg inhalation and in the pyloric and gastrointestinal tracts after oral administration.

Dermal irritation has been observed in humans after exposure to liquid NMP used as a cleaner or paint stripper. A low potential for skin irritation was reported in a repeated-insult patch test in humans, as well as in a primary skin irritation study in rabbits. NMP was negative for skin sensitization in humans and animals and caused moderate eye irritation in animals.

NMP did not show carcinogenic potential in a 2-year inhalation study in rats. No genotoxic potential of NMP was reported in a series of *in vitro* and *in vivo* studies.

In a repeated whole-body exposure study in which rats were exposed to 1000 mg NMP/m^3 for 2 weeks, there was extensive mortality, and autopsy revealed myelotoxicity and atrophy of lymphoid tissue.

Inhalation exposure to NMP did not induce changes in the male reproductive tract or semen quality in rats. Administration of NMP parenterally or at maternally toxic doses to experimental animals induced fetal toxicity and teratogenicity.

One study by inhalation reported a slight decrease in fetal weight in the absence of clinical signs of maternal toxicity at an exposure level of 478 mg/m^3 and a non-dose-dependent, transient minor decrease in pup weight at exposure levels of 41, 206, and 478 mg/m^3 (Solomon et al., 1995). A transient decrease in pup weight, late arrival at some of the measured postnatal development milestones, and impaired results in some of a large number of functional neurobehavioural tests were observed in rats after exposure to 622 mg NMP/m^3, a concentration that was accompanied by a minor decrease in maternal weight gain (Hass et al., 1994). Another study reported preimplantation loss with no significant effect on the number of implantations per dam or the number of live fetuses and an increase in the incidence of skeletal variations and delayed ossification, but no increased incidence of malformations, at an exposure level of 680 mg/m^3, which did not induce clinical toxicity in dams (Hass et al., 1995). No effects of exposure to NMP at the highest concentration tested, 360 mg/m^3, on the outcome of pregnancy, embryonal growth rate, or development in vital organs and skeletons of the fetuses were observed in a further study in rats (Lee et al., 1987).

In a range-finding study on dermal exposure to NMP with few animals, all dams died or aborted before day 20 of gestation at a daily dose level of 2500 mg/kg body weight; 1100 mg/kg body weight caused resorption

of 65 of 66 fetuses and a depression in dam body weight gain. A daily dermal dose of 500 mg/kg body weight had no adverse effect on pregnancy, dam body weights, implantations, or gestation. In a follow-up study with a proper number of experimental animals, a dose of 750 mg/kg body weight during days 6–15 of gestation decreased dam body weight gain, increased resorption of fetuses, decreased fetal body weight, and induced skeletal abnormalities and delayed/incomplete ossification, but there was no increase in the incidence of soft tissue anomalies. No effects were observed at the lower dose levels studied, 75 and 237 mg/kg body weight per day (Becci et al., 1982).

In studies not published in the open literature, skeletal variations, reduced fetal weight, and, at exposure levels toxic to dams, soft tissue terata have been observed. These studies cannot be assessed, as few details have been provided.

11.1.2 Criteria for setting tolerable intakes/ concentrations or guidance values for N-methyl-2-pyrrolidone

At high and maternally toxic exposure levels, NMP clearly induces adverse developmental effects, including terata. However, at exposure levels close to the NOAEL for maternal toxicity, effects are minor or, as in the case of the reported possible neurobehavioural toxicity, need confirmation by independent studies. With respect to the risk assessment, however, tolerable intakes and tolerable concentrations derived from either reproductive toxicity studies or studies on other end-points are very similar.

The NOAEL from the 4- to 13-week repeated-dose inhalation exposure studies, based on mortality, effects on haematopoietic and lymphatic organs, and nasal irritation, is 500 mg/m^3 (BASF, 1994). Thus, the tolerable concentration (TC) can be calculated as follows:

TC = [500 mg/m^3 × (6/24) × (5/7)] / 300
= 0.3 mg/m^3

where:

- 500 mg/m^3 is the NOAEL,
- 6/24 and 5/7 adjust the intermittent exposure in the animal experiment to continuous human exposure, and
- 300 is the combined uncertainty factor. In the absence of specific data on NMP, the uncertainty factors are the default values, i.e., 10 for species differences, 10 for interindividual variation in humans, and 3 for adjustment from a 90-day study to a lifelong exposure (IPCS, 1994).

Considering 400 mg/m^3 as a LOAEL in the Lee et al. (1987) long-term study, a very similar tolerable concentration would be obtained.

In the reproductive studies, effects on offspring, mostly accompanied by changes in the mother, have generally been observed at exposure levels of 500 mg/m^3, and a no-effect level has been reported at 360 mg/m^3 (Lee et al., 1987). A TC may be thus be derived as follows:

TC = [360 mg/m^3 × (6/24)] / 100
= 0.9 mg/m^3

For dermal exposure, using the reproductive toxicity NOAEL of 237 mg/kg body weight per day as the starting point (Becci et al., 1982), a TC may be derived as follows:

TC = 237 mg/kg body weight per day / 100
= 2.37 mg/kg body weight per day

For oral exposure, a NOAEL from the 90-day study by E.I. du Pont de Nemours and Company (1995b), 169 mg/kg body weight per day, leads to the following TC:

TC = 169 mg/kg body weight per day / 300
= 0.6 mg/kg body weight per day

using the same default uncertainty factors as for the 90-day inhalation study above.

11.1.3 Sample risk characterization

Because of non-existent data on the exposure of the general population and very limited information on occupational exposure, a meaningful risk characterization cannot be performed.

11.1.4 Uncertainties of the health effects evaluation

Reproductive effects have been observed following inhalation exposure to NMP. However, the calculated TC, based on other effects in experimental animals, is also protective against reproductive effects. The dermal and oral tolerable intakes have been calculated using different end-points, the former a reproductive toxicity study and the latter a 90-day toxicity study. These studies give very similar tolerable intakes. As absorption via the skin and gastrointestinal tract are both very effective, it is again not important from the risk characterization point of view whether full weight is given to the reproductive toxicity studies.

There is an important discrepancy between the tolerable daily intake via inhalation and the tolerable intakes via other routes of exposure. The inhalation TC of 0.3 mg/m^3 will lead to a total daily dose by inhalation of [0.3 mg/m^3 × 20 m^3/day] / 64 kg = 0.1 mg/kg body weight per day (where 20 m^3 is the diurnal volume of respiration, and 64 kg the weight of the average human), i.e., approximately 5–15% of that by other routes. The reasons for the disproportionately high inhalation toxicity of NMP are not known. This disproportionate inhalation toxicity is also apparent in the oral/dermal LD_{50} / short-term LC_{50} values. LD_{50} values (oral, dermal, rat) are in the order of 5000 mg/kg body weight, but 2-week exposure (6 h/day × 5 days/week) to 1000 mg NMP/m^3 (calculated total dose in the order of 300 mg/kg body weight) led to the death of 9 out of 10 animals.

The inhalation toxicity of NMP is quite variable depending on the conditions of exposure; there is no apparent explanation for this discrepancy either.

Reliable analysis of the hazards and risks due to inhalation exposure to NMP requires further experimental work.

11.2 Evaluation of environmental effects

Water and air are considered to be the most relevant compartments for NMP, since the substance may be released both as volatile emissions to the atmosphere and as a component of wastewater, municipal as well as industrial. Since the substance shows high mobility in soil, leaching from landfills is a possible route of contamination of groundwaters. NMP is expected to be removed from air by wet deposition or by reaction with hydroxyl radicals. The substance is not transformed by chemical hydrolysis but is rapidly biodegraded under aerobic conditions. The substance is not expected to bioconcentrate.

Very few reliable ecotoxicological data were found. However, the available results from short-term tests on aquatic species (fish, crustaceans, algae, and bacteria) and terrestrial species (birds) indicate that NMP has low acute toxicity.

Also, very few data on measured concentrations in the environment were identified. The available eco-toxicological data should not be used for a quantitative risk assessment until fully evaluated. As a tentative conclusion, however, based on the biodegradability of the substance, the absence of bioconcentration tendency, and the indicated low acute aquatic toxicity, NMP is not expected to present a significant risk to the environment.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

No previous evaluations were identified.

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APPENDIX 1 — SOURCE DOCUMENTS

Åkesson (1994): *N-Methyl-2-pyrrolidone (NMP)*, Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals, *Arbete och hälsa*, 40:1–24

Copies of the *Arbete och hälsa* document on NMP (ISSN 0346-7821; ISBN 91-7045-288-1), prepared by the Nordic Expert Group, may be obtained from:

National Institute of Working Life
Publications Department
S-171 84 Solna
Sweden

In the peer review procedure of documents prepared in the series Criteria Documents from the Nordic Expert Group (focused on human health only), one member of the Nordic Expert Group serves as a primary reviewer for the first draft. A second draft is forwarded to all members of the Nordic Expert Group, who in turn consult appropriate specialists to review the document. The specialists are chosen either because they have an extended knowledge of the substance itself or because they are specialists in the critical effect area of the substance evaluated. The second review is performed by a review board, including the Nordic Expert Group participants with the ad hoc experts, for further comments. The review board meeting is repeated if necessary.

HSE (1997): *N-Methyl-2-pyrrolidone: Risk assessment document EH72/10*, Sudbury, Suffolk, HSE Books

The authors' draft version is initially reviewed internally by a group of approximately 10 Health and Safety Executive experts (mainly toxicologists, but also scientists from other relevant disciplines, such as epidemiology and occupational hygiene). The toxicology section of the amended draft is then reviewed by toxicologists from the United Kingdom Department of Health. Subsequently, the entire risk assessment document is reviewed by a tripartite advisory committee to the United Kingdom Health and Safety Commission, the Working Group for the Assessment of Toxic Chemicals (WATCH). This committee is composed of experts in toxicology and occupational health and hygiene from industry, trade unions, and academia.

The members of the WATCH committee at the time of the peer review were:

Mr Steve Bailey (Confederation of British Industries)
Professor Jim Bridges (University of Surrey)
Dr Ian Guest (Confederation of British Industries)
Dr Alastair Hay (Trades Union Congress)
Dr Jenny Leeser (Confederation of British Industries)
Dr Len Levy (Institute of Occupational Hygiene, Birmingham)
Dr Mike Molyneux (Confederation of British Industries)
Mr Alan Moses (Confederation of British Industries)
Dr Ron Owen (Trades Union Congress)
Mr Jim Sanderson (Independant Consultant)
Dr Mike Sharratt (University of Surrey)

HSDB (1997): *Hazardous substances data bank*, Bethesda, MD, National Library of Medicine

The version of HSDB used for this CICAD is included in the CD-ROM CHEM-BANK (February 1998), published by:

Silver Platter Information Inc.
100 River Ridge Drive
Norwood, MA 02062-5043
USA

HSDB is also available on CD-ROM from the Canadian Centre for Occupational Health and Safety (CCINFOdisc D2) and on-line by Data-Star, DIMDI, STN International, and TOXNET.

HSDB is built, reviewed, and maintained on the National Library of Medicine's Toxicology Data Network (TOXNET). HSDB is a factual data bank, referenced and peer reviewed by a committee of experts (the Scientific Review Panel). All data extracted from HSDB to this CICAD were preceded by the symbol denoting the highest level of peer review.

The date for the last revision or modification of the record on NMP was November 1997.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on *N*-methyl-2-pyrrolidone was sent for review to institutions and organizations identified by IPCS after contact with IPCS national contact points and Participating Institutions, as well as to identified experts. Comments were received from:

A. Aitio, World Health Organization, Switzerland

M. Baril, Institut de Recherche en Santé et en Sécurité du Travail du Québec, Canada

R. Benson, US Environmental Protection Agency Region VIII, USA

R. Cary, Health and Safety Executive, United Kingdom

R.S. Chhabra, National Institute of Environmental Health Sciences, USA

P. Edwards, Department of Health, United Kingdom

T. Fortoul, National University of Mexico, Mexico

E. Frantik, National institute of Public Health, Czech Republic

R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Germany

R. Montaigne, European Chemical Industry Council (CEFIC), Belgium

D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Australia

P. Yao, Chinese Academy of Preventive Medicine, People's Republic of China

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Stockholm, Sweden, 25–28 May 1999

Members

Mr H. Abadin, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, GA, USA

Dr B. Åkesson, Department of Occupational and Environmental Health, University Hospital, Lund, Sweden

Dr T. Berzins (*Chairperson*), National Chemicals Inspectorate (KEMI), Solna, Sweden

Mr R. Cary, Health and Safety Executive, Bootle, Merseyside, United Kingdom

Dr R.S. Chhabra, General Toxicology Group, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Dr S. Dobson (*Rapporteur*), Institute of Terrestrial Ecology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Dr G. Koennecker, Chemical Risk Assessment, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Dr A. Nishikawa, National Institute of Health Sciences, Division of Pathology, Tokyo, Japan

Professor K. Savolainen, Finnish Institute of Occupational Health, Helsinki, Finland

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Ms D. Willcocks (*Vice-Chairperson*), Chemical Assessment Division, National Occupational Health and Safety Commission (Worksafe Australia), Sydney, Australia

Professor P. Yao, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Ministry of Health, Beijing, People's Republic of China

Observers

Dr N. Drouot (representing the European Centre for Ecotoxicology and Toxicology of Chemicals [ECETOC]), Elf Atochem, DSE-P Industrial Toxicology Department, Paris, France

Ms S. Karlsson, National Chemicals Inspectorate (KEMI), Solna, Sweden

Dr A. Löf, National Institute of Working Life, Solna, Sweden

Dr A. Poole (representing the European Chemical Industry Council [CEFIC]), Dow Europe S.A., Horgen, Switzerland

Dr K. Ziegler-Skylakakis, Institute for Toxicology, GSF - National Research Center for Environment and Health, Neuherberg, Oberschleissheim, Germany

Secretariat

Dr A. Aitio, Programme for the Promotion of Chemical Safety, World Health Organization, Geneva, Switzerland

Ms M. Godden, Health and Safety Executive, Bootle, United Kingdom

Ms L. Regis, Programme for the Promotion of Chemical Safety, World Health Organization, Geneva, Switzerland

Dr P. Toft, Division of Health and Environment, World Health Organization, Regional Office for the Americas/Pan American Sanitary Bureau, Washington, DC, USA

Dr M. Younes, Programme for the Promotion of Chemical Safety, World Health Organization, Geneva, Switzerland

N-METHYL-2-PYRROLIDONE

0513
April 1997

CAS No: 872-50-4
RTECS No: UY5790000
UN No:
EC No: 606-021-00-7

1-Methyl-2-pyrrolidinone
1-Methyl-2-pyrrolidone
N-Methylpyrrolidone
C_5H_9NO
Molecular mass: 99.1

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 96°C explosive vapour/air mixtures may be formed.	Above 96°C use a closed system, ventilation.	
EXPOSURE		**PREVENT GENERATION OF MISTS!**	
Inhalation	Headache.	Ventilation.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED! Dry skin. Redness.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain. Blurred vision.	Safety spectacles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	Rinse mouth. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place (extra personal protection: filter respirator for organic gases and vapours).	Xi Symbol R: 36/38 S: (2-)41

EMERGENCY RESPONSE	STORAGE
NFPA Code: H2; F1; R0.	Separated from oxidants, rubber, plastics, aluminium, light metals. Dry. Ventilation along the floor.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
COLOURLESS HYGROSCOPIC LIQUID, WITH CHARACTERISTIC ODOUR. TURNS YELLOW ON EXPOSURE TO HEAT.

Chemical Dangers
The substance decomposes on heating or on burning producing toxic fumes including nitrogen oxides, carbon monoxide. Attacks aluminium, light metals, rubber, plastic.

Occupational Exposure Limits
TLV not established.
MAK: 20 ppm; 80 mg/m^3; skin (1996).

Routes of Exposure
The substance can be absorbed into the body by inhalation and through the skin.

Inhalation Risk
A harmful contamination of the air will not or will only very slowly be reached on evaporation of this substance at 20°C, on spraying however much quickly.

Effects of Short-term Exposure
The substance irritates the eyes and the skin. Swallowing the liquid may cause aspiration into the lungs with the risk of chemical pneumonitis.

Effects of Long-term or Repeated Exposure
Repeated or prolonged contact with skin may cause dermatitis. Animal tests show that this substance possibly causes toxic effects upon human reproduction.

PHYSICAL PROPERTIES

Boiling point: 202°C
Melting point: -24°C
Relative density (water = 1): 1.03
Solubility in water: very good
Vapour pressure, Pa at 25°C: 66
Relative vapour density (air = 1): 3.4
Relative density of the vapour/air-mixture at 20°C (air = 1): 1.00
Flash point: 96°C o.c.
Auto-ignition temperature: 270°C
Explosive limits, vol% in air: 0.99-3.9

ENVIRONMENTAL DATA

NOTES

N-Methyl-2-pyrrolidone enhances the skin permeability for other substances. Insufficient data are available on the effect of this substance on human health, therefore utmost care must be taken.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif à la *N*-méthyl-2-pyrrolidone (NMP) repose principalement sur deux mises au point, l'une préparée à l'intention du Groupe d'experts nordiques (Åkesson, 1994) et l'autre rédigée par le *Health and Safety Executive* du Royaume-Uni au sujet des effets que ce composé pourrait avoir sur la santé humaine (HSE, 1997). En ce qui concerne les données sur le devenir et le comportement de cette molécule dans l'environnement, on n'a pas repéré de document de niveau équivalent. On a donc utilisé l'HSDB (1997) à titre de source documentaire complémentaire. D'autres données non validées, principalement de nature écotoxicologiques, ont été trouvées dans IUCLID (1995) et d'autres articles ont été repérés dans les publications accessibles (dépouillement jusqu'à fin juillet 1998). On trouvera à l'appendice 1 des indications sur la nature des sources documentaires existantes. Les renseignements concernant l'examen du CICAD par des pairs font l'objet de l'appendice 2. Ce document a été examiné lors de la réunion du Comité d'évaluation finale qui s'est tenue à Stockholm (Suède) du 25 au 28 mai 1999. La liste des participants à cette réunion figure à l'appendice 3. Après la réunion, on a demandé l'avis d'un groupe consultatif composé de B. Heinrich-Hirsch (BgVV , Allemagne), Frank Sullivan (Consultant, Royaume-Uni), Robert Chapin (*National Institute of Environmental Health Sciences*, Etats-Unis), Gary Kimmel (*US Environmental Protection Agency*, Etats-Unis) et Rolf Hertel (BgVV, Allemagne, Président), pour l'interprétation des données sur la toxicité génésique de la *N*-méthyl-2-pyrrolidone. Sur la base des avis émis par ce groupe et avec l'aide du Secrétariat, l'auteur a révisé les sections correspondantes du document. Le CICAD révisé a été approuvé en tant qu'évaluation internationale par les membres du Comité d'évaluation finale, qui se sont exprimés par correspondance. La fiche d'information internationale sur la sécurité chimique (ICSC 0513) relative à la *N*-méthyl-2-pyrrolidone, établie par le Programme international sur la sécurité chimique (IPCS, 1993), est également reproduite dans ce document.

La *N*-méthyl-2-pyrrolidone (NMP) (No CAS 872-50-4) est un solvant organique miscible à l'eau. Elle se présente sous la forme d'un liquide hygroscopique incolore dégageant une légère odeur d'amine. On l'utilise dans l'industrie pétrochimique et dans la fabrication de composants microélectroniques; elle entre également dans la composition de divers produits tels que pigments, cosmétiques, médicaments, insecticides, herbicides et fongicides. Elle est en outre de plus en plus utilisée en remplacement des hydrocarbures chlorés.

La NMP peut pénétrer dans l'environnement soit sous la forme d'émissions dans l'atmosphère car le composé est volatil et très largement utilisé comme solvant, soit en étant déversée dans l'eau avec les eaux usées municipales et industrielles dont elle est un constituant. Elle est mobile dans le sol et elle peut venir contaminer les eaux souterraines par lessivage des décharges.

Elle s'élimine vraisemblablement de l'atmosphère par dépôt humide ou à la faveur de réactions photochimiques avec les radicaux hydroxyles. Etant totalement miscible à l'eau, elle ne devrait pas être adsorbée aux particules du sol, aux sédiments ou aux matières organiques en suspension, ni subir une bioconcentration. La NMP n'est pas décomposée par hydrolyse chimique. Les essais de biodégradabilité montrent que la NMP subit une biodégradation rapide.

Chez le rat, le composé est rapidement résorbé après inhalation, ingestion ou application cutanée; il se répartit dans l'organisme puis est éliminé après hydroxylation en dérivés polaires qui sont excrétés par voie urinaire. La dose initiale est excrétée dans les 24 h à environ 80 % sous la forme de NMP et de métabolites. Chez les rongeurs, on observer une coloration jaune des urines, qui est probablement liée à la dose. Le principal métabolite est la 5-hydroxy-*N*-méthyl-2-pyrrolidone.

Les études sur l'Homme donnent des résultats analogues. On a montré que la pénétration percutanée était très rapide. La NMP subit une transformation rapide en 5-hydroxy-*N*-méthyl-2-pyrrolidone, qui est ensuite oxydée en *N*-méthyl-succinimide, cet intermédiaire subissant à son tour une hydroxylation en 2-hydroxy-*N*-méthyl-succinimide. Tous ces métabolites sont incolores. On a constaté qu'après inhalation ou ingestion, la quantité de métabolites excrétés dans les urines représentait respectivement 100 % ou 65 % de la dose administrée.

Chez le lapin, la NMP n'a qu'un faible pouvoir irritant pour peau et elle est modérément irritante pour la muqueuse oculaire. Des doses quotidiennes répétées de 450 mg par kg de poids corporel appliquées sur la peau de lapins ont provoqué des hémorragies et des escarres graves et douloureuses. Ces effets indésirables ne sont pas observés chez les travailleurs exposés à de la NMP pure, mais on les a constatés après exposition cutanée à de la NMP utilisée pour le nettoyage. Aucun pouvoir sensibilisateur n'a été constaté.

Les études toxicologiques effectuées sur des rongeurs révèlent une faible toxicité aiguë. L'administration de doses toxiques aiguës par voie orale, percutanée ou respiratoire provoque des troubles fonctionnels et une dépression du système nerveux central. Une irritation locale a été observée au niveau des voies respiratoires après inhalation ainsi qu'au niveau du pylore et de l'ensemble des voies digestives après ingestion. Chez

l'Homme, on n'a pas constaté d'irritation des voies respiratoire après exposition à 50 mg/m^3 pendant 8 h.

Après administration de doses multiples, le profil toxicologique de la NMP ne se dégage pas clairement. Lors d'une étude alimentaire de 28 jours sur des rats, on a observé chez les mâles une diminution du gain de poids liée à l'administration du composé pour une dose de 1234 mg/kg de poids corporel (p.c.), le même phénomène se produisant chez les femelles à la dose de 2268 mg/kg p.c. A ces doses, on a également observé une dégénérescence testiculaire chez les mâles et une atrophie du thymus chez les femelles. La dose sans effet indésirable observable (NOAEL) était de 429 mg/kg p.c. pour les mâles et de 1548 mg/kg p.c. pour les femelles. Dans une étude de 28 jours au cours de laquelle de la NMP a été administrée par intubation à des rats, on a constaté une augmentation, liée à la dose, du poids relatif du foie et des reins et une diminution du nombre des lymphocytes chez les deux sexes à la dose de 1028 mg/kg p.c. La NOAEL obtenue dans cette étude était égale à 514 mg/kg p.c. Lors d'une autre étude sur des rats, la prise quotidienne de NMP avec la nourriture pendant 90 jours a provoqué une diminution du poids corporel à la dose de 433 mg/kg p.c. chez les mâles et de 565 mg/kg p.c. chez les femelles. Des effets neuro-comportementaux ont également été observés à ces doses. La NOAEL était respectivement égale à 169 et à 217 mg/kg p.c. pour les mâles et les femelles.

Après exposition à de la NMP présente dans l'air, le profil de toxicité dépend fortement du rapport vapeurs/aérosol et de la région exposée (par ex. tête seule ou totalité du corps). Comme l'aérosol est plus absorbé par voie percutanée, la NMP est davantage résorbée, à concentration égale, lorsque l'animal est exposé à un aérosol que lorsqu'il est exposé à des vapeurs. Chez des femelles dont seule la tête était exposée à une concentration de 1000 mg/m^3, on n'a constaté qu'une légère irritation nasale, mais à la même concentration, la mortalité a été massive avec de graves lésions au niveau des principaux organes lorsque ces femelles avaient le corps entièrement exposé à de grosses gouttelettes dans un milieu présentant une forte humidité relative. Plusieurs études sur des rats ont montré qu'à des concentrations comprises entre 100 et 1000 mg/m^3, une exposition répétée à la NMP provoquait des effets toxiques généraux aux doses les plus faibles de cette fourchette. Dans la plupart des études, les effets ne se sont pas manifestés au bout de 4 semaines d'observation.

Chez des rats exposés (tête seulement) à une concentration de 3000 mg/m^3, 6 h par jour, 5 jours par semaine, pendant 13 semaines, on a observé une diminution du gain de poids, une augmentation des érythrocytes, du taux d'hémoglobine, de l'hématocrite et du volume globulaire moyen, une réduction du poids des testicules et une perte cellulaire dans l'épithélium germinal des testicules. La NOAEL était de 500 mg/m^3.

On ne dispose d'aucune donnée concernant une exposition répétée chez l'Homme.

On n'a pas observé de signes clairs de cancérogénicité chez des rats exposés à des concentrations de NMP allant jusqu'à 400 mg/m^3 lors d'études d'inhalation de longue durée.

Le pouvoir mutagène de la NMP est faible. On n'a observé qu'une légère augmentation des mutants réverses lors d'un test sur salmonelles avec des souches présentant une substitution des paires de bases. Il a été montré que la NMP produisait une aneuploïdie dans des cellules de levure (*Saccharomyces cerevisiae*). Aucune étude portant sur des effets mutagènes chez l'Homme n'est disponible.

Lors d'une étude sur la reproduction portant sur deux générations de rats, l'exposition du corps entier des mâles et des femelles à vapeurs de NMP à la concentration de 478 mg/m^3 6 heures par jour, 7 jours par semaine pendant au moins 100 jours (avant l'accouplement, pendant l'accouplement, pendant la gestation et pendant la lactation) a provoqué une diminution de 7 % du poids des foetus dans la génération F_1. Une diminution passagère, non liée à la dose, de 4 à 11 % du poids corporel moyen des ratons s'est produite à toutes les concentrations étudiées (41, 206 et 478 mg/m^3).

L'administration de NMP à des rats par application cutanée a eu un effet toxique sur leur développement à la dose de 750 mg/kg p.c. Les effets suivants ont été observés : perte avant la nidation, diminution du poids foetal et retard à l'ossification. La NOAEL relative aux effets sur le développement et à la toxicité pour les mères (diminution du gain de poids) était de 237 mg/kg p.c.

Des études d'inhalation sur des rats (exposition du corps entier) ont mis en évidence des effets toxiques sur le développement se traduisant par une augmentation des pertes avant la nidation sans conséquence pour le taux de nidation ou le nombre de foetus vivants à la concentration de 680 mg/m^3 et des effets toxiques comportementaux à la concentration de 622 mg/m^3. Lors d'une étude d'inhalation (exposition du corps entier), la NOAEL relative aux effets toxiques sur les mères a été évaluée à 100 mg/m^3, la NOAEL relative aux effets sur le développement étant égale à 360 mg/m^3.

Plusieurs autres études ont été consacrés aux effets de la NMP sur la reproduction, mais elles n'ont pas été publiées et en général, elles ne sont pas disponibles. Un résumé en est donné à titre d'information à la section 8.7.3 du présent document.

Ces études n'ont cependant pas été prises en compte pour l'évaluation des effets sanitaires de la NMP.

En se basant sur la mortalité et les lésions observées au niveau des organes, une dose tolérable par inhalation de 0,3 mg/m^3, devrait assurer contre tout risque d'effets toxiques sur la reproduction. Il devrait en être de même avec une dose tolérable par ingestion de 0,6 mg par kg p.c., basée sur les résultats d'une étude de 90 jours. Comme il n'existe aucune donnée sur l'exposition de la population générale et que les informations sur l'exposition professionnelle sont très limitées, on ne peut pas procéder à une caractérisation valable du risque.

Il est impossible d'évaluer quantitativement le risque écotoxicologique sur la base des données actuelles. Cependant, compte tenu de la biodégradabilité du composé, du fait qu'il ne subit pas de bioconcentration (selon le coefficient de partage [log K_{ow}] = !0,38), et qu'il est peu toxique pour les organismes aquatiques ainsi que les oiseaux, on peut provisoirement conclure que la NMP ne devrait pas constituer un risque environnemental important.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre la *N*-metil-2-pirrolidona se basó fundamentalmente en un estudio preparado por el Grupo de Expertos Nórdicos (Åkesson, 1994) y en un examen de los problemas relativos a la salud humana preparado por la Dirección de Salud y Seguridad del Reino Unido (HSE, 1997). Para los datos relativos al destino y el comportamiento en el medio ambiente, no se identificó ningún documento amplio del mismo nivel. En su lugar, se utilizó el HSDB (1997) como documento original adicional. En IUCLID (1995) se encontraron datos complementarios no validados, fundamentalmente ecotoxicológicos, y en la bibliografía abierta se identificaron algunos artículos (búsqueda hasta julio de 1998). La información relativa al carácter y a la disponibilidad de los documentos originales figura en el apéndice 1. La información sobre el examen colegiado de este CICAD se presenta en el apéndice 2. Este CICAD se examinó en una reunión de la Junta de Evaluación Final, celebrada en Estocolmo (Suecia) del 25 al 28 de mayo de 1999. La lista de participantes en esta reunión figura en el apéndice 3. Tras la reunión de la Junta de Evaluación Final, se pidió asesoramiento a un grupo consultivo formado por el Dr. B. Heinrich-Hirsch, BgVV (Alemania), el Sr. Frank Sullivan, consultor (Reino Unido), el Dr. Robert Chaplin, Instituto Nacional de Ciencias de la Salud Ambiental (EE.UU.), el Dr. Gary Kimmel, Agencia para la Protección del Medio Ambiente de los Estados Unidos (EE.UU.) y el profesor Rolf Hertel, BgVV (Alemania) (Presidente), con respecto a la interpretación de los datos sobre la toxicidad reproductiva de la *N*-metil-2-pirrolidona. Sobre la base del asesoramiento de este grupo, el autor, en colaboración con la Secretaría, revisó las secciones correspondientes del documento. Los miembros de la Junta de Evaluación Final aprobaron el CICAD revisado como evaluación internacional en una votación por correo. La Ficha internacional de seguridad química (ICSC 0513) para la *N*-metil-2-pirrolidona, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

La *N*-metil-2-pirrolidona (CAS Nº 872-50-4) es un disolvente orgánico miscible con el agua. Es un líquido incoloro higroscópico con un ligero olor a amina. Se utiliza en la industria petroquímica y en la microelectrónica, así como en la fabricación de varias sustancias, entre ellas pigmentos, productos de cosmética, medicamentos, insecticidas, herbicidas y fungicidas. Se está registrando un creciente uso de la *N*-metil-2-pirrolidona como sustitutivo de los hidrocarburos clorados.

La *N*-metil-2-pirrolidona puede incorporarse al medio ambiente mediante emisiones a la atmósfera, puesto que la sustancia es volátil y se utiliza ampliamente como disolvente, o bien puede liberarse al agua

como componente de las aguas residuales municipales e industriales. La sustancia es móvil en el suelo y, por consiguiente, la lixiviación a partir de los vertederos es una posible vía de contaminación del agua freática.

En el aire, cabe suponer la eliminación de la *N*-metil-2-pirrolidona mediante deposición húmeda o por reacciones fotoquímicas con radicales hidroxilo. Puesto que la sustancia es totalmente miscible con el agua, no es previsible su adsorción en el suelo, los sedimentos o la materia orgánica suspendida ni su bioconcentración. La *N*-metil-2-pirrolidona no se degrada por hidrólisis química. Los datos de las pruebas de detección sobre su biodegradabilidad ponen de manifiesto que la sustancia se biodegrada con rapidez.

Tras la administración a ratas por inhalación o por vía oral o cutánea, la *N*-metil-2-pirrolidona se absorbe con rapidez, se distribuye por todo el organismo y se elimina sobre todo mediante hidroxilación a compuestos polares, que se excretan en la orina. Alrededor del 80% de la dosis administrada se excreta como *N*-metil-2-pirrolidona y sus metabolitos en un plazo de 24 horas. En los roedores se observa una coloración amarilla de la orina, probablemente dependiente de la dosis. El principal metabolito es la 5-hidroxi-*N*-metil-2-pirrolidona.

En los estudios con personas, se observan resultados comparables. Se ha comprobado que la penetración a través de la piel humana es muy rápida. La *N*-metil-2-pirrolidona se biotransforma con rapidez por hidroxilación a 5-hidroxi *N*-metil-2-pirrolidona, que se oxida nuevamente a *N*-metil-succinimida. Todos estos metabolitos son incoloros. La concentración de metabolitos de la *N*-metil-2-pirrolidona excretados en la orina tras la inhalación o la ingesta por vía oral es de alrededor del 100% y el 65% de las dosis administradas, respectivamente.

La *N*-metil-2-pirrolidona tiene en los conejos un potencial de irritación cutánea bajo y un potencial de irritación ocular moderado. La administración cutánea de dosis diarias repetidas de 450 mg/kg de peso corporal produjo en los conejos hemorragia grave dolorosa, así como la formación de escara. Estos efectos adversos no se han detectado en trabajadores ocupacionalmente expuestos a la *N*-metil-2-pirrolidona pura, pero se han observado tras la exposición cutánea a la utilizada en procesos de limpieza. No se ha observado potencial de sensibilización.

En estudios de toxicidad aguda en roedores, la *N*-metil-2-pirrolidona mostró una toxicidad baja. La administración oral, cutánea o por inhalación de dosis muy tóxicas provoca trastornos funcionales y depresión del sistema nervioso central. Tras la administración por inhalación y por vía oral de *N*-metil-2-pirrolidona se observaron efectos de irritación local, respectivamente, en las vías respiratorias y en los tractos pilórico y gastrointestinal. En las personas, no se observó ningún efecto irritante en el sistema respiratorio tras una exposición de ocho horas a 50 mg/m^3.

No hay un perfil claro de toxicidad de la *N*-metil-2-pirrolidona después de una administración múltiple. En un estudio de alimentación de 28 días con ratas, se observó una disminución del aumento del peso corporal relacionada con el compuesto a 1234 mg/kg de peso corporal en los machos y a 2268 mg/kg de peso corporal en las hembras. A estos niveles de dosis se detectó degeneración y atrofia testicular en los machos y atrofia del timo en las hembras. La concentración sin efectos adversos observados (NOAEL) fue de 429 mg/kg de peso corporal en los machos y de 1548 mg/kg de peso corporal en las hembras. En un estudio de intubación de 28 días en ratas, se observó un aumento dependiente de la dosis del peso relativo del hígado y el riñón y una disminución del recuento de leucocitos en ambos sexos a 1028 mg/kilo de peso corporal. La NOAEL en este estudio fue de 514 mg/kg de peso corporal. En otro estudio realizado en ratas, la ingesta diaria con los alimentos durante 90 días provocó una disminución del peso corporal a concentraciones de 433 y 565 mg/kg de peso corporal en las hembras y los machos, respectivamente. A esos niveles de dosis también se observaron efectos en el neurocomportamiento. La NOAEL de los machos y las hembras fue de 169 y 217 mg/kg de peso corporal, respectivamente.

El perfil de la toxicidad tras la exposición a la *N*-metil-2-pirrolidona suspendida en el aire depende considerablemente de la razón vapor:aerosol y de la superficie de exposición (es decir, exposición sólo de la cabeza o de todo el cuerpo). Debido a la mayor absorción cutánea del aerosol, a concentraciones semejantes la asimilación de los animales expuestos al aerosol es superior a la de los expuestos al vapor. En estudios con ratas hembras con la cabeza solamente expuesta a 1000 mg/m^3, sólo se observó una ligera irritación nasal, pero se registró una mortalidad masiva y efectos graves en los órganos principales tras la exposición de todo el cuerpo de las hembras a la misma concentración de gotas gruesas con una humedad relativamente alta. Varios estudios en ratas después de una exposición repetida a concentraciones de *N*-metil-2-pirrolidona de 100 a 1000 mg/m^3 han puesto de manifiesto efectos de toxicidad sistémica a los niveles de dosis más bajos. En la mayoría de los estudios no se observaron estos efectos tras un período de observación de cuatro semanas.

En ratas, la exposición a 3000 mg de *N*-metil-2-pirrolidona/m^3 (sólo en la cabeza) seis horas al día, cinco días a la semana, durante 13 semanas provocó una disminución del aumento del peso corporal, un incremento de los eritrocitos, la hemoglobina, el hematocrito y

el volumen corpuscular medio, una reducción del peso absoluto de los testículos y pérdida celular en el epitelio germinal de los testículos. La NOAEL fue de 500 mg/m^3.

No hay datos en las personas después de una exposición a dosis repetidas.

En un estudio de inhalación prolongado, la *N*-metil-2-pirrolidona no mostró ningún signo claro de carcinogenicidad en las ratas expuestas a concentraciones de hasta 400 mg/m^3.

El potencial mutagénico de la *N*-metil-2-pirrolidona es débil. Sólo se observó un ligero aumento del número de revertientes cuando se sometió a prueba en una valoración de *Salmonella* con cepas con un par de bases sustituidas. Se ha demostrado que la *N*-metil-2-pirrolidona induce aneuploidía en las células de levadura de *Saccharomyces cerevisiae*. No se dispone de investigaciones relativas a la mutagenicidad en el ser humano.

En un estudio de reproducción de dos generaciones en ratas, la exposición de todo el cuerpo, tanto de machos como de hembras, a 478 mg/m^3 de vapor de *N*-metil-2-pirrolidona seis horas al día, siete días a la semana, durante un mínimo de 100 días (períodos de preacoplamiento, acoplamiento, gestación y lactación) produjo una disminución del 7% en el peso fetal de las crías F_1. Se observó una reducción transitoria no dependiente de la dosis del 4% al 11% en el peso medio de las crías a todos los niveles de exposición sometidos a prueba (41, 206 y 478 mg/m^3).

Tras la administración cutánea de *N*-metil-2-pirrolidona a ratas, se registró toxicidad en el desarrollo a 750 mg/kg de peso corporal. Los efectos observados fueron un aumento de las pérdidas antes de la implantación, una reducción del peso fetal y un retraso de la osificación. La NOAEL tanto para los efectos en el desarrollo como para la toxicidad materna (reducción del aumento del peso corporal) fue de 237 mg/kg de peso corporal.

En estudios de inhalación en ratas (exposición del cuerpo completo), a 680 mg/m^3 se observó toxicidad en el desarrollo mediante el aumento de las pérdidas antes de la implantación, sin un efecto significativo en la tasa de implantación o el número de fetos vivos, y a 622 mg/m^3 toxicidad en el desarrollo del comportamiento. En un estudio de inhalación (exposición del cuerpo completo), la NOAEL para los efectos maternos fue de 100 mg/m^3 y para los efectos en el desarrollo de 360 mg/m^3.

Se han realizado varios estudios más sobre los efectos reproductivos de la *N*-metil-2-pirrolidona, pero no se han publicado ni están en general disponibles. Para información del lector, en la sección 8.7.3 de este documento se presenta una breve sinopsis de estos estudios. Sin embargo, los estudios no se utilizan para la evaluación de los efectos de la *N*-metil-2-pirrolidona en la salud.

Cabe prever que la inhalación de una concentración tolerable, de 0,3 mg/m^3, basada en la mortalidad y en los daños de los órganos, no protegerá de una posible toxicidad reproductiva. Igualmente, se supone que una ingesta oral tolerable de 0,6 mg/kg de peso corporal al día, basada en un estudio de 90 días, proporcionará una protección adecuada contra posibles efectos reproductivos. Debido a la falta de datos sobre la exposición de la población general y a la información muy limitada sobre la exposición ocupacional, no se puede realizar una caracterización válida del riesgo.

No es posible realizar una evaluación cuantitativa del riesgo ecotoxicológico a partir de los datos presentes. Sin embargo, teniendo en cuenta la biodegradabilidad observada, la falta de bioconcentración prevista (basada en un log del coeficiente de reparto octanol-agua de ! 0,38) y la baja toxicidad aguda indicada para los organismos acuáticos, así como para las aves, se puede llegar a la conclusión provisional de que la *N*-metil-2-pirrolidona no debería representar un riesgo importante para el medio ambiente.

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