UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**DATE:** **June 1, 2006**

**ACTION MEMORANDUM**

**SUBJECT:** Inert Reassessments: *N*-methylpyrrolidone (CAS Reg. No. 872-50-4)

**FROM:** Pauline Wagner, Chief Pauline M Wagner 6/1/06
Inert Ingredient Assessment Branch

**TO:** Lois A. Rossi, Director
Registration Division

## I. FQPA REASSESSMENT ACTION

**Action:** Reassessment of one inert ingredient exemption from the requirement of a tolerance. The current exemption is to be maintained.

**Chemical:** *N*-methylpyrrolidone (NMP)
**CFR:** 40 CFR 180.920 formerly 40 CFR 180.1001(d)
**CAS #:** 872-50-4

**Table 1. Tolerance Exemptions Expression**

| 40 CFR | Inert Ingredients | Limits | Uses (Pesticidal) | CAS Reg. No. and 9 CI Name |
|---|---|---|---|---|
| 180.920 | *N*-Methylpyrrolidone (CAS Reg. No. 872-504) | (none) | Solvent, cosolvent | 872-50-4 2-Pyrrolidinone, 1-methyl- |

**Use Summary:** NMP is used by various industries as a solvent for processing of petroleum, resins, acetylene, olefins, diolefins, and gas as well as for aromatic extraction from feedstock. This chemical also has plastic solvent applications in the microelectronics industry. It is also used as a pigment dispersant, a chemical intermediate, and a spinning agent for polyvinyl chloride. NMP is used by the pharmaceutical industry as a penetration enhancer for a more rapid transfer of

substances through the skin, and is approved by the U.S FDA as a solvent for slimicide applications to food packaging materials. NMP is also used as a solvent/cosolvent in a variety of pesticide products for agricultural and home garden use.

## II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient *N*-Methylpyrrolidone (CAS Reg. No. 872-50-4). I consider the exemption established in 40 CFR 180.920 [formerly 40 CFR 180.1001(d)] to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi, Director
Registration Division

Date: 6/1/06

CC: Debbie Edwards, SRRD
Joe Nevola, SRRD

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June 1, 2006

**MEMORANDUM**

SUBJECT: Reassessment of one Exemption from the Requirement of a Tolerance for *N*-methylpyrrolidone (NMP; CAS Reg. No. 872-50-4)

FROM: R. Tracy Ward, Biologist
Inert Ingredient Assessment Branch
Registration Division (7505P)

And

Whang Phang, Toxicologist
Reregistration Branch II
Health Effects Division (7509P)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch
Registration Division (7505P)

## Background

Attached is the science assessment for *N*-methylpyrrolidone (NMP; CAS Reg. No. 872-50-4). This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of NMP. The purpose of this document is to reassess the one existing exemption from the requirement of a tolerance for residues of NMP as required under the Food Quality Protection Act (FQPA).

## Executive Summary

This document evaluates NMP, a pesticide inert ingredient for which there is one exemption from the requirement of a tolerance under 40 CFR 180.920 for its use as a solvent, cosolvent in pesticide formulations applied to growing crops only.

In studies NMP had low acute toxicity via oral, dermal, and inhalation exposures. NMP was practically non-irritating to the skin, but caused moderate eye irritation. In subchronic repeat dose studies, decreased weight, food consumption, and body weight gain were observed at high oral doses, and neurotoxic effects were observed at high doses. Chronic effects were observed at high doses in males including progressive nephropathy and decreased survival rate from oral exposure, and alveolitis from inhalation exposure. NMP did not induce reproductive toxicity in animal studies. Developmental NOAELs and LOAELs were typically observed at maternal NOAELs and LOAELs and quantitative sensitivity was not observed for NMP. The chemical was non-carcinogenic in studies, and non-mutagenic in a majority of studies.

Residential inhalation exposures to NMP are not expected because of its physical and chemical properties. Dermal exposures are possible, but as an inert ingredient in pesticide formulations, it is not expected to be available at levels that would cause toxic effects or produce skin irritation. Due to reduced rates in pesticide formulations and because NMP readily biodegrades, dietary exposures (food and drinking water) at levels of concern are not likely.

NMP appears to have low acute toxicity to aquatic species and terrestrial animals, and low subchronic toxicity to terrestrial animals.

Taking into consideration all available information on NMP, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to NMP when used as an inert ingredient in pesticide formulations when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of NMP can be considered reassessed as safe under section 408(q) of the FFDCA.

## I. Introduction

This report provides a qualitative assessment for NMP, an inert ingredient in pesticide products for which one exemption from the requirement of a tolerance exists when used as a solvent, cosolvent in pesticide formulations used on growing crops only under 40 CFR 180.920.

## II. Use Information

### A. Pesticide Uses

NMP is used as an inert ingredient in a variety of pesticide products for agricultural and home garden use. There are no active ingredient uses for NMP registered at this time. The one tolerance exemption for this chemical is provided below

in Table 1.

**Table 1. Tolerance Exemption Being Reassessed in this Document**

| 40 CFR | Inert Ingredient | Limits | Uses | CAS Reg. No. and 9CI Name |
|---|---|---|---|---|
| 180.920[1] | *N*-Methylpyrrolidone (CAS Reg. No. 872-504[2]) | None | Solvent, cosolvent | 872-50-4 2-Pyrrolidinone, 1-methyl- |

1. Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.
2. The CAS Reg. No. for NMP in the CFR is incorrect. The correct CAS Reg. No. is 872-50-4. This error will be corrected in the future through a Federal Register notice.

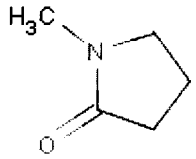
## B. Other Uses

NMP is used by various industries as a solvent for processing/purification of petroleum, resins, acetylene, olefins, diolefins, and gas as well as for aromatic extraction from feedstocks. The chemical also has plastic solvent applications in the microelectronics industry. It is also used as a pigment dispersant, a chemical intermediate, and a spinning agent for polyvinyl chloride. NMP is used by the pharmaceutical industry as a penetration enhancer for a more rapid transfer of substances through the skin, and is approved by the U.S. Food and Drug Administration (FDA) as a solvent for slimicide applications to food packaging materials under 21 CFR 176.300(d) (http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/cfr_2003/aprqtr/21cfr176.300.htm).

## III. Physical and Chemical Properties

The physical and chemical properties for NMP are provided in Table 2.

**Table 2. Physical and Chemical Properties of NMP**

| Parameter | Value | Reference |
|---|---|---|
| Structure |  | ChemIDPlus 2004 |
| CAS Reg. No. | 872-50-4 | |
| Molecular formula | $C_5$-$H_9$-N-O | ChemIDPlus 2004 |
| Molecular Weight | 99.13 | HSDB 2002 |
| Physical State | Colorless liquid | HSDB 2002 |
| Melting Point | -24°C (Measured) | ChemIDPlus 2004 |
| Water Solubility | 1.00 x $10^6$ mg/L @ 25°C (Measured) | ChemIDPlus 2004 |

| Parameter | Value | Reference |
|---|---|---|
| Log P (octanol-water) | -0.38 (Measured) | ChemIDPlus 2004 |
| Henry's Law Constant | 3.20 x $10^{-9}$ atm-$m^3$/mole (Measured) | ChemIDPlus 2004 |
| Vapor Pressure | 0.345 mm Hg @ 25°C (Measured) | ChemIDPlus 2004 |
| Atmospheric OH Rate Constant | 7.40 x 10-11 $cm^3$/molecule-sec @ 25°C (Estimated) | ChemIDPlus 2004 |

## IV. Hazard Assessment

### A. Hazard Profile

The toxicology data of NMP were previously reviewed and published in the International Programme on Chemical Safety (IPCS) report (WHO 2001). This assessment includes a small fraction of the information covered in the IPCS report. A more detailed description of the relevant toxicity studies on NMP is presented in Appendix A (Tables A-1 to A-7).

In studies NMP had low acute toxicity via oral, dermal, and inhalation exposures. NMP was practically non-irritating to the skin, but caused moderate eye irritation. In subchronic repeat dose studies, decreased weight, food consumption, and body weight gain were observed at high oral doses, and neurotoxic effects were observed at high doses. Chronic effects were observed at high doses in males including progressive nephropathy and decreased survival rate from oral exposure, and alveolitis from inhalation exposure. NMP did not induce reproductive toxicity in animal studies. Developmental NOAELs and LOAELs were typically observed at maternal NOAELs and LOAELs and quantitative sensitivity was not observed for NMP. The chemical was non-carcinogenic in studies, and non-mutagenic in a majority of studies.

### B. Metabolism

In animal metabolism studies, NMP was readily absorbed via the oral, inhalation, and dermal routes of administration. The chemical was distributed rapidly in the body and eliminated mainly as hydroxylated polar metabolites via urine (≈80% within 24 hours after exposure). After exposure to NMP, the urine of the test animals turned yellow, and the major metabolite was identified as 5-hydroxy-N-methyl-2-pyrrolidone.

### C. Toxicological Data

**Acute Toxicity:**

The available data on NMP indicate low acute toxicity with oral, dermal, and inhalation exposure as indicated in Table 3. The magnitude of inhalation toxicity depended on the method of exposure. Whole body inhalation exposure was shown to be more toxic than nose-only exposure due to absorption through the skin. NMP was practically non-irritating to the skin, but caused moderate eye irritation. No acute

neurotoxicity screening studies were available for NMP.

**Table 3. Summary of Acute Toxicity Data for N-methyl-2-pyrrolidone**

| Parameter | Toxicity Value* | Reference |
|---|---|---|
| Oral $LD_{50}$ (rats, mice, guinea-pigs, and rabbits) | 3900 – 7900 mg/kg (Tox. Cat. III – IV) | Ansell and Fowler 1988, as cited in WHO 2001 |
| Dermal $LD_{50}$ (rats & rabbits) | 4000 – 10,000 mg/kg (Tox. Cat. III – IV) | Bartsch et al., as cited in WHO 2001; Wallen 1992 |
| Inhalation $LC_{50}$ (rats; heads only) | >5.1 mg/L (5100 mg/$m^3$) (Tox. Cat. IV) | BASF, 1988, as cited in WHO 2001 |
| Inhalation $LC_{50}$ (rats; whole body exposure) | ≈1.7 mg/L (1700 mg/ $m^3$) (Tox. Cat. III) | E.I. du Pont de Nemours & Co. 1977, as cited in WHO 2001 |
| Primary Eye Irritation (rabbits) | Moderate (causing corneal opacity, iritis and conjunctivitis); recovered after 21 days post dosing | Ansell and Fowler, as cited in WHO 2001 |
| Primary Skin Irritation (rabbits) | Practically non-irritating | Ansell and Fowler, as cited in WHO 2001 |

* Some of these values were also reported in a submission to the Office of Toxic Substances under TSCA (US EPA/OTS; Doc #000080937Y)

**Subchronic Toxicity:**

Repeated oral exposure (**2 to 4 weeks**): With oral dosing to rats or mice (2 to 4 weeks) either by gavage or via the diet, NMP produced adverse effects at high dose levels (> 1000 mg/kg). The adverse effects consisted of decreased body weight ranging from 17% to 33%, hypocellular bone marrow, thymus atrophy, or swelling of epithelium of the renal tubuli (WHO 2001; Malek et al. 1997). Discoloration of urine was also seen; this finding was considered a sign of exposure to NMP.

With **90-day** dietary exposure in rats, NMP produced slight decreases in body weight and food consumption at 433 mg/kg. In the neurotoxicity portion of this study, an increase in foot splay at dose levels of 433 mg/kg or above was found. The report did not indicate any other related findings such as decreases in grip strength and in motor activity. A higher incidence of low arousal and slight palpebral closure were also seen at 1057 mg/kg (Malley et al. 1999; WHO 2001). This study had a NOAEL of 169 mg/kg and a LOAEL of 433 mg/kg.

When dogs were fed NMP in the diet for **90 days**, no significant adverse effects were seen at doses ranging from 25 to 250 mg/kg (Becci et al. 1983; as cited in WHO 2001).

Inhalation exposure (**2 weeks**): The data from a series of inhalation studies in

rats with varied particle sizes and exposure conditions indicated that NMP as coarse droplets, at high relative humidity (70%), and with whole body exposure produced most severe toxicity (including death of the test animals) at 1 mg/L (1000 mg/m$^3$; WHO 2001).

The results of a 90-day nose-only inhalation study in rats (relative humidity, 52-61%; particle size, 2.1-3.5 $\mu$m) showed that at concentrations levels of 0.5, 1.0, & 3 mg/L (500, 1000, & 3000 mg/m$^3$), NMP caused dark yellow discoloration of urine. At 1 and 3 mg/L, nasal irritation was seen. At 3 mg/L, testicular germinal epithelial cell loss was seen in males, and slight increases in red blood cells and other hematological parameter changes were also seen in females (WHO 2001). The NOAEL for this study was 0.5 mg/L (500 mg/m$^3$), and the LOAEL was 1 mg/L (1000 mg/m$^3$).

**Chronic Toxicity:**

Dietary exposure: When rats and mice were fed diets containing NMP for two years, male rats showed signs of progressive nephropathy/uremia at 678 mg/kg. No adverse effects were seen in rats at 207 mg/kg or below, and no increase in tumor incidence was found (Malley et al. 2001). In mice (B6C3F1), increases in absolute and relative liver weights and associated cellular changes such as hepatocellular hypertrophy and foci of cellular alteration at the highest dose (1089 mg/kg) were reported (Malley et al. 2001). Increases in the incidence of hepatocellular adenomas and carcinomas were reported in both male and female mice at 1089 mg/kg or higher. The increase in hepatocellular carcinomas, however, was reported to be within the historical control range. In rats, the NOAEL was 207 mg/kg, and the LOAEL was 678 mg/kg. In mice, the NOAEL was 173 mg/kg, and the LOAEL was 1089 mg/kg.

Inhalation exposure: Rats were exposed (whole body) to NMP for two years at concentrations of 0.04 or 0.4 mg/L (40 and 400 mg/m$^3$). No significant compound related effects were reported, except discoloration of the urine (Lee et al. 1987).

**Neurotoxicity:**

A 90-day dietary study in rats with a neurotoxicity examination component showed that at 433 mg/kg or above an increase in landing foot splay was reported, and at 1057 mg/kg a decrease in arousal was also seen. The increase in landing foot splay was not accompanied by any other effects at 433 mg/kg (WHO 2001). Nevertheless, these observations suggested that NMP at high doses might affect the nervous system. A NOAEL of 169 mg/kg, and a LOAEL of 433 mg/kg were reported for this 90-day dietary study.

**Genetic Toxicity:**

The majority of the data indicated that NMP was not mutagenic. In a range of bacterial mutagenicity assays, NMP did not produce mutagenic activity (BASF 1978, as

cited in WHO 2001). Two assays in yeast, *Saccharomyces cerevisiae*, showed NMP induced aneuploidy (Zimmermann et al., as cited in WHO 2001). NMP was shown to be negative in an unscheduled DNA synthesis assay in rat primary hepatocyte cultures (WHO 2001). No clastogenic effect was seen in a micronucleus test in mice at doses as high as 3800 mg/kg (WHO 2001). A bone marrow chromosomal aberration study in hamsters indicated no mutagenic activity at 1900 mg/kg and 3800 mg/kg (WHO 2001).

**Developmental and Reproductive Toxicity:**

**Developmental Toxicity:** There were several developmental toxicity studies available and they were carried out by either inhalation or dermal routes of exposure. There were also two TSCA Section 8(e) submissions consisting of an abstract and a report on developmental toxicity studies by oral exposure (gavage).

By the inhalation route (whole body) in rats, no developmental effects were found at concentrations of 0.36 mg/L (360 mg/m$^3$; Lee et al. 1987). Developmental toxicity at higher concentrations consisted of decrease in fetal body weight at 0.478 mg/L (478 mg/m$^3$; Solomon et al., 1995, as cited in WHO 2001), neurobehavioral effects (occasional increases in latency in the Morris swimming maze and borderline impairment in operant behavior with delayed spatial alteration) at 0.622 mg/L (622 mg/m$^3$; Hass et al., as cited in WHO 2001), and pre-implantation loss, delayed ossification at 0.68 mg/L (680 mg/m$^3$; Hass et al. 1994, as cited in WHO 2001).

In two dermal developmental toxicity studies 500 mg/kg NMP or below had no adverse effects in rats (Becci et al. 1982, as cited in WHO 2001). When dosed with 750 mg/kg or higher of NMP, rats had developmental effects such as increase in resorptions, decreased fetal body weight, incomplete closing of the skull, reduced or incomplete hyoid bone, and incomplete ossification of vertebrae. At a dose of 1100 mg/kg, 98% resorption was reported. In one study, the developmental and maternal NOAELs were 237 mg/kg, and the LOAELs were 750 mg/kg. The developmental and maternal NOAELs for the range-finding study were 500 mg/kg, with a LOAEL of 1100 mg/kg.

An abstract of an oral developmental toxicity study in rats reported that at 250 mg/kg or above there were reductions in fetal body weights and increases in the incidence of malformations characterized by anal atresia and the absence of a tail (TSCA: 8EHQ-0202-15084; Feb 27, 2002). However, neither the purity of NMP nor the data were available for analysis or to confirm information presented in this abstract.

The results of another oral developmental toxicity study in rats showed that, at 400 mg/kg (the highest dose tested) there was an increase in the number of fetuses with stunted growth and decreased fetal weight (10% in males and 11% in females; TSCA: 8EHQ-0492-3206; April 17, 1992).

**Reproductive toxicity:** Some older studies indicated that when rats were

exposed for 4 weeks to NMP in the diet at 2060 mg/kg per day (BASF 1978a, as cited in WHO 2001), or to 3 mg/L (3000 mg/m$^3$) by inhalation for 6 h/day, 5 days/week for 13 weeks (BASF 1994, as cited in WHO 2001), testicular effects were seen. However, in a 1993 submission to the Agency's Office of Toxic Substances (OTS), the results of a study specifically designed to explore the effects of NMP on the testes, central nervous system, embryogeny, and sperm in rats showed no testicular effect. The rats were exposed by inhalation at a concentration of 0.618 mg/L (618 mg/m$^3$) for 90 days (TSCA: 8EHQ-0195-0695).

In a 2-generation reproduction study (Solomon et al. 1995), male and female rats were exposed to NMP by inhalation at concentrations from 0.04 to 0.478 mg/L (40 to 478 mg/m$^3$). The results showed no effects on testicular weights and reproductive parameters. There was a sporadic decrease in mean pup weights at 0.478 mg/L (4-11%) on different days of measurement.

**Carcinogenicity:**

The carcinogenicity data from rats and mice indicated no increase in tumor incidence for rats. An increase, however, in hepatocellular adenomas and carcinomas were observed in male mice and hepatocellular adenomas in female mice fed 1089 mg/kg/day of NMP (Malley et al. 2001).

### D. Special Considerations for Infants and Children

Developmental and reproductive toxicity from NMP is observed only after repeated exposures at high concentrations that are not expected from its use as an inert ingredient in pesticide formulations. Developmental NOAELs and LOAELs were typically observed at maternal NOAELs and LOAELs. Quantitative sensitivity, therefore, was not observed for NMP. Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to NMP when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

## V. Environmental Fate Characterization/Drinking Water Considerations

From the Hazardous Substance Data Bank (2002):

"...If released to air, a vapor pressure of 0.345 mm Hg at 25 deg C indicates that 1-methyl-2-pyrrolidinone will exist in the vapor phase in the ambient atmosphere. Vapor-phase 1-methyl-2-pyrrolidinone will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 5 hrs. If released to soil, 1-methyl-2-pyrrolidinone is expected to have very high mobility based upon an estimated Koc of 12. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated

Henry's Law constant of 4.46 $X10^{-8}$ atm-cu m/mole (measured value in Table 2 is 3.20 x $10^{-9}$). The half-life of 1-methyl-2-pyrrolidinone in clay, loam and sand soils was 4.0, 8.7, and 11.5 days, respectively. If released into water, 1-methyl-2-pyrrolidinone is not expected to adsorb to suspended solids and sediment in the water column based upon the estimated Koc. 1-Methyl-2-pyrrolidinone appears to undergo biodegradation in aqueous environments as indicated through the Japanese MITI test and various screening experiments using activated sludge inoculum. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 0.23 suggests the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to occur due to the lack of hydrolyzable functional groups."

NMP is not expected to bioaccumulate in fish tissue, based on its low $P_{ow}$(log $P_{ow}$ = -0.38) and low BCF of 0.23 (HSDB 2002).

## VI. Exposure Assessment

Residential inhalation exposures to NMP are not expected because of its physical and chemical properties. Dermal exposures are possible, but as an inert ingredient in pesticide formulations it is not expected to be available at levels that would cause toxic effects or produce skin irritation. Due to reduced rates in pesticide formulations and because NMP readily biodegrades, dietary exposures (food and drinking water) at levels of concern are not likely.

## VII. Aggregate Exposure

In examining aggregate exposure, the FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For NMP, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to NMP as an inert ingredient in pesticide formulations.

## VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism

of toxicity finding as to NMP and any other substances, and this material does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that NMP has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative.

## IX. Human Health Risk Characterization

For NMP, toxic effects were only observed at high concentrations for repeat exposures of subchronic and chronic durations. As an inert ingredient in pesticide formulations, NMP will likely be at lower exposure concentrations with few applications, and the risk is, therefore, expected to be low.

In studies NMP had low acute toxicity via oral, dermal, and inhalation exposures. NMP was practically non-irritating to the skin, but caused moderate eye irritation. In subchronic repeat dose studies, decreased weight, food consumption, and body weight gain were observed at high oral doses, and neurotoxic effects were observed at high doses. Chronic effects were observed at high doses in males including progressive nephropathy and decreased survival rate from oral exposure, and alveolitis from inhalation exposure. NMP did not induce reproductive toxicity in animal studies. Developmental NOAELs and LOAELs were typically observed at maternal NOAELs and LOAELs and quantitative sensitivity was not observed for NMP. The chemical was non-carcinogenic in studies, and non-mutagenic in a majority of studies.

Residential inhalation exposures to NMP are not expected because of its physical and chemical properties. Dermal exposures are possible, but as an inert ingredient in pesticide formulations it is not expected to be available at levels that would cause toxic effects or produce skin irritation. Due to reduced rates in pesticide formulations and because NMP readily biodegrades, dietary exposures (food and drinking water) at levels of concern are not likely.

Taking into consideration all available information on NMP, there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of NMP under 40 CFR 180.920 when applied as a solvent, cosolvent in pesticide formulations used on growing crops only can be considered reassessed as safe under section 408(q) of the FFDCA.

The CAS Reg. No. for NMP in the CFR is incorrect. The correct CAS Reg. No. is

872-50-4. This error will be corrected in the future through a federal register notice.

## X. Ecotoxicity and Ecological Risk Characterization

From the WHO (2001) CICAD 35 for NMP:

"In a static test on the acute toxicity of NMP to the freshwater guppy (*Poecilla 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."

"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)."

**References:**

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HSDB. 2002. Hazardous Substance Databank. National Library of Medicine, National Institute of Health. *N*-Methylpyrrolidone Profile Updated: February 13, 2002. <http://www.toxnet.nlm.nih.gov>.

Lee, KP, Chromey, NC, Culik, R, et al. (1987). Toxicity of N-methyl-2-pyrrolidone (NMP): Teratogenic, subchronic, and two-year inhalation studies. *Fundamental and Applied Toxicology*, 9, pp 222-235.

Malek, DE, Malley, LA, Slone, TW, et al. (1997). Repeated dose toxicity study (28 days) in rats and mice with N-methylpyrrolidone (NMP). *Drug and Chemical Toxicology*, 20 (1 & 2), pp 63-77.

Malley, LA, Kennedy, GL, Elliot, GS et al. (1999). 90-Day subchonic toxicity study in rats and mice fed N-methylpyrrolidone (NMP) including neurotoxicity evaluation in rats. *Drug and Chemical Toxicology*, 22 (3), pp 455-480.

Malley, LA, Kennedy, GL, Elliot, GS et al. (2001). Chronic toxicity study of N-methyl-pyrrolidone (NMP) in rats and mice by dietary administration. *Drug and Chemical Toxicology*, 24 (4), pp 315-338.

Solomon, HM, Burgess, BA, Kennedy, Jr., GL et al. (1995). 1-methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat. *Drug and Chemical Toxicology*, 24 (4), pp 315-338.

US EPA: TSCA 8EHQ-04920-3206; April 17, 1992. Developmental toxicity study in rats with *N*-Methylpyrrolidone. Exxon Biomedical Sciences, Inc., Toxicology Lab. East Millstone, NJ. (no date). Submitted by International Specialty Products Wayne NJ. April 10, 1992.

US EPA: TSCA 8EHQ-0202-15084; Feb 27, 2002. Saillenfait, AM et al (2001) Developmental toxicity of N-methyl-2-pyrrolidone administered by gavage or inhalation to rats. (an abstract in the proceedings of the 29th Conference of the European Teratology Society, Balatonfured- Hungary , 2001).

US EPA: TSCA 8EHQ-0195-0695; Jan. 17, 1995. The effects of *N*-metylpyrrolidone on embryogeny, central nervous system, testicles, and sperm in the rats. Nat'l. Institute of

Occupational Health, Denmark. Submitted by BASF Corporation, June 21, 1991.

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# APPENDIX A

## Summary of Toxicity Studies on NMP

**Table A-1. Two-week[a] inhalation toxicity studies in female rats exposed to NMP at 1000 mg/m$^3$ (1mg/L)[+]**

| Exposure characterization[b] | Mode of exposure | Effects observed | Reference |
|---|---|---|---|
| Fine/dry (<3 μm; RH, 10%)c | Whole body | No deaths; slight decrease in body weight gain ($p<0.05$); and slight decreases in lymphocyte and neutrophil counts. | BASF, 1995c |
| Fine/dry (3.8-4.4 μm; RH, 35%) | Nose only | No deaths. | BASF, 1992 |
| Coarse/wet (4.8 μm; RH, 70%) | Whole body | Nine deaths; congestion in nearly all organs, and lesions in spleen and lungs. Survivors recovered in 2 weeks. | BASF, 1995f |
| Coarse/wet (4.4-4.5 μm; RH, 70%) | Head only | No deaths; nasal irritation. | BASF, 1995g |
| Coarse/wet (4.4-4.5 μm; RH, 70%) | Whole body | Nine deaths; serious lesions in spleen (depletion and necrosis of lymphocytes) and bone marrow (panmyelophthisis and gelatinous bone marrow). Survivors' body weight and absolute organ weight "different" from means of controls. | BASF, 1995g |
| Coarse/wet (5.1-5.2 μm; RH, 70%) | Whole body | Eight deaths; apathy, irregular respiration, convulsions, tremor, and poor general health state. Pulmonary edema and multifocal purulent pneumonia; necrotic alterations in liver; cell depletion in bone marrow; necrosis in spleen; ulceration in the glandular stomach; increased adrenal weight. Survivors had no significant gross or microscopic findings. | BASF, 1995d |
| Fine/dry (<3 μm; R, 10%) | Whole body | No deaths; sensory irritation characterized by decreased respiratory rate and minute volume and increased inspiration time. | BASF, 1995a |

| Exposure characterization[b] | Mode of exposure | Effects observed | Reference |
|---|---|---|---|
| Fine/wet (>3 μm; RH, 70%) | Whole body | No deaths; slightly (p=0.05) decreased lymphocyte counts and increased liver weights. Increased relative lung weight. Symptoms of nasal irritation. | BASF, 1995e |

+ Table excerpted from the from the Literature Summary Report: N-Methyl-2-pyrolidone (NNMP) prepared by Oak Ridge National Laboratory (July 12, 2005). It was originally taken from WHO, 2001, by Oak Ridge National Laboratory.
a All BASF references as cited in WHO.
b Ten female rats were exposed to NMP for five 6-hours/day, 5 days/week for 2 weeks. Ten female control rats were exposed to air.
c RH = relative humidity.

**Table A-2. Subchronic and Chronic Toxicity Studies**

| Species/study type/ exposure | LOAEL NOAEL | Effects seen at LOAEL or above | References |
|---|---|---|---|
| **Subchronic Toxicity Studies** | | | |
| Rats: 90-day **inhalation** study; nose only exposure to aerosol (2.1-3.5 μm): 0.5, 1.0, 3.0 mg/L | 1 mg/L<br>0.5 mg/L | At 1.0 mg/L, nasal irritation at the end of exposure period. At 3mg/L, respiratory tract irritation, ↓ body weight (34%), ↓ testes weight and germinal epithelial cell loss in the testes. | WHO 2001 |
| Rats: 4-week **inhalation** study (whole body); aerosol-vapor; 0.1, 0.5, & 1.0 mg/L; | 1.0 mg/L<br>0.5 mg/L | At 1.0 mg/L, lethargy, respiratory difficulty, and excessive mortality were seen. Focal pneumonia, bone marrow hypoplasia, and atrophy of lymphoid tissue in the spleen and thymus were also found, but these effects were shown to be reversible after two weeks of recovery. | Lee et al., 1987; WHO 2001 |

| Table A-2. Subchronic and Chronic Toxicity Studies | | | |
|---|---|---|---|
| **Species/study type/ exposure** | **LOAEL NOAEL** | **Effects seen at LOAEL or above** | **References** |
| Rats: 4-week study by **intubation**; 257, 514, 1028, & 2060 mg/kg | 1028 mg/kg<br>514 mg/kg | At 1028 mg/kg, ↓ body weight (11%), ↓ lymphocyte counts, ↓ body weight gain, and increased relative kidney and liver weights. At 2060 mg/kg, all the effects seen in 1028 mg/kg plus ↓ relative and absolute testes weights, formation of multinucleate giant cells and clumping of sloughed-cells in seminiferous tubule epithelium. | WHO 2001 |
| Rats: 28-day **feeding** study; 2,000; 6,000; 18,000; & 30,000ppm (149, 429, 1234, & 2019 mg/kg for ♂; 161, 493, 1548, 2268 mg/kg for ♀) | 1234 mg/kg<br>429 mg/kg | At 1234 mg/kg & above, ↓ body weight (17%), ↓ body weight gains (40%), ↓ food consumption and efficiency, hypocellular bone marrow, & testicular degeneration & atrophy. Female at 2268 mg/kg also had thymic atrophy. | Malek et al., 1997; WHO 2001 |
| Mice: 28-day **feeding** study; 500; 2,500; 7,500; & 10,000 ppm (130, 720, 2130, & 2670 mg/kg for ♂; 180, 920, 2970, & 4060 mg/kg for ♀) | 2130 mg/kg<br>720 mg/kg | Males at 2130 mg/kg has swelling of epithelium of the distal tubule in males (2/5). At next dose levels 4/5 males and 3/5 females were affected. | Malek et al., 1997; WHO 2001 |

| Table A-2. Subchronic and Chronic Toxicity Studies | | | |
|---|---|---|---|
| **Species/study type/ exposure** | **LOAEL NOAEL** | **Effects seen at LOAEL or above** | **References** |
| Mice:28-day & 90-day **feeding** study; 1000, 2500, 7500 ppm (289, 773, & 2153 mg/kg) | 28-day: NOAEL = 2153 mg/kg<br><br>90-day: NOAEL=2153 mg/kg | For 28-day study, there were slight increases in cholesterol and decreases in triglycerides at 2500 and 7500 ppm groups, but these changes were not seen after 90-day feeding. In 90-day feeding groups, increased in absolute & relative liver weights were seen 2500 & 7500 ppm males associated with dose-related increase in incidence of hepatocellular hypertrophy in both males and females in these two dose groups.<br>The effects seen in 90-day treatment groups appeared to be treatment-related adaptive effects and might not be adverse. | Malley et al., 1999; WHO 2001<br><br>This study should be considered in conjunction with the chronic study (Malley et al. 2001) in mice because this was part of the work to examine the short, medium, and long-term effects of NMP in the mouse. |
| Rats: 90-day feeding; 3000, 7500, & 18000 ppm (♂:169, 433, & 1057mg/kg; ♀: 217, 565, & 1344 mg/kg) | 433 mg/kg<br>169 mg/kg | At 7500 ppm, a slight decrease in body weight reflecting a reduction in food consumption. At 7500 ppm or above there was an increase in foot splay. At 18000 ppm, an increase in "higher incidence of low arousal & slight papebral closure suggestive of sedative effect" was seen. | Malley et al. 1999; WHO 2001 |
| **Chronic Toxicity Studies** | | | |
| Rats: 2-year **inhalation** study (whole body); 0.04 & 0.4 mg/L (6 h/d; 5 d/wk) | | At 0.4 mg/kg, there was an increase in the incidence of alveolitis in males, but similar effect was not seen in females. | Lee et al., 1987; WHO 2001 |

| Table A-2. Subchronic and Chronic Toxicity Studies | | | |
|---|---|---|---|
| **Species/study type/ exposure** | **LOAEL NOAEL** | **Effects seen at LOAEL or above** | **References** |
| Rats: 2-year **feeding** study; 1600, 5000, 15000 ppm (♂: 66.4, 207, & 678 mg/kg; ♀: 87.8, 283, & 939 mg/kg) | 678 mg/kg<br>207 mg/kg | At 678 mg/kg, there was an increase in the incidence of severe chronic progressive nephropathy in males, and a decrease in survival rate was also found in males of this dose level.<br>No increase in tumor incidence was seen | Malley et al., 2001 |
| Mice: 2-year **feeding** study; 600, 1200, 7200 ppm (♂: 89, 173, & 1089 mg/kg; ♀: 115, 221, & 1399 mg/kg) | 1089 mg/kg<br>173 mg/kg | At 1089 mg/kg (7200 ppm), there were an increase in liver weight, increase in the incidences of hepatocellular clear foci, eosinophilic foci, hypertrophy, and alterations. At 173 mg/kg, there was an increase in liver hypertrophy, but the increase was not statistically significant and no other effect was increased relative to the controls. An increase in hepatocellular adenomas and carcinomas was seen in the highest-dose males and females (1089 mg/kg for ♂; 1399 mg/kg for ♀) relative to the controls. | Malley et al., 2001 |

| Table A-3. Reproductive Toxicity Studies on NMP in rats[a]: Inhalation | | | | | |
|---|---|---|---|---|---|
| **Species/type of study/exposure** | **Concentration/ dose** | **Toxicity** | | **NOAEL/LOAEL** | **Reference[b]** |
| | | **Fetal** | **Maternal** | | |
| Rat/ two-generation/ inhalation (whole body), 6 h/day, 7 days/week | 0 mg/m3<br>41 mg/m$^3$<br>206 mg/m$^3$<br>478 mg/m$^3$ | None<br>None<br>None<br>Decrease of 4-11% in pup body weight | None<br>None<br>None<br>Decrease in response to sound | Reproductive toxicity: NOAEL = 478 mg/m$^3$; LOAEL = ND<br><br>Maternal toxicity: NOAEL = 206 mg/m$^3$; LOAEL = 478 mg/m$^3$ | Solomon et al., 1995 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Offspring toxicity: NOAEL = 206 mg/m$^3$ LOAEL = 478 mg/m$^3$ | |
| Rat/ testes and semen toxicity study/ inhalation (whole body); 6 h/day, 7 days/week; 90 days | 0 mg/m$^3$ 618 mg/m$^3$ | None None | None None | Reproductive toxicity: NOAEL = 618 mg/m$^3$ | Fries et al., 1992 |

a: Table excerpted from the Literature Summary Report: N-Methyl-2-pyrolidone (NMP) prepared by Oak Ridge National Laboratory (July 12, 2005). It was originally taken from WHO, 2001, by Oak Ridge National Laboratory.
b: References as cited in WHO, unless otherwise indicated.
ND = not determined

**Table A-4. Developmental toxicity Studies on NMP in rats[a]**

| Species/type of study/ exposure | Concentration/ dose | Toxicity | | NOAEL/LOAEL | Reference[b] |
|---|---|---|---|---|---|
| | | Fetal | Maternal | | |
| **Inhalation** | | | | | |
| Rat; developmental toxicity; inhalation (whole body); days 4–20 of gestation, 6 h/day | 0 mg/m$^3$ 680 mg/m$^3$ | None Increased preimplantation loss but no effect on # of implantations per dam or # of live fetuses; delayed ossification | None None | Developmental toxicity: NOAEL = ND LOAEL = 680 mg/m$^3$<br><br>Maternal toxicity: NOAEL = 680 mg/m$^3$ LOAEL = ND | Hass et al., 1995 |
| Rat; two-generation study; inhalation (whole body): M/F exposed for 14 weeks, mated and pregnant females examined at day 21 of | 0 mg/m$^3$ 478 mg/m$^3$ | None Decrease of 7% in fetal body wt. | None None | Developmental toxicity: NOAEL = ND LOAEL = 478 mg/m$^3$<br><br>Maternal toxicity: NOAEL = 478 mg/m$^3$ LOAEL = ND | Solomon et al., 1995 |

| Table A-4. Developmental toxicity Studies on NMP in rats[a] | | | | | |
|---|---|---|---|---|---|
| **Species/type of study/ exposure** | **Concentration/ dose** | **Toxicity** | | **NOAEL/LOAEL** | **Reference[b]** |
| | | **Fetal** | **Maternal** | | |
| gestation | | | | | |
| Rat; developmental toxicity; inhalation (whole body); days 7–20 of gestation, 6 h/day | 0 mg/m$^3$<br>622 mg/m$^3$ | None<br>Decreased body weight; Neurobehavioral effects | None<br>None | Developmental toxicity: LOAEL = 622 mg/m$^3$<br><br>Maternal toxicity: NOAEL = 622 mg/m$^3$<br>LOAEL = ND | Hass et al., 1994 |
| Rat; developmental toxicity; inhalation (whole body); days 6–15 of gestation, 6 h/day | 0 mg/m$^3$<br>100 mg/m$^3$<br>360 mg/m$^3$ | None<br>None<br>None | None<br>Lethargy and irregular respiration during the first 3 days of exposure (100 and 360 mg/m$^3$) | Developmental toxicity: NOAEL = 360 mg/m$^3$<br>LOAEL = ND<br><br>Maternal toxicity:[c] NOAEL = 100 mg/m$^3$; LOAEL = 360 mg/m$^3$ | Lee et al., 1987 |
| Rat: Develop. Toxicity; inhalation (whole body or nose only not specified); GD 6 to 20. 6 hr/day | ppm mg/m$^3$<br>30 125<br>60 250<br>120 500 | None<br>None<br>Decreased fetal body weight | None<br>↓ bwtg<br>↓ bwtg<br><br>Bwtg= body weight gain | Developmental toxicity: NOAEL =250 mg/m$^3$<br>LOAEL = 500 mg/m$^3$<br><br>Maternal toxicity: NOAEL = 125 mg/m$^3$<br>LOAEL = 250 mg/m$^3$ | TSCA 8EHQ-0202-15084; Feb 27, 2002 |
| **Dermal Administration** | | | | | |
| Rat; range-finding developmental | 0 mg/kg<br>500 mg/kg<br>1100 mg/kg | –<br>–<br>Resorptions | None<br>None<br>Massive | Developmental toxicity: NOAEL = 500 | Becci et al 1982 |

| Table A-4. Developmental toxicity Studies on NMP in rats[a] | | | | | |
|---|---|---|---|---|---|
| Species/type of study/ exposure | Concentration/ dose | Toxicity | | NOAEL/LOAEL | Reference[b] |
| | | Fetal | Maternal | | |
| toxicity study; dermal; days 6–15 of gestation | 2500 mg/kg | Resorptions | resorption; decreased body weight gain<br>Lethal | mg/kg<br>LOAEL = 1100 mg/kg<br><br>Maternal toxicity[c]: NOAEL = 500 mg/kg LOAEL = 1100 mg/kg | |
| Rat; developmental toxicity study; dermal; days 6–15 of gestation | 0 mg/kg<br>75 mg/kg<br>237 mg/kg<br>750 mg/kg | None<br>None<br>None<br>Increased resorptions, decreased body weights, delayed ossification, skeletal abnormalities | None<br>None<br>None<br>Decreased body weight gain; increased resorptions | Developmental toxicity: NOAEL = 237 mg/kg LOAEL = 750 mg/kg<br><br>Maternal toxicity: NOAEL = 237 mg/kg LOAEL = 750 mg/kg | Becci et al 1982 |

a: Table excerpted from the from the Literature Summary Report: N-Methyl-2-pyrolidone (NMP) prepared by Oak
Ridge National Laboratory (July 12, 2005). It was originally taken from WHO 2001 by Oak Ridge National Laboratory.
b: References as cited in WHO, 2001
c: NOAEL and LOAEL stated as in WHO, 2001; however, the reviewer would place maternal LOAEL at ND and the NOAEL at 360 mg/m3.
ND = not determined

| Table A-5. Developmental Toxicity Information on N-Methyl-2-pyrrolidone with Oral Exposure Submitted Under TSCA | | | |
|---|---|---|---|
| Study Type | Dose levels | Effects | References |
| Develop. Tox. In SD rats (gavage) (25-27/dosegroup) | 125, 250, 500, & 750 mg/kg.<br>GD days 6 to 20; Cesarean section on GD 21. | Maternal toxicity was seen at 500 & 750 consisted of reduced body weight gain and food consumption. Developmental toxicity was seen at 250 mg/kg or above. At 250 mg/kg, a dose-related decrease in fetal | US EPA:TSCA 8EHQ-0202-15084. Feb 27, 2002. This submission consisted of an abstract.<br><br>(It should be noted that neither the purity of NMP nor the data were available |

| Table A-5. Developmental Toxicity Information on N-Methyl-2-pyrrolidone with Oral Exposure Submitted Under TSCA | | | |
|---|---|---|---|
| **Study Type** | **Dose levels** | **Effects** | **References** |
| | | body weight was seen. An increase in the incidence of malformation ( anal atresia and absence of tail) was seen at 250 (one fetus) & 500 (11 fetuses) mg/kg. At 750 mg/kg one case of proboscis and one case of anasarca were reported. No effect was seen at 125 mg/kg. | to be analyzed and to confirm the information reported in the abstract.) |
| Develop. Tox. In SD rats (gavage) 25/dose group | 20, 125, & 400 mg/kg GD 6 through 15. Cesarean section on GD21. | Maternal toxicity was seen at 400 mg/kg characterized by statistically significant reduction in body weight gain during treatment period (22%). Developmental effects were seen at 400 mg/kg, and these were decreased fetal body weight (10% in males and 11% in females) and increase incidence of stunted fetuses (fetal data: 1/340 in controls vs 12/397 in 400 mg/kg; litter data: 1/21 in controls vs 6/25 in 400 mg/kg). | US EPA: TSCA 8EHQ-0492-3206. April 17, 1992. This submission was a study report stamped as Draft. The study was conducted by Exxon Biomedical Sciences, Inc., Tox. Laboratory East Millstone, NJ. |

in WHO 2001), or to 3 mg/L (3000 mg/m$^3$) by inhalation for 6 h/day, 5 days/week for 13 weeks (BASF 1994, as cited in WHO 2001), testicular effects were seen. However, in a 1993 submission to the Agency's Office of Toxic Substances (OTS), the results of a study specifically designed to explore the effects of NMP on the testes, central nervous system, embryogeny, and sperm in rats showed no testicular effect. The rats were exposed by inhalation at a concentration of 0.618 mg/L (618 mg/m$^3$) for 90 days (TSCA: 8EHQ-0195-0695).

In a 2-generation reproduction study (Solomon et al. 1995), male and female rats were exposed to NMP by inhalation at concentrations from 0.04 to 0.478 mg/L (40 to 478 mg/m$^3$). The results showed no effects on testicular weights and reproductive parameters. There was a sporadic decrease in mean pup weights at 0.478 mg/L (4-11%) on different days of measurement.

**Carcinogenicity:**

The carcinogenicity data from rats and mice indicated no increase in tumor incidence for rats. An increase, however, in hepatocellular adenomas and carcinomas were observed in male mice and hepatocellular adenomas in female mice fed 1089 mg/kg/day of NMP (Malley et al. 2001).

### D. Special Considerations for Infants and Children

Developmental and reproductive toxicity from NMP is observed only after repeated exposures at high concentrations that are not expected from its use as an inert ingredient in pesticide formulations. Developmental NOAELs and LOAELs were typically observed at maternal NOAELs and LOAELs. Quantitative sensitivity, therefore, was not observed for NMP. Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to NMP when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

## V. Environmental Fate Characterization/Drinking Water Considerations

From the Hazardous Substance Data Bank (2002):

"...If released to air, a vapor pressure of 0.345 mm Hg at 25 deg C indicates that 1-methyl-2-pyrrolidinone will exist in the vapor phase in the ambient atmosphere. Vapor-phase 1-methyl-2-pyrrolidinone will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 5 hrs. If released to soil, 1-methyl-2-pyrrolidinone is expected to have very high mobility based upon an estimated Koc of 12. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 4.46 X10$^{-8}$ atm-cu m/mole (measured value in Table 2 is 3.20 x

$10^{-9}$). The half-life of 1-methyl-2-pyrrolidinone in clay, loam and sand soils was 4.0, 8.7, and 11.5 days, respectively. If released into water, 1-methyl-2-pyrrolidinone is not expected to adsorb to suspended solids and sediment in the water column based upon the estimated Koc. 1-Methyl-2-pyrrolidinone appears to undergo biodegradation in aqueous environments as indicated through the Japanese MITI test and various screening experiments using activated sludge inoculum. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 0.23 suggests the potential for bioconcentration in aquatic organisms is low. Hydrolysis is not expected to occur due to the lack of hydrolyzable functional groups."

NMP is not expected to bioaccumulate in fish tissue, based on its low $P_{ow}$(log $P_{ow}$ = -0.38) and low BCF of 0.23 (HSDB 2002).

## VI. Exposure Assessment

Residential exposures and inhalation exposures in the general population to NMP are not expected because of its physical and chemical properties. Dermal exposures are possible, but as an inert ingredient in pesticide formulations it is not expected to be available at levels that would cause toxic effects or produce skin irritation. Due to reduced rates in pesticide formulations and because NMP readily biodegrades, dietary exposures (food and drinking water) at levels of concern are not likely.

## VII. Aggregate Exposure

In examining aggregate exposure, the FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For NMP, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to NMP as an inert ingredient in pesticide formulations.

## VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism

| Table A-6. Additional Reproductive/developmental toxicity of NMP+ | | | |
|---|---|---|---|
| **Type of study/species** | **Exposure** | **Effects** | **Reference** |
| **Oral** | | | |
| Multigeneration reproductive toxicity, rats (number not given) | 50-500 mg/kg/day in the diet from pre-mating to weaning of last litter | 500 mg/kg: decreased parental body weight and food consumption; reduction in survival and growth rates of the pups. 50 and 160 mg/kg: slightly lower male fertility and female fecundity indices. NOAEL not demonstrated. | EXXON (1991)<br>It should be noted that there were no data available for analysis and a confirmation of the conclusion could not be made on this study. |
| Developmental toxicity, pregnant rats (25/dose) | 0, 40, 125, or 400 mg/kg/day by gavage on days 6-15 of gestation | 400 mg/kg: decreased maternal body weight gain, reduced fetal body weights and increased fetal stunting. | EXXON (1992) |
| Developmental toxicity, pregnant rats (number not given) | 0, 332, or 997 mg/kg/day by gavage on days 6-15 of gestation | 997 mg/kg: no maternal toxicity; increased incidence of resorptions (95%) and malformations in 8/15 (53%) surviving fetuses; fetal mortality, reduced placental and fetal weights, reduced fetal length. No adverse effects at 332 mg/kg/day | U.S. EPA (1988) |
| **Inhalation** | | | |
| Developmental toxicity, pregnant rabbits (15/dose) | 0, 200, 500, or 1000 mg/m3, 6 h/day on days 7-19 of gestation | No maternal toxicity. 1000 mg/m$^3$: slight increase in skeletal variations in fetuses, accessory 13$^{th}$ rib | BASF (1991) |
| **Dermal Application** | | | |
| Developmental toxicity, pregnant rabbits (15/dose) | 0, 100, 300, or 1000 mg/kg, 6h/day on days 7-19 of gestation, dermal application | No maternal toxicity. 1000 mg/kg: slight fetal toxicity (skeletal variations, accessory 13$^{th}$ rib) | BASF (1993a) |

+: Table excerpted from the Literature Summary Report: N-Methyl-2-pyrolidone (NMP) prepared by Oak

Ridge National Laboratory (July 12, 2005). These studies were cited in the WHO 2001 document, but they were not found in the published literature search.

**Table A-7. Genotoxicity assays with NMP**

| Type of test/test system | NMP Dose/Metabolic activation | Results | References[a] |
|---|---|---|---|
| ***In vitro* studies** | | | |
| Direct plate incorporation, *Salmonella typhumurium* strains TA97, TA98, TA100, TA102 and TA104 | 0.01-1000 μmol/plate (0.99 μg-99 mg/plate), with and without Aroclor-induced rat liver S9 | Signs of cytotoxicity at highest dose. Without activation, strains TA102 and TA104 exhibited a minor and non-dose-related increase in the number of revertants | Wells et al. |
| Preincubation, *Salmonella typhimurium* strains TA98 and TA104 | 0.01-1000 μmol/plateb (0.99 μg-99 mg/plate), with and without Aroclor-induced rat liver S9 | No effect | Wells et al. |
| Preincubation, Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 | up to 10 mg/plate, with and without Aroclor-induced rat or hamster liver S9 | No mutagenic activity | Mortelmans et al. |
| Induction of aneuploidy *Saccharomyces cerevisiae* strain D61.M | 77-230 mmol/L (7.6-23 g/L) | Toxicity and decreased survival (by>50%) at 179 mmol/liter (18 g/L) and higher | Mayer et al. |
| Induction of aneuploidy *Saccharomyces cerevisiae* strain D61.M | 2.44% | Decreased survival (by >50%) | Zimmerman n et al. |
| Unscheduled DNA synthesis in rat primary hepatocyte cultures | Not given | Negative for unscheduled DNA synthesis | GAF |
| Unscheduled DNA synthesis in L5178y mouse lymphoma cells | Not given | Negative for unscheduled DNA synthesis | E.I. du Pont de Nemours and Company (1976a) |
| ***In vivo* studies** | | | |

| Table A-7. Genotoxicity assays with NMP | | | |
|---|---|---|---|
| **Type of test/test system** | **NMP Dose/Metabolic activation** | **Results** | **References[a]** |
| Micronucleus test in NMRI male and female mice | Single oral doses of 950, 1900, or 3800 mg/kg body weight | Signs of general poor health. No clastrogenic effects or aneuploidy observed at 24, 48, and 72 hours after administration. | Engelhardt and Fleig |
| Chromosomal aberration study in male and female Chinese hamsters | Single oral doses of 1900 or 3800 mg/kg | Signs of general poor health. No structural or numerical chromosomal alterations observed in samples taken 16 (high dose only) and 24 hours after administration. | Engelhardt and Fleig |

a: Table excerpted from the Literature Summary Report: N-Methyl-2-pyrolidone (NMP) prepared by Oak Ridge National Laboratory (July 12, 2005). It was originally taken from WHO, 2001, by Oak Ridge National Laboratory. All references as cited in WHO.
b: Experimental details for this study are not clear in the WHO document. The reviewer assumes the concentrations and test conditions, based on the wording of the WHO document.