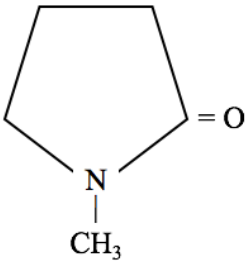
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

n-METHYL-2-PYRROLIDONE (NMP) (2022)

I. IDENTIFICATION (OECD, 2007)

Chemical Name: n-Methyl-2-Pyrrolidone
Synonyms: NMP; l-Methyl-2-Pyrrolidone; m-Pyrol; n-Methyl Pyrrolidinone
CAS Number: 872-50-4
Molecular Formula: C_5H_9NO
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES (OECD, 2007; OECD, 2008)

Molecular Weight: 99.1 g/mol
Physical Description: Liquid, almost colorless
Odor Description: Mild, amine-like odor
Odor Threshold: 8 mg/m^3 (2 ppm) (van Thriel et al., 2007)
Conversion Factor: 1 ppm = 4 mg/m^3, 1 mg/m^3 = 0.25 ppm
Boiling Point: 395°F (202 °C) at 760 mmHg; 302°F (150°C) at 162 mmHg; 212°F (100°C) at 24 mmHg
Melting Point: -11.9°F (-24.4°C)
Vapor Density (air = 1): 3.40
Vapor Pressure: 0.32 hPa at 20°C (68°F); 0.46 hPa at 25°C (77 °F)
Flash Point: 199°F (93°C) closed cup; 204°F (96°C) open cup
Flammability Limits in Air (by volume): Upper explosive limit - 12.24% at 370°F (188°C); Lower explosive limit - 2.18% at 360°F (182°C)
Autoignition Temperature: 518°F (270°C)
Specific Gravity (Water = 1): 1.027 at 25°C (77°F)
Solubility: Completely miscible with water and most organic solvents
Reactivity and Incompatibilities: NMP is stable

III. USES

NMP is a widely used solvent with a large variety of applications including paint stripping; coating systems; spinning, molding, and extruding synthetic fibers; manufacture of wire insulation enamels; fuel and lube oil additive; and pharmaceutical solvent (OECD, 2007; OECD, 2008).

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

For inhalation studies, NMP can exist as a vapor and aerosol depending on air temperature and humidity. Depending on chamber conditions (i.e., humidity), it is possible that the test atmospheres for the toxicology studies conducted via inhalation contained NMP aerosol as well as vapor. Under such conditions, the deposition of aerosol on exposed body surfaces can contribute to the total exposure (inhalation, dermal absorption, and incidental oral ingestion via grooming) exceeding that due to inhalation alone. During vapor phase exposures, data in humans show that dermal absorption of NMP at a concentration as low as 80 ppm significantly contributes to total exposure (i.e., 42% of total whole-body NMP exposure) (Bader et al., 2008). The air concentration of NMP contributes to the degree of dermal absorption under the conditions of the test system and needs to be considered when interpreting study results.

1. Lethality Data

Table 1. Lethality in Various Animal Species

Species	Route	4-hr LC_{50}
Mouse (strain not specified)	Oral	4050 mg/kg (OECD, 2008)
Mouse (NMRI)	Oral	7725 mg/kg (OECD, 2008)

Species	Route	4-hr LC_{50}
Rat (strain not specified)	Oral	3605 mg/kg (OECD, 2008)
Rat (Sprague-Dawley)	Oral	3914 mg/kg (OECD, 2008)
Rat (Sprague-Dawley)	Oral	4150 mg/kg (OECD, 2008)
Rat (Sprague-Dawley)	Dermal	>5000 mg/kg (OECD, 2008)
Rat (Wistar)	Dermal	5000-7000 mg/kg (OECD, 2008)
Rabbit	Dermal	8000 mg/kg (Bartsch et al., 1976)
Rat (Wistar)	Inhalation	>5100 mg/m^3 (1275 ppm) (4h) (OECD, 2008)

In most cases, the study summaries do not specify the effects that occurred at sublethal doses. However, one study in rats reported clinical signs of ataxia and diuresis at high but sublethal doses (at 1/8 LD_{50}). In acute inhalation studies, effects during or after exposure appeared to reflect changes in breathing (e.g., accelerated, irregular breathing), irritation (e.g., slightly reddish nasal secretion), or effects on responsiveness (e.g., reduced pain sensitivity or lethargy).

2. Eye Irritation

Undiluted NMP (0.1 mL) was placed in the eyes of New Zealand white rabbits. Corneal effects were reversible within 14 days for unwashed eyes and within 7 days for washed eyes. Conjunctival effects cleared in unwashed eyes by the end of the 21-day observation period and in washed eyes by day 14. The ocular effects were rated as moderate (Ansell and Fowler, 1988; OECD, 2008).

3. Skin Absorption

The dermal toxicity of five chemicals, including NMP, was evaluated by applying the chemical to shaved areas (20–25% of body surface) of Sprague-Dawley rats. This reference reports two separate tests of NMP; one non-occluded and one occluded with adhesive bandages backed with aluminum foil. The authors concluded that NMP had an LD_{50} in rats approximately the same as that in rabbits (Clark et al., 1984).

4. Skin Irritation

In a primary dermal irritation study, 0.5 mL of undiluted NMP was applied to intact and abraded skin of 6 albino rabbits. The primary irritation index (PII) was 0.5 (for both intact and abraded skin and the averaged reading was from 24 and 72 hours) with no responses observed after 72 hours. The dermal response was rated as minimal (OECD, 2008).

5. Skin Sensitization

Based on the study summaries, NMP did not produce a dermal sensitization response after initial exposure to intradermal injections of either 5 or 50% NMP solution and subsequent challenge with a 5% solution on the shaved intact skin of male guinea pigs (OECD, 2008). In a human repeat insult patch test in 50 volunteers, the exposure of 15 volunteers for 24h reportedly caused minor to moderate transient dermal irritation, but no sensitization (OECD, 2008).

6. Inhalation Toxicity

Wistar rats (5/sex) were exposed by head-nose only for 4 hours to a single concentration of 5100 mg/m^3 (1275 ppm) NMP (respirable fraction was 87%). During the 14-day observation period no animals died and all gained body weight. This study was conducted on a vapor/aerosol mixture with a mass median aerodynamic diameter (MMAD) of 4.6 µm (ECHA, 1988). In another study, rats exposed via whole body to a supersaturated concentration (>370 ppm) of NMP (110°C) for an uninterrupted 6-h period showed no toxic effects (Saillenfait et al., 2003).

B. Subacute Toxicity

1. Inhalation

Several inhalation studies have been conducted to assess the impacts of exposure mode (head-nose versus whole-body), humidity and chemical form (vapor versus aerosol including number and size of droplets) on the toxicity of NMP. Female Sprague-Dawley or Wistar rats were exposed to control air or 1.0 mg/L (1000 mg/m^3) NMP for 6 h/day, 5 days/week, for 2 or 4 weeks. These studies are summarized in the SIDS (Screening Information Dataset) Initial Assessment Report (SIAR) (OECD, 2007; OECD, 2008) and concluded that: "The head-nose exposure caused independently of aerosol fraction or humidity no effects other than slight nasal irritation and colored urine. Whole-body exposure with 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, while whole body exposure with fine droplets and low or high relative humidity caused no deaths and less severe effects." These studies identify the important role of both dermal uptake and the need to consider oral dose contributions from coat grooming when evaluating the toxicity of airborne NMP from studies using whole-body exposed animals.

A 14-day range finding study was conducted in Wistar rats exposed head-nose only to nominal aerosol concentrations of 4000, 7000, or 10,000 mg/m^3 for 6 h/day, 5 days/week, but at the

two highest concentration groups high mortality was observed requiring termination of those exposures after 3 or 4 days (OECD, 2008). Exposure to 4000 mg/m^3 caused signs of systemic toxicity including target organs effects in the lung, liver and testes as substantiated by weight changes, gross findings, and histopathological cellular depletion in the testes. In a study at lower concentrations following OECD Test Guideline 412, Wistar rats were exposed 6 h/day, 5 days/week, for 4 weeks to aerosolized NMP at concentrations of 0, 10, 30, or 100 mg/m^3 in a nose-head only chamber. The animals of the high NMP concentration group (100 mg/m^3) showed yellow-orange discolored urine and bedding indicative of systemic availability (author suggested probably caused by metabolite). The study NOAEL was 100 mg/m^3 (25 ppm).

Fifteen CD rats per sex per group were exposed, in whole body chambers to an aerosol/vapor mixture of NMP at 0, 100, 500 or 1000 mg/m^3 (0, 25, 125 or 250 ppm) for 6 h/day, 5 days/week for 4 weeks with an additional five animals per group kept for a 2-week recovery period. Greater than 95% of the particles had a diameter of <10 µm. Comprehensive blood and urine analyses were conducted after 10 and 20 days of exposure. Animals were examined grossly and microscopically at the end of exposure or after the 2-week recovery. All NMP exposed rats showed signs of lethargy and irregular respiration which persisted at the end of the exposure period in a concentration-dependent manner. At 1000 mg/m^3, rats exhibited excessive mortality by day 9, and exposure was discontinued on day 10. Decreased body weight gain was observed in this group. In the animals that died *in extremis*, pulmonary edema and congestion, focal interstitial pneumonia, atrophy, hypoplasia, hemorrhage and necrosis of the bone marrow, thymus, spleen, and lymph nodes were observed. These animals also had microscopic findings in the lung and lymphoid tissue. There were no other adverse effects noted in the treated animals or remarkable findings in the recovery group animals. The NOAEL for males and females was 500 mg/m^3 (125 ppm) (Lee et al., 1987). The toxicity observed in this study using whole body exposure was greater than toxicity seen at higher concentrations studies with nose only exposures. The whole-body exposure allowed for dermal (deposited on the fur and skin) and oral (grooming) route contributions to the overall systemic exposure and toxicity (OECD, 2007).

2. Oral

In a GLP 28-day dietary toxicity study following OECD Guideline 407, B6C3F1 mice (5/sex/group) were given 500, 2500, 7500 or 10,000 ppm (130, 720, 2130 or 2670 mg/kg/day for males and 180, 920, 2970 or 4060 mg/kg/day for females, respectively) NMP in the diet. At ≥2500 ppm NMP, urine was discolored indicating systemic exposure. One high dose male died. A decrease in alkaline phosphatase was observed but was only statistically significant in high dose females. Microscopic findings included increased incidence of cloudy swelling of the epithelia in the distal portion of the renal tubules, in males at 7500 ppm and in both sexes of the high dose group. The NOAEL was 2500 ppm, 720 mg/kg/day for males and 920 mg/kg/day for females (Malek et al., 1997).

In a GLP 28-day dietary toxicity study following OECD Guideline 407, Crl:CD BR Sprague-Dawley rats (5/sex/group) were given 2000, 6000, 18,000 or 30,000 ppm NMP (149, 429, 1234 or 2019 mg/kg/day for males and 161, 493, 1548 or 2268 mg/kg/day for females, respectively). At ≥18,000 ppm, dark yellow staining of cage boards was observed indicating systemic exposure. A decrease in body weights/weight gain and food consumption was observed at ≥18,000 ppm in males and the high dose in females. Findings at ≥18,000 ppm included hepatocellular hypertrophy. Findings at ≥30,000 ppm included testicular degeneration, thymus gland atrophy (females only), hypocellular bone marrow as well as reduction in lymphocyte counts (statistically significant in males), increased serum cholesterol, decreased total protein, albumin and alkaline phosphatase activity and serum glucose (males only). The NOAEL for males was 6000 ppm (429 mg/kg/day) and 18,000 ppm (1548 mg/kg/day) for females (Malek et al., 1997).

3. Dermal

In a GLP 20-day dermal toxicity study (similar to OECD 410) 0.4, 0.8 or 1.6 mL/kg NMP was placed on abraded and normal skin sites of 4 male rabbits per group. The study description does not provide the dose in mg NMP/kg body weight; however, assuming the standard density of NMP these doses are calculated to be 411, 822, and 1643 mg/kg. Body weight, hematological, clinical chemistry, gross pathology, and histopathology endpoints were examined. Mild local skin irritation was observed at all doses. One of four animals treated with 1.6 mL/kg (1643 mg NMP/kg) died (abraded skin). There were no effects noted in the surviving animals at this dose or any animals at the lower doses (ECHA, 1963). The NOAEL was not stated by the authors.

C. Subchronic Toxicity

1. Inhalation

In a 90-day nose-only inhalation toxicity study following OECD 413, Wistar rats (10/sex/group) were exposed to air, 500, 1000 or 3000 mg/m^3 (0, 125, 250 or 750 ppm) nominal NMP aerosol concentrations for 6 h/day, 5 days/week for 3 months with an additional 10 rats in the control and high concentration kept as a 4-week recovery group. The mass median aerodynamic diameter (MMAD) ranged from 1.6–3.5 µm (+/- 2.1-9.6 GSD). Body

weight, ophthalmoscopic, hematological, clinical chemistry, gross pathological and histopathological examinations were conducted. All NMP exposed groups showed discolored urine indicative of systemic bioavailability. Reddish crust formation on nasal edges in males and females at 1000 or 3000 mg/m^3 indicated irritation. However, there was no histopathological correlate for the nasal clinical signs. At 3000 mg/m^3, clinical signs included ruffled fur (at 2 weeks) and high stepping gait (at end of exposure). A statistically significant decrease in body weight was observed after 3000 mg/m^3 exposure in males in the recovery animals during the exposure and recovery. Decreased body weight gain was observed in males at 1000 mg/m^3 and 3000 mg/m^3. There was no significant body weight loss in the animals terminated at 90-days except at day 33 in the high concentration males. Also, in the high concentration males and females, there were statistically significant changes in red blood cell parameters and alanine aminotransferase (ALT), inorganic phosphate, albumin, triglycerides and/or glucose at both the end of exposure and recovery period, which were inconsistent between the 90-day and recovery animals. Of the organs weighed, there was decreased testes absolute weight in the 90-day animals, which was not present at the end of the recovery period. One animal of the high concentration group and two in the recovery group had decreased testes size upon gross examination. Cellular depletion of the testes germinal epithelium was observed in 5 animals (control: 0/10, low concentration: 1/10, mid concentration: 0/10, high concentration: 4/10) of the main study and 7 animals (control: 0/10, high concentration 7/10) of the recovery group. The NOAEL was 500 mg/m^3 (125 ppm) based on a statistically significant decreased body weight gain in males and slight irritation observed at the ≥1000 mg/m^3 concentration (Malley et al., 1999).

2. Oral

In a GLP three-month dietary toxicity study (similar to OECD 408), 20 to 26 male and female Crl:CD®BR rats per group were given 0, 3000, 7500 or 18,000 ppm NMP (0, 169, 433 or 1057 mg/kg/day for males and 0, 217, 565 or 1344 mg/kg/day for females, respectively). Ten animals per sex from the control and high dose groups were allowed to recover for one month. Clinical pathology, hematology, urinalysis, ophthalmoscopic, functional and morphological evaluations of neurotoxicity, gross pathology and histopathology were performed. The urine showed a discoloration at ≥3000 ppm which indicated systemic bioavailability. Decreased body weight and body weight gain (percentages not given) were observed at 7500 ppm during the first half of the study; however, these rats appeared to recover during the second half of the study. Body weight gain was also significantly reduced, 28% for males and 25% for females in the 18,000 ppm dose group. The authors concluded that the lower body weight and body weight gain were correlated with lower food consumption and efficiency. Body weight gain and food consumption increased for rats in the high dose recovery group once NMP was removed from the diet. At 18,000 ppm the liver weights in females were increased (increased incidence of centrilobular hypertrophy) and the kidney weights of males and females were increased without corresponding histopathological findings. In addition, animals of both sexes showed a minimal increase in splenic hemosiderin at this dose. In males, only 3 of 36 neurotoxicity parameters were affected by NMP exposure; females were unaffected. Males exhibited an increase in foot splay at ≥7500 ppm. A higher incidence in low arousal and slight light palpebral closure, suggestive of a sedative effect, were observed at 18,000 ppm. These effects were no longer observed after a one-month recovery period. The NOAEL was 3000 ppm for both sexes (approximately 169 mg/kg/day in males and 217 mg/kg/day in females) for reduced body weight, body weight gain, and food consumption. A specific target organ for compound-related adverse systemic toxicity was not identified (Malley et al., 1999).

In an OECD Guideline 408 study, groups of mice (10/sex/group) were administered dietary concentrations of 0, 1000, 2500 or 7500 ppm NMP for 3 months. Daily doses were 229, 561 or 1704 mg/kg/day and 324, 676 or 2158 mg/kg/day, for males and females, respectively. Dark yellow staining of the urine of all animals in the two higher exposure groups was observed. There were significantly increased mean absolute and relative liver weights (relative to terminal body weight and to brain weight) in males in the two higher exposure groups. In addition, histopathological examinations revealed centrilobular hypertrophy of the liver cells in males (9/10) and females (10/10). There were no substance-related effects in the 1000 ppm exposed group. The NOAEL of the study was 1000 ppm (229 and 324 mg/kg/day, respectively, for males and females) (Mellert et al., 1995).

Male and female beagle dogs were fed NMP doses of 25, 79 or 250 mg/kg/day for 13 weeks. Clinical signs, ophthalmoscopy, body weight, food consumption, hematology, clinical pathology, gross pathology, organ weights and histopathology were examined. At the highest dose there were decreased body weight gains of 54% (males) and 37% (females) as well as decreased food consumption; although these effects were not statistically significant compared to controls. Serum cholesterol was decreased at all dose levels. Serum protein and albumin were decreased in the mid- and high-dose group males. The NOAEL was stated to be 250 mg/kg/day based on lack of systemic toxicity (Becci et al., 1983).

D. Chronic Toxicity

1. Inhalation

In a two-year inhalation study, 120 CD rats per sex per concentration were exposed to air, 40 (10 ppm) or 400 mg/m^3 (100 ppm) NMP vapor concentrations for 6 h/day, 5 days/week. Only trace aerosol was detected. Ten animals per group were evaluated at 1, 3, 6, 12 and 18 months and the remaining animals at 2 years of exposure. Serum hematology and clinical chemistry, gross and a comprehensive histopathological examination were conducted. Since there were no findings at the high concentration, the low concentration animals were not examined microscopically. All high concentration animals had stained wet perinea (includes low concentration females) and dark yellow urine. At the end of 2 years, a 6% decrease in body weight gain was observed in males exposed to 400 mg/m^3 NMP. A few clinical chemistry changes were observed in the high concentration rats only at 18 months. There were no meaningful differences in either the incidence or severity of the neoplastic or nonneoplastic lesions between the control and treated groups. For females, the NOAEL was 400 mg/m^3 (100 ppm), the highest concentration tested, and for males the NOAEL was 40 mg/m^3 (10 ppm) based on 6% reduced body weights gains (Lee et al., 1987).

2. Oral

In an 18-month dietary toxicity study following OECD 451 (Carcinogenicity Study), B6C3F1 mice (50/sex/group) were given unchanged diet or feed containing 600, 1200, or 7200 ppm NMP (0, 89, 173 or 1089 for males and 0, 115, 221 or 1399 mg/kg/day for females). Food consumption, body weights, blood smears, and detailed physical examinations were taken during the in-life phase. At the end of exposure, liver, kidney, adrenal glands, testes, ovaries, and brain were weighed and a comprehensive histopathological examination was conducted. In mid- and high-dose groups, discoloration of urine was observed indicating systemic bioavailability. There was a treatment-related effect on liver weight. In addition, at the high dose, liver foci were increased 14/50 (males) and 6/50 (females) compared to 2/50 and 3/50 in the controls. The liver foci were described as eosinophilic and clear cell type in males and eosinophilic and basophilic type in females. A centrilobular hypertrophy of hepatocytes was observed in most high-dose males and in a few mid-dose males. The number of males and females with hepatocellular adenomas and carcinomas was increased in the top dose group. Liver masses (adenomas and carcinomas) were increased 18/50 (males) and 16/50 (females)in the highest dose group compared to 10/50 and 2/50 in the controls. Liver adenomas were also increased in the top dose group 12/50 (males) and 7/50 (females) compared to 5/50 and 2/50, respectively, in the controls. Similarly, liver carcinomas were increased 13/50 (males) and 3/50 (females) compared to 4/50 and 0/50, respectively, in the controls. There was no substance-related mortality. There was no effect on body weight, food consumption, hematology, or other organ weights. The NOAEL for toxicity was 89 and 221 mg/kg/day for males and females, respectively, based on increased liver weights and histological changes in the liver. The NOAEL for carcinogenicity was 173 or 221 mg/kg/day for males and females, respectively, based on significantly increased incidence of hepatocellular adenoma in males and females and on increased incidence of hepatocellular carcinoma in males. These effects were interpreted to be due to enzyme induction, consistent with a non-genotoxic mode of action, to which B6C3F1 mice are highly sensitive (Malley et al., 2001).

In a two-year dietary carcinogenicity study following EPA OTS 798.3300 (Carcinogenicity) Guideline, Sprague-Dawley CD rats (62/sex/group) were given 0, 1600, 5000 or 15,000 ppm NMP (approximately 66, 207 or 678 mg/kg/day for males and 88, 283 or 939 mg/kg/day for females). Food consumption and body weights, clinical signs, ophthalmological, and hematological endpoints were examined. At the end of exposure, hematology, gross pathology, and histopathology were examined. There were no relevant clinical signs of toxicity in any group. Discoloration of urine was observed in mid- and high-dose animals, which was an indication of systemic exposure. There was NMP-related decrease in survival in the 15,000 ppm males associated with chronic progressive nephropathy/uremia. No other effect on survival was noted in males or females. At the high dose in both sexes, there was pigment accumulation in the spleen, a statistically significant decrease in body weight and body weight gain, and a decrease in food consumption (not statistically significant) compared to controls. In addition, the males also had increased incidence of large kidneys, a diagnosis of chronic nephropathy, fluid in the pleural cavity, and small testes. There was no increased incidence in treatment-related benign or malignant tumors in male or female rats at any dose level. The NOAEL for toxicity was 5000 ppm (207 or 283 mg/kg/day) in males and females, respectively, based on decreased body weights, body weight gain, and food consumption in the high dose males/females and morphological kidney changes in high dose males (Malley et al., 2001).

E. Reproductive/Developmental Toxicity

1. Inhalation

The reproductive and developmental toxicity potential of NMP has been evaluated in rats following inhalation exposures under

several study designs. The available studies include *in utero* developmental toxicity studies with gestational exposure, a two-generation reproduction study, and a study focused on postnatal developmental and behavioral effects. These studies were conducted using whole-body exposures at concentrations up to the transition from vapor to aerosol phase. The maximum vapor concentration is dependent on relative humidity; at 50% relative humidity the transition from vapor to aerosol occurs at 128 ppm OECD, 2007; OECD, 2008 This value is consistent with the saturated vapor concentrations observed by Solomon et al. (1995) and Saillenfait et al. (2003) to occur between 120 -140 ppm. Consequently, the effects observed in the inhalation studies potentially reflect a combination of inhalation, dermal, and oral exposure to NMP.

The developmental toxicity of inhaled NMP was studied in Sprague-Dawley rats. Groups of 20-25 pregnant rats were exposed whole body to NMP (>99.5% purity) vapor at concentrations of 0, 30, 60 or 120 ppm (124, 247 or 494 mg/m^3), 6 h/day, from gestation days (GD) 6-20. A statistically significant decrease in maternal body weight gain was seen during the first half of the study in the 60 and 120 ppm dose groups on GD 6-13 but no differences were observed in absolute weight gain in any dose group. A statistically significant decrease in maternal food consumption was observed in the 120 ppm group on GD 6-21. No significant difference in the gestational weight change corrected for the weight of the gravid uterus was observed at any NMP exposure level. The number of implantations of live fetuses and the incidences of non-live implants and resorptions were comparable across groups. No malformations were observed at any of the NMP concentrations tested. Fetal body weights were decreased (5-6%) at 120 ppm. The NOAEL for maternal and developmental toxicity was 30 and 60 ppm, respectively (Saillenfait et al., 2003).

Groups of 25 pregnant CR-CD rats were exposed whole-body for 6 h/day on days 6-15 of gestation to aerosol concentrations of 0, 100 mg/m^3 (25 ppm) or 360 mg/m^3 (90 ppm) of NMP. Twenty-two, 20 and 23 rats were pregnant in each of the control, low and high concentration groups, respectively. Some dams in each of the NMP treatment groups displayed periodic lethargy and irregular respiration during the first 3 days of exposure, however no other clinical signs were observed and there were no significant differences in body weights or food consumption among groups. The types and incidence of fetal malformations and variations was comparable among all groups. At the high NMP exposure concentration, the incidence and type of resorptions, final maternal body weight, and fetal length and body weight were similar to the controls. However, at the low NMP exposure concentration, pregnant females had fewer corpora lutea and lower conception rates. Specifically, 7/20 pregnant females had less than 10 corpora lutea, as compared with 1/22 and 1/23 pregnant rats in the control and high NMP exposure groups, respectively. In addition, 2 of the 7 females with low numbers of corpora lutea had only 4 and 1 corpora lutea, and only one implantation each. The mean number of resorptions/litter was 1.9, 1.3 (statistically different from controls) and 2.5 in the control, 100 mg/m^3 and 360 mg/m^3 NMP groups, respectively. However, the authors stated that although the pregnant animals were randomly assigned to treatment groups, random distribution was not obtained, since 5/25 females in the 100 mg/m^3 NMP group were not pregnant and 2/20 had only one implantation. When those 2 dams were removed from the group, the calculated mean values were similar to the control. The conception rate and number of corpora lutea could not have been affected by NMP, since exposure started after implantation on gestation day 6. Therefore, the NOAELs for maternal and developmental toxicity are considered to be >360 mg/m^3 (90 ppm), based on the results of this study (Lee et al., 1987).

Groups of 20-23 pregnant rats (Mol:WIST) were exposed by inhalation (whole body) on gestation days 4-20 to the highest technically achievable concentration of NMP (BASF commercial grade, purity ≥99.5%) or clean air (control) for 6 h/day. During the exposure periods, the mean concentration after reaching equilibrium in the NMP exposure chamber was 165 ± 2 ppm (660 mg/m^3) NMP. The pregnant animals were observed daily after exposure for signs of toxicity, and body weight and food consumption were recorded on days 4, 7, 14 and 21 of pregnancy. The animals were sacrificed on day 21 and examined along with the fetuses. No clinical signs of maternal toxicity were seen during the exposure period, and similar values for maternal food consumption, body weight and growth were observed in the NMP and control groups during pregnancy. There were no statistically significant differences between the two groups regarding the number of corpora lutea, implantations, resorptions or live fetuses per dam. In the NMP exposed group, a higher incidence of pre-implantation loss and significantly more dams with pre-implantation loss were observed. Pre-implantation loss was observed for 87% of the NMP-exposed dams compared to 55% of dams in the control group ($p<0.05$). The mean fetal body weight in the NMP-exposed litters was slightly lower than the control, but the difference was not statistically significant**.** However, mean fetal body weight adjusted for litter size was significantly reduced ($p <0.05$) in the treatment group. The incidences of external, skeletal or visceral anomalies and malformations were similar in the two groups. Fetuses in the NMP litters exhibited delayed ossification of the skeleton, and the differences were statistically significant for cervical vertebrae 4**,** 5, 6 and 7 and for digital bones. Therefore, the NOAELs for maternal and developmental toxicity are considered to be >165

ppm and <165 ppm, respectively, based on the results of this study (Haas et al., 1995).

In a two-generation reproductive inhalation toxicity study, male and female rats were exposed whole body to 0, 10.3 (40.9 mg/m^3), 50.8 (203 mg/m^3), or 116.4 ppm (466 mg/m^3) NMP 6 h/day, 7 days/week from 34 days of age. Exposure continued for the males until the end of the mating period (134 days of age). Exposure continued in the reproductive toxicity phase females until day 21 post-partum (exposure was suspended from day 20 of gestation through day 4 postpartum). On day 70 post-partum, one F1 pup of each sex/litter/exposure level was selected and mated with unexposed adults to produce an F2 generation (Solomon et al., 1995).

Three P0 rats died during the study, two in the control group and one in the 50.8 ppm group. The cause of death of the NMP-exposed animal was not described by the study authors. In the 116 ppm group rats, decreased response to sound was observed while they were inside the inhalation chambers, in comparison with controls. This was determined by tapping the chamber with a coin during the exposure period and was considered as a 'qualitative index' of overall responsiveness. A concentration-related and statistically significant ($p \leq 0.05$) slight decrease in mean F1 pup body weight (affecting mainly the female pups) was observed in the 116 ppm NMP group from birth to 21 days of age at which time dam exposures ceased and pups were weaned. These body weight decrements grew progressively smaller over the 21-day period and seven days post-weaning and were not significantly different from those of control rats, indicating recovery after cessation of exposure. No other adverse effects were noted in these offspring or their pups (F2 generation) and the reproductive performance of the offspring was not affected. Therefore, the NOAELs for maternal and developmental toxicity are 50.8 ppm (203 mg/m^3) based on the results of this study (Solomon et al., 1995).

In the teratology phase of the two-generation reproductive inhalation toxicity study, groups of 14-15 female Sprague-Dawley rats were exposed whole body to NMP vapor (99.9% purity) at a concentration of 0 or 115 ppm (460 mg/m^3) for 6 h/day, 7 days per week. Exposure of both sexes was initiated when the rats were 34 days old, and continued through the 12-week premating period, the 2-week mating period, and the 21-day gestation period (females only). In the table describing the experimental design for the P0 generation, the authors state that an extra 10 males and 20 females were assigned to study groups C1 and E3 for use in the developmental phase of the study. However, in Table 5 Developmental Phase: Summary of Reproduction Data, the number of females pregnant/mated in group C1 and E3 is listed as 14/14 and 13/15, respectively. Consequently, it is unclear what happened to the extra 6 and 5 females that were allocated to groups C1 and E3 for the developmental toxicity part of the study. Dams were euthanized on day 21 and fetuses examined. The body weights of NMP-exposed females did not significantly differ from controls. None of the dams died during gestation and there were no remarkable clinical signs observed during gestation. Mean fetal body weight in the NMP-exposed group was significantly ($p<0.05$) reduced versus control (3.37 g versus 3.62 g). Therefore, the NOAELs for maternal toxicity and developmental toxicity (decreased fetal body weight) are considered to be >115 ppm and <115 ppm, respectively (Solomon et al., 1995).

A group of 16 pregnant rats (Mol:WIST) was exposed by inhalation (whole body) to 150 ppm (600 mg/m^3) NMP (BASF, commercial grade, purity ≥99.5%) 6 h/day on GD 7-20 (Haas et al., 1994). This study was intended to measure postnatal developmental and behavioral effects, so the exposure level was selected to avoid maternal toxicity and maintain viability of offspring. The exposure to NMP caused no signs of maternal toxicity (i.e., no clinical signs were seen) and no significant differences between the control and exposed group were observed for maternal weight gain during the gestation period, pregnancy length, number of pups and sex distribution in the litters, neonatal death, or the number of implants per dam. In the pre-weaning period, the exposed offspring had lower body weight and their physical development was delayed. The decrease in mean fetal body weight between the control and the NMP exposed group observed at parturition in both male and female pups was still present during the pre-weaning period until PND 22. However, the difference in body weight from control decreased from approximately 8% to 5% during the post-weaning period and was not statistically significant when pups reached 5 weeks of age. The authors concluded that a relatively small decrease in fetal body weight observable at parturition may persist and still be detectable at weaning. Although the inhalation exposure to NMP was stopped at GD 20 in this study, it was suggested that systemic exposure may have continued during the perinatal growth period, based on a published abstract NMP has a half-life of more than 16 h in fetuses and dams and there may also have been exposure through maternal milk during the neonatal period (Ravn-Jonsen et al., 1992). However, it should be noted that the half-life in male and nulipareous female rats was 2-3.4 h after inhalation exposure (Ghantous, 1995). Neurobehavioral evaluation revealed no effects on basal functions of the central nervous system. The animals appeared normal, and the motor function and activity level, as well as the performance in learning tasks with a low grade of complexity, such as learning in Morris maze and autoshaping and visual discrimination in Skinner boxes were comparable among the two

groups. However, more extensive testing revealed effects on higher cognitive functions related to solving more difficult tasks such as reversal of learning in Morris maze and delayed spatial alternation. These effects may be long lasting as they were observed 4 to 7 months after exposure. In more difficult tasks (e.g., delayed spatial alternation), rats from the exposed group showed a progressive deficit as compared to controls in outcomes that measure learning performance in this schedule (performance, accuracy, corrected responses, and error persistence). Therefore, the NOAELs for maternal and developmental toxicity are considered to be >150 ppm and <150 ppm (600 mg/m^3), respectively (Haas et al., 1994).

2. Oral

Developmental toxicity studies involving oral dosing during gestation have been conducted in mice, rats, and rabbits. In addition, a series of two-generation studies have also been conducted. These studies generally involved high doses.

Pregnant New Zealand white rabbits, 15-20 per group, were given doses of 0, 55, 175 or 540 mg/kg NMP by gavage on days 6-18 of gestation. Does were euthanized on day 29, and the fetuses were examined. Maternal toxicity was noted in the form of transient reduction in mean body weight gain in the mid- and high-dose groups. Also, reduced food consumption was noted in the high-dose group. One spontaneous abortion was also noted in the high-dose group. Developmental toxicity in the form of misshapen skull bones and cardiovascular malformations was evident in the offspring of the 540 mg/kg dose group. The NOAEL for maternal toxicity was 55 mg/kg/day, and for developmental toxicity was 175 mg/kg/day (OECD, 2008).

The database of oral dosing studies for reproductive and developmental effects also includes a series of 3 two-generation studies. In the initial study, Sprague-Dawley rats were administered doses of 0, 50, 160 or 500 mg/kg NMP via their diet. Maternal toxicity (significant reduction in body weight and food consumption) was noted at 500 mg/kg. Exposure to all doses down to 50 mg/kg resulted in reproductive toxicity in the F1 generation (reductions in the male fertility index and female fecundity index). Additional reproductive and developmental effects were seen at 500 mg/kg in the F1 generation, and developmental effects (reduced litter size, reduced postnatal survival, and reduced pup body weight) were seen at 500 mg/kg in the F2 generation. The authors concluded that effects observed at lower doses were spurious and not treatment related since all parameters where in the range of historical control data (OECD, 2007). However, EPA concluded that reductions in male fertility and female fecundity indices observed at the lower dose levels were biologically (although not statistically) significant, and that a NOAEL was not achieved (US EPA, 1993).

Subsequently, two additional multi-generation reproductive dietary toxicity studies were conducted in Sprague-Dawley and Wistar rats. The initial dose levels were 0, 50, 160 or 500 mg/kg/day but the high dose was reduced to 350 mg/kg/day due to high F1 pup mortality. There were no effects on fertility or reproductive performance in F0 or F1 animals in either study. A decrease in the number of pups surviving lactation and a decrease in pup body weights/weight gain were observed in the F1 and F2 offspring at the high dose. The NOAEL for parental toxicity was 350 mg/kg/day. The NOAEL for developmental toxicity was 160 mg/kg/day (OECD, 2007; OECD, 2008).

3. Dermal

Only one developmental toxicity study for dermal administration of NMP was identified. Doses of 75, 237 or 750 mg/kg NMP were administered dermally to groups of 25 pregnant Sprague-Dawley rats on days 6 through 15 of gestation (Becci et al., 1982). Maternal toxicity was observed at 750 mg/kg as reduced body weight gain during gestation. Treatment with NMP resulted in dose-dependent brightly colored yellow urine (indicative of systemic exposure) and dry skin. The highest dermal dose level resulted in fewer live fetuses per dam, an increase in the percentage of resorption sites and skeletal abnormalities. There was neither evidence of teratogenic effects, nor adverse effects on the dams at 75 and 237 mg/kg. The NOAEL for maternal and developmental toxicity was 237 mg/kg. Important additional data were obtained from the results of a range-finding study conducted by the same authors. In this study, all dams from a 2500 mg/kg exposure group died before GD 20. In the 1100 mg/kg exposure group, 65 of 66 fetuses were resorbed. The NOAEL of 237 mg/kg is essentially within a factor of 4-fold of a totally lethal outcome for the fetus (US EPA, 2015).

F. Genotoxicity/Mutagenicity

The genotoxicity of NMP has been evaluated in a variety of *in vitro* and *in vivo* test systems that assessed mutagenic and chromosome level effects. Based on these studies NMP showed no mutagenic or clastogenic potential (OECD, 2007).

1. In Vitro

The mutagenicity of NMP has been tested in several test systems. It was negative in four Ames assay studies (summarized in OECD, 2007) including studies that used 5 *Salmonella typhimurium* strains (TA-1535, TA-1537, TA-1538, TA-98, TA-100), both S-9 activated and nonactivated. NMP was also not mutagenic in mammalian cell assays including in the hypoxanthine-guanine phosphoribosyltransferase (HGPRT)

assay in Chinese Hamster ovary (CHO) cells and the mouse lymphoma assay using L5178Y cells (OECD, 2007). NMP did not induce unscheduled DNA synthesis (as an indicator of DNA damage) in rat primary hepatocytes. Aneuploidy was induced in yeast *(Saccharomyces cerevisae)* by 150-230mM concentrations of NMP; gene mutation or conversion was not induced (Mayer et al., 1988).

2. In Vivo

Investigations of the effects of NMP in the mouse micronucleus test (Charles River mice) and the Chinese hamster bone marrow test were negative after single oral doses of up to 3800 mg/kg (Engelhardt and Fleig, 1993; ECHA, 1993, 1989). No mutagenic activity was identified in a dominant lethal assay in NMRI mice administered an intraperitoneal (IP) dose of 393 mg/kg NMP (OECD, 2008).

G. Metabolism/Pharmacokinetics

Pharmacokinetic and disposition studies in rats were conducted via the following routes: intravenous (IV) (50 mg/kg), inhalation (10 or 100 ppm NMP vapor, nose only for 6 h), oral (5 or 50 mg/kg), and dermal (10 mg/kg - 0.1 mL over a 2x3 inch area for 6 h) (Ghantous, 1995). Dosing routines consisted of a single exposure to ^{14}C-radiolabeled NMP to 4-10 rats/sex. Blood, urine, feces, and tissue samples were collected from among the following post-exposure time points: 1, 3, 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96 and 120 h and analyzed for parent NMP, metabolite and radioactivity.

1. Absorption

The presence of NMP in urine following inhalation exposures indicates the systemic uptake of NMP following exposure via this route. After inhalation exposures to NMP vapor at concentrations of 10 ppm or 100 ppm, approximately 43% or 64%, respectively, of the inspired NMP was absorbed (Ghantous, 1995).

After oral exposure, mean intestinal absorption was rapid and similar in males and females, ranging from approximately 50 to 100%. Peak blood levels were reached within 0.4 and 2 h in males and females, respectively, and were somewhat delayed at high doses (Ghantous, 1995).

NMP is also well-absorbed via the skin, but the rate and degree of absorption are affected by water or other solvents. Dermal uptake has been a consideration in the interpretation of the body of toxicology studies: therefore, this aspect of toxicokinetics has been studied in detail. Application of (calculated to be approximately 2%) NMP 10 mg/kg- 0.1 mL over a 2x3 inch area for 6 h, resulted in peak plasma concentrations reached at 6.0 and 4.4 h and 44 and 43% systemic absorption in males and females, respectively (Ghantous, 1995). The mean percentage systemically available was higher in males compared to females (ECHA, 2003). The dermal application of 2% NMP in water resulted in a steady-state absorption rate of 4.65 and 4.0 µg/h-cm^2 for male and female rats, respectively, with permeability constants (Kp) of approximately 1.9 x 10^{-4} cm/h (OECD, 2008). Similar absorption rates were identified in an *in vitro* study using human skin conducted according to test guideline OECD 428. This study found that the absorption rate of NMP in water progressively decreased with increasing dilution over a wide concentration range (30% - 0.1%), while the Kp values remained relatively constant (1 to 2 x 10^{-4} cm/h) among the concentrations tested. Absorption rates were similar for NMP dissolved in water versus synthetic sweat (SafePharm Laboratories, 2004). These Kp results are consistent with values reported *in vivo* (Ghantous, 1995). In contrast, the dermal absorption rate for neat NMP during the first several h post-application was higher at 6.6 mg/cm^2-h (*in vivo*) (Payan et al., 2003). These higher rates are reflected by the ability of neat NMP to increase dermal permeability to ^3H_2O by ~4-fold (at 0.5 h) to 14-fold (at 4 h) (Payan et al., 2003), indicating NMP can increase skin permeability. These observations may explain the higher flux of neat NMP (17 mg/cm^2-h) seen with protracted (6-h) dermal application (Ursin et al., 1995). In contrast to the ability of water to decrease NMP flux, the presence of an organic solvent (*i.e.*, d-limonene) significantly increased the absorption of NMP compared to neat NMP (US EPA, 2015). In an *in vivo* study on the effect of occlusion (Inveresk, 2003), neat NMP was rapidly absorbed 1-h post-application; an un-occluded application resulted in the highest mean absorbed dose (69% of dose applied), followed by semi-occluded (57%) and occluded (50%). The difference between the absorption of neat NMP under non-occluded and occluded states may reflect dilution of neat NMP by the transdermal movement of water that cannot vaporize from the occluded application site (Payan et al., 2003). The fact that this difference was not significant when measured 24-h post application (Payan et al., 2003) is consistent with the progressive loss of skin integrity seen as early as 0.5-h post-exposure to neat NMP and that volatilization of liquid NMP may not be a limiting factor in dermal uptake.

Desquamation increased the percutaneous absorption of NMP slightly. The flux was dependent on the thickness of the skin and was proportional to the concentration of NMP. The authors suggest a passive diffusion of NMP through the skin. The skin does not metabolize NMP (Payan et al., 2003).

2. Distribution

Studies with radiolabeled NMP showed that 6 h after an IV dose, radioactivity was present in all major organs, with the highest levels in the liver (2%) and intestines (3%) (Wells and Digenis, 1988). Negligible radioactivity remained in tissues 4 to 5 days post-dosing via the IV, oral and inhalation routes. The highest residual radioactivity was found in organs of metabolism (liver) and excretion (kidney); no bioaccumulation occurred in any tissue (Ghantous, 1995). A similar widespread distribution of radiolabel among multiple organ systems was observed 4 h after an intraperitoneal dose of ^{14}C-NMP to male and female rats; only trace levels remained 72 h post-dosing. There was no significant difference in the distribution of radiolabel between male and female rats (Sitarek and Kilanowicz, 2006). The apparent volume of distribution was calculated to be 0.7 L/kg (Ravn-Jonsen et al., 1992; Ghantous, 1995; Payan et al., 2003), a value approximating total body water.

3. Metabolism

The major metabolite after dermal, IP, inhalation or oral routes was 5-hydroxy-N-methylpyrrolidone (5-HNMP) with two other peaks reported (Ansell et al., 1984; Haas et al., 1995; ECHA, 1995; Ligocka et al., 2003; Wells and Digenis, 1988; Wells et al., 1992; Carnerup et al., 2005). The same metabolites were found in both rats and humans (Carnerup et al., 2005). It was shown that CYP2E1 plays a role in the metabolism and elimination of NMP in rats but has a lesser role in humans (Ligocka et al., 2003).

4. Elimination

In the rat, the main route of excretion is via the urine with greater than 80% of the administered IP, IV or oral dose measured as metabolites without detectable conjugation in the urine and less than 5% as parent NMP (Haas et al., 1995; ECHA, 1995). Approximately 4 to 9% appeared in the feces and approximately, 0.5 to 1% was found in tissues. Two studies have reported a low percentage, 1-2%, of the administered dose to be eliminated with expired air (Wells and Digenis, 1988; Wells et al., 1992). The dermal route varies from other routes with respect to the contributions of different elimination pathways to total clearance. During the first 6 h after a 40 mg/kg NMP dermal administration to rats (sex not specified in study summary), about 22% of the dose was excreted in urine; however, whether this represents the percentage of the absorbed or administered dose is not clear from the available study summary (ECHA, 2006). After 120 h, the urine contained 57% (males) and 36% (females) of the absorbed NMP, the feces contained 5% (males) and 3% (females), while 26% (males) and 54% (females) of the absorbed dose remained at the dermal application site (Ghantous, 1995). The mean plasma half-life for NMP following IV, oral, dermal and inhalation exposures varied slightly depending on route and sex and ranged from 1.0 to 3.3 h; the half-life for total radioactivity ranged from 2.0 to 6.8 h (Ghantous, 1995).

Non-pregnant female Sprague-Dawley rats were given a single oral dose of either 125 or 500 mg/kg NMP. NMP, 5-HNMP, N-methylsuccinimide and 2-hydroxy-N-methylsuccinimide (2-HMSI) and 2-pyrrolidone (2-P) were identified in both plasma and urine. In urine, 48% of the administered dose was recovered as 5-HNMP, 2–5% as 2-HMSI and 2-3% as NMP; peak concentrations were measured 6-12 h after dosing. The total recovery in urine was 53-59% (Carnerup et al., 2005). After an oral exposure to a non-toxic dose of 125 mg/kg/day in female rats, the peak plasma concentrations were: 1.2 mmol/L for NMP (1 h to peak); 0.42 mmol/L for 5-HNMP (4 h to peak); 0.07 mmol/L for MSI (4 h to peak); and 0.02 mmol/L for 2-HMSI (12 h to peak) (Carnerup et al., 2005). After an oral exposure to a developmentally toxic dose of 500 mg/kg/day in female rats, the peak plasma concentrations were: 6.9 mmol/L for NMP (2 h to peak); 0.76 mmol/L for 5-HNMP (12 h to peak); 0.31 mmol/L for MSI (12 h to peak); 0.05 mmol/L for 2-HMSI (12 h to peak) (Carnerup et al., 2005). This study indicates some dose-dependent shifts in the peak plasma concentrations for low versus high-dose oral exposures and may reflect saturation of NMP metabolism (Payan et al., 2002). To the degree that peak concentrations are important for developmental toxicity, the high dose exposures yield a greater proportion of the dose as the parent compound, the moiety of toxicological interest.

H. Other

In vitro and *in vivo* studies have been conducted to determine the effects of NMP versus major metabolites on developmental toxicity. Taken together, the data support the conclusion that the parent compound is the primary toxic moiety. These results are important in using PBPK modeling to estimate the relevant dose metric for deriving a point of departure for risk assessment.

In vitro assays including the rat whole embryo culture (WEC), and BALB/c 3T3 cytotoxicity test were conducted, and these results were then applied to an European Centre for the Validation of Alternative Methods (ECVAM) prediction model to evaluate the embryotoxicity of NMP, and NMP metabolites: 5-hydroxy-N-methyl-pyrrolidone (5- HNMP), 2-hydroxy-N-methylsuccinimide (2-HMSI) and N-methylsuccinimide (MSI). Specific dysmorphogeneses induced by NMP and 5-HNMP were aberrations in the head region of the embryos, abnormal development of the second visceral arches and open neural pores. Under the conditions of the WEC assay and subsequent modelling, NMP and 5-HNMP were shown to be weakly embryotoxic; although NMP was twice as potent as the 5-HNMP

metabolite. The other two metabolites were not embryo- toxic in this assay (Flick et al., 2009).

The NMP metabolites were also examined in an oral developmental toxicity studies in Sprague-Dawley rats. Pregnant rats were dosed on gestational days 6–20 with 5-HNMP (0, 250, 500, 750 or 1000 mg kg/day), 2-HMSI (0, 250, 500, 1000 or 1500 mg/kg/day) or MSI (0, 500, 750, 1000 or 1250 mg/kg/day). Maternal weights, food consumption, number of implantation sites, resorptions, dead and live fetuses, and corpora lutea in each ovary were recorded. Live fetuses were weighed, sexed and examined for external anomalies and processed and examined for visceral or skeletal changes. The 5-HNMP metabolite did not result in maternal or embryo-fetal toxicity. The 2-HMSI metabolite caused a significant decrease in maternal weight gain and food consumption at ≥500 mg/kg/day, but no embryo-fetal toxicity was observed. The MSI metabolite resulted in significantly decreased maternal weight gain and food consumption at ≥750 mg/kg/day, and developmental toxicity at maternally toxic doses. At ≥750 mg/kg/day the incidence of skeletal variations (predominantly rudimentary cervical ribs, and delayed ossification of skull bones and sternebrae) was increased and at ≥1000 mg/kg/day, reduced fetal weight, and malformations described as anasarca, cardiovascular defects and diaphragmatic hernia were observed. At 1250 mg/kg/day, there was an increase in postimplantation loss. The authors stated that MSI was much less potent than NMP. The author also concluded that embryotoxic and teratogenic effects of NMP are not attributable to these metabolites (Saillenfait et al., 2007).

V. HUMAN USE AND EXPERIENCE

A. Human Studies

1. Effects and Dose Response

Human experience has demonstrated irritation and dermatitis on repeated contact.

Ten of twelve workers in a small electrotechnical company in Norway experienced acute irritant contact dermatitis after 2 days of work with NMP (Leira et al., 1992).

In a repeated insult patch test using 50 human subjects, no irritation was produced during the first 24-h exposure. Repeated exposures caused mild transient irritation. No evidence of sensitization was shown (OECD, 2008).

Effects following workplace NMP exposures have been reported. An investigation was described of an industry vessel cleaner, who reported eye and upper respiratory tract irritation, and headaches. Measured air concentrations were 15.5 mg/m^3 (3.9 ppm) TWA with peak exposures of 18 mg/m^3 (4.5 ppm) for 102 min and a maximum 5-minute exposure at 85 mg/m^3 (21.3 ppm). The authors stated that some NMP-associated health complaints might be due in part to excessive dermal exposure (Bader et al., 2005). In a second report, workers exposed to NMP in areas with air concentrations up to 60 ppm (280 mg/m³) reported severe eye irritation and headache. Due to the methods of assessing the exposure level (sampling on charcoal and tracer gas method) and the response (observation and informal interview), a concentration–response relationship could not be developed (Beaulieu and Schmerber, 1991; WHO, 2001). These two workplace NMP exposure situations may be confounded due to mixed exposures to other compounds, precluding direct use for concentration response determination.

A controlled exposure experimental study of 15 healthy male subjects examined the chemosensory effects of NMP at vapor concentrations of 10, 40 or 80 mg/m³ (2.5, 10 or 20 ppm, respectively) for two sessions of 4-h exposures with an exposure-free lunch break of 30 min. To maximize chemosensory effects, a peak exposure scenario included exposure to a 25 mg/m³ baseline, with 160 mg/m³ (40 ppm) peaks 4 times for 15 min, resulting in a time-weighted average of 72 mg/m³ (18 ppm). The four different conditions were conducted with and without moderate physical workload. Chemosensory effects were measured physiologically by anterior rhinomanometry, eye blink rate and breathing frequency. Subjective ratings of acute health symptoms and intensity of olfactory and trigeminal sensations were collected. All physiological variables were unaffected by the different NMP concentrations and even the peak exposures did not have an effect on these measures. Olfactory-mediated health symptoms (e.g., odor intensity, annoyance) increased concentration-dependently. For these symptoms, a strong adaptation was observable, especially during the first 4 h of the exposures. Other acute symptoms were not significantly affected. Comparable to the symptoms, only olfactory sensations increased concentration-dependently. Odor intensity ranged from barely to nearly weakly detectable at the lower concentration of 10 mg/m³, observations consistent with the odor threshold of 8 mg/m^3 postulated by the author. Trigeminal sensations (e.g., eye and nose irritations) were evaluated as being barely detectable during the different exposures, only during 160 mg/m³ exposure peak, weak and transient eye irritation were reported. The results suggest that NMP concentrations of up to 160 mg/m³ (40 ppm) did not cause clearly adverse sensory irritation or undue annoyance (van Thriel et al., 2007).

An eight-hour experimental exposure in a chamber to 10, 25, and 50 mg/m³ (2.5, 6.25 and 12.5 ppm) did not induce discomfort to eyes or upper airways. There were no acute changes in the nasal cavity as assessed by continuous acoustic rhinometry, and no

significant differences were observed in FEV1 (forced expiratory volume in 1 second), vital capacity or forced expiratory capacity, measured by spirometry. In the blood there were no significant change in number of leukocytes, neutrophils, eosinophils, lymphocytes, basophils, monocytes, platelets or in the concentrations of IgE; bilirubin, alkaline phosphatase, g-glutamyl transferase, aspartate aminotransferase or alanine aminotransferase (Akesson and Paulsson, 1997). Two of the six volunteers reported detecting an odor at 50 mg/m³.

A study compared neurological endpoints in 15 NMP-exposed workers to 15 control male workers as determined by assessed exposures of NMP in the breathing zone and the urine. Clinical examinations, motor and sensory nerve conduction velocities in the dominant arm, and neurobehavioral tests were carried out. The subjects completed self-administered questionnaires for subjective symptoms and psychological assessment. The mean NMP exposure concentrations ranged from 0.14 to 0.26 ppm, and urinary NMP levels at the end of each workday ranged from 0.17 to 0.22 mg/L, throughout the work week. There were no differences in motor and sensory nerve conduction velocities, neurobehavioral tests, or subjective symptom assessments between NMP-exposed and non-exposed workers (Nishimura et al., 2009).

A 23-year-old laboratory technician was occupationally-exposed to NMP during her first 20 weeks of pregnancy (Solomon et al., 1996). An exposure evaluation was conducted after the technician experienced a stillbirth. Air concentrations of NMP were detectable at 0.05 ppm in an industrial hygiene study of different technicians. The study authors, however, thought that the patient's actual inhalation exposure was higher than reflected in these measurements, and skin absorption may have contributed significantly to her exposure. Her work duties included rinsing of glassware with NMP by hand and cleaning- up of an NMP spill in week 16 of pregnancy. During the 4 days following the spill, malaise, headache, and nausea were experienced but she was not removed from the exposure for 4 more weeks. 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. Solomon et al. (1996) noted that according to Feldman (1992) stillbirths at 31 weeks of pregnancy are unusual and occur with a frequency of 4.8 stillbirths/1000 births. However, as the level of exposure to this worker is unknown, it is impossible to establish if exposure to NMP is the causative factor in this case.

B. Metabolism/Pharmacokinetics

1. Absorption

The absorption of NMP has been studied in humans. NMP is absorbed by the inhalation, dermal and oral routes in humans (Ligocka et al., 2003; Akesson and Paulsson, 1997; Bader et al., 2007; Jönsson and Akesson, 2003; Keener et al., 2007; OECD, 2007). Bader et al. (2008) exposed 16 volunteers to 80 mg/m^3 NMP for 8 h under either whole-body (i.e., inhalation plus dermal) or dermal only conditions. Under resting conditions, whole-body exposure resulted in the elimination of 169 mg NMP equivalents compared to 71 mg NMP equivalents (i.e., 42% of whole-body) for dermal-only exposure. Under moderate workload, whole-body exposure resulted in the elimination of 238 mg, while 79 mg NMP (i.e., 33%) was eliminated under dermal-only exposure (Bader et al., 2008). Dermal absorption from the vapor phase contributed significantly to the total uptake of NMP and may contribute significantly to total workplace exposure (Bader et al., 2007; Jönsson and Akesson 2003; Keener et al., 2007). Moderate workload conditions enhanced the total uptake of NMP by approximately one third; this increase was attributed to inhalation since the uptakes of NMP vapor through the skin under both conditions were comparable (Bader et al., 2008). Studies in humans showed that NMP absorption after inhalation exposure was similar in dry and humid air (Carnerup et al., 2006). There was a large variability among individuals in this study.

Absorption by the dermal route of administration has also been evaluated. An application of 300 mg NMP to the skin of 12 volunteers resulted in a percutaneous absorption of 67.9% (Ligocka et al., 2003). In another study (Keener et al., 2007), an average dermal absorption of 5.4 ± 1.5 mg NMP/cm^2/h was calculated for a 2-h exposure to undiluted NMP and 6.5 ± 2.0 mg NMP/cm^2/h for a 30-minute exposure. A 50% NMP aqueous solution decreased the absorption to 0.9 ± 0.5 mg NMP/cm^2/h. Note that the reported rates may be artificially high because they were calculated based on the mass excreted in 72 h under the assumption that all the absorption occurred during the exposure period (i.e., 2 h or 0.5 h). The rates do not consider that the skin was likely “loaded” with NMP during the short application time and was absorbed systemically for some unknown period of time post-exposure (Keener et al., 2007). Other sources state the human dermal absorption rate is 1-2 mg/cm^3/h, about 2 to 3-fold lower than the rat (OECD, 2007).

2. Distribution

There are two studies that reported on distribution parameters of NMP. Six male volunteers exposed for 8 h to 10, 25, or 50 mg/m^3 NMP; 3 of the 6 subjects were exposed a second time at 50

mg/m^3. The apparent volumes of distribution were 41, 28, 120 and 281 L for NMP, 5-HNMP, MSI and 2-HMSI, respectively (Akesson and Paulsson, 1997). In a separate study, the mean apparent volume of distribution of NMP was 41 liters (range 10–81 L) (Jönsson and Akesson, 2003). These results are consistent with a chemical that is widely distributed in the body water volume suggesting distribution to most tissues.

3. Metabolism

The same metabolites were found in both rats and humans (Carnerup et al., 2006). NMP, 5-HNMP, 2-HMSI and MSI were detected in the urine of humans exposed to NMP by oral, inhalation and dermal routes (Ligocka et al., 2003; Akesson and Paulsson, 1997; Jönsson and Akesson, 2003; Keener et al., 2007; Bader et al., 2007). There was a significant relationship between CYP2E1 mRNA content in the peripheral blood lymphocytes of volunteers administered NMP and metabolites excreted in the urine. The authors state that these results indicate that CYP2E1 is involved in the first steps of NMP metabolism in humans but to a lesser degree than in the rat (Ligocka et al., 2003). In an oral study with 3 male volunteers, 100 mg NMP was administered on day 1; 24-h urine collections were analyzed for metabolites for one week. The mean excreted fractions (%) for NMP, 5-HNMP, MSI, and 2-HMSI were 0.8, 44, 0.4, and 20, respectively by day 7. NMP was detected only on day 1, 5-HNMP on day 1 and 2, MSI on days 1-3, and 2-HMSI on days 1-6; none of these metabolites was detected on day 7. One third of the oral dose of NMP was not recovered in urine as any of the above molecules (Bader et al., 2008).

4. Elimination

An inhalation exposure study with NMP was conducted in human volunteers under unique frequency, duration, concentration, or workload conditions (constant: 2 x 4 h [30 min break], 10, 40 or 80 mg/m^3; variable: 4 x 15 minutes [every 2h], peak 160 mg/m^3, baseline 25 mg/m^3), (Bader et al., 2007). The mean systemic half-lives based on urinary excretion for NMP, 5-HNMP and 2-HMSI were 3.8 h, 7.4 h and 24 h, respectively. These results were similar to urinary half-lives after an oral exposure, which were approximately 4, 8, and 17 h, respectively (Akesson and Paulsson, 1997).

The Bader study described above examined elimination pharmacokinetics. Percutaneous uptake delayed the elimination peak times and the apparent biological half-lives of NMP and 5-HNMP (Bader et al., 2008). The elimination half-life of NMP after whole body versus dermal only exposure under workload conditions was 3.7 and 7.5 h respectively. For NMP, the mean renal clearance was 0.13 (range 0.02–0.26) L/h. The mean total clearance was 11.4 (range 5.0–17.5) L/h (Jönsson and Akesson, 2003). Bader and colleagues stated that there was no significant influence of physical workload, intensity or variation of exposure on the peak times, half-lives and total elimination times (Bader et al., 2007). In addition, the differences in kinetics between male and female volunteers were small (Åkesson et al., 2004).

C. Exposure

Monitoring data supplied by DuPont to the US EPA in 1990 ranged from 12 ppm (48 mg/m^3) to 17 ppm (68 mg/m^3); however, US EPA also stated that a "typical inhalation exposure" according to DuPont was 0.2 ppm (0.8 mg/m^3) (US EPA, 1993). In the manufacture of adhesives and glues, the exposure ranged from 0.9-15.5 mg/m^3 (0.23-3.9 ppm, TWA) with some peak exposure at 18 mg/m^3 (4.5 ppm, 45 min) or 85 mg/m^3 (21.3 ppm, 5 min) (ECHA, 2011). In the electronics industry, measurements reported in 1991 indicated that workers in the microelectronics fabrication industry may be exposed up to 6 mg/m^3 (1.5 ppm) (personal breathing zones; 8-h TWA). NMP air concentrations up to 280 mg/m^3 (70 ppm) for a full shift were reported for fixed point area monitoring when warm NMP (80°C) was present. The authors stated that it was unclear whether these measurements were representative of personal exposure concentrations (ECHA, 2011).

D. Physiologically Based Pharmacokinetic (PBPK) model

PBPK models allow for the use of specific understanding of the toxicokinetics of NMP and the physiology of both rats and humans to obtain a more accurate human equivalent concentration (HEC) exposure and point of departure (POD) for the WEEL calculation.

Three PBPK models for NMP were developed building from an original model (Poet et al., 2010) to determine the internal NMP dose [i.e., as the area under the plasma concentration versus time curve; (AUC)] associated with developmental toxicity in rats following oral, dermal or inhalation exposures. For each exposure route, decreased fetal/pup body weights in rats, were identified as the critical effect. The AUC values were analyzed utilizing Benchmark Dose (BMD) software to identify the POD for developmental toxicity. The AUC corresponding to the benchmark dose lower confidence limit (BMDL) is considered equivalent to the use of a NOAEL for this response for WEEL derivation. The internal rat BMDL (as an AUC) becomes the human equivalent internal exposure NOAEL (as an AUC), which is then extrapolated to a HEC, the external worker inhalation exposure of NMP in air that would generate this internal dose based on a human PBPK model (Poet et al., 2010; US EPA, 2015; Poet et al., 2016). The three available PBPK models are compared in Table 2.

For the Poet et al. (2010) PBPK and BMD modeling, the rat internal AUCs were derived from exposures over GD 5-20 and 6-20 used in the Saillienfait et al. (2003) and Solomon et al. (1996) studies, respectively, and were used in the BMD evaluation. A $BMDL_{1SD}$, the lower confidence limit on the dose estimated to result in a change in response corresponding to 1 standard deviation for unexposed animals, was selected as the benchmark response rate (BMR) because it serves as the default value for continuous data sets. The geometric mean of the $BMDL_{1SD}$ from each study was considered the rat developmental toxicity NOAEL (Saillenfait et al., 2003; Solomon et al., 1995; Poet et al., 2010). The human PBPK model used to estimate the HEC values were based on simulations conducted for a pregnant woman (8 h/day, 5 days/week) with dermal absorption of NMP vapors. The internal dose value for NMP for the POD was 350 mg/h/L which corresponds to a human equivalent external exposure as an air concentration of 480 ppm.

The original PBPK model of Poet et al. (2010) was reparameterized and published as Poet et al. (2016) in a joint effort with US EPA. US EPA modified and adapted that model for application to human health risk assessment of NMP under TSCA (US EPA, 2015). The rat version of the model allowed for estimation of NMP time-courses in rat blood from inhalation, oral and dermal exposures. The human version of the model, based on non-pregnant and pregnant women, also included skin compartments for portions of the skin in contact with NMP vapor and liquid. The US EPA model was optimized based on the low human concentration data (i.e., 2.5 ppm) of Bader and van Thriel (2006). The BMD assessment only used the Saillenfait et al. (2003) study because it was considered to have a more robust dose-response. A benchmark response (BMR) of 5% relative deviation for decreased fetal body weight was selected based on the suggestion (Kavlock et al., 1995) that it may be appropriate for some developmental endpoints in the absence of knowledge as to what level of response is considered adverse. The human PBPK model developed for various paint stripping tasks was able to account for length of exposure and to include both the inhalation and dermal routes. From the various exposure scenarios, it was clear that dermal absorption, especially through liquid contact via the hands significantly contributed to the internal dose. The US EPA risk assessment compared the internal dose associated with various occupational scenarios, for which all included some dermal exposure to liquid NMP, to the 411 mg-h/L point of departure (POD) derived from their model using a margin of exposure approach. However, the human equivalent air concentration that corresponded to an internal dose of approximately 411 mg.h/L was not provided. Using the data in Table 2 and assuming linear toxicokinetics, the US EPA (2015) derived an internal dose of 411 mg-h/L from inhalation and dermal vapor uptake that is equivalent to a HEC of approximately 310 ppm using the EPA model (with zero dermal absorption of NMP liquid) and 430 ppm using the Poet et al. (2016) model, which includes dermal absorption.

In the third model portrayed by Poet and colleagues (2016), a number of metabolic parameters for both rats and humans were optimized. This PBPK model was then used to predict the average daily internal maternal exposure of NMP (from GD 13 - 20) for the two inhalation developmental toxicity studies (Saillenfait et al., 2003; Solomon et al., 1995). The $BMDL_{1SD}$ was determined for each of five developmental toxicity studies by the inhalation, dermal and oral routes, and the geometric mean of the $BMDL_{1SD}$ AUC from the inhalation studies was utilized to identify the rat inhalation NOAEL. The $BMDL_{1SD}$ was stated to be appropriate because statistically significant decrements in pup/fetal body weights fell within one standard deviation (5% to 10%) of the control body weights and the $BMDL_{1SD}$ is expected to fall between alternative BMRs ($BMDL_{05}$ and $BMDL_{10}$). In addition, there has been precedent for US EPA using $BMDL_{1SD}$ for developmental toxicity end points for other chemicals in the US EPA IRIS database (https://www.epa.gov/iris). The rat internal AUC were then converted to a human equivalent concentration using the human PBPK model for NMP, which was optimized based on the human concentration data of Bader and van Thriel (2006) (2.5, 10 and 20 ppm) as compared to only the low concentration (2.5 ppm) of the US EPA model. The resulting internal dose for NMP was 470 mg/h/L and a human equivalent external concentration of 490 ppm using Poet et al. (2016) and 350 ppm using US EPA (2015). Variability of HEC range also reflects differences in the BMR (5% versus 1SD) selected for POD determination.

The authors pointed to several uncertainties in the PBPK models. While pregnancy attributes were taken into account to develop the models, the chemical specific PK data were from nullipareous females or males. There was also uncertainty in the model regarding NMP metabolism with the variability in pregnant women and the lack of CYP2E1 in the fetus. A second point was regarding the derivation of the rat PBPK model for NMP being based on developmental toxicity data from a whole-body inhalation study, while the plasma NMP levels associated within this toxicity were derived solely from nose-only exposure. The PBPK-predicted internal NMP doses associated with rat developmental toxicity, which is seen only at saturated NMP vapor concentrations, likely underestimated the true internal exposures because they did not consider contributions from either the dermal absorption of NMP vapor or the incidental ingestion of NMP during grooming and the dermal uptake in rats is greater than in humans. Thirdly, the internal human dose was

based on data from the uptake of NMP vapor via inhalation as well as its absorption through the skin in healthy male volunteers. These models indicate that at the same external air concentrations, rats will achieve relatively higher internal blood concentrations than humans, which makes the reliance on these models protective.

VI. RATIONALE

NMP has low acute and chronic toxicity and is neither genotoxic nor carcinogenic. In human volunteers exposed under controlled conditions, 20 ppm NMP (80 mg/m³) was considered a NOEL for irritation for an 8-h exposure period, although weak and transient eye irritation was reported following shorter-term peak exposures of 40 ppm (160 mg/m³; the highest concentration tested). In workplace investigations, irritation and headache were reported among workers at these and higher air concentrations of NMP with potential exposure to other chemicals. Chronic studies in the rat provided a NOAEL of 10 ppm (40 mg/m^3) with a minimal LOAEL of 100 ppm (400 mg/m^3) causing only minor effects in males (slightly reduced mean body weight). Three developmental/reproductive inhalation studies in rats showed toxicological effects in the offspring, with a fourth giving indications of behavioral changes, indicating that developmental toxicity is an endpoint of concern. Saillenfait and colleagues (2003), identified as the key study, observed fetal body weight decreases (5-6%) at an exposure concentration of 120 ppm, with no malformations observed at any of the tested concentrations. The NOAEL for maternal and developmental toxicity was 30 and 60 ppm, respectively, which was associated with a BMDL internal dose for developmental effects ranging from 350-470 mg.h/L AUC among several PBPK models (Table 2).

The PBPK modeled exposure concentration is preferred for the POD in the development of the WEEL. The human equivalent concentrations associated with the rat NOAEL for decreased fetal weights from the US EPA (2015) and Poet et al. (2016) models ranged from 310 ppm to 490 ppm. While there is uncertainty in the PBPK model, adjustment factors for animal toxicodynamics and human intraspecies variability are applied to address these uncertainties. The calculation of a WEEL from either PBPK model results in similar values that differ by less than 20%, considering a conservative approach and to address any residual variability of the model, the WEEL derived from the POD range was rounded to 15 ppm.

Examination of the irritation concentration-response information for NMP indicates that a 15-minute Short Term Exposure Limit (STEL) is appropriate. A NOEL of 20 ppm and a LOEL of 40 ppm for causing weak and transient irritation after a short- term peak exposure was obtained from a controlled exposure study in human volunteers. A value of 30 ppm is expected to be a reasonable STEL, protective of irritation in the majority of the worker population.

The time weight average WEEL of 15 ppm (60 mg/m^3) is expected to be protective of irritation and chronic target organ effects, including developmental effects. A STEL of 30 ppm (120 mg/m^3) is recommended to prevent eye and upper respiratory irritation. Because of the ability of NMP to be absorbed through the skin, and because developmental and reproductive effects have been shown in dermal studies, a skin notation is assigned to NMP.

VII. RECOMMENDED WEEL GUIDE

8-Hour Time-Weighted Average (TWA): 15 ppm (60 mg/m^3), Skin

Short-term exposure level (STEL): 30 ppm (120 mg/m^3)

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Table 2. Human equivalent external concentration derived from rat internal dose

					Rat			Human		
Assessment	**Endpoint**	**Data Set(s)**	**Dose Measure**	**BMR**	**PBPK Model**	**POD Internal Dose (mg*h/L)**	**Routes of Exposure**	**PBPK Model**	**POD HEC (ppm occupational)**	**Routes of Exposure**
Poet et al. (2010)	Fetal/pup body weight changes	Geometric mean of Saillenfait et al. (2003) and Solomon et al. (1995)	Average daily AUC NMP in maternal blood during gestation period	1SD	Original model	350	Inhalation (nose-only)	Original model	480	Inhalation and dermal absorption of vapors
US EPA (2015)	Fetal body weight changes	Saillenfait et al. (2003)	Average daily AUC NMP in maternal blood during gestation period	5%	Minor corrections and reoptimization of original model parameters[a]	411[c]	Inhalation (nose-only)	US EPA refined model[b]	[d]Poet Model: 430 USEPA Model: 310	Inhalation and dermal absorption of vapors, plus dermal absorption of liquid (under paint stripper scenario-specific assumptions)
Poet et al. (2016)	Fetal/pup body weight changes	Geometric mean of Saillenfait et al. (2003) and Solomon et al. (1995)	Average daily AUC NMP in maternal blood during late gestation period (GD 13-20), based on a window-of-susceptibility analysis	1SD	Minor corrections and reoptimization of original model parameters[a]	470	Inhalation (nose-only)	Poet et al. refined model[b]	Poet Model: 630 USEPA Model: 460	Inhalation of vapors, only
									Poet Model: 490 USEPA Model: 350	Inhalation and dermal absorption of vapors

[a]Revised rat models used by US EPA (2015) and Poet et al. (2016) are effectively the same.

[b]The primary difference between the revised human models pertain to the use of Bader et al. (2007, 2008) data for optimizing metabolism parameters: (1) US EPA (2015) used data only collected at the lowest concentration (i.e., 2.5 ppm; below the POD HEC); and (2) Poet et al. (2016) utilized data from all concentrations (i.e., 2.5, 10 and 20 ppm; nearer to the POD HEC).

[c]For the Saillenfait et al. (2003), a BMR of 5% results in a POD internal dose (411 mg*h/L) that is lower than the internal dose (530 mg*h/L) associated with BMR of 1SD.

[d]Values derived from POD AUC and POD HEC of 411 mg*h/L and the assumption of linear toxicokinetics and no dermal exposure to NMP liquid.