

Initial Risk-Based Prioritization of High Production Volume (HPV) Chemicals

SPONSORED CHEMICAL

N-Methylformamide (CASRN 123-39-7)
(CA Index Name: Formamide, N-methyl-)

SUPPORTING CHEMICAL

N,N-Dimethylformamide (CASRN 68-12-2)
(CA Index Name: Formamide, N,N'-dimethyl-)

Prioritization Decision: Low Priority.

- **No further action suggested at this time.**
- **Because of the high developmental toxicity associated with this chemical, EPA notes that occupational exposures of women of childbearing age should be avoided. The chemical's use as an intermediate is expected generally to limit potential exposures.**

Screening-level prioritizations are interim evaluations that do not constitute either final Agency determinations as to risk or final determinations as to whether sufficient data are available to characterize risk. They are based predominantly on screening-level hazard, exposure, and risk characterizations prepared by EPA using data submitted to the Agency under the HPV Challenge Program¹ and the 2006 Inventory Update Reporting (IUR)², and data publicly available through other selected sources. These screening-level characterizations do not constitute full risk assessments. They are intended only to support initial decisions to determine the relative priority for further assessment or risk management activities concerning HPV chemicals, and to identify data needs for individual chemicals or chemical categories. The methodology used in preparing these characterizations and prioritization decisions is available on the EPA website.³

Screening-Level Characterization Summary

Risk Characterization

Potential Risk to Aquatic Organisms from Environmental Releases: *LOW*. The low potential that aquatic organisms might be exposed to this chemical and the low acute hazard for fish, aquatic invertebrates, and plants suggests a low potential risk to aquatic organisms.

¹ US EPA, HPV Challenge Program information: <http://www.epa.gov/hpv/>.

² US EPA, IUR information: <http://www.epa.gov/oppt/iur/index.htm>.

³ US EPA, Methodology for Risk-Based Prioritization Under ChAMP: <http://www.epa.gov/champ/pubs/rbp/method.pdf>.

Potential Risk to the General Population from Environmental Releases, Workers, Consumers, and Children: *LOW*. Although the potential human health hazard is moderate in adults and high for the developing fetus, the low potential for exposure suggests a low potential risk to the general population from environmental releases, and to workers, consumers and children.

Production Volume, Use, and Release Information

This chemical had an aggregated production and/or import volume in the United States between 1 million and 10 million pounds in 2005.

Non-confidential IUR information indicates that the industrial processing and uses of the chemical include intermediates in the manufacturing of pesticides and other agricultural chemicals. The HPV Challenge Program submission indicates that the predominant use (greater than 95%) of this chemical is as a DuPont-limited intermediate. Less than 5% of DuPont's production is sold to external customers. These customers, located in Europe and Japan, use this chemical for industrial purposes only: as a solvent in electronics manufacture and as a solvent for chemical synthesis of resins. The Hazardous Substances Data Bank (HSDB) information for this chemical states that the chemical is used primarily as an intermediate in the synthesis of pesticides, as an extraction solvent for aromatic hydrocarbons, and in the manufacture of methyl isocyanate.

No information is available on releases of this chemical to the environment.

Hazard Characterization Summary

This chemical is a liquid with high water solubility and moderate vapor pressure. It is expected to have high mobility in soil. Volatilization of this chemical is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible and the rate of atmospheric photooxidation is expected to be slow. This chemical is considered to be readily biodegradable. It is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The evaluation of available toxicity data for aquatic organisms indicates that the potential acute hazard of this chemical to fish, aquatic invertebrates, and aquatic plants is low.

The acute oral and inhalation toxicity of CASRN 123-39-7 in rats is low. It is irritating to the eyes of rabbits. Toxicity was moderate to rats that were repeatedly exposed to this chemical via inhalation for 14 days. Rats and mice showed moderate toxicity when exposed to supporting chemical CASRN 68-12-2 via inhalation in repeated-dose toxicity studies. In prenatal developmental toxicity studies, CASRN 123-39-7 showed high developmental toxicity in both rats and rabbits via the oral route, and in rats following exposure via inhalation. These same prenatal developmental toxicity studies showed moderate maternal toxicity. In a multigeneration reproductive toxicity study in mice exposed to supporting chemical CASRN 68-12-2 in their drinking water, with both prenatal and postnatal evaluations, showed high prenatal developmental toxicity and low toxicity to young animals (following postnatal exposures), adult animals, and for reproductive effects. No genotoxicity studies were available for this chemical.

Supporting chemical CASRN 68-12-2 did not induce gene mutation or chromosomal aberrations. No carcinogenicity studies have been conducted with CASRN 123-39-7. Rats and mice were exposed via inhalation to the supporting chemical in a cancer study and showed no increase in tumors.

No data gaps were identified under the HPV Challenge Program.

Exposure Characterization Summary

EPA identifies a low potential that the general population and environment might be exposed to this chemical based on its limited use as an intermediate with no further processing and use, low expected releases, and low environmental persistence.

EPA identifies a low relative ranking for potential worker exposure based primarily on the moderate vapor pressure of the chemical and its limited use domestically as an intermediate.

EPA identifies a low potential that consumers and children might be exposed to this chemical based on its limited use as an intermediate with no further processing and use.

Additional Considerations For Prioritization Decision

Regulatory and Related Information Summary

- This chemical is on the TSCA Inventory and is not otherwise regulated under TSCA.

Assumptions and Uncertainties

- EPA has no information on releases of this chemical, and has made assumptions about potential exposures based on generic use scenarios associated with reported uses. Releases of this chemical to the environment are presumed to be low based on its use. The lack of environmental release data for a chemical is a source of uncertainty in the potential that the general population and the environment might be exposed to that chemical.

Appendix A: Screening-Level Hazard Characterization

SPONSORED CHEMICAL

N-Methylformamide (CASRN 123-39-7)
(CA Index Name: Formamide, N-methyl-)

SUPPORTING CHEMICAL

***N,N*-Dimethylformamide (CASRN 68-12-2)**
(CA Index Name: Formamide, *N,N'*-dimethyl-)

Introduction

The sponsor, E. I. du Pont de Nemours & Co, submitted a Test Plan and Robust Summaries to EPA for N-methylformamide also known as monomethylformamide (MMF) (CASRN 123-39-7; CA Index Name: Formamide, N-methyl-) on March 30, 2004. EPA posted the submission on the ChemRTK HPV Challenge website on April 13, 2004 (<http://www.epa.gov/chemrtk/pubs/summaries/monomthf/c15159tc.htm>). EPA comments on the original submission were posted to the website on August 30, 2005. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on June 15, 2006 and October 27, 2006, which were posted to the ChemRTK website on September 5, 2006 and January 31, 2007, respectively.

Justification for Supporting Chemical

For repeated-dose, reproductive and genetic toxicity endpoints, the sponsor indicated data on MMF are not available. The sponsor submitted data on an analog, *N,N*-dimethylformamide (DMF, CASRN 68-12-2), to address these endpoints. DMF was evaluated in the OECD HPV Chemicals Program (<http://www.chem.unep.ch/irptc/sids/OECD/SIDS/DIMETHYLFORM.pdf>). The structure of DMF is closely related to MMF, in that both contain an N-substituted formamide moiety. The substances differ only in the degree of substitution on the nitrogen atom; MMF contains one methyl group and DMF contains two. As stated in the summary of the metabolism of MMF and DMF provided in the test plan, the pathways for biotransformation of DMF and MMF have been extensively studied and are qualitatively similar. The major pathway for metabolism of DMF is oxidation to form N(hydroxymethyl)-N-methylformamide and an alternative pathway is demethylation to MMF. Hepatotoxicity of both compounds is thought to be mediated by a reactive intermediate formed by further metabolism of MMF. For the purposes of both the HPV Challenge Program and the ChAMP, EPA considered DMF to be a suitable analog for MMF based on similarities in their structures, physical-chemical properties and metabolism pathways showing similar target organ toxicity.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of MMF and a supporting chemical DMF are summarized in Table 1a, while the environmental fate properties are provided in Table 1b. The structures of these compounds are provided in Table 2 at the end of Appendix A.

Physical-Chemical Properties Characterization

MMF is a liquid with high water solubility and moderate vapor pressure.

Property	<i>N</i> -Methylformamide (MMF)	<i>N,N</i> -Dimethylformamide (DMF)
CASRN	123-39-7	68-12-2
Molecular Weight	59.07	73.10
Physical State	Liquid	Liquid
Melting Point	-3.8°C (measured)	-61°C (measured)
Boiling Point	199.5°C (measured)	152.5–153.5°C (measured)
Vapor Pressure	0.253 mm Hg at 25°C (measured)	3.6 mm Hg at 25°C (measured)
Water Solubility	1×10 ⁶ mg/L at 25°C (measured)	200,000 mg/L at 20°C (measured)
Dissociation Constant (pK _a)	Not applicable under environmental conditions	Not applicable under environmental conditions
Henry's Law Constant	1.97×10 ⁻⁸ atm·m ³ /mole (estimated) ²	7.4×10 ⁻⁸ atm·m ³ /mole (estimated) ²
Log K _{ow}	-0.97 (measured)	-0.85 (measured)

¹E.I. du Pont de Nemours & Company, Inc. January 31, 2007. Revised Robust Summary and Test Plan for Monomethylformamide.

<http://www.epa.gov/oppt/chemrtk/pubs/summaries/monomthf/c15159tc.htm>.

²USEPA. 2008. Estimation Programs Interface Suite™ (version 3.20). United States Environmental Protection Agency, Washington, DC, USA Available online at: <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

Environmental Fate Characterization

MMF is expected to have high mobility in soil. MMF is considered to be readily biodegradable based on the results of an OECD 301B test. The rate of volatilization of MMF from water and moist soil is considered low based on its estimated Henry's Law constant. The rate of hydrolysis is considered negligible under environmental conditions and the rate of atmospheric photooxidation is considered slow. MMF is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Property	N-Methylformamide (MMF)	N,N-Dimethylformamide (DMF)
CASRN	123-39-7	68-12-2
Photodegradation Half-life	57 hours (estimated) ²	22 hours (estimated) ²
Hydrolysis Half-life	Stable	Stable
Biodegradation	80% in 28 days (readily biodegradable, OECD 301B) ³	4.4–8.8% in 14 days (not readily biodegradable) ⁴
Bioconcentration	BCF = 3 (estimated) ²	BCF = 0.3–1.2 (measured in carp) ⁴
Log K _{oc}	0.32 (estimated) ²	0.38 (estimated) ²
Fugacity (Level III Model) ²	Air = 0.43% Water = 39.7% Soil = 59.8% Sediment = 0.073%	Air = 1.23% Water = 41.5% Soil = 57.2% Sediment = 0.076%
Persistence ⁵	P1 (low)	P2 (moderate)
Bioaccumulation ⁵	B1 (low)	B1 (low)

¹E.I. du Pont de Nemours & Company, Inc. January 31, 2007. Revised Robust Summary and Test Plan for Monomethylformamide.

<http://www.epa.gov/oppt/chemrtk/pubs/summaries/monomthf/c15159tc.htm>.

²US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA.

<http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

³OECD, 1992. OECD Guideline for Testing of Chemicals, 301: Ready Biodegradability.

⁴National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Accessed September 18, 2008.

http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

⁵Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: MMF is a liquid with high water solubility and moderate vapor pressure. It is expected to have high mobility in soil. Volatilization of MMF is considered low based on its Henry’s Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow. MMF is considered to be readily biodegradable. MMF is expected to have low persistence (P1) and low bioaccumulation potential (B1).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

(1) Fathead minnows (*Pimephales promelas*) were exposed to MMF at nominal concentrations of 0, 100, 1000 or 10,000 mg/L under static conditions for 96 hours. No mortality occurred at the highest concentration. A 96-hour LC₅₀ for fish, estimated by ECOSAR v 1.0, was used to support evaluation of the acute toxicity of MMF.

96-h LC₅₀ > 10,000 mg/L

96-h LC₅₀ = 26,635 mg/L (estimated)

(2) Fathead minnows (*Pimephales promelas*) were exposed to MMF at nominal concentrations of 0, 0.5, 1.0, 50, 500 or 5,000 mg/L under static conditions for 96 hours. No mortality occurred at the highest concentration. Rapid breathing was seen in all fish at the highest concentration.

96-h LC₅₀ > 5000 mg/L

Acute Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to MMF at nominal concentrations of 0, 62.5, 125, 250 or 500 mg/L under static conditions for 48 hours. No mortality/immobility occurred at any concentration. A 48-hour EC₅₀ for *Daphnia*, estimated by ECOSAR v1.0, was used to support evaluation of the acute toxicity of MMF.

48-h EC₅₀ > 500 mg/L

48-h EC₅₀ = 9,435 mg/L (estimated)

Toxicity to Aquatic Plants

Green algae (*Scenedesmus subspicatus*) were exposed to MMF at nominal concentrations of 0, 5,000, 8,000, 12,800, 20,500, 32,800 or 42,400 mg/L under static conditions for 72 hours. No effect on growth was detected at concentrations of 8,000 mg/L or less. A 96-hour EC₅₀ for green algae, estimated by ECOSAR v1.0, was used to support evaluation of the acute toxicity of MMF.

96-h EC₅₀ (biomass) = 17,300 mg/L

96-h EC₅₀ = 1,142 mg/L (estimated)

Conclusion: The evaluation of available toxicity data for aquatic organisms indicates that the potential acute hazard of MMF to fish, aquatic invertebrates and aquatic plants is low.

3. Human Health Effects

Acute Oral Toxicity

(1) Female mice (BALB/C, number not reported) were administered MMF a single oral dose at 5 dose levels (doses not reported) and were observed for 30 days.

LD₅₀ = 2600 mg/kg-bw

(2) Two other studies were reported in rats, but no information was provided except for the LD₅₀ values (4000 and 7077 mg/kg-bw).

Acute Inhalation Toxicity

Male rats (Crl:CD, 6) were exposed to MMF vapor at concentrations of 0.69, 1.0, 5.6 and 10.76 mg/L for 4 hours and were observed for an unspecified time after exposure. No deaths occurred but rats in the two highest exposure groups exhibited severe weight loss followed by recovery. Gasping was observed during exposure in 2 of 6 rats at the highest concentration.

LC₅₀ > 10.76 mg/L

Repeated-Dose Toxicity

N-methylformamide (MMF; CASRN 123-39-7)

Male rats (15/dose) were exposed to MMF vapor via nose-only inhalation, at mean measured concentrations of 0, 0.12, 0.32, or 0.97 mg/L for 6 hours/day, 5 days/week for 2 weeks (10 exposures total). Five rats/dose were sacrificed after the 10th exposure, five rats/dose were sacrificed on day 14 of the study and five rats per group were held for a two-week recovery period and used solely for MMF analysis in urine. No mortality was reported at any exposure level. At 0.12 mg/L, no adverse effects were reported. At 0.32 mg/L, rats exhibited significantly decreased body weights during the two week exposure period. However, during the two-week recovery period, the body weight gains were comparable to controls. Relative liver weights and cholesterol were increased at this concentration. Adverse histopathological effects in the liver were seen at the end of the treatment period in mid- and high-dose animals (pale cytoplasm, increase in mitotic figures and cytoplasmic lipid vacuolation). Following the two-week recovery period, no adverse effects were noted.

At 0.97 mg/L, rats exhibited significantly reduced body weights and increased cholesterol levels, aspartate aminotransferase (AST) activity and alanine aminotransferase (ALT) activity. In recovery animals, these parameters were unaffected. Increased relative liver and testes weights were seen at the end of the exposure, which returned to normal after 14 days recovery. Absolute weights of heart, lung, spleen, and thymus were decreased compared to controls at the end of the exposure period (robust summary did not include the evaluation of these organs during the recovery period). Histopathological evaluation of liver revealed degenerative/regenerative changes as described above in mid-dose animals.

LOAEL = 0.32 mg/L (based on decreased body weight and liver effects)

NOAEL = 0.12 mg/L

N,N-Dimethylformamide (DMF; CASRN 68-12-2, supporting chemical)

Fischer 344 rats (30/sex/dose) and B6C3F1 mice (10/sex/dose) were administered the supporting chemical, dimethylformamide via whole-body inhalation at 0, 50, 100, 200, 400 and 800 ppm (approximately 0, 0.15, 0.30, 0.60, 1.2, or 2.4 mg/L, respectively) for 6 hours/day, 5 days/week for 13 consecutive weeks. The studies were conducted by the National Toxicology Program (NTP).

Rats: No mortality occurred at any DMF concentration. Body weight gains were decreased in the two highest exposure groups, markedly at the highest concentration. Clinical chemistry parameters measured on days 4, 24, and 91, revealed significantly ($p < 0.05$ and $p < 0.01$) elevated activities of alanine aminotransferase and sorbitol dehydrogenase, in animals exposed to 200 ppm or higher by as early as day 4 of exposure. Serum cholesterol levels were significantly increased ($p < 0.01$) in all exposed rats at all time points. Relative liver weights were significantly ($p < 0.01$) increased at 100 ppm and higher in males and at all concentrations in females with slight to moderate centrilobular necrosis at 400 and 800 ppm (more severe in females). Relative testes weights were increased at 400 and 800 ppm; no microscopic findings or adverse effects on sperm density or motility were seen. Prolonged diestrus was noted in females (7/10) exposed to 800 ppm. NTP determined a LOAEL for DMF at 401 ppm based on liver toxicity, even though some clinical chemistry parameters indicative of liver injury were observed at lower exposure concentrations.

LOAEL = 1.2 mg/L (based on adverse effects on the liver)

NOAEL = 0.60 mg/L

Mice: No mortality occurred that was attributable to DMF exposure. Female body weight gains were reduced compared to controls at 800 ppm. Absolute and relative liver weights (significant, $p < 0.01$) were increased in all mice exposed to DMF with accompanying slight hepatocyte hypertrophy in all mice exposed to 100 ppm DMF and higher and in males at 50 ppm. In females, a trend toward an increase in the estrus cycle length was seen. No effects on the reproductive system of male mice were noted. The NTP report authors apparently did not consider liver changes (increased weights and hepatocyte size) as anything more than an adaptive response (i.e., mixed function oxidase induction) as there was no accompanying centrilobular necrosis when examined histologically, leaving a NOAEL greater than or equal to the highest exposure tested of 804 ppm.

NOAEL (male) = > 2.4 mg/L (no effects at highest dose tested)

LOAEL (female) = 0.60 mg/L (based on increased estrus cycle length)

NOAEL (female) = 0.30 mg/L

Reproductive Toxicity

N-methylformamide (MMF; CASRN 123-39-7)

The single MMF study available was performed using an irrelevant route exposure (i.p.).

N,N-Dimethylformamide (DMF; CASRN 68-12-2, supporting chemical)

In a continuous breeding study, CD-1 mice (male and female) were administered DMF in the drinking water at 0, 1000, 4000, 7000 ppm (approximately 219, 820, and 1455 mg/kg-bw/day). The study consisted of 4 segments: (1) F0 cohabitation and lactation phase, (2) a crossover mating trial of the F0 generation, (3) a fertility assessment of the F1 generation and (4) reproductive performance of the second generation.

During F0 cohabitation and lactation phase, mice (40/sex for controls and 20/sex/dose for treated animals) were housed in breeding pairs within dose groups. Litter interval, number, sex, weight of pups per litter, number of litters per breeding pair, and the post-natal day (PND) 0 body weights were monitored. F0 females were allowed to deliver and rear the final litter until

PND 21. Pups were sexed, counted, and weighed periodically through the postnatal phase. On PND 21, randomly selected F1 pups from each dose group were weaned and housed in same-sex pairs by dose and saved for the F1 fertility assessment phase (described below). After completion of the cohabitation and lactation phase, all F0 animals were maintained on their respective treatment until scheduled sacrifice following the completion of the crossover mating phase.

There was no effect on survival, dose-related clinical signs of toxicity, body weight in males, food consumption or water consumption. Female body weight was significantly ($p < 0.05$) decreased at 7000 ppm at weeks 8 and 16. Maternal body weight decreased at all doses. Maternal food consumption was decreased during the lactation period. Reduced fertility was noted at 4000 ppm; and at 7000 ppm. The average number of litters per pair, average litter size, proportion of pups born alive, and average pup weight were all reduced compared to control pairs. Pups showed external malformations and other abnormalities, including domed head and hematomas along the nose and on the head. Those pups most severely affected died shortly after birth, and many were cannibalized prior to examination. The proportion of litters with one or more pups with an abnormal appearance was 7.9, 10.5, 90.0, and 77.8% for the 0, 1000, 4000, and 7000 ppm groups, respectively. The reduction in the proportions of litters with malformed pups in the high-dose group, compared to the mid-dose group, was influenced by the decreased fertility, increased prenatal death, and postnatal cannibalism observed in the high dose group. During the lactation phase, average post-natal survival was reduced in the 4000 and 7000 ppm groups.

For crossover mating, only the control and high-dose mice were used. This experiment was performed because fertility was affected in the F0 cohabitation/lactation study. Three breeding groups of F0 animals were created: 1) control male mated with control female, 2) high-dose male mated with control female, and 3) control male mated with high-dose female. No treatments were administered during cohabitation. Dosing was resumed after confirmation of pregnancy.

High-dose females treated with 7000 ppm produced fewer live pups per litter and pups with lower weights when compared to the males treated with 7000 ppm. However, males treated with 7000 ppm had an increased incidence of incomplete ossification of the cranial bones. Malformations observed in the control male mated with 7000 ppm-females included abnormal ossification of the cranial plates, abnormal suture formation in the cranium, and abnormal or incomplete formation of the sternbrae. Pups born to DMF-treated mothers had malformations, including agenesis of the cerebrum, agnathia, abnormally shaped centrum or cranium, cleft palate, or enlarged cerebral ventricles. The number of females having normal estrous cycles was also affected by DMF. At necropsy, DMF-treated F0 females had significantly depressed body weights. Male liver weights and female absolute and relative liver weight, kidney and adrenal weights were increased at all doses. Caudal epididymal weight was significantly increased at all doses of DMF. A slight decrease in testicular spermatid concentration in the DMF-treated animals showed a significant ($p < 0.01$) trend. However, no correlation of this finding was noted during the histopathological examination of the reproductive organs. Therefore, the effect on testicular spermatids was not considered biologically relevant.

For F1 fertility assessment, randomly selected F1 pups from all groups began directly receiving DMF via the drinking water at PND 21. At 74 ± 10 days of age, males and females in the control

or treated groups were cohoused as nonsibling breeding pairs. Food consumption was unaffected in the F1 generation. Water consumption was increased for the males in the mid- and high-dose groups and body weights were reduced at these doses in both sexes. Selected F2 litters were preserved on PND 1 and evaluated for whole body skeletal malformations and soft tissue malformations of the head. Selected adult F1 males and females were evaluated for skeletal malformations. The survival of F1 pups in the final litter and postnatal survival on PND 4 was reduced at 4000 and 7000 ppm and continued to decline throughout the lactation period. Pup weight during lactation was reduced at the mid and high doses prior to PND7. The F1 pups at these doses also exhibited craniofacial malformations. Pups that were severely malformed did not survive the pre-weaning period. The surviving F1 pups were small and had foreshortened, domed heads. After weaning, pups were randomly selected for rearing and inclusion in the reproductive performance evaluation of the F1 generation.

During reproductive performance evaluation of the second generation, the following observations were made: The mating index was significantly ($p < 0.05$) decreased at 7000 ppm. Fertility was reduced in the 4000 and 7000 ppm groups. The average days to litter was increased, and the number of live pups per litter, pup body weight, and the proportion of pups born alive was decreased in the 4000 and 7000 ppm groups. Live pup weight was also decreased in the 1000 ppm pups. F2 pups born to DMF-treated F1 pairs exhibited malformations similar to those observed for the F1 litters described above. The proportion of litters with 1 or more externally malformed pups was 0, 27.7, 60, and 75% for the 0, 1000, 4000 and 7000 ppm groups, respectively. Females in the 7000 ppm group had significantly longer estrus cycles and tended to be in either metestrus or diestrus longer than the control animals. At necropsy, F1 male and female body weights were reduced in the 4000 and 7000 ppm groups. Absolute and relative liver weights were markedly increased in all DMF-treated animals of both sexes. Female relative kidney plus adrenal weight was increased in the 4000 and 7000 ppm groups. Histopathological examination of the animals with gross lesions (high and low dose groups) revealed treatment-related centrilobular hepatocellular hypertrophy. Absolute prostate weight was decreased in males at 4000 and 7000 ppm and relative prostate weight was decreased at all doses. Epididymidal spermatozoa concentration was decreased at 7000 ppm. Malformations observed in the mid- and high-dose animals consisted of abnormal or incomplete ossification of the cranial plates, abnormal cranial suture formation and abnormally formed sternbrae. Histopathological examination of additional F1 animals in the mid- and high-dose group revealed dysplasia of the cranial bones, primarily at the midline.

Significant reproductive and developmental toxicity was observed in both generations at 4000 and 7000 ppm DMF in the presence of some general toxicity. The liver appeared to be the primary non-reproductive target organ. Reduced F2 pup weight at birth was noted at 1000 ppm DMF.

LOAEL (systemic toxicity) = 219 mg/kg-bw/day (based on decreased body weight and various organ weights, including some pathological changes in the liver)

NOAEL (systemic toxicity) = Not established

LOAEL (reproductive toxicity) = 820 mg/kg-bw/day (based on decreased pup survival, decreased pup viability to weaning, decreased prostate weights and reduced fertility)

NOAEL (reproductive toxicity) = 219 mg/kg-bw/day

LOAEL (offspring) = 219 mg/kg-bw/day (based on malformations and reduced pup weight in F2 offspring at birth)

NOAEL (offspring) = Not established

Developmental Toxicity

N-methylformamide (MMF; CASRN 123-39-7)

(1) Pregnant CrI:CD, BR rats (25 /group) were administered MMF by gavage at doses of 0, 1, 5, 10, or 75 mg/kg-bw/day during gestation days 6 through 15. Significantly decreased food consumption and decreased maternal weight gain ($p < 0.01$) were observed in the high-dose group. There was no effect on the number of corpora lutea or fetal sex ratios. Post-implantation loss was significant ($p < 0.01$), fetal viability was reduced due to a marked increase in early resorptions and fetal weights were significantly decreased ($p < 0.01$) at 75 mg/kg-bw/day. Over 50% of the fetuses at 75 mg/kg-bw/day were malformed. Malformations included cephalocele (protrusion of a part of the cranial contents) and sternoschisis (cleft sternum) and skeletal variations included incomplete ossification of various skeletal structures including reduced ossification of the skull, 13th rib and sternbrae. Malformations seen at 10, 5, and 1 mg/kg-bw/day were not dose dependent or were within the historical control range. No malformations occurred in the pups from the control or 1 mg/kg-bw/day dose groups. One pup (from one litter) was malformed at 5 mg/kg-bw/day, 3 pups had malformations (from 3 different litters) at 10 mg/kg-bw/day and 150 pups showed malformations (from 21 affected litters) at 75 mg/kg-bw/day. Malformations consisted primarily of cephalocele and sternoschisis.

LOAEL (maternal toxicity) = 75 mg/kg-bw/day (based on significant decreased weight gain and decreased food consumption)

NOAEL (maternal toxicity) = 10 mg/kg-bw/day

LOAEL (developmental toxicity) = 75 mg/kg-bw/day (based on post-implantation loss, decreased fetal viability, and increases in gross malformations and skeletal variations)

NOAEL (developmental toxicity) = 10 mg/kg-bw/day

(2) Pregnant New Zealand White rabbits (20/group) were administered MMF via gavage at 0, 5, 10 or 50 mg/kg-bw/day during gestation days 6 through 18. There were no treatment-related maternal deaths, or effects on clinical signs or gross pathology. Body weight and food consumption were decreased and there was a statistically significant increase ($p < 0.05$) in post-implantation loss at 50 mg/kg-bw/day. The number of implantations and sex ratio at lower doses were unaffected by treatment. Fetal viability was reduced at 50 mg/kg-bw/day. Significant ($p < 0.05$) treatment-related malformations observed at 50 mg/kg-bw/day included cephalocele, domed head, bent hyoid, other skull and sternum anomalies, flexed paw, and gastroschisis. No increase in pup malformations was observed at 5 or 10 mg/kg-bw/day.

LOAEL (maternal toxicity) = 50 mg/kg-bw/day (based on decreased weight gain and decreased food consumption)

NOAEL (maternal toxicity) = 10 mg/kg-bw/day

LOAEL (developmental toxicity) = 50 mg/kg-bw/day (based on post-implantation loss, increases in gross malformations and decreased survival)

NOAEL (developmental toxicity) = 10 mg/kg-bw/day

(3) Pregnant rats (CrI:CD BR, 25/group) were exposed (nose-only) to MMF vapor at concentrations of 0, 15, 50 or 150 ppm (approximately 0, 0.04, 0.12 and 0.40 mg/L/day, respectively), 6 hours/day during gestation days 7 through 16. Dams in the mid- and high-exposure groups exhibited mild respiratory distress characterized as rales and wheezing. At 150 ppm there was one treatment-related mortality plus the following significant adverse effects: decreased food consumption, decreased body weight and decreased thymus weights (both relative and absolute). Dams at this exposure level also showed significantly increased resorptions. The mean number of live fetuses per litter was also decreased. Pups from the 50 and the 150 ppm exposure groups had reduced fetal body weights (significant at 150 ppm only). At 150 ppm, pups had the following malformations: subcutaneous head cysts, microphthalmia, hydrocephaly, distended ventricles of the brain, fused ribs and vertebrae, and hemivertebrae. An increased incidence of skeletal anomalies and retarded bone ossification also were evident in pups from the 150 ppm group.

LOAEL (maternal toxicity) = 0.12 mg/L/day (based on respiratory distress)

NOAEL (maternal toxicity) = 0.04 mg/L/day

LOAEL (developmental toxicity) = 0.12 mg/L/day (based on fetal body weight depression)

NOAEL (developmental toxicity) = 0.04 mg/L/day

Genetic Toxicity – Gene Mutation

In vitro

N-methylformamide (MMF; CASRN 123-39-7)

No reliable in vitro gene mutation tests were submitted for MMF.

N,N-Dimethylformamide (DMF; CASRN 68-12-2, supporting chemical)

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to DMF, at concentrations of 0, 9400, 24000, 47000, 94000, 190,000 or 470,000 µg/plate in the presence or absence of metabolic activation. The two highest concentrations were cytotoxic in the presence and absence of metabolic activation. Both positive and negative control responses were appropriate.

DMF was not mutagenic in this assay.

(2) The National Toxicology Program reports three mouse lymphoma studies, two negative and one positive for the supporting chemical DMF (see http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=mouselymphoma.choosestudytype&cas_no=68-12-2&endpointlist=ML%2CML-N).

Genetic Toxicity – Chromosomal Aberration

In vitro

N,N-Dimethylformamide (DMF; CASRN 68-12-2, supporting chemical)

The supporting chemical, DMF, was examined, no increase in chromosome aberrations or sister chromatid exchanges were detected in Chinese hamster ovary cells in two trials at concentrations ranging from 50 to 5000 µg/mL in the presence or absence of metabolic activation. Positive and negative controls gave appropriate responses.

DMF did not induce chromosomal aberrations in this assay.

In vivo

N,N-Dimethylformamide (DMF; CASRN 68-12-2, supporting chemical)

A micronucleus assay was conducted with DMF in male BALB/c mice (5/dose), administered via intraperitoneal injection at doses of 0, 0.2, 20 or 2000 mg/kg-bw. Whether animals received more than one dose was not reported and other methodological details were absent from the robust summary. The positive and negative controls gave appropriate responses.

DMF did not induce chromosomal aberrations in this assay.

Genetic Toxicity – Other DNA Effects

In Vivo

N,N-Dimethylformamide (DMF; CASRN 68-12-2, supporting chemical)

In the dominant lethal assay, rats (10/group) were exposed to *N,N*-dimethylformamide via the inhalation route of exposure 6 hours/day, for 5 days at concentrations of 0, 30, or 300 ppm (equivalent to 0, 0.09 or 0.90 mg/L). Individual males were housed with 2 untreated females for two weeks before treatment. Immediately after the treatment phase, males were housed with two new untreated females for two weeks, then two more untreated females. This was repeated over the 6-week cycle of sperm development in order to assess all phases of spermatogenesis. Females were sacrificed 18 days after the first day of caging and implantation sites were counted to assess dominant lethality. DMF did not affect implantation rates or fetal deaths indicating a negative response for dominant lethality. The positive control responded appropriately.

DMF was negative in this assay.

Additional Information

Eye Irritation

MMF (100 µl) was instilled into the lower conjunctival sac of one eye of six New Zealand White rabbits with the opposite eye as control. Effects on the cornea, iris and conjunctivae were evaluated according the scoring criteria of Draize at 4, 24, 48, 72, and 96 hours. Corneal opacity reached a severity of 1 (on a scale of 0 to 4) at the 4-hour observation point, after which scores diminished to 0.3 at the 72 hour observation period and clearing almost completely by 96 hours. Observation after 96 hours showed that conjunctivitis was still persistent. MMF was irritating to rabbits' eyes.

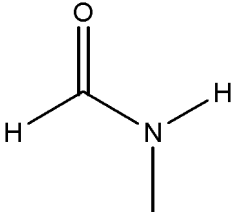
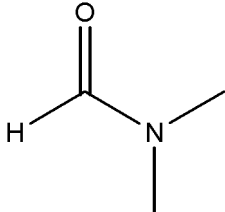
Carcinogenicity

No carcinogenicity studies have been conducted with MMF. The International Agency for Research on Cancer (IARC) has reviewed the supporting chemical, DMF, for carcinogenicity and concluded that this chemical has been adequately characterized in rats and mice by the inhalation route of exposure showing no increase in tumor incidence above controls.

Conclusion: The acute oral and inhalation toxicity of MMF in rats is low. MMF is irritating to the eyes of rabbits. In rats repeatedly exposed to MMF via inhalation for 14-days, toxicity was moderate. Rats and mice showed moderate toxicity when exposed to the supporting chemical, DMF, via inhalation in repeated-dose toxicity studies. In prenatal developmental toxicity studies, MMF showed high developmental toxicity in both rats and rabbits via the oral route, and in rats following exposure via inhalation. These same prenatal developmental toxicity studies showed moderate maternal toxicity. In a multigeneration reproductive toxicity study in mice exposed to DMF in their drinking water, DMF with both prenatal and postnatal evaluations, showed high prenatal developmental toxicity and low toxicity to young animals (following postnatal exposures), adult animals and for reproductive effects. No genotoxicity studies were available for MMF. DMF did not induce gene mutation or chromosomal aberrations. No carcinogenicity studies have been conducted with MMF. Rats and mice were exposed via inhalation to DMF in a cancer study and showed no increase in tumors.

No data gaps were identified under the HPV Challenge Program.

Table 2

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program		
Endpoints	SPONSORED CHEMICAL N-methylformamide 123-39-7	SUPPORTING CHEMICAL N,N-Dimethylformamide ¹ 68-12-2
Structure		
Summary of Environmental Effects – Aquatic Toxicity Data		
Fish 96-h LC ₅₀ (mg/L)	> 5,000	—*
Aquatic Invertebrates 48-h EC ₅₀ (mg/L)	> 500	—*
Aquatic Plants 72-h EC ₅₀ (mg/L) (growth and biomass)	17,300	—*
Summary of Human Health Data		
Acute Oral Toxicity LD ₅₀ (mg/kg-bw)	4000 – 7077 (rat) 2600 (mouse)	—*
Acute Inhalation Toxicity LC ₅₀ (mg/L)	> 10.8 (rat, 4-hr)	—*
Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/day)	<p>Rat</p> <p>NOAEL = 0.12 LOAEL = 0.32 (10 days of exposure over 14-day period)</p> <p>Mice</p> <p>—*</p>	<p>NOAEL = 0.60 LOAEL = 1.2</p> <p>NOAEL (male) > 2.40 LOAEL (male) = Not established NOAEL (female) = 0.30 LOAEL (female) = 0.60</p>
Reproductive Toxicity NOAEL/LOAEL (mg/kg- bw/day)	No Data NOAEL = Not established	NOAEL = Not established

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program		
Endpoints	SPONSORED CHEMICAL N-methylformamide 123-39-7	SUPPORTING CHEMICAL N,N-Dimethylformamide ¹ 68-12-2
Systemic Toxicity	LOAEL = 219 (RA)	LOAEL = 219
Reproductive Toxicity	NOAEL = 219 LOAEL = 820 (RA)	NOAEL = 219 LOAEL = 820
Offspring Toxicity	NOAEL = Not established LOAEL = 219 (RA)	NOAEL = Not established LOAEL = 219
Developmental Toxicity Oral NOAEL/LOAEL(mg/kg- bw/day) Maternal/Developmental Toxicity	(Rat) NOAEL = 10 LOAEL = 75	—*
Developmental Toxicity Maternal Toxicity	(Rabbit) NOAEL = 10 LOAEL = 50 NOAEL = 10 LOAEL = 50	—*
Developmental Toxicity Inhalation (mg/L/day) Maternal/Developmental Toxicity	NOAEL = 0.04 LOAEL = 0.12	—*
Genetic Toxicity – Gene Mutation <i>In vitro</i>	No Data Negative (RA)	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	No Data Negative (RA)	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	No Data Negative (RA)	Negative
Genetic Toxicity – Other Dominant Lethal	No Data	Negative

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program		
Endpoints	SPONSORED CHEMICAL N-methylformamide 123-39-7	SUPPORTING CHEMICAL N,N-Dimethylformamide¹ 68-12-2
	Negative (RA)	
Additional Information Eye Irritation	Irritating	—*
Additional Information Carcinogenicity	—*	DMF has been adequately characterized in rats and mice by the inhalation route of exposure showing no increase in tumor incidence above controls (IARC).

— indicates endpoint was not addressed for this chemical; * indicates endpoint not required for this chemical; RA = Read Across

¹ Supporting chemical data was used for addressing the repeated-dose, reproductive and genetic toxicity endpoints.

Appendix B: IUR Data Summary

SPONSORED CHEMICAL

N-Methylformamide (CASRN 123-39-7)
(CA Index Name: Formamide, N-methyl-)

This data summary was completed using both public, non-confidential sources, and one or more IUR submissions that were available as of this writing.

Non Confidential IUR Data Summary

Manufacturing/Import Information

Production and import volume:	1 million to 10 million pounds
List of non-CBI companies*:	E. I. du Pont de Nemours and Company
Maximum number of potentially exposed workers**:	between 100 and 999
Highest non-CBI maximum concentration*:	greater than 90%
Non-CBI physical forms*:	liquid

* There may be other companies, concentrations and physical forms that are claimed confidential.

** Includes all manufacturing and industrial processing and use workers. There may be additional potentially exposed industrial workers that are not included in this estimate since not all submitters were required to report on industrial processing and use and/or there may be at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions.

Table 1		
Industrial Processing and Use Information		
Processing Activity	Industrial Sector	Function in Industrial Sector
Processing as a reactant	Pesticide and Other Agricultural Chemical Manufacturing	Intermediates
One or more items may have been claimed as confidential.		

Table 2		
Commercial/Consumer Uses Information		
Commercial/Consumer Product Category Description	Highest Maximum Concentration Range	Use in Children's Products
None reported		