SCREENING-LEVEL HAZARD CHARACTERIZATION

N-Methylphthalimide
(CASRN 550-44-7)

The High Production Volume (HPV) Challenge Program[1] was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

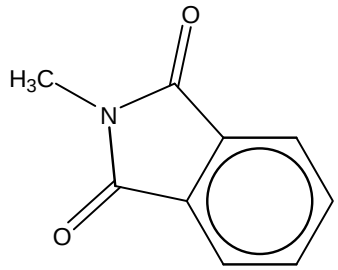
The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental

[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.

authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	**550-44-7**
Chemical Abstract Index Name	**H-Isoindole-1,3(2H)-dione, 2-methyl-**
Structural Formula	

Summary

CASRN 550-44-7 is a solid with moderate water solubility and moderate vapor pressure. It is expected to possess 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 under acidic conditions, moderate at basic pH, and slow under neutral conditions. The rate of atmospheric photooxidation is considered moderate. CASRN 550-44-7 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute toxicity of CASRN 550-44-7 is low via the oral (rats) and dermal (rabbits) routes of exposure. Repeated oral exposure of rats to CASRN 550-44-7 for 30 days showed effects on body weight and liver at 250 mg/kg-bw/day and above, with a NOAEL of 125 mg/kg-bw/day. In an one-generation reproductive toxicity study in rats, the LOAEL for systemic toxicity was 600 mg/kg-bw/day (highest dose tested) based on effects on body weight, liver and kidneys. The LOAEL for reproductive toxicity was 50 (males) to 150 (females) mg/kg-bw/day based on delayed puberty in F1 pups; the NOAEL for reproductive toxicity for males was not established and for females it was 150 mg/kg-bw/day. In the same study, the LOAEL for developmental toxicity was 50 (males) to 150 (females) mg/kg-bw/day based on decreased post-weaning body weights. The NOAEL for developmental toxicity for male pups was not established and for females it was 150 mg/kg-bw/day. In the prenatal developmental toxicity study in rabbits, no effects on maternal or developmental parameters were seen at 500 mg/kg-bw/day (only does tested). CASRN 550-44-7 did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells in *in vitro* tests.

The measured 96-hour LC_{50} of CASRN 550-44-7 for fish is 110 mg/L. The measured 24-hour EC_{50} of CASRN 550-44-7 for aquatic invertebrates is 112 mg/L, and the measured 72-hour EC_{50} for aquatic plants is 57 mg/L.

No data gaps were identified under the HPV Challenge Program.

The sponsor, General Electric (GE), submitted a Test Plan and Robust Summaries to EPA for N-methylphthalimide (CASRN 550-44-7) on December 31, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on January 30, 2003 (http://www.epa.gov/hpv/pubs/summaries/nmethylp/c14220tc.htm). EPA comments on the original submission were posted to the website on June 16, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 5, 2003 and November 30, 2005, which were posted to the ChemRTK website on September 5, 2003 and January 10, 2006, respectively.

1. Chemical Identity

1.1 Identification and Purity

The HPV submission[4] for this chemical did not include information on purity in the Test Plan (2003). However, in response to EPA comments, GE Plastics indicates that the purity of the test material was consistently > 99% and usually ~ 99.9% (August 2003).

1.2 Physical-Chemical Properties

The physical-chemical properties of *N*-methylphthalimide are summarized in Table 1. *N*-Methylphthalimide is a solid with moderate water solubility and moderate vapor pressure.

Table 1. Physical-Chemical Properties of *N*-Methylphthalimide[1]

Property	Value
CASRN	550-44-7
Molecular Weight	161.16
Physical State	Solid
Melting Point	136–137°C (measured)
Boiling Point	275°C (measured)
Vapor Pressure	0.000385 mm Hg at 24.15°C (measured)
Water Solubility	420 mg/L at 22.6°C (measured)
Dissociation Constant (pK_a)	Not applicable
Henry's Law Constant	2.2×10^{-8} atm-m^3/mole (estimated)[2]
Log K_{ow}	1.29 (measured)

[1]General Electric Company. December 1, 2005. Revised Robust Summary and Test Plan for *N*-Methyl-phthalimide. http://www.epa.gov/chemrtk/pubs/summaries/nmethylp/c14220tc.htm.
[2]U.S. 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.

[4]General Electric Company (2003). Robust Summary N-methylphthalimide CASRN 550-44-7. http://www.epa.gov/chemrtk/pubs/summaries/nmethylp/c14220tc.htm

2. General Information on Exposure

2.1 Production Volume and Use Pattern

N-Methylphthalimide had an aggregated production volume in the United States of 1 million to 10 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include processing as an intermediate in other basic organic chemical manufacturing. The HPV submission for this chemical states that it is primarily used as a site-limited intermediate in the production of a high molecular weight polyetherimide polymer.

2.2 Environmental Exposure and Fate

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

The environmental fate properties are provided in Table 2. *N*-Methylphthalimide is a solid with moderate water solubility and moderate vapor pressure. It is expected to possess high mobility in soil. Volatilization of *N*-methylphthalimide is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible under acidic conditions, moderate at basic pH, and slow under neutral conditions. The rate of atmospheric photooxidation is considered moderate. *N*-Methylphthalimide is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of *N*-Methylphthalimide[1]	
Property	**Value**
Photodegradation Half-life	15.7 hours (estimated)
Hydrolysis Half-life	10,148 hours at pH 4 and 25°C (measured); 88 hours at pH 7 and 25°C (measured); 2.2 hours at pH 9 and 25°C (measured)
Biodegradation	77% in 23 days (readily biodegradable)
Bioconcentration	BCF = 2 (estimated)[2]
Log K_{oc}	1.1 (estimated)[2]
Fugacity (Level III Model)[2]	Air = 5.3% Water = 44.4% Soil = 50.2% Sediment = <0.1%
Persistence[3]	P1 (low)
Bioaccumulation[3]	B1 (low)

[1]General Electric Company. December 1, 2005. Revised Robust Summary and Test Plan for *N*-Methyl-phthalimide. http://www.epa.gov/chemrtk/pubs/summaries/nmethylp/c14220tc.htm.
[2]U.S. 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.
[3]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3. Human Health Hazard

The human health hazard data are summarized in Table 3.

Acute Oral Toxicity

Male Spartan rats (2/dose) were administered N-methylphthalimide in corn oil via gavage at 500 or 5000 mg/kg-bw and observed for 14 days following dosing. Mortality occurred at 5000 mg/kg-bw.
LD50 > 500 mg/kg-bw < 5000 mg/kg-bw

Acute Dermal Toxicity

New Zealand White rabbits (1/sex/dose) were administered N-methylphthalimide dermally at 200 or 2000 mg/kg-bw to clipped intact skin under occluded conditions for 24 hours. Following exposure animals were observed for 14 days. No mortality was reported.
LD_{50} > 2000 mg/kg-bw

Repeated-Dose Toxicity

Sprague-Dawley rats (10/sex/dose) were administered N-methylphthalimide via the diet at 0, 0.25, 0.5 or 1.0% (approximately 0, 125, 250 or 500 mg/kg-bw/day) for 30 days. One male rat in the low-dose level died on day 26 of the study. Marked decreases in relative body weights occurred in the 250 and 500 mg/kg-bw groups, in both males (6 and 18%, respectively) and females (4 and 11%, respectively). Mean food consumption was sporadically decreased compared to controls throughout the study. Gross pathology showed no treatment-related effects at any dose. Mean relative liver weight was increased in both sexes and mean relative kidney weight was increased in males at the high-dose level. Microscopic evaluation revealed compound-related centrilobular to diffuse hepatocellular enlargement in rats of both sexes in the mid- and high-doses. The severity of chronic progressive nephropathy was increased slightly in male rats at the high-dose. There were no compound-related findings in the tissues of low-dose males or females.
LOAEL ~ 250 mg/kg-bw/day (based on decreased body weight and liver effects)
NOAEL ~ 125 mg/kg-bw/day

Reproductive/Developmental Toxicity

In the one-generation reproductive toxicity study, Sprague-Dawley rats (10 sex/dose) were administered N-methylphthalimide in corn oil via gavage at 0, 50, 150 or 600 mg/kg-bw/day. F0 males were dosed for 4 weeks (beginning 2 weeks prior to breeding and continuing for 2 weeks during breeding) and females were dosed for 10 weeks (2 weeks pre-breeding, 2 weeks during mating, 3 weeks during gestation, 3 weeks during lactation). F1 litters were culled on postnatal day (pnd) 4 to five per sex. At pnd 21, at least one male and female from each litter was selected to continue treatment from pnd 22 until at least 70 days of age. Four unscheduled deaths occurred in high-dose F0 females. No other treatment-related deaths were reported. Clinical signs of toxicity in F0 male rats included ataxia, audible breathing and piloerection at the high dose. Absolute and relative liver weight and brain weights were significantly increased in high-dose males, and absolute and relative prostate weight was significantly decreased. Histopathological findings included centrilobular hepatocellular hypertrophy in livers of the high-dose animals of both sexes and hyaline droplets in kidney in males which is consistent with alpha 2µ-globulin nephropathy. Pre-coital interval was markedly decreased at the high-dose. There was a significant reduction in mean body weight during gestation and lactation in high-dose females. No effects were observed on gestational length or reproductive indices. Total number of implantation sites per litter and the number of total and live pups per litter at birth were decreased at the high dose. In F1 offspring, there were significant reductions in body weight, body weight gain and food consumption in males at all doses and in females at the two highest doses from postnatal days 22-71. The absolute and adjusted acquisition of puberty was significantly delayed in all F1 male groups and high-dose F1 females. In F1 males, hemoglobin was significantly increased in high-dose males, platelet count was significantly decreased in mid- and high-dose males and mean platelet volume was significantly decreased at all doses. In F1 females, total cholesterol was significantly increased at the high dose. Histological findings in high-dose F1 animals consisted of centrilobular hepatocellular hypertrophy in both sexes and hyaline droplets in male kidneys which is consistent with alpha 2µ-globulin nephropathy. In

offspring sacrificed at pnd 21, absolute spleen weights were significantly decreased in males and relative brain and epididymal weights were significantly increased in high-dose males. In female offspring sacrificed at pnd 21, relative brain weight was significantly increased, and absolute spleen and thymus weights were significantly decreased at the high-dose level.
LOAEL (systemic toxicity) = 600 mg/kg-bw/day (based on decreased body weight, liver and kidney effects)
NOAEL (systemic toxicity) = 150 mg/kg-bw/day
LOAEL (reproductive toxicity – male/female) = 50/150 mg/kg-bw/day (based on delayed puberty in F1 pups)
NOAEL (reproductive toxicity- male/female) = Not established/50 mg/kg-bw/day
LOAEL (developmental toxicity– male/female) = 50/150 mg/kg-bw/day (based on reduced post-weaning body weights)
NOAEL (developmental toxicity – male/female) = Not established/50 mg/kg-bw/day

Developmental Toxicity

Female New Zealand White rabbits (16/dose) were administered N-methylphthalimide in 0.5% carboxymethyl cellulose via gavage at 500 mg/kg-bw/day on days 6 through 18 of gestation. There was no maternal or developmental toxicity.
NOAEL (maternal toxicity) = 500 mg/kg-bw/day (only dose tested)
NOAEL (developmental toxicity) = 500 mg/kg-bw/day (only dose tested)

Genetic Toxicity – Gene Mutation

In vitro
(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to N-methylphthalimide at concentrations of 0, 1, 10, 100, 500, 1000, 2500, 5000 or 10,000 μg/plate in the presence and absence of metabolic activation. Positive and solvent controls were tested concurrently and responded appropriately. The cytotoxic concentration was 10,000 μg/plate for TA1537. The test substance did not exhibit mutagenic activity in any tested strain.
N-Methylphthalimide was not mutagenic in this assay.

(2) *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and *Saccharomyces cerevisiae* strain D4 were exposed to N-methylphthalimide at concentrations of 0, 0.1, 1, 10, 100 and 500 μg/plate in the presence and absence of metabolic activation. Positive and solvent controls were tested concurrently and responded appropriately. Cytotoxicity was observed at 500 μg/plate in strains TA1535, TA1537, TA1538 and TA98. The test substance did not exhibit mutagenic activity in any tested strain.
N-Methylphthalimide was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Chinese Hamster Ovary (CHO) cells were exposed to N-methylphthalimide at concentrations of 0, 201.25, 402.5, 805 or 1610 µg/mL in the presence or absence of metabolic activation. In the absence of metabolic activation, tests were conducted with exposure periods of 4 and 20 hours; in the presence of metabolic activation, tests were conducted with an exposure period of 4 hours. Solvent and positive controls were tested concurrently and responded appropriately. The cytotoxic concentration was > 1610 µg/mL. The test substance was negative for the induction of structural and numerical chromosome aberrations in Chinese hamster ovary cells.
N-Methylphthalimide did not induce chromosomal aberrations in this assay.

Conclusion: The acute toxicity of CASRN 550-44-7 is low via the oral (rats) and dermal (rabbits) routes of exposure. Repeated oral exposure of rats to CASRN 550-44-7 for 30 days showed effects on body weight and liver at 250 mg/kg-bw/day and above, with a NOAEL of 125 mg/kg-bw/day. In one-generation reproductive toxicity study in rats, the LOAEL for systemic toxicity was 600 mg/kg-bw/day (highest dose tested) based on effects on body weight, liver and kidneys. The LOAEL for reproductive toxicity was 50 (males) to 150 (females) mg/kg-bw/day based on delayed puberty in F1 pups. The NOAEL for reproductive toxicity for males was not established and for females it was 150 mg/kg-bw/day. In the same study, the LOAEL for developmental toxicity was 50 (males) to 150 (females) mg/kg-bw/day based on decreased post-weaning body weights. The NOAEL for developmental toxicity for male pups was not established and for females it was 150 mg/kg-bw/day. In the prenatal developmental toxicity study in rabbits, no effects on maternal or developmental parameters were seen at 500 mg/kg-bw/day (only dose tested). CASRN 550-44-7 did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells in *in vitro* tests.

4. Hazard to the Environment

The environmental hazard data are summarized in Table 3.

Acute Toxicity to Fish

Rainbow trout (*Oncorhynchus mykiss*) were exposed to *N*-methylphthalimide at measured concentrations of 0, 34.6, 100.3 and 293.3 mg/L under static conditions for 96 hours. At the higher concentration, seven fish were dead. Total mortality was 0, 0, 0, 33.3, 100 and 100% for the control, 40, 68, 116, 200 and 293 mg/L, respectively.
96-h LC_{50} = 110 mg/L

Acute Toxicity to Aquatic Invertebrates

Daphnia magna were exposed to *N*-methylphthalimide at measured concentrations of 26.9, 126.0 and 313.7 mg/L under static conditions for 24 hours. At 126 mg/L, 75% immobilization occurred and 100% immobilization occurred at the two highest concentration levels.
24-h LC_{50} = 112 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to *N*-methylphthalimide at measured concentrations of 0, 27.6, 80.4 and 360.2 mg/L for 46, 110 and 400 mg/L under static conditions for 72 hours. Control samples produced a satisfactory cell increase during the exposure period. Mean relative cell growth rates were 100, 84, 75, 7, 1, 0 and -1% for the control, 46, 70, 110, 170, 260 and 400 mg/L samples, respectively.
72-h EC_{50} (growth) = 57 mg/L

Conclusion: The measured 96-hour LC_{50} of CASRN 550-44-7 for fish is 110 mg/L. The measured 24-hour EC_{50} of CASRN 550-44-7 for aquatic invertebrates is 112 mg/L, and the measured 72-hour EC_{50} for aquatic plants is 57 mg/L.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL N-Methylphthalimide (550-44-7)**
Summary of Human Health Data	
Acute Oral Toxicity **LD_{50} (mg/kg-bw)**	**> 500, < 5000**
Acute Dermal Toxicity **LD_{50} (mg/kg-bw)**	**> 2000**
Repeated-Dose Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)**	(30-day) **NOAEL = 125** **LOAEL = 250**
Reproductive/Developmental Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)** **Systemic Toxicity**	**NOAEL = 150** **LOAEL = 600**
Reproductive/Developmental Toxicity Male/Female	**NOAEL = Not established/50** **LOAEL = 50/150**
Developmental Toxicity **NOAEL/LOAEL** **Oral (mg/kg-bw/day)**	(Rabbits)
Maternal Toxicity	**NOAEL = 500 (odt)**
Developmental Toxicity	**NOAEL = 500 (odt)**
Genetic Toxicity – Gene Mutation*In vitro*	**Negative**
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	**Negative**
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish **96-h LC_{50} (mg/L)**	**110**
Aquatic Invertebrates **48-h EC_{50} (mg/L)**	**112 (24-h)**
Aquatic Plants **72-h EC_{50} (mg/L)** **(growth)**	**57**

odt = only dose tested;