SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL
2-Pyrrolidone (CASRN 616-45-5)

SUPPORTING CHEMICAL
1-Methyl-2-pyrrolidone (CASRN 872-50-4)

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 Set1[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

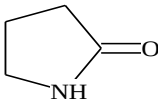
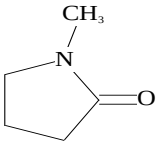
The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness 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.), Science Direct and ECHA[4]. 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

[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.
[4]European Chemicals Agency, http://echa.europa.eu

presented in an international forum that involves review and endorsement by governmental 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)	**Sponsored Chemical** **616-45-5** **Supporting Chemical** **872-50-4**
Chemical Abstract Index Name	**Sponsored Chemical** **2-Pyrrolidone** **Supporting Chemical** **1-methyl-2-pyrrolidone**
Structural Formula	**Sponsored Chemical**  SMILES: O=C(NCC1)C1 **Supporting Chemical**  SMILES: O=C1CCCN1C

Summary

2-Pyrrolidone is a clear liquid with moderate vapor pressure and high water solubility. It is expected to have high mobility in soil. Volatilization of 2-pyrrolidone is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible under environmental conditions. The rate of atmospheric photooxidation is considered moderate. Based on data for the supporting chemical 1-methyl-2-pyrolidone, 2-pyrrolidone is expected to be readily biodegradable. 2-Pyrrolidone is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute oral and dermal toxicity of 2-pyrrolidone in rats and rabbits, respectively, is low. In a three-month repeated-dose toxicity study, male rats given 2-pyrrolidone via drinking water exhibited increased urinary specific gravity, reduced urinary volume and increased mean relative kidney weights at $\geq$ 529 mg/kg-bw/day, with a NOAEL of 184 mg/kg-bw/day. Females exhibited histopathological changes in thymocytes at all doses, with a LOAEL of ~ 42 mg/kg-bw/day. In another three-month repeated-dose study, female rats administered 2-pyrrolidone via drinking water exhibited decreased body weight gains of 16% at 1339 mg/kg-bw/day and 8% at 5 mg/kg-bw/day. No specific reproductive toxicity studies are available for 2-pyrrolidone. However, in the three-month drinking water study with female rats only, decreased relative and absolute uterine weights and increased absolute pituitary weights were

observed. No histopathological changes in the reproductive organs were observed in the other three month drinking water study in either sex. In an oral gavage prenatal developmental toxicity study in rats, dams exhibited decreased body weights at $\geq$ 600 mg/kg-day (with decreased gravid uterine weights at 1900 mg/kg-day); the NOAEL for maternal toxicity is 190 mg/kg-day. In this study, fetuses exhibited increased incidences of malformations, visceral and skeletal anomalies and decreased fetal weights at 1900 mg/kg-day, resulting in a developmental NOAEL of 600 mg/kg-day. In another prenatal oral gavage developmental toxicity study in rats, the developmental NOAEL was 1875 mg/kg-day (only dose tested); data were inadequate to establish a maternal NOAEL. 2-Pyrrolidone induced gene mutations in yeast *in vitro*, but did not induce gene mutations in bacteria *in vitro* or chromosomal aberrations in mammalian cells *in vitro*. 2-Pyrrolidone did not induce micronuclei in mice *in vivo*. 2-Pyrrolidone is irritating to rabbit skin and eyes.

For 2-Pyrrolidone, the 96-h LC_{50} for fish is 580 mg/L, the 48-h EC_{50} for aquatic invertebrates is 13.21 mg/L. For the toxicity to aquatic plants, the 96-h EC_{50} values are 84 mg/L for biomass and 353 mg/L for growth rate.

No data gaps were identified under the HPV Challenge Program.

The sponsor, BPPB Consortium, submitted a Test Plan and Robust Summaries to EPA for 2-pyrrolidone (CASRN 616-45-5; CA Index name: 2-pyrrolidone) on January 2, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on January 31, 2003 (http://www.epa.gov/chemrtk/pubs/summaries/2pyrroli/c14223tc.htm). EPA comments on the original submission were posted to the website on June 19, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 13, 2003, which were posted to the ChemRTK website on October 22, 2003.

Supporting Chemical Justification

The sponsor provided data from a ready biodegradation test for a supporting chemical, 1-methyl-2-pyrrolidone (CASRN 872-50-4). These data were used to support the inherent biodegradation data for the sponsored compound based on structural similarities between the two compounds. In addition to data provided by the industry sponsor for 1-methyl-2-pyrrolidone, an assessment of this compound is available through the OECD Cooperative Chemicals Assessment Program (http://www.oecd.org/env/hazard/data).

1. Chemical Identity

1.1 Identification and Purity

2-Pyrrolidone, a cyclic amide, is a clear liquid with unpleasant ammonia-like odor. A discussion of purity was not included in the submitted test plan. However, purity was stated for several individual studies (in robust summaries); values ranged from ≥ 97% to 99.9% in all cases except one, which noted use of 'crude' 2-pyrrolidone with no further description.

1.2 Physical-Chemical Properties

The physical-chemical properties and are summarized in Table 1. 2-Pyrrolidone is a clear liquid with moderate vapor pressure and high water solubility.

Table 1. Physical-Chemical Properties of 2-Pyrrolidone[1]	
Property	**Value**
CASRN	616-45-5
Molecular Weight	85.11
Physical State	Clear liquid
Melting Point	25°C (measured)
Boiling Point	245°C (measured)
Vapor Pressure	0.0095 mm Hg at 25°C (measured)
Dissociation Constant (pK_a)	Not applicable
Henry's Law Constant	1.0×10^{-9} atm-m^3/mole (estimated)[2]
Water Solubility	Miscible; 1×10^6 mg/L at 20 °C (measured)[3]
Log K_{ow}	-0.71 at 25°C (measured)

[1]BPPB Consortium. 2003. Revised Test Plan and Robust Summary for 2-Pyrrolidone. Available online at http://www.epa.gov/chemrtk/pubs/summaries/2pyrroli/c14223tc.htm as of December 8, 2011.
[2]U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of December 8, 2011.
[3]SRC. 2011. The Physical Properties Database (PHYSPROP). Syracuse, NY: SRC Inc. Available online at http://www.syrres.com/esc/physprop.htm as of December 8, 2011.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

2-Pyrrolidone had an aggregated production and/or import volume in the United States between 50 to 100 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the chemical is processed and used in the following industrial categories and in the following ways: (1) in other basic organic chemical manufacturing, both as intermediates but also as uses for which information was not readily obtainable (NRO); and (2) in printing ink manufacturing, as solvents that become part of product formulation or mixture.

Non-confidential commercial and consumer uses of this chemical were reported as "Other" and "NRO."

2.2 Environmental Exposure and Fate

2-Pyrrolidone is expected to have high mobility in soil. It was degraded approximately 99% over 9 days using non-adapted activated sludge in a Zahn-Wellens test (OECD 302B), which means that it was inherently biodegradable. A structural analog, 1-methyl-2-pyrrolidone (CASRN 872-50-4), achieved 73% of its theoretical biochemical oxygen demand (BOD) in 28 days using the modified MITI (OECD 301C) test. Therefore, it is concluded that 2-pyrrolidone is likely to be readily biodegradable. Volatilization of 2-pyrrolidone is considered low based on its Henry's Law constant. The rate of atmospheric photooxidation is considered moderate. 2-Pyrrolidone is expected to have low persistence (P1) and low bioaccumulation potential (B1). The environmental fate properties are summarized in Table 2.

Table 2. Environmental Fate Properties of 2-Pyrrolidone[1]

Property	Value
Photodegradation Half-life	10.8 hours (estimated)[2]
Hydrolysis Half-life	>1 year
Biodegradation	99% after 9 days (inherently biodegradable); 73% after 28 days (readily biodegradable)[4]
Bioaccumulation Factor	BAF = 0.9 (estimated)[2]
Log K_{oc}	0.9 (estimated)[2]
Fugacity (Level III Model)[2]	
Air (%)	<0.1
Water (%)	32.2
Soil (%)	67.7
Sediment (%)	0.1
Persistence[3]	P1 (low)
Bioaccumulation[3]	B1 (low)

[1]BPPB Consortium. 2003. Revised Test Plan and Robust Summary for 2-Pyrrolidone. Available online at http://www.epa.gov/chemrtk/pubs/summaries/2pyrroli/c14223tc.htm as of December 8, 2011.
[2]U.S. EPA. 2011. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of December 8, 2011.
[3]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.
[4]Data for 1-Methyl-2-pyrrolidone CASRN 872-50-4

Conclusion: 2-Pyrrolidone is a clear liquid with moderate vapor pressure and high water solubility. It is expected to have high mobility in soil. Volatilization of 2-pyrrolidone is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible under environmental conditions. The rate of atmospheric photooxidation is considered moderate. Based on data for the supporting chemical 1-methyl-2-pyrolidone, 2-pyrrolidone is expected to be readily biodegradable. 2-Pyrrolidone is expected to have low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

A summary of the human health toxicity data for SIDS and other endpoints is provided in Table 3.

Acute Oral Toxicity

Sprague-Dawley rats (5/sex) were administered a 50% solution of 2-pyrrolidone via gavage at 5000 mg/kg in distilled water and observed for 14 days following dosing. No mortalities were observed.
LD_{50} > 5000 mg/kg

Acute Dermal Toxicity

New Zealand White rabbits (5/sex) were administered 2-pyrrolidone via the dermal route at 2000 mg/kg under occluded conditions for 24 hours and observed for 14 days following dosing. No mortalities were observed.
LD_{50} > 2000 mg/kg

Repeated-Dose Toxicity

(1)Wistar rats (10/sex/dose) were administered 2-pyrrolidone (99.7% pure) via drinking water at 0, 600, 2400, 7200 or 15,000 ppm (~ 33, 184, 529 and 1062 mg/kg-bw for males and 42, 230, 643 and 1189 mg/kg-bw for females) for 3 months. No mortalities were observed. Effects included decreased food consumption in both sexes at 15,000 ppm and females at 7200 ppm, decreased water consumption in both sexes at15,000 and 7200 ppm and decreased body weight gain in both sexes at 15,000 (~8 and 9% in females and males, respectively) and 7200 ppm (~ 16% and 7% in females and males, respectively). Hematological effects included prolonged prothrombin time in both sexes at 15,000 ppm. Clinical chemistry effects included decreased total protein, globulins, triglycerides and creatinine in both sexes at 15,000 ppm. Decreased creatinine and total protein were also observed at the 7200 ppm dose level in both sexes and females, respectively. Urinalysis revealed increased urinary specific gravity, reduced urinary volume and dark yellow discoloration in 15,000 and 7200 ppm males. Increased mean relative kidney weights were observed in both sexes at 15,000 ppm and in males at 7200 ppm. Females exhibited altered thymocytes of irregular size and shape with increased numbers of large, pale blast-like lymphocytic thymocytes among smaller, dark-staining cells. A clear dose-response was not obvious and no changes in the cortex/medulla ratio, thymic medulla, or T-cell areas of other organs were seen. Although the sponsor's submission notes that other studies show these thymocyte changes occur in controls, the lack of such an effect in controls in the current study indicates a possible effect of the test substance (robust summary from HPV submission; TSCATS OTS0521310-3).

LOAEL (males) ~ 529 mg/kg-bw/day (based on effects on clinical chemistry, urinalysis and increased kidney weights)
NOAEL (males) ~ 184 mg/kg-bw/day
LOAEL (females) ~ 42 mg/kg-bw/day (based on histopathological changes in thymocytes)
NOAEL (females) ~ Not established

(2) Female Wistar rats (5/dose) were administered 0, 50 and 15,000 ppm (~0, 5 and 1339 mg/kg-bw/day) 2-pyrrolidone (99.7% pure) via drinking water for 3 months. Additional rats at 0 and 15,000 ppm were followed without dosing for an additional 4 weeks. The purpose of the study was to further evaluate the thymic effects seen in females in the repeated-dose study (#1). Food and water consumption and body weight were measured each week and rats were observed for signs of toxicity each day. Hematological examinations were conducted at the end of the dosing period. All rats were subjected to gross and histological pathology examinations, although the organs examined were not listed. Estrous cycle determination was prepared in three intervals (start, mid and end of study). At 15,000 ppm, food and water consumption were impaired up to 21.5 and 33.1% lower than controls, respectively. At 50 ppm, the changes were 17.6 and 15% lower than controls, respectively. Body weight gain was 8 and 16% lower than controls at 50 and 15,000 ppm, respectively. At the highest dose, relative and absolute uterine weights were significantly decreased at 4 weeks and absolute pituitary gland weight was significantly increased. After 3 months, altered cellular composition was seen in the thymic cortex in both controls and treated rats, due to the incidences observed, the authors concluded that there was no treatment-related effect. A NOAEL and LOAEL were not established (ECHA database).

Reproductive Toxicity

No reproductive toxicity studies are available.

In the three-month drinking water repeated-dose toxicity study in male and female Wistar rats, described above, no gross lesions or microscopic findings were detected in male or female reproductive organs, which included all genital tract organs (except oviducts) as well as pituitary and adrenal glands. Some reproductive and related organs (uterus, epididymides, seminal vesicles, prostate, pituitary gland and spleen) were not weighed in this study.

In the three-month drinking water repeated-dose toxicity study with female Wistar rats, described above, relative and absolute uterine weights were significantly decreased at 4 weeks and absolute pituitary gland weight was significantly increased at the highest dose tested. No effects on the estrous cycle were observed (ECHA database).

Developmental Toxicity

(1) Pregnant Sprague-Dawley rats (25/group) were administered 2-pyrrolidone via gavage at 0, 190, 600 or 1900 mg/kg in distilled water from days 6 to 15 of gestation. No mortalities or treatment-related clinical signs of toxicity were observed. Maternal effects included reduced body weight gain and food consumption in mid- and high-dose animals and reduced gravid

uterine weight at the highest dose. Developmental effects in high-dose pups included reduced fetal weight, malformations (acaudia, microcaudia, anal atresia, missing vertebrae and missing ribs), increased incidence of visceral anomalies as well as skeletal anomalies (reduced ossification of frontal bones, irregular ossification of supraoccipital bones, reduced pre-sacral vertebrae and ossification centers on the seventh cervical vertebra). The submitted robust summary notes that statistically significant differences in incidence of reduced ossification (of the interparietal bone, first lumbar vertebra, pubic bones, ischial bones) or absent ribs were observed at 190 and 600 mg/kg, but the submitters attributed these effects to intergroup variation. The accuracy of this claim could not be verified due to limited information in the robust summary.
LOAEL (maternal toxicity) = 600 mg/kg-day (based on decreased body weights)
NOAEL (maternal toxicity) = 190 mg/kg-day
LOAEL (developmental toxicity) = 1900 mg/kg-day (based on increased incidence of malformations, visceral and skeletal anomalies and decreased fetal weights)
NOAEL (developmental toxicity) = 600 mg/kg-day

(2) Pregnant Sprague-Dawley rats (25/group) were administered 2-pyrrolidone via gavage at 1700 µL/kg (approximately 1875 mg/kg) in distilled water from days 6 to 15 of gestation. One death was observed on day 17 post-coitum, presumably in a dosed dam (although this is not clear in the summary of this study). There were no data on maternal body weight gain and therefore, maternal toxicity could not be fully evaluated. No treatment-related maternal effects were observed in the mean number of implantations, percentage of resorptions or following macroscopic examination. No treatment-related fetal effects were observed for mean weight and length of fetuses, mean placental weight, percentage of malformed live fetuses or skeletal malformations.
NOAEL (developmental toxicity) ~ 1875 mg/kg-day (based on no effects at the highest dose tested)

(3) Pregnant female NMRI mice (12/dose; 14/control) were administered 2-pyrrolidone (unknown purity) at 0, 1279 and 3199 mg/kg-day via gavage from gestation days 11 through 15. Implantation and fetal resorption sites were recorded and the number of live and dead fetuses and body length, weight and sex were determined. Fetuses were examined macroscopically for any malformations. At 3199 mg/kg-day, the mean weight and length of fetuses were somewhat lower than 'comparative values' (without further elaboration other than noting only 2 runts were seen at the highest dose). A total of 4 malformations were seen at 3199 mg/kg-day (3 in a single fetus, with 2 dams effected), which matched the number of malformations in the control group (again, with 3 seen in a single fetus, with two dams affected). At 1279 mg/kg-day, mean litter size (along with mean number of implantations) were decreased but the effect was considered not to be treatment-related due to the timing (i.e., nidation takes place on the gestation day 5-6). The malformation rate at 1279 mg/kg-day was somewhat increased vs. controls; 4 of 6 malformations at this dose were cleft palates. The slightly increased incidence of malformations was considered in the 'range of physiological fluctuations' (ECHA database).
NOAEL (maternal toxicity) = 3199 mg/kg-day (highest dose tested)
NOAEL (developmental toxicity) = 3199 mg/kg-day (highest dose tested)

Genetic Toxicity – Gene Mutations

In vitro

Salmonella typhimurium strains TA1535, TA1538, TA100, TA1537 and TA98 were exposed to 2-pyrrolidone (99.9% purity) in distilled water up to 150 µL/plate with and without metabolic activation. The positive control produced appropriate responses. The cytotoxic concentration was 150 µL/plate. 2-Pyrrolidone did not exhibit genetic activity with or without metabolic activation.

2-Pyrrolidone was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

(1) Human lymphocytes were exposed to 2-pyrrolidone (99.9% purity) in distilled water at 1250, 2500 or 3500 µg/mL without metabolic activation or 2500, 5000 or 6000 µg/mL with metabolic activation. Positive and negative controls produced appropriate responses. High doses were considered minimally cytotoxic.

2-Pyrrolidone did not induce chromosomal aberrations in this assay.

(2) *Saccharomyces cerevisiae* strain D61.M was exposed to 2-pyrrolidone up to 445.0 mM without metabolic activation. Negative controls produced appropriate responses. Information on the use and response of positive controls was not provided. The cytotoxic concentration was 321 mM. The frequency of aneuploidy increased with dose.

2-Pyrrolidone induced aneuploidy in this assay.

In vivo

NMRI mice (5/sex/dose) were administered 2-pyrrolidone (>99.5% purity) in distilled water via intraperitoneal injection at 500, 1000 or 2000 mg/kg and were sacrificed at 24 hours post-administration (and at 16 and 48 hours at 2000 mg/kg) and bone marrow was collected for analysis. Negative and positive controls produced appropriate responses. Clinical signs of toxicity included irregular respiration, piloerection, abdominal position, apathy and squatting posture. The ratio of polychromatic to normochromatic erythrocytes containing micronuclei did not differ from negative controls or in the various dose groups at any sacrifice interval.

2-Pyrrolidone did not induce micronuclei in mice in this assay.

Additional Information

Skin Irritation

(1) Six male Vienna white rabbits were administered 0.5 mL undiluted 2-pyrrolidone (crude) for 24 hours under occlusive cover to intact and ‘scarified’ skin and observed for 8 days. Skin reddening and edema were seen on both intact and scarified skin and were both more severe on the scarified skin. Necrosis was seen in one rabbit. The overall primary irritation value was 2.5 (between mild (2) and severe (3) values) (TSCATS OTS0522884; additional details from ECHA

database). There were several deviations from OECD test guidelines, including use of a 24 hour exposure period.
2-Pyrrolidone was irritating to rabbit skin.

(2) Three New Zealand white rabbits were exposed to 0.5 g of the undiluted test substance under semiocclusive conditions on the shaved dorsal area for 4 hours and observed up to 72 hours. The test site was washed after exposure. One rabbit exhibited slight erythema, which resolved after 24 hours. No corrosion was observed (ECHA database).
2-Pyrrolidone was not irritating to rabbit skin.

Eye Irritation

Vienna white rabbits (1 male; 5 females) were administered 0.1 mL undiluted 2-pyrrolidone (crude) in the eye and observed for 15 days. Effects were seen in the cornea, iris and conjunctivae and were severe in some rabbits. By day 15, not all effects were reversed and severe effects were still seen in one rabbit. The overall primary irritation value was 42 (TSCATS OTS0522884).
2-Pyrrolidone was irritating to rabbit eyes.

(2) Two Vienna white rabbits were administered 0.05 mL of the undiluted test substance to the conjunctival sac of one eye and not washed; the eyes were observed up to 8 days after instillation. At 24-72 hours, the mean corneal opacity score was 2 (out of 2 as a maximum score). The iris score for the same time period was zero. The mean conjunctivae score for redness was 1 (out of 2 as a maximum) but no conjunctival swelling occurred. Complete reversal was seen by day 7 (ECHA database).
2-Pyrrolidone was irritating to rabbit eyes.

Conclusion: The acute oral and dermal toxicity of 2-pyrrolidone in rats and rabbits, respectively, is low. In a three-month repeated-dose toxicity study, male rats given 2-pyrrolidone via drinking water exhibited increased urinary specific gravity, reduced urinary volume and increased mean relative kidney weights at $\geq$ 529 mg/kg-bw/day, with a NOAEL of 184 mg/kg-bw/day. Females exhibited histopathological changes in thymocytes at all doses, with a LOAEL of ~ 42 mg/kg-bw/day. In another three-month repeated-dose study, female rats administered 2-pyrrolidone via drinking water exhibited decreased body weight gains of 16% at 1339 mg/kg-bw/day and 8% at 5 mg/kg-bw/day. No specific reproductive toxicity studies are available for 2-pyrrolidone. However, in the three-month drinking water study with female rats only, decreased relative and absolute uterine weights and increased absolute pituitary weights were observed. No histopathological changes in the reproductive organs were observed in the other three month drinking water study in either sex. In an oral gavage prenatal developmental toxicity study in rats, dams exhibited decreased body weights at $\geq$ 600 mg/kg-day (with decreased gravid uterine weights at 1900 mg/kg-day); the NOAEL for maternal toxicity is 190 mg/kg-day. In this study, fetuses exhibited increased incidences of malformations, visceral and skeletal anomalies and decreased fetal weights at 1900 mg/kg-day, resulting in a developmental NOAEL of 600 mg/kg-day. In another prenatal oral gavage developmental toxicity study in rats, the developmental NOAEL was 1875 mg/kg-day (only dose tested); data were inadequate to establish a maternal

NOAEL. 2-Pyrrolidone induced gene mutations in yeast *in vitro*, but did not induce gene mutations in bacteria *in vitro* or chromosomal aberrations in mammalian cells *in vitro*. 2-Pyrrolidone did not induce micronuclei in mice *in vivo*. 2-Pyrrolidone is irritating to rabbit skin and eyes.

Table 3. Summary Table of the Screening Information Data Set under the U.S. HPV Challenge Program – Human Health Data

Endpoint	2-Pyrrolidone (616-45-5)
Acute Oral Toxicity LD_{50} (mg/kg)	**> 5000**
Acute Dermal Toxicity LD_{50} (mg/kg)	**> 2000**
Repeated-Dose Toxicity Oral (mg/kg-bw/day)	**(rat; 3-m)** **$NOAEL_{males}$ ~ 184** **$LOAEL_{males}$ ~ 529** **$NOAEL_{females}$ = Not Established** **$LOAEL_{females}$ ~ 42**
Reproductive Toxicity Oral	In the 3-month repeated-dose toxicity study in female rats, decreased absolute uterine weight and increased pituitary weights were observed. No histopathological changes in male and female reproductive organs were observed in the other 3-month study.
Developmental Toxicity Oral (mg/kg-day)	
Maternal	**NOAEL = 190** **LOAEL = 600**
Developmental	**NOAEL = 600** **LOAEL = 1900**
Genetic Toxicity – Gene Mutations *In vitro*	**Negative**
Genetic Toxicity – Chromosomal Aberrations	
In vitro	**Positive** **[Aneuploidy in yeast]**
In vivo	**Negative**
Additional Information	
Skin Irritation	**Irritating**
Eye Irritation	**Irritating**

Measured data in bold

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4.

Acute Toxicity to Fish

Zebra fish (*Brachydanio rerio*) were exposed to 2-pyrrolidone (purity 99.7%) at nominal concentrations of 0, 50, 100, 1000, 2150, 4640 or 10,000 mg/L under static conditions for 96 hours. Measured concentrations were 0, 38, 98, 947, 2084, 4600 and 9935 mg/L at 96 hours. At 10,000 mg/L, 100% mortality was observed at 96 hours. Clinical signs included apathy and tumbling.
96-h LC_{50} = 6783 mg/L

Acute Toxicity to Aquatic Invertebrates

(1) *Daphnia magna* were exposed to 2-pyrrolidone (purity > 99.5%) at nominal concentrations of 0, 31.25, 62.5, 125, 250 or 500 mg/L under static conditions for 48 hours. Measured concentrations were not provided. No daphnids were found immobilized by treatment and no adverse effects were noted at any concentration.
48-h EC_{50} > 500 mg/L

(2) *Daphnia magna* were exposed to 2-pyrrolidone at nominal concentrations of 10, 100 or 1000 mg/L under static conditions for 96 hours. Daphnia were observed for 21 days. Measured concentrations were not provided. No mortality occurred in the first 96 hours of exposure in any group. At the end of the 3-week exposure period the numbers of surviving daphnids were 17/20, 18/20 and 12/20 for the 10, 100 and 1000 mg/L groups, respectively.
96-h EC_{50} > 1000 mg/L

(3) *Daphnia pulex* were exposed to 2-pyrrolidone (purity ≥ 97%) at unspecified concentrations under static conditions for 48 hours. Measured concentrations were not provided. The mean effective concentration was taken from three valid tests.
48-h EC_{50} = 13.21 mg/L

Toxicity to Aquatic Plants

Green algae (*Desmodesmus subspicatus*) were exposed to 2-pyrrolidone (purity > 99.5%) at nominal concentrations of 0, 25, 50, 100, 250 or 500 mg/L for 96 hours. Measured concentrations were not provided.
96-h EC_{50} (biomass) = 84 mg/L
96-h EC_{50} (growth rate) = 353 mg/L

Conclusion: For 2-pyrrolidone, the 96-h LC_{50} for fish is 580 mg/L, the 48-h EC_{50} for aquatic invertebrates is 13.21 mg/L. For the toxicity to aquatic plants, the 96-h EC_{50} values are 84 mg/L for biomass and 353 mg/L for growth rate.

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data

Endpoint	2-Pyrrolidone (616-45-5)
Fish 96-h LC_{50} (mg/L)	**6783**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**13.21**
Aquatic Plants 96-h EC_{50} (mg/L)	
(Growth rate)	**353**
(Biomass)	**84**

Bold = measured data (i.e., derived from testing)