SCREENING-LEVEL HAZARD CHARACTERIZATION
Pyridine and Pyridine Derivatives Category

SUB-CATEGORY I

Pyridine (CASRN 110-86-1)

2-Picoline (CASRN 109-06-8)

3-Picoline (CASRN 108-99-6)

4-Picoline (CASRN 108-89-4)

Pyridine, alkyl derivatives (CASRN 68391-11-7)

SUB-CATEGORY II

Nicotinonitrile (CASRN 100-54-9)

Picolinonitrile (CASRN 100-70-9)

SUB-CATEGORY III

Piperidine (CASRN 110-89-4)

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 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

[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.

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 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.

[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.

Chemical Abstract Service Registry Number (CASRN)	**Sub-Category I** **110-86-1** **109-06-8** **108-99-6** **108-89-4** **68391-11-7** **Sub-Category II** **100-54-9** **100-70-9** **Sub-Category III** **110-89-4**
Chemical Abstract Index Name	**Sub-Category I** **Pyridine** **Pyridine, 2-methyl-** **Pyridine, 3-methyl-** **Pyridine, 4-methyl-** **Pyridine, alkyl derivs.** **Sub-Category II** **3-Pyridinecarbonitrile** **2-Pyridinecarbonitrile** **Sub-Category III** **Piperidine**
Structural Formula	See Section 1

Sub-Category I:
CASRNs 110-86-1, 109-06-8, 108-99-6, 108-89-4 and 68391-11-7 are liquids with high water solubility and high vapor pressure. They are expected to have high mobility in soil. Volatilization is considered moderate based on their Henry's Law constants; however, these compounds will partially exist as cations in the environment which will attenuate the potential to volatilize. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow to negligible. The rate of biodegradation is considered rapid to moderate. These chemicals are expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute toxicity of sub-category I is low via the oral (rats), high via the dermal (rabbits) and moderate via the inhalation (rats) routes of exposure. The alkyl pyridines are corrosive to rabbit skin and severely irritating to rabbit eye. CASRN 110-86-1 is not a skin sensitizer in guinea pigs. Oral repeated-dose studies with CASRN 110-86-1 in rats showed systemic toxicity ranging from changes in body weights to histopathological changes in the liver at 33 mg/kg-bw/day; the NOAEL was 14 mg/kg-bw/day. In mice, repeated oral exposures showed effects on body weight gain and liver at 200 mg/kg-bw/day; the NOAEL for systemic toxicity was 100 mg/kg-bw/day. Repeated inhalation exposures of male rats to CASRN 108-99-6 showed no effects at the highest concentration tested; the NOAEC for systemic toxicity was 1.10 mg/L. Repeated inhalation exposures of rats to CASRN 109-06-8 showed no effects at the highest concentration tested; the NOAEC for systemic toxicity was 0.38 mg/L. Effects were observed on body weights and liver; the NOAEC for systemic toxicity was not established. No specific reproductive toxicity studies were available but effects on the male reproductive system were observed after repeated oral exposures to CASRN 110-86-1 in mice and rats. No developmental toxicity studies were available. Sub-category I did not induce gene mutations *in vitro*. CASRN 110-86-1 did not induce chromosomal aberrations *in vitro* or *in vivo*. In two-year bioassays in rats and mice exposed via drinking water, CASRN 110-86-1 increased the incidence of tumors.

The acute hazard to fish is based on the toxicity values for CASRNs 108-89-4, 108-99-6, 109-06-8, 110-86-1 and 68391-11-7 ranging from 40 to 897 mg/L. The acute hazard to aquatic invertebrates is based on the toxicity values for CASRNs 108-99-6, 110-86-1 and 68391-11-7 ranging from 69 to 2470 mg/L. The acute hazard to aquatic plants is based on the toxicity value for CASRN 108-99-6 of 320 mg/L.

The reproductive and developmental toxicity endpoints remain as data gaps under the HPV Challenge Program.

Sub-Category II:
CASRNs 100-54-9 and 100-70-9 are solids at ambient temperature with high water solubility and moderate vapor pressure. They are expected to have high mobility in soil. Volatilization is considered moderate based on their Henry's Law constants. The rates of hydrolysis and atmospheric photooxidation are considered negligible. The rate of biodegradation is considered rapid to moderate and they are expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute toxicity of sub-category II is low via the oral (rats) and dermal (rabbits) routes of exposure. Repeated oral exposures with CASRN 100-54-9 in rats showed histopathological changes in the liver at 30 mg/kg-bw/day; the NOAEL for systemic toxicity was 5 mg/kg-bw/day. At higher doses, there was necrosis of spermatocytes and spermatids. No specific reproductive toxicity studies were available but effects on the male reproductive system were observed after repeated oral exposures to CASRN 100-54-9 in rats. No developmental toxicity studies were available. CASRN 100-54-9 did not induce gene mutations or chromosomal aberrations *in vitro*.

The acute hazard to fish is based on the toxicity value for CASRN 100-70-9 of 726 mg/L. The acute hazard to aquatic invertebrates is based on the estimated toxicity values for CASRNs 100-54-9 and 100-70-9 of 1000 mg/L. The acute hazard to aquatic plants is based on the estimated toxicity values for CASRNs 100-54-9 and 100-70-9 of 232 mg/L.
The reproductive and developmental toxicity, and the acute toxicity to aquatic invertebrates and aquatic plants endpoints remain as data gaps under the HPV Challenge Program.

Sub-Category III:
CASRN 110-89-4 is a colorless liquid with high water solubility and high vapor pressure. It is expected to have moderate mobility in soil. Volatilization of CASRN 110-89-4 is considered moderate based on its Henry's Law constant; however, it is a weak base that is expected to exist as a cation in water and cations do not volatilize. The rate of hydrolysis is considered negligible.

The rate of atmospheric photooxidation is considered moderate. CASRN 110-89-4 was found to be readily biodegradable and is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute oral toxicity of CASRN 110-89-4 is moderate in rats and low in mice. Acute dermal toxicity in rabbits and inhalation toxicity in rats is moderate. CASRN 110-89-4 is corrosive to rabbit skin, severely irritating to rabbit eye and a skin sensitizer in guinea pigs. After repeated inhalation exposures, no adverse effects were observed in rats at the highest dose tested; the NOAEC for systemic toxicity was 0.348 mg/L. No data were available for the reproductive toxicity endpoint. In a prenatal developmental toxicity study in rats via the inhalation route, dams showed decreased weight gains at 0.015 mg/L; the NOAEC for maternal toxicity was 0.003 mg/L. Fetal body weights were decreased at 0.003 mg/L. The NOAEC for developmental toxicity was not established. CASRN 110-89-4 did not induce gene mutations *in vitro* and did not induce micronuclei *in vivo*. No data were available for the chromosomal aberrations endpoint. In a two-year bioassay in rats exposed via drinking water, CASRN 110-89-4 did not increase the incidence tumors.

The acute hazard to fish is based on the estimated toxicity value for CASRN 110-89-4 of 46 mg/L. The acute hazard to aquatic invertebrates is based on the estimated toxicity value for CASRN 110-89-4 of 4 mg/L. The acute hazard to aquatic plants is based on the estimated toxicity values for CASRN 110-89-4 of 1.2 mg/L.

The reproductive toxicity and the acute toxicity to fish, aquatic invertebrates and aquatic plants endpoints remain as data gaps under the HPV Challenge Program.

The sponsor, the American Chemistry Council's Pyridine and Pyridine Derivatives High Production Volume Work Group, submitted a Test Plan and Robust Summaries to EPA for the Pyridine and Pyridine Derivatives category on December 17, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on January 28, 2004 (http://www.epa.gov/chemrtk/pubs/summaries/pyriderv/c14925tc.htm). EPA comments on the original submission were posted to the website on July 15, 2004. Public comments were also received and posted to the website. The pyridine and pyridine derivatives category consists of eight substances described in Section 1.

Category Justification

The pyridine and pyridine derivatives category was submitted comprising nine chemicals that are structurally-related derivatives of pyridine: piperidine is the saturated ring structure derivative of pyridine. The sponsor grouped the chemicals into one category based on similarities in structure and functional features and similar or predictable physical-chemical, environmental fate, ecotoxicity and mammalian toxicities. Two of the sponsored substances are mixtures; pyridine, alkyl derivatives (CASRN 68391-11-7) and pyridinium, 1-(phenylmethyl)-ethyl methyl derivatives, chlorides (CASRN 68909-18-2) for which the sponsor did not provide the composition.

EPA did not support the category formation as submitted because of significant differences in the chemical structures, in the metabolism of some of the category members and a lack of evidence of their similar mammalian toxicities. In addition, it was questionable whether data for the alkylpyridines could be read across to the alkylpyridine derivatives or pyridinium chlorides because composition for these mixtures is unknown. The sponsor did not provide a category justification for the ecotoxicity endpoints; however, EPA concluded that the observed differences in structures are also likely to lead to differences in ecological toxicity. In its letter (to Charlie Auer), dated November 15, 2006, the sponsor withdrew the sponsorship for pyridinium, 1(phenylmethyl)- Et Me derivs., chlorides (CASRN 68909-18-2). For the remaining category members, EPA proposed grouping of the chemicals into the following sub-categories:

Sub-category I: pyridine (CASRN 110-86-1), 2-picoline (CASRN 109-06-8), 3-picoline (CASRN 108-99-6), 4-picoline (CASRN 108-89-4) and pyridine, alkyl derivatives (CASRN 68391-11-7);

Sub-category II: nicotinonitrile (CASRN 100-54-9) and picolinonitrile (CASRN 100-70-9); and

Sub-category III: Piperidine (CASRN 110-89-4)

The Sponsor agreed with EPA's suggested sub-categories and EPA agrees that the sub-categories of the pyridine and pyridine derivatives category are acceptable but read-across between the sub-categories is not supported.

1 Chemical Identity

1.1 Identification and Purity

The following description is taken from the Test Plan (2003):

Pyridine and pyridine derivatives are industrial solvents and chemical intermediates. CASRN 68391-11-7 is a TSCA unknown of variable composition or of biological origin (UVCB) chemical which has an unspecified molecular formula and weight. The chemical structures are presented in Table 1.

Table 1. Chemical Structures of Pyridine and Pyridine Derivatives

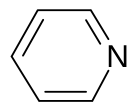
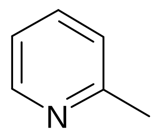
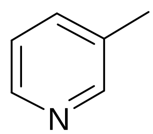
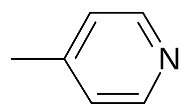
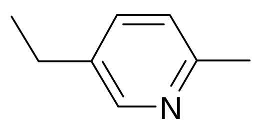
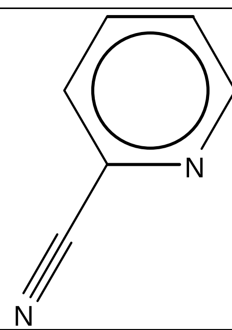
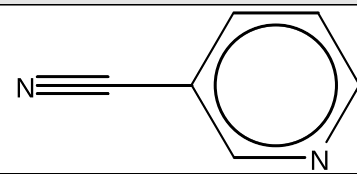
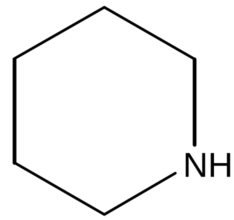
Chemical Name	CASRN	Structure
Pyridine	110-86-1	
2-Picoline	109-06-8	
3-Picoline	108-99-6	
4-Picoline	108-89-4	
Pyridine, alkyl derivatives	68391-11-7	Representative structure: 
Picolinonitrile	100-70-9	

Table 1. Chemical Structures of Pyridine and Pyridine Derivatives		
Chemical Name	**CASRN**	**Structure**
Nicotinonitrile	100-54-9	
Piperidine	110-89-4	

1.2 Physical-Chemical Properties

Sub-Category I
The physical-chemical properties of the pyridine and alkylpyridines sub-category are summarized in Table 2. The pyridine and alkylpyridines sub-category primarily contains liquids with high water solubility and high vapor pressure.

Sub-Category II
The physical-chemical properties of picolinonitrile and nicotinonitrile are summarized in Table 3. Picolinonitrile and nicotinonitrile are solids at ambient temperature with high water solubility and moderate vapor pressure.

Sub-Category III
The physical-chemical properties of piperidine are summarized in Table 4. Piperidine is a colorless liquid with high water solubility and high vapor pressure.

Table 2. Physical-Chemical Properties Sub-Category I[1]

Property	Pyridine	2-Picoline	3-Picoline	4-Picoline	Pyridine, alkyl derivs.
CASRN	110-86-1	109-06-8	108-99-6	108-89-4	68391-11-7
Molecular Weight	79	93	93	93	UVCB[2]
Physical State	Liquid	Liquid	Liquid	Liquid	No data[2]
Melting Point	**-41.6°C (measured)**	**-70 to -66.8°C (measured)**	**-18.3°C (measured)**	**3.66°C (measured)**	No data[2]
Boiling Point	**115.2°C (measured)**	**128–129°C (measured)**	**143–144°C (measured)**	**144.9–145°C (measured)**	No data[2]
Vapor Pressure	**20 mm Hg at 25°C (measured)**	**10–12.6 mm Hg at 25°C (measured)**	5.32 mm Hg at 25°C (estimated); **6.05 mm Hg at 25°C (measured)[3]**	**7.99 mm Hg at 25°C (measured)**	No data[2]
Water Solubility	**1×10^6 mg/L, miscible (measured)**	**1×10^6 mg/L, freely soluble, very soluble, miscible (measured)**	**1×10^6 mg/L, miscible (measured)**	**1×10^6 mg/L, soluble, infinite solubility, miscible (measured)**	No data[2]
Dissociation Constant (pK_a)	**5.23 (measured)[3]**	**6.00 (measured)[3]**	**5.63 at 25°C (measured)**	**5.98 at 25°C (measured)**	No data[2]
Henry's Law Constant	**1.1×10^{-5} atm-m^3/mole (measured)**	**9.96×10^{-6} atm-m^3/mole (measured)**	**7.73×10^{-6} atm-m^3/mole (measured)**	**6.0×10^{-6} atm-m^3/mole (measured)**	No data[2]
Log K_{ow}	**0.64 (measured)**	**1.11 (measured)**	1.35 (estimated); **1.20 (measured)[3]**	**1.22 (measured)**	No data[2]

[1]The American Chemistry Council's Pyridine and Pyridine Derivatives HPV Work Group. December 19, 2003. Revised Robust Summary for the Pyridine and Pyridine Derivatives Category. http://www.epa.gov/chemrtk/pubs/summaries/pyriderv/c14925tc.htm.
[2]UVCB chemicals, which are TSCA Unknown, of Variable Composition, or of Biological Origin, have unspecified molecular formulas and molecular weights. According to the Robust Summary, properties are not calculable for UVCB chemicals.
[3]HSDB. 2008. Hazardous Substances Data Bank. Accessed December 17, 2008. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

Table 3. Physical-Chemical Properties of Sub-Category II[1]		
Property	**Picolinonitrile**	**Nicotinonitrile**
CASRN	100-70-9	100-54-9
Molecular Weight	104	104
Physical State	Solid at ambient temperature	Solid at ambient temperature
Melting Point	**29°C (measured)**	**50°C (measured)**
Boiling Point	**222°C (measured)**	**240°C (measured)**
Vapor Pressure	0.102 mm Hg at 25°C (estimated)	0.0262 mm Hg at 25°C (estimated); **0.296 mm Hg at 25°C (measured)[2]**
Water Solubility	35,710 mg/L at 25°C (estimated)	27,920 mg/L at 25°C (estimated); **1.35×10^5 mg/L at 20°C (measured)[2]**
Dissociation Constant (pK_a)	**-0.26 (measured)[2]**	**1.39 (measured)[2]**
Henry's Law Constant	6.8×10^{-8}atm-m^3/mole (estimated); 3.4×10^{-7}atm-m^3/mole (estimated)[3]	**2.7×10^{-7} atm-m^3/mole (measured)[2]**
Log K_{ow}	0.35 (estimated); **0.45 (measured)[2]**	0.35 (estimated); **0.36 (measured)[2]**

[1]The American Chemistry Council's Pyridine and Pyridine Derivatives HPV Work Group. December 19, 2003. Robust Summary and Test Plan for Pyridine and Pyridine Derivatives. http://www.epa.gov/chemrtk/pubs/summaries/pyriderv/c14925tc.htm.
[2]SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available from http://www.syrres.com/esc/physprop.htm as of December 2008.
[3]USEPA. 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.

Table 4. Physical-Chemical Properties of Sub-Category III[1]	
Property	**Piperidine**
CASRN	110-89-4
Molecular Weight	85.2
Physical State	Colorless liquid
Melting Point	**-11.03°C (measured)**
Boiling Point	**106.3°C (measured)**
Vapor Pressure	**32.1 mm Hg at 25°C (measured)**
Water Solubility	**1×10^6 mg/L at 20°C (measured)**
Dissociation Constant (pK_a)	**11.28 (measured)[2]**
Henry's Law Constant	**4.4×10^{-6} atm-m^3/mole (measured)[2]**
Log K_{ow}	**0.84 (measured)**

[1]The American Chemistry Council's Pyridine and Pyridine Derivatives HPV Work Group. December 19, 2003. Robust Summary and Test Plan for Pyridine and Pyridine Derivatives. http://www.epa.gov/chemrtk/pubs/summaries/pyriderv/c14925tc.htm.
[2]SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available from http://www.syrres.com/esc/physprop.htm as of October 15, 2008.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

The Pyridine and Pyridine Derivatives Category chemicals had an aggregated production and/or import volume in the United States of 35 million to 200 million pounds during the calendar year 2005.

- CASRN 100-54-9 1 to 10 million pounds
- CASRN 100-70-9 1 to 10 million pounds
- CASRN 108-89-4 1 to 10 million pounds
- CASRN 108-99-6 10 to 50 million pounds
- CASRN 109-06-8 10 to 50 million pounds
- CASRN 110-86-1 10 to 50 million pounds
- CASRN 110-89-4 1 to 10 million pounds
- CASRN 68391-11-7 1 to 10 million pounds

Non-confidential information in the IUR indicated that the industrial processing and uses of these chemicals include intermediates and corrosion inhibitors and anti-scaling agents. Non-confidential information in the IUR indicated that the commercial and consumer products containing the chemical under CASRN 68391-11-7 include "other." IUR information also indicates there were no commercial/consumer uses for other chemicals in the category. The HPV submission for this category states that the chemicals are used as industrial solvents and chemical intermediates in the production of drugs and vitamins, as well as industrial products such as paints, dyes, rubber products and adhesives. In addition, the HSDB states that CASRN 110-86-1 and 110-89-4 are used in food flavorings.

2.2 Environmental Exposure and Fate

There is potential for environmental releases of these chemicals to various media including water, land and air.

Sub-Category I

The environmental fate properties are provided in Table 5. The pyridine and alkylpyridines category contains liquids with high water solubility and high vapor pressure. The pyridine and alkylpyridines are expected to have high mobility in soil. Volatilization of the pyridine and alkylpyridines is considered moderate based on their Henry's Law constants; however, these compounds will partially exist as cations in the environment which will attenuate the potential to volatilize. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered slow to negligible. The rate of biodegradation is considered rapid to moderate. Pyridine and alkylpyridines are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 5. Environmental Fate Characteristics of Sub-Category I[1]

Property	Pyridine	2-Picoline	3-Picoline	4-Picoline	Pyridine, alkyl derivs.
CASRN	110-86-1	109-06-8	108-99-6	108-89-4	68391-11-7
Photodegradation Half-life	28.9 days (estimated)	9.707 days (estimated)	9.707 days (estimated)	9.707 days (estimated)	No data[2]
Hydrolysis Half-life	Stable (estimated)	Stable (estimated)	Stable (estimated)	Stable (estimated)	Stable (estimated)
Biodegradation	11-15% after 14 days 58-97% after 28 days 0% after 19 days 100% after 21 days 98% after 13 days 100% after 8 days at 20 mg/L in river water 92-100% in 28 days (readily biodegradable)[3]	100% after 9 days with benzoate 100% after 13 days with glucose 94% after 7 days 56- 100% in 24 days by soil suspension. 1-2% in 28 days (not readily biodegradable)[3]	85% after 29 days 95% after 10 days 45% after 30 days by soil suspension 100% after 14 days by river water 100% after 9 days with benzoate 100% after 48 days with glucose 3-12% in 28 days (not readily biodegradable)[3]	68-100% in 24 days by soil suspension 90% after 14 days in river water 100% in 66–170 days by soil suspension 30% in 7 days at 20 mg/L 100% in 32 days by soil suspension	No data[2]
Bioconcentration	BCF = 3 (estimated)[4]	BCF = 1 (estimated)[4]	BCF = 2 (estimated)[4]	BCF = 2 (estimated)[4]	No data[2]
Log K_{oc}	1.5 (estimated)[4]	1.7 (estimated)[4]	1.7 (estimated)[4]	1.7 (estimated)[4]	No data[2]
Fugacity (Level III Model)[4] Air Water Soil Sediment	 9.52% 42.9% 47.5% 0.0818%	 5.5% 46.3% 48.1% 0.1%	 5.12% 45.1% 49.7% 0.1%	 4.87% 44.8% 50.2% 0.1%	No data[2]
Persistence[5]	P1 (low)	P1 (low)	P1 (low)	P1 (low)	No data
Bioaccumulation[5]	B1 (low)	B1 (low)	B1 (low)	B1 (low)	No data

[1]The American Chemistry Council's Pyridine and Pyridine Derivatives HPV Work Group. December 19, 2003. Revised Robust Summary for the Pyridine and Pyridine Derivatives Category. http://www.epa.gov/chemrtk/pubs/summaries/pyriderv/c14925tc.htm.
[2]UVCB chemicals, which are TSCA Unknown, of Variable Composition, or of Biological Origin, have unspecified molecular formulas and molecular weights. According to the Robust Summary, properties are not calculable for UVCB chemicals.
[3]National 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.
[4]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.
[5]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Sub-Category II

The environmental fate properties are provided in Table 6. CASRN 100-54-9 and CASRN 100-70-9 are solids at ambient temperature with high water solubility and moderate vapor pressure. Both compounds are expected to have high mobility in soil. Volatilization is considered moderate based on their Henry's Law constants. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered negligible. The rate of biodegradation is considered rapid to moderate. CASRN 100-54-9 and CASRN 100-70-9 are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 6. Environmental Fate Characteristics of Sub-Category II[1]

Property	Picolinonitrile	Nicotinonitrile
CASRN	100-70-9	100-54-9
Photodegradation Half-life	164 days (estimated)	164 days (estimated)
Hydrolysis Half-life	Stable[2]	Stable[2]
Biodegradation	20–61% after 7 days under aerobic conditions; Half-life = <1 days under anaerobic conditions	Half-life = <1 days under anaerobic conditions; 91–97% after 7 days under aerobic conditions; 1% after 28 days (not readily biodegradable)[3]
Bioconcentration	BCF = 3.2 (estimated)[4]	BCF = 3.2 (estimated)[4]
Log K_{oc}	1.99 (estimated)[4]	1.99 (estimated)[4]
Fugacity (Level III Model)	Air = 3% Water = 34% Soil = 63% Sediment = <0.1%	Air = 11% Water = 33% Soil = 56% Sediment = <0.1%
Persistence[5]	P1 (low)	P1 (low)
Bioaccumulation[5]	B1 (low)	B1 (low)

[1]The American Chemistry Council's Pyridine and Pyridine Derivatives HPV Work Group. December 19, 2003. Robust Summary and Test Plan for Pyridine and Pyridine Derivatives. http://www.epa.gov/chemrtk/pubs/summaries/pyriderv/c14925tc.htm.
[2]HSDB. 2008. Hazardous Substances Data Bank. Accessed December 10, 2008. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.
[3]National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.
[4]USEPA. 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.
[5]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Sub-Category III

The environmental fate properties are provided in Table 7. CASRN110-89-4 is expected to have moderate mobility in soil. CASRN110-89-4 was readily biodegradable using a modified MITI biodegradation test (OECD 301C). Volatilization of CASRN110-89-4 is considered moderate based on its Henry's Law constant; however, it is a weak base that is expected to exist as a cation in water and cations do not volatilize. The rate of hydrolysis is considered negligible under environmental conditions. CASRN110-89-4 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 7. Environmental Fate Characteristics of Sub-Category III[1]	
Property	**Piperidine**
Photodegradation Half-life	0.12 days (estimated)
Hydrolysis Half-life	Stable
Biodegradation	67% after 14 days (readily biodegradable)[2]
Bioconcentration	BCF = 3.2 (estimated)[3]
Log K_{oc}	1.97 (estimated)[3]
Fugacity (Level III Model)	Air = 70% Water = 16% Soil = 14% Sediment = <0.1%
Persistence[4]	P1 (low)
Bioaccumulation[4]	B1 (low)

[1]The American Chemistry Council's Pyridine and Pyridine Derivatives HPV Work Group. December 19, 2003. Robust Summary and Test Plan for Pyridine and Pyridine Derivatives. http://www.epa.gov/chemrtk/pubs/summaries/pyriderv/c14925tc.htm.
[2]National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.
[3]USEPA. 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]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

A summary of health effects data submitted for SIDS endpoints is provided in Table 8. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

Sub-Category I
Pyridine (CASRN 110-86-1)
(1) Male albino rats (5/dose) were administered undiluted pyridine by the oral route at 464, 681, 1000 or 1470 mg/kg-bw and observed for 14 days. No mortality was observed at the lowest dose. Two rats died at each mid-dose in the first seven days post exposure and all rats died within two days at the highest dose. (http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384)
LD_{50} = 891 mg/kg-bw

(2) In studies with rats and mice, the LD_{50} was determined (no other information available). (http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384)
LD_{50} = 800-1600 mg/kg-bw
4-Picoline (CASRN 108-89-4)

In two studies, Sprague-Dawley rats (4 females/dose in one study and 2-3/sex/dose in the other) were administered 4-picoline via gavage at doses from 125 to 2000 mg/kg-bw and observed for up to 14 days. Mortality was observed at all doses > 500 mg/kg-bw.
LD_{50} = 700 – 841 mg/kg-bw

3-Picoline (CASRN 108-99-6)
(1) Sprague-Dawley rats (2-3/sex/dose) were administered 3-picoline via gavage at 501, 631, 794 or 1000 mg/kg-bw and observed for seven days. Mortality was observed at all doses within four days of dosing.
LD_{50} = 710 mg/kg-bw

(2) Fischer rats (3 males/dose) were administered 3-picoline via gavage at 320, 630, 1300, 2000, 3200 or 5000 mg/kg-bw and observed for 14 days. No rats died at 320 mg/kg-bw and one rat died at 630 mg/kg-bw. All rats died at doses greater than 630 mg/kg-bw.
LD_{50} = 630 mg/kg-bw

2-Picoline (CASRN 109-06-8)
In two studies, Sprague-Dawley rats (10 males/dose in one study and 2-3/sex/dose in the other) were administered 2-picoline via gavage at doses from 550 to 1260 mg/kg-bw and observed daily for up to 28 days. Mortality was observed at doses greater than 790 mg/kg-bw.
LD_{50} = 810 to > 950 mg/kg-bw

Pyridine, alkyl derivs (CASRN 68391-11-7)
Sherman-Wistar rats (5 males/dose) were administered pyridine, alkyl derivatives via gavage at 1000, 2000, 4000, 8000 or 16,000 mg/kg-bw and observed for 14 days. At 4000 mg/kg-bw and above, all rats died; in most cases less than five to six hours post dosing.

LD_{50} = 2500 mg/kg-bw

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)
(1) Sherman-Wistar rats (5 males/dose) were administered nicotinonitrile via gavage at 250, 500, 1000, 2000 or 4000 mg/kg-bw and observed for 14 days. All rats at the two high doses died within 3 hours of exposure. Mortality was also observed at the 1000 mg/kg-bw. No rats died at the two lower doses.

LD_{50} = 1100 mg/kg-bw

(2) Sprague-Dawley rats (5/sex/dose) were administered nicotinonitrile via gavage at 0, 1297, 1388, 1485, 1589 or 1700 mg/kg-bw and observed for 14 days. In males, mortality was observed at all doses; no females dying at 1297 mg/kg-bw..
LD_{50} (males) = 633 mg/kg-bw
LD_{50} (females) = 1455 mg/kg-bw

Picolinonitrile (CASRN 100-70-9)

Sprague-Dawley rats (2-3/sex/dose) were administered picolinonitrile via gavage at 500 or 1000 mg/kg-bw as a 5% solution of test substance in corn oil. Two of 3 rats from the high dose died within three days of dosing. No mortality occurred at 500 mg/kg-bw. No other information provided.
LD_{50} = not calculated

Sub-Category III
Piperidine (CASRN 110-89-4)
(1) Sprague-Dawley rats (5/sex/dose) were administered piperidine via gavage at 300, 550 or 800 mg/kg-bw and observed for 14 days. Mortality was observed (7 of 10) at the highest dose.
LD_{50} = 740 mg/kg-bw

(2) Sprague-Dawley rats (5 females) were administered piperidine one at a time with the estimated LD_{50} dose in an up and down method and observed for 14 days.
LD_{50} = 337 mg/kg-bw

(3) Sprague-Dawley rats (10/sex/dose) were administered piperidine via gavage at 5, 50, 500 or 2000 mg/kg-bw using the fixed-dose procedure and up and down method and observed for 14 days (number of deaths not stated).
LD_{50} (males) = 405 mg/kg-bw
LD_{50} (females) = 488 mg/kg-bw

(4) ddY Mice (10/sex/dose) were administered piperidine (doses not specified) via gavage and observed for 14 days (number of deaths not stated).
LD_{50} (males) = 633 mg/kg-bw
LD_{50} (females) = 536 mg/kg-bw

Acute Dermal Toxicity

Sub-Category I
Pyridine (CASRN 110-86-1)
Albino rabbits (2/dose) were administered 500, 1000 or 2000 mg/kg-bw pyridine dermally on to the hair-clipped skin under occluded conditions for 24 hours. All animals in the high dose group died within a day post exposure. Severe chemical burn was seen topically at all doses.
1000 mg/kg-bw < LD_{50} < 2000 mg/kg-bw

4-Picoline (CASRN 108-89-4)
(1) New Zealand White rabbits (4 males/dose) were administered 4-picoline dermally (concentration not stated) on to the hair-clipped skin under occluded conditions for 24 hours and observed for 14 days.
LD_{50} ~ 257 mg/kg-bw

(2) In two similar studies, New Zealand White rabbits (1/sex/dose) were administered 4-picoline dermally on to hair-clipped skin at 50.1 (male), 79.4 (female), 126 (male), 200 (female), 501 (male), 1000 (female) or 2000 (male) mg/kg-bw under occluded conditions for 24 hours and

observed for 14 days. In both studies, rabbits at 316 mg/kg-bw and above died within one day. In one study, the animals also died at 126 and 200 mg/kg-bw.
79.4 mg/kg-bw < LD_{50} < 126 mg/kg-bw

3-Picoline (CASRN 108-99-6)
(1) New Zealand White rabbits (2/dose, sex not stated) were administered 3-picoline dermally at 200, 800 or 2000 mg/kg-bw for 24 hours and observed for 14 days. All animals at the highest dose died.
200 mg/kg-bw < LD_{50} < 800 mg/kg-bw

(2) New Zealand White rabbits (1/sex/dose) were administered 3-picoline dermally on to hair-clipped skin at 79.4 (male), 126 (female), 200 (male), 316 (female), 501 (male), 1000 (female) or 2000 (male) mg/kg-bw under occluded conditions for 24 hours and observed for 14 days. Rabbits at 501 mg/kg-bw and above died. Mortality was also seen at 200 mg/kg-bw.
126 mg/kg-bw < LD_{50} < 200 mg/kg-bw

(3) New Zealand White rabbits (5/sex/dose) were administered 3-picoline dermally on to hair-clipped skin at 200 and 1000 mg/kg-bw under occluded conditions for 24 hours and observed for 14 days. All animals at the higher dose died.
200 mg/kg-bw < LD_{50} < 1000 mg/kg-bw

2-Picoline (CASRN 109-06-8)
(1) New Zealand White rabbits (1/sex/dose) were administered 2-picoline dermally on to clipped hair at 79.4 (female), 200 (male), 316 (female), 501 (male), 1000 (female), or 2000 (male) mg/kg-bw under occluded conditions and observed for 14 days post exposure. All rabbits exposed to 316 mg/kg-bw or above died within one day of exposure.
200 mg/kg-bw < LD_{50} < 316 mg/kg-bw

(2) Rabbits (strain and number not reported) were administered 2-picoline (dose not stated) dermally and observed for 14 days. No other information provided.
LD_{50} ~385 mg/kg-bw

(3) Rabbits (strain not stated, 2/dose) were administered 2-picoline dermally at 252 or 500 mg/kg-bw under occluded conditions for 24 hours. All animals at the higher dose died. Upon removal of the cuff, animals in the lower dose group showed signs of moderate necrosis with slight edema.
252 mg/kg-bw < LD_{50} < 500 mg/kg-bw

Pyridine, alkyl derivatives (CASRN 68391-11-7)
New Zealand White rabbits (2/sex/dose) were administered pyridine, alkyl derivatives dermally at 0.5, 1.0 or 2.0 mL/kg-bw to abraded skin under an occluded conditions for 24 hours and observed for 14 days. The only mortality was a female in the high dose group which died on day 12.
LD_{50} > 2.0 mL/kg-bw

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)
Rabbits (2/sex/dose, strain not reported,) were administered nicotinonitrile dermally at 500, 1000, 2000, or 4000 mg/kg-bw u on to the clipped and abraded backs under occluded condition and observed for 14 days (exposure duration not reported). All rabbits at the highest dose died. One male at 2000 mg/kg-bw died.
2000 mg/kg-bw < LD_{50} < 4000 mg/kg-bw

Sub-Category III
Piperidine (CASRN 110-89-4)
New Zealand White rabbits were treated with piperidine by the dermal route of exposure and observed for 14 days. No other information provided.
http://www.bgchemie.de/files/95/ToxBew72-L.pdf
LD_{50} = 276 mg/kg-bw

Acute Inhalation Toxicity

Sub-Category I
Pyridine (CASRN 110-86-1)
(1) Sprague-Dawley rats (5/sex/concentration) were exposed (whole body) to pyridine (concentrations not stated) for one hour.
1-h LC_{50} ~29.1 mg/L

(2) Sprague-Dawley rats (6 males/concentration) were exposed (nose only) to pyridine at 1600, 4900 or 6000 ppm (approximately 5.18, 14.7 or 18 mg/L, respectively) for 4 hours and were observed for 14 days. Mortality occurred at 4900 ppm (2 of 6 rats within four days) and 6000 ppm (5 of 6 rats during exposure).
14.7 mg/L < LD_{50} < 18 mg/L

(3) Six rats (strain and sex not reported) were exposed to pyridine at 4000 ppm (12 mg/L) for 4 hours and were observed for 14 days. Five rats died within 14 days after exposure.
LC_{50} < 12 mg/L

4-Picoline (CASRN 108-89-4)
(1) Rats (6 males, strain not reported) were exposed (whole body) to 4-picoline at an average chamber concentration of 9.2 g/m^3 (approximately 9.2 mg/L) for five hours. All animals died during exposure.
LC_{50} < 9.2 mg/L

(2) Rats (6 males, strain not reported) were exposed (whole body) to 4-picoline at an average chamber concentration of 17.5 g/m^3 (approximately 17.5 mg/L) for two and half hours. All animals died during exposure.
2.5 h-LC_{50} < 17.5 mg/L

(3) Albino rats (6 males) were exposed to 4-picoline at 1000 ppm (approximately 3.8 mg/L) for 4 hours and observed for 14 days post exposure. One rat died during the study.

LC_{50} > 3.8 mg/L

3-Picoline (CASRN 108-99-6)
(1) Sprague-Dawley rats (6 males) were exposed (whole body) to 3-picoline at an average chamber concentration of 11.82 g/m^3 (approximately 11.8 mg/L) for 5 hours. All animals died during exposure.
LC_{50} < 11.8 mg/L

(2) Sprague-Dawley rats (6 males) were exposed (nose only) to 3-picoline at concentrations of 1300 and 3300 ppm (approximately 4.95 and 12.7 mg/L, respectively) for 4 hours. All animals at the higher concentration died during exposure.
5.0 mg/L <LD_{50} < 12.7 mg/L

2-Picoline (CASRN 109-06-8)
(1) Sprague-Dawley rats (6 males) were exposed (whole body) to 2-picoline at an average chamber concentration of 13.2 g/m^3 (approximately 13.2 mg/L) for 4 hours. All animals died during exposure.
LC_{50} < 13.2 mg/L

(2) Six rats (strain and sex distribution not stated) were exposed to 2-picoline at concentrations of 2000 and 4000 ppm (approximately 7.6 and 15.2 mg/L, respectively) for 4 hours and observed for 14 days post exposure. All animals at the higher concentration died during the 14 days post exposure.
7.6 < LD_{50} < 15.2 mg/L

Sub-Category III
Piperidine (CASRN 110-89-4)
(1) Rats (6, sex distribution and strain not reported) were exposed to piperidine at 2000 ppm (approximately 6.96 mg/L) for 4 hours and were observed for 14 days. No deaths occurred.
LC_{50} > ~ 6.96 mg/L

(2) Wistar rats (number and sex/concentration not stated) were exposed via inhalation to piperidine at 6960 or 13,920 mg/m^3 (approximately 6.96 or 13.9 mg/L) for four hours and observed for 14 days. No mortalities occurred at the lower concentration. At 13,920 mg/m^3, all rats died (http://www.bgchemie.de/files/95/ToxBew72-L.pdf).
~ 6.96 < LC_{50} < ~13.9 mg/L
(3) Sprague-Dawley rats of both sexes (number/dose not stated) were exposed to piperidine (concentrations not stated) via inhalation for four hours and observed for 14 days (http://www.bgchemie.de/files/95/ToxBew72-L.pdf).
LC_{50} ~ 4.8 mg/L

Repeated-Dose Toxicity

Sub-Category I
Pyridine (CASRN 110-86-1)

(1) In a 13-week study, Sprague-Dawley rats (10/sex/dose) were administered pyridine via gavage at 0, 0.25, 1.0, 10, 25 or 50 mg/kg-bw/day 7 days/week. No treatment-related mortalities occurred. Males at the highest dose had statistically significant (significance not provided) decreased body weights and weight gains and increased food consumption. Absolute and relative liver weights were significantly increased (significance not provided) at 10, 25 and 50 mg/kg-bw/day in females. Elevated (though not significant) cholesterol levels were observed in females at the two higher doses. Inflammatory hepatic lesions were observed in both sexes: males at 0.25, 1.0 and 50 mg/kg-bw/day and females at 50 mg/kg-bw/day. There were no treatment-related effects on the hematological parameters or macroscopic and microscopic changes noted during histopathological examination of the tissues. No neuropathological lesions were observed.
LOAEL = 50 mg/kg-bw/day (based on decreased body weights effects on liver)
NOAEL = 25 mg/kg-bw/day

(2) In a 13-week study, Fischer F344 rats (10/sex/dose) were administered pyridine via gavage at 0, 12.5, 25, 50, 100 or 200 mg/kg-bw/day. Mortality was observed at 100 mg/kg-bw/day (1 male) and at 200 mg/kg-bw/day (1 male and two females). Decreased body weights, when compared to controls, were noted in females at all doses (11 to 14%) and in males at and above 50 mg/kg-bw/day (13 to 41%). Gross pathological observations of the liver (doses not stated) indicated granular visceral surfaces with depressed discolored areas. At 100 and 200 mg/kg-bw/day, multiple foci or diffuse necrosis, hepatocytomegaly, bile duct hyperplasia and fatty metamorphosis were noted during microscopic evaluation of the liver. A proliferation of connective tissue forming collagenous bands altering the parenchyma was also observed. At 200 mg/kg-bw/day, focal interstitial myocarditis was also observed in both sexes.
LOAEL = 100 mg/kg-bw/day (based on reduced body weights and effects on liver)
NOAEL = 50 mg/kg-bw/day

(3) In a 13-week NTP study, Fischer F344 rats (10/sex/concentration) were administered pyridine via drinking water at 0, 50, 100, 250, 500 or 1000 ppm (equivalent to 0 and approximately 5, 10, 25, 55 or 90 mg/kg-bw/day) for 13 weeks. Mortality was observed at the highest dose (2 females). Body weights were significantly ($p<0.01$) depressed at the two highest doses. Clinical chemistry at these doses indicated increases in serum alanine aminotransferase (ALT) and sorbitol dehydrogenase (SDH) activity as well as increased bile acid concentrations. The estrous cycle length at the highest dose was longer than controls. Significantly increased ($p<0.01$) absolute and relative liver weights were seen in both sexes at 25 mg/kg-bw/day and above. Incidences of centrilobular degeneration, hypertrophy, chronic inflammation and pigmentation were also increased at the two highest doses in both sexes. Kidney lesions in males at the two highest doses included protein casts, chronic inflammation and mineralization. The incidences of granular casts and hyaline degeneration (hyaline droplets) were increased in males of the two high doses; these lesions were consistent with alpha 2μ-globulin nephropathy.
LOAEL ~ 55 mg/kg-bw/day (based on effects on body weight and liver effects)
NOAEL ~ 25 mg/kg-bw/day

(4) In a 13-week NTP study, Wistar rats (10 males/concentration) were administered pyridine via drinking water at 0, 50, 100, 250, 500 or 1000 ppm (0 and approximately 5, 10, 30, 60 or 100 mg/kg-bw/day) pyridine. Mortality was observed at 60 mg/kg-bw/day (one male). Body

weights and body weight gains were significantly decreased (p<0.01) at 30 mg/kg-bw/day and above. Clinical chemistry at the two highest doses indicated increases in serum alanine aminotransferase (ALT) and sorbitol dehydrogenase (SDH) activity and increased bile acid concentrations. In the liver, incidences of centrilobular degeneration, hypertrophy, chronic inflammation and pigmentation were generally increased at the two highest doses.
LOAEL ~ 60 mg/kg-bw/day (based on changes in clinical chemistry and effects on liver)
NOAEL ~ 30 mg/kg-bw/day

(5) In a two-year drinking water study, described in the carcinogenicity section, Fischer 344 rats (50/sex/dose) were exposed to pyridine in drinking water at 0, 100, 200 or 400 ppm (0 and approximately 7, 14 or 33 mg/kg-bw/day). Treatment-related non-neoplastic lesions were observed in the liver of both sexes at 400 ppm (~33 mg/kg-bw/day). These included centrilobular cytomegaly, cytoplasmic vacuolization, periportal fibrosis, fibrosis, centrilobular degeneration and necrosis and pigmentation.
LOAEL ~ 33 mg/kg-bw/day (based on liver effects)
NOAEL ~ 14 mg/kg-bw/day

(6) In a two-year drinking water study, described in the carcinogenicity section, male Wistar rats (50/sex/dose) were exposed to pyridine in drinking water at 0, 100, 200 or 400 ppm (0 and approximately 8, 17 or 36 mg/kg-bw/day). Survival of rats exposed to 200 or 400 ppm was significantly less than that of controls. Severity of nephropathy was marked in all groups and additional evidence of systemic toxicity, including mineralization in the glandular stomach, parathyroid gland hyperplasia and fibrous osteodystrophy was observed at 200 and 400 ppm. Incidences of hepatic centrilobular degeneration and necrosis, fibrosis, periportal fibrosis and/or pigmentation were increased (significance not stated) in exposed groups.
LOAEL ~ 17 mg/kg-bw/day (based on mortality and systemic effects)
NOAEL ~ 8 mg/kg-bw/day

(7) In a four-day study, Fischer 344 rats (5 males/dose) were exposed (nose only) to pyridine at 5 or 444 ppm (approximately 0.02 or 1.44 mg/L) for 6 hours/day. Olfactory epithelial lesions in rats exposed to both concentrations of pyridine included vacuolar degeneration of sustentacular cells; focal, marked attenuation of the epithelium; loss of neurons and the presence of intraepithelial luminal structures.
LOAEC ~ 0.02 mg/L (based on lesions in the olfactory epithelium)
NOAEC ~ not established

(8) In a 13-week study, B6C3F1 mice (10/sex/dose) were administered pyridine via gavage at 25, 50, 100, 200 or 400 mg/kg-bw/day, five days/week. Six males at 400 mg/kg-bw/day and one male in the 200 mg/kg-bw/day group died during exposure. Males in all exposure groups experienced body weight depression (6 to 40%) in a dose-dependant manner. Males at 400 mg/kg-bw/day were lethargic or moribund and females were emaciated. At 400 mg/kg-bw/day, some males and females had prominent lobular markings in the livers. These coincided with histopathological changes in some animals at 200 mg/kg-bw/day and above. The hepatic lesions consisted of fatty metamorphosis, hepatocytomegaly and multifocal necrosis and occasional parenchymal degeneration, indicated by an increase in the number of normal mitotic figures.
LOAEL = 200 mg/kg-bw/day (based on mortality and effects on liver)

NOAEL = 100 mg/kg-bw/day

(9) In a 13-week National Toxicology Program (NTP) study, B6C3F1 mice (10/sex/concentration) were administered pyridine in drinking water at 0, 50, 100, 250, 500 or 1000 ppm (0, 10, 20, 50, 85 or 160 mg/kg-bw/day for males and 0, 10, 20, 60, 100 or 190 mg/kg-bw/day for females). One female mouse in the 60 mg/kg-bw/day group died during week 2. The final mean body weights and body weight gains of females were significantly ($p<0.01$) reduced at the highest dose. Sperm motility was significantly decreased ($p<0.01$) in exposed mice relative to controls. Absolute and relative liver weights were increased in males at 20 mg/kg-bw/day and higher ($p<0.01$) and in females at 60 and 100 mg/kg-bw/day and higher ($p<0.01$). No treatment-related lesions were observed in either sex.
$NOAEL_{males}$ = 160 mg/kg/bw/day (based on no treatment-related effects at highest dose tested)
$LOAEL_{females}$ = 190 mg/kg-bw/day (based on decreased body weight gain)
$NOAEL_{females}$ = 100 mg/kg-bw/day

3-Picoline (CASRN 108-99-6)
In a two-week study, Sprague-Dawley rats (10 males/dose) were exposed (nose only) to 3-picoline at 0 or 290 ppm (0 or 1.10 mg/L) for 6 hours/day, 5 days/week. Five rats were allowed to recover for 13 days post exposure. No clinical signs of toxicity were observed during exposure. The exposed rats had changes in liver weights which were not present after the recovery period. No other treatment-related effects were observed. No treatment-related effects were observed on hematological or clinical chemistry analysis.
NOAEC ~ 1.10 mg/L

2-Picoline (CASRN 109-06-8)
In a six-month study, Sprague-Dawley rats (10/sex/dose) were exposed to 2-picoline vapor at 0, 5, 35, 100 ppm (0 and approximately 0.019, 0.133 or 0.38 mg/L/day) for 6 hours/day, 5 days/week. No signs of treatment-related toxicity were observed at any treatment level at any time.
NOAEC ~ 0.38 mg/L

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)
In a 28-day study, Sprague-Dawley rats (6/sex/dose) were administered nicotinonitrile via gavage at 0, 5, 30 or 180 mg/kg-bw/day. Additional groups of control and high dose animals were allowed to recover for 14 days post exposure. At 180 mg/kg-bw/day significant ($p<0.05$) decreased body weight gain was observed. Changes in urinalysis parameters (volume increased, osmotic pressure decreased, changes in pH and specific gravity) in both sexes at the highest dose were reversible. Changes in hematological parameters (increased leukocyte count, decreased erythrocyte count) were observed at the highest dose in both sexes. Histopathological examination showed hemosiderin deposits in the red pulp of the spleen in both sexes at the highest dose. However, these changes were not considered toxicologically significant because they were within normal physiological limits. Changes (significance not stated) in blood chemistry values (increases in total protein, albumin, A/G ratio, GPT, total cholesterol and phospholipids) were not altered during the recovery period. Treatment-related (significance not stated) changes in relative kidney and liver weights were observed in both sexes at the highest

dose. Males at this dose also exhibited increased absolute and relative adrenal weights which did not correlate to any histological changes. For females, kidney and liver weight changes (significance not stated) were observed at 30 mg/kg-bw/day. Histopathology indicated centrilobular hypertrophy of hepatocytes in both sexes at 30 mg/kg-bw/day and higher. These were present after recovery at the highest dose in both sexes. In males, the incidence of hyaline droplets increased in the proximal tubules at 30 mg/kg-bw/day and higher. There was also hypertrophy of zona hepatoblast of the adrenal and extramedullary hematopoiesis and hemosiderin deposits in spleen at the highest dose in both sexes.
LOAEL = 30 mg/kg-bw/day (based on effects on the liver)
NOAEL = 5 mg/kg-bw/day

Sub-Category III
Piperidine (CASRN 110-89-4)
In a 28-day study, Wistar rats (10/sex/concentration) were exposed via inhalation (whole-body) to piperidine at 5, 20 or 100 ppm (approximately 0.017, 0.07 or 0.348 mg/L, respectively) for six hours/day five days/week. No treatment-related changes were observed at the two lower concentrations. At the highest concentration, there was a slight increase in relative liver weights and decrease in body weight gain. The increase in liver weights was significant in females but no histopathologic correlation was observed. No differences from control were observed in hematology, clinical chemistry, ophthalmology, pathology or histopathology. No evidence of neurotoxicity was observed (http://www.bgchemie.de/files/95/ToxBew72-L.pdf).
NOAEL ~ 0.348 mg/L (based on no adverse effects at highest concentration tested)

Reproductive Toxicity

Sub-Category I
Pyridine (CASRN 110-86-1)
Data from an oral repeated-dose study in mice, described above, indicate effects on sperm motility in mice. These data are inadequate to address the reproductive toxicity endpoint for the purposes of the HPV Challenge Program. The reproductive toxicity endpoint remains a data gap sub-category I under the HPV Challenge Program.

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)
Data from an oral repeated-dose study in rats, described above, showed necrosis of spermatocytes and spermatids, and vacuolation of the Sertoli cells. These data are inadequate to address the reproductive toxicity endpoint for the purposes of the HPV Challenge Program. The reproductive toxicity endpoint remains a data gap for sub-category II under the HPV Challenge Program.

Sub-Category III
Data gap.

Developmental Toxicity

Sub-Category I

Data gap.

Sub-Category II
Data gap.

Sub-Category III
Piperidine (CASRN 110-89-4)
Pregnant rats were exposed to piperidine at 0, 3, 15 or 100 mg/m^3 (approximately 0, 0.003, 0.015 or 0.10 mg/L, respectively) via inhalation for three different exposure scenarios: throughout pregnancy, day 4 (3 and 100 mg/m^3 only) of gestation or day 9 of gestation. There was a treatment-related decrease in body weight gain in the maternal animals at the two higher exposure concentrations. There was a treatment-related decrease in fetal body weight with increasing exposure concentrations and exposure times; only the low dose groups being affected during the one day exposures.
LOAEL (maternal) ~ 0.015 mg/L (based on decrease in weight gain)
NOAEL (maternal) ~ 0.003 mg/L
LOAEL (developmental toxicity) ~ 0.003 mg/L (based on reduced fetal body weight)
NOAEL (developmental toxicity) ~ not established

Genetic Toxicity – Gene Mutation

In vitro

Sub-Category I
Pyridine (CASRN 110-86-1)
(1) In seven reverse-mutation bacterial assays, *Salmonella typhimurium* strains (TA98, TA100, TA102, TA1535, TA1537 and/or TA1538) were exposed to pyridine at concentrations ranging from 0.05 to 100 µL/plate with and without metabolic activation. Positive and negative controls were tested concurrently; however, their responses were not provided. Cytotoxicity was observed in two assays at 25 and 50 µL/plate. No mutagenicity was observed in the presence or absence of metabolic activation in these assays.
Pyridine was not mutagenic in these assays.

(2) *Escherichia coli* strains 343/113 polA$^+$ and KMBL1787 polA$^-$ were exposed to pyridine at 10 µg/plate without metabolic activation. The positive control showed appropriate response.
Pyridine was not mutagenic in this assay.

(3) Chinese hamster lung cells (V79) were exposed to pyridine at concentrations up to 9.25 µL/mL without metabolic activation. Positive and negative controls were tested concurrently; however, the results were not provided. Cytotoxic concentration was observed at 8.75 µL/mL. The test substance was not mutagenic under these test conditions.
Pyridine was not mutagenic in this assay.

4-Picoline (CASRN 108-89-4)
(1) In three reverse-mutation bacterial assays, *Salmonella typhimurium* strains TA98, TA100, TA 1535, TA 1537, TA1538 were exposed to 4-picoline at concentrations up to 5000 µg/plate with

and without metabolic activation. Positive and negative controls were tested concurrently; however, the results were not provided. The test substance was not mutagenic under these test conditions in the presence or absence of metabolic activation.
4-Picoline was not mutagenic in this assay.

(2) Chinese hamster lung cells (V79) were exposed to 4-picoline at concentrations up to 4.5 µL/mL without metabolic activation. Positive and negative controls were tested concurrently; however, the results were not provided. Cytotoxic concentration was 4.5 µL/mL. The test substance was not mutagenic under these test conditions.
4-Picoline was not mutagenic in this assay.

3-Picoline (CASRN 108-99-6)
(1) In four reverse-mutation bacterial assays, *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA 1535 and/or TA 1537 were exposed to 3-picoline at concentrations up to 5000 µg/plate with and without metabolic activation. Positive and negative controls were tested concurrently; however, the results were not provided. The test substance was not cytotoxic or mutagenic under these test conditions in the presence or absence of metabolic activation.
3-Picoline was not mutagenic in this assay.

(2) Chinese hamster lung cells (V79) were exposed to 3-picoline at concentrations up to 4.0 µL/mL without metabolic activation in a mammalian cell forward mutation assay. Positive and negative controls were tested concurrently; however, the results were not provided. Cytotoxic concentration was 4.0 µL/mL. The test substance was not mutagenic under these test conditions.
3-Picoline was not mutagenic in this assay.

2-Picoline (CASRN 109-06-8)
(1) In a reverse-mutation bacterial assay, *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA 1535 and/or TA 1537 were exposed to 2-picoline at concentrations up to 5000 µg/plate with and without metabolic activation. Positive and negative controls were tested concurrently; however, the results were not provided. The test substance was not cytotoxic or mutagenic under these test conditions in the presence or absence of metabolic activation.
2-Picoline was not mutagenic in this assay.

(2) Chinese hamster lung cells (V79) were exposed to 2-picoline at concentrations up to 5.5 µL/mL without metabolic activation. Positive and negative controls were tested concurrently; however, the results were not provided. Cytotoxic concentration was 5.25 µL/mL. The test substance was not mutagenic under these test conditions.
2-Picoline was not mutagenic in this assay.

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)

In reverse-mutation bacterial assays, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli*/WP2 uvrA were exposed to nicotinonitrile at concentrations up to 5000 µg/plate with and without metabolic activation. Positive and negative controls were tested concurrently; however, the results were not provided. No cytotoxicity or mutagenicity was observed in the presence or absence of metabolic activation.
Nicotinonitrile was not mutagenic in this assay.

Sub-Category III
Piperidine (CASRN 110-89-4)
(1) In a reverse-mutation bacterial assay, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to piperidine at a concentration of 3 µmol/plate, with and without metabolic activation. The controls behaved as expected. Piperidine was negative for mutagenesis in this assay in the presence or absence of metabolic activation.
Piperidine was not mutagenic in this assay.

(3) *Escherichia coli* strains 343/113 $polA^+$ and KMBL1787 $polA^-$ were exposed to piperidine at 10 µg and 40 mM without metabolic activation. The positive control behaved appropriately. At the lower concentration the results were inconclusive but at the higher concentration, the results were negative.
Piperidine was not mutagenic in this assay.

(3) Mouse lymphoma L5178Y/TK^+ cells were examined for mutations following exposure to 0, 2.00, 4.01 or 6.01 mM piperidine in the absence of metabolic activation and 0, 2.00, 4.01, 6.01 or 8.02 mM piperidine in the presence of metabolic activation. The cytotoxic concentration was 6.01 mM with activation and 8.02 mM with activation. No mutagenic activity was observed in the presence of metabolic activation. With metabolic activation, piperidine was positive for mutagenicity.
Piperidine was mutagenic in this assay in the absence of metabolic activation and not mutagenic in the presence of metabolic activation.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Sub-Category I
Pyridine (CASRN 110-86-1)
(1) Chinese hamster fibroblast cells (CHL) were exposed to pyridine at concentrations up to 505.7 mg/mL without metabolic activation. Negative controls were tested concurrently; however, the results were not provided. Based on the criteria for the assay, pyridine did not cause an increase in chromosomal aberrations.
Pyridine did not induce chromosomal aberrations in this assay.

(2) Chinese hamster ovary (CHO) cells were exposed to pyridine concentrations up to 2325 µg/mL without metabolic activation and 5000 µg/mL with metabolic activation. Positive and negative controls were tested concurrently; however, the results were not provided. Cytotoxicity occurred at concentrations >2325 µg/mL without metabolic activation and

>5000 µg/mL with metabolic activation. Pyridine did not induce chromosomal aberrations with or without metabolic activation.
Pyridine did not induce chromosomal aberrations in this assay.

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)
Chinese hamster ovary (CHO) cells were exposed to nicotinonitrile concentrations up to 5000 µg/mL with and without metabolic activation for six hours or up to 3000 µg/mL without activation for 24 and 48 hours. Positive and negative controls were tested concurrently; however, the results were not provided. No cytotoxicity was observed. Nicotinonitrile did not induce chromosomal aberrations with or without metabolic activation under these test conditions.
Nicotinonitrile did not induce chromosomal aberrations in this assay.

In vivo

Sub-Category I
Pyridine (CASRN 110-86-1)
(1) B6C3F1 mice (10 males/dose) were administered pyridine via intraperitoneal injection at 400, 500 and 600 mg/kg-bw. Positive and negative controls were tested concurrently; however, the results were not provided. Two hours before sacrifice, the animals were administered colchicine intraperitoneally. The mice were sacrificed at 17 or 36 hours. No induction of aberrations was noted in bone marrow cells at either sampling time at any dose.
Pyridine did not induce chromosomal aberrations in this assay.

(2) B6C3F1 mice (5 males/dose) were administered pyridine via intraperitoneal injection at 31.25, 62.5, 125, 250 and 500 mg/kg-bw three times at 24-hour intervals. Positive and negative controls were tested concurrently; however, the results were not provided. The animals were sacrificed 24 hours after the third injection and blood smears were prepared from bone marrow cells obtained from the femurs. The micronucleated polychromatic erythrocytes (MPCEs) per 1000 PCEs and the percent PCEs in the treated animals were not significantly different ($p>0.025$) to the controls at any dose tested.
Pyridine did not increase micronuclei in this assay.

Sub-Category III
Piperidine (CASRN 110-89-4)
In a mouse micronucleus assay (OECD TG 474) NMRI mice of both sexes (6 mice/dose) were treated with a single oral dose of piperidine at 40, 120 or 400 mg/kg-bw (maximum tolerated dose). Five of the 18 animals died within 72 hours. No increase in polychromatic erythrocytes was observed. (No other information provided). (http://www.bgchemie.de/files/95/ToxBew72-L.pdf).
Piperidine did not increase micronuclei in this assay.

Genetic Toxicity – Other Effects
In vitro

Sub-Category I

Pyridine (CASRN 110-86-1)
(1) In a sister chromatid exchange (SCE) assay, Chinese hamster cells were exposed to pyridine up to 0.005 M without metabolic activation. Positive controls were tested concurrently; however, the results were not provided. The test substance did not induce SCE in this assay.
Pyridine did not induce chromosomal aberrations in this assay.

(2) In a sister chromatid exchange (SCE) assay, Chinese hamster ovary (CHO) cells were exposed to pyridine up to 5020 μg/mL with and without metabolic activation. Negative and positive controls were tested concurrently and showed appropriate response. Cytotoxicity was observed at 5020 μg/mL without metabolic activation. The test substance did not induce SCE in this assay.
Pyridine did not induce chromosomal aberrations in this assay.

In vivo

Sub-Category I
Pyridine (CASRN 110-86-1)
In an unscheduled DNA synthesis (UDS) assay, B6C3F1 mice (4 males/dose) were administered pyridine via gavage at 175, 350 or 700 mg/kg-bw. Mice were sacrificed 2 and 16 hours post exposure. Primary hepatocytes were isolated, cultured and counted. Negative and positive controls were tested; the negative control results were discussed. No treatment-related increase in the UDS response was observed at any dose tested.
Pyridine did not induce unscheduled DNA synthesis in this assay.

Additional Information

Skin Irritation
The following information was retrieved from the TSCATS database accessible at:
(http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384)

Sub-Category I
Pyridine (CASRN 110-86-1)
Six albino rabbits (sex not stated) were treated with 0.5 mL undiluted pyridine on intact and abraded skin and observed at 24 and 72 hours.
Pyridine was corrosive to rabbit skin.

4-Picoline (CASRN 108-89-4)
(1) Six New Zealand white rabbits were exposed to 0.5 mL 4-picoline dermally on to the clipped area of the skin under occluded condition for 4 hours. The skin was washed and observed at 24 and 48 hours. Corrosion was seen at the application site.
4-Picoline was corrosive to rabbit skin.

(2) Rabbits (strain not stated 1 male/2females) exposed to 0.2 mL 4-picoline dermally on to the intact skin and evaluated after 1, 24 48, 72, 120 and 168 hours. The clinical observations ranged from no changes through slight erythema and moderate edema ending with no erythema or

edema at 168 hours. A de-fatting effect was observed whereby flaking of the skin was observed at 10-14 days.
4-Picoline was severely irritating to rabbit skin.

(3) New Zealand albino rabbits were exposed to 4-picoline dermally at dilutions of 8, 12.5, 25, or 50%. Except for 8% dilution, all doses were lethal to the rabbits. Additional rabbits were exposed to 4-picoline at 0.5 or 1.0 g/kg-bw. All animals applied 1.0 g/kg-bw died. Animals applied 0.5 g/kg survived. (No other information available)

3-Picoline (CASRN 108-99-6)
(1) Six New Zealand white rabbits were exposed to 3-picoline dermally. Corrosion was observed. (No other information available).

3-Picoline was corrosive to rabbit skin.

(2) When tested in guinea pigs, 3-picoline was moderately irritating to the skin. (No additional information available).
3-Picoline was moderately irritating to guinea pig skin.

2-Picoline (CASRN 109-06-8)
(1) Six albino rabbits were exposed to 2-picoline dermally and observed at 4, 24 and 48 hours. Moderate to severe erythema and corrosion were observed.

2-Picoline was corrosive to rabbit skin.

(2) Rabbits were exposed to undiluted 2-picoline six times on to the intact skin of the ear. Slight hyperemia was observed during the first week which became moderate by week two. After the sixth application, moderate burning was apparent. After 21 days, a slight scab remained.
2-Picoline was severely irritating to rabbit skin.

(3) Rabbits were exposed to undiluted 2-picoline dermally on to the intact and abraded skin. Severe burning was accompanied by severe hyperemia and moderate edema after one application. A severe scar with moderate scabbing remained after 21 days.
2-Picoline was severely irritating to rabbit skin.

(4) In a skin patch test, undiluted 2-picoline was applied to rabbit skin for 15 minutes, 5 minutes or 1 minute. Moderate hyperemia was observed after two minutes; moderate burn after 15 minutes. The burn appeared to be severe with severe hyperemia one day later. A severe scab remained in six days. After the five minute exposure, skin looked normal in a week. After the one minute exposure, no irritation was observed the next day or a week later.
2-Picoline was severely irritating to rabbit skin.

Sub-Category III
Piperidine (CASRN 110-89-4)
(1) New Zealand White rabbits (2 male/4 females) were exposed to 0.5 mg Haccure 200 (a mixture containing piperidine and 2-ethyl-4-methylimidazole) and Epon 828 dermally on to the

clipped skin under semi-occluded conditions 4 hours. After four hours, the gauze was removed and the animals were scored for erythema and edema at 30-60 minutes and at 24, 48 and 72 hours, and days four and 14 following exposure. The study was terminated after 14 days. At 30-60 minutes, there was slight to moderate edema in 5/6 rabbits. Moderate or severe erythema and edema were observed on all rabbits from 24 hours to seven days. On day 14, except for one rabbit, severe erythema with eschar formation and slight to severe edema were observed.
Piperidine was irritating to rabbit skin.

(2) New Zealand White rabbits (2 male/4 females) were exposed to 0.5 mL Haccure 200 (a mixture containing piperidine and 2-ethyl-4-methylimidazole (4:6)) dermally on to the clipped skin under semi-occluded condition for 4 hours. After four hours, the gauze was removed and the animals were scored for erythema and edema at 30-60 minutes and at 24hours, and observed for 14 days following exposure. At 30-60 minutes, there was slight to moderate edema in all rabbits. Severe erythema and moderate to severe edema were observed on all rabbits at 24 hours. Necrosis was observed at all test sites at both 30-60 minutes and 24 hours. The study was terminated after 24 hours since the lesions were not considered reversible within the 14-day study design.
Piperidine was corrosive to rabbit skin.

(3) Piperidine (0.5 mg) was tested in rabbits in a standard Draize test for 24 hours. Severe dermal reaction was seen. (No other information available).
Piperidine was severely irritating to rabbit skin.

Eye Irritation
The following information was retrieved from the TSCATS database accessible at:

(http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384)

Sub-Category I
Pyridine (CASRN 110-86-1)
Six albino rabbits (sex not stated) were instilled with 0.1 mL undiluted pyridine into the eyes and observed at 24, 48 and 72 hours.
Pyridine was severely irritating to rabbit eye.

4-Picoline (CASRN 108-89-4)
(1) New Zealand albino rabbits were instilled with 4-picoline in to the eyes. Both eyes were observed for conjunctival, corneal or internal responses. One eye was washed within 30 seconds while the other eye was unwashed. Severe conjunctival inflammation and swelling, severe corneal injury and severe iritis were observed.
4-Picoline was severely irritating to rabbit eye.

(2) Albino rabbits (3 male and females) were instilled with undiluted 4-picoline (0.1 mL) in the right eye and observed for seven days. The eyes were rinsed with warm isotonic saline solution after either a 24 hour exposure or 15 minute exposure. The left eye served as the control. At 24 hours, opacity of the eye was observed with accompanying discharge, at both exposures. The test substance was considered a severe eye irritant at both exposure times.
4-Picoline was severely irritating to rabbit eye.

3-Picoline (CASRN 108-99-6)
When tested in rabbit eye, 3-picoline was a severe eye irritant.
3-Picoline was severely irritating to rabbit eye.

2-Picoline (CASRN 109-06-8)
Rabbit was instilled with undiluted 2-picoline with and without washing. There was slight pain upon direct contact followed by severe conjunctival and corneal injury resulting in permanent impairment of vision and possibly total loss of sight. Corneal injury was apparent immediately after contact.
2-Picoline was severely irritating to rabbit eye.

Sub-Category III
Piperidine (CASRN 110-89-4)
Rabbits were instilled with 250 μg piperidine in a standard Draize test for 24 hours. The reaction was severe. (No other information provided).
Piperidine was severely irritating in rabbit eye.

Sensitization
The following information was retrieved from the TSCATS database accessible at:

(http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384)

Sub-Category I
Pyridine (CASRN 110-86-1)
Pyridine was evaluated for dermal sensitization in guinea pigs and was determined not to be a sensitizer. No other information is available.
Pyridine is not a skin sensitizer.

Sub-Category III
Piperidine (CASRN 110-89-4)
Haccure 200 is a mixture containing (piperidine and 2-ethyl-4-methylimidazole, 4:6).
In a contact dermal sensitization test, ten female guinea pigs were applied 0.5 mL Haccure 200 (piperidine) as a 30% (v/v) suspension in propylene glycol to a 4 x 4 cm patch and attached to hair clipped skin. A concentration of 30% was chosen due to severe dermal reactions at higher concentrations. The induction applications were made 3 times each week until all nine induction applications had been made. Animals were challenged two weeks after the last induction with 0.5 mL test substance. Sites of application were evaluated for erythema, edema and other lesions approximately 24 and 48 hours after the test substance application. The positive control behaved as expected. The test substance was considered a contact dermal sensitizer.
Piperidine is a skin sensitizer.

Carcinogenicity

Sub-Category I
Pyridine (CASRN 110-86-1)
(1) In a two-year NTP study, B6C3F1 mice (50/sex/concentration) were exposed to pyridine in drinking water at 0, 250, 500 or 1000 ppm (males; 0, 35, 65, 110 mg/kg-bw/day or 0, 125, 250 or

500 ppm (females; 0, 15, 35 or 70 mg/kg-bw/day). Hepatocellular neoplasm, including hepatoblastomas in exposed male and female mice were treatment-related. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchresults&searchterm=110-86-1
Pyridine increased the incidence of tumors in this study.

(2) In a two-year NTP study, Fischer 344 rats (50/sex/concentration) were exposed to pyridine in drinking water at 0, 100, 200 or 400 ppm (0 and approximately 7, 14 or 33 mg/kg-bw/day). Incidences of renal tubular adenoma or carcinoma were observed in males and were considered treatment-related. Similarly, incidences of mononuclear cell leukemia in females were also considered treatment-related.
http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchresults&searchterm=110-86-1
Pyridine increased the incidence of tumors in this study.

(3) In a two-year NTP study, male Wistar rats (50/sex/concentration) were exposed to pyridine in drinking water at 0, 100, 200 or 400 ppm (0 and approximately 8, 17 or 36 mg/kg-bw/day). Survival of rats exposed to 200 or 400 ppm was significantly less than that of controls. Incidences of testicular adenoma were considered treatment-related.
http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchresults&searchterm=110-86-1
Pyridine increased the incidence of tumors in this study.

Sub-Category III
Piperidine (CASRN 110-89-4)
In a 50-week study, Sprague-Dawley rats (15/sex/concentration) were exposed to piperidine in drinking water at 0 or 0.09% (approximately 50 mg/kg-bw/day) with and without 0.2% sodium nitrite 5 days/week. There was no significant increase in the tumor incidence in rats chronically exposed to 0.09% piperidine with or without sodium nitrite as compared to control rats receiving 0.2% sodium nitrite in drinking water.
Piperidine did not increase the incidence of tumors in this study.

Other

Sub-Category I
Pyridine (CASRN 110-86-1)
Sprague-Dawley rats (5 males/dose) were administered 1.25 mmol pyridine intraperitoneally daily for five days. The animals were sacrificed 18 hours after the last injection. Serum sorbitol dehydrogenase (SDH), blood urea nitrogen (BUN), serum creatinine and *p*-nitrophenol hydroxylase were measured. Pyridine was hepatotoxic as indicated by increased SDH activity. An increase in *p*-nitrophenol hydroxylase activity indicated that pyridine induced the metabolism of *p*-nitrophenol.
Pyridine is potentially hepatotoxic.

Conclusion:
Sub-Category I: The acute toxicity of sub-category I is low via the oral (rats), high via the dermal (rabbits) and moderate via the inhalation (rats) routes of exposure. The alkyl pyridines are corrosive to rabbit skin and severely irritating to rabbit eye. CASRN 110-86-1 is not a skin sensitizer in guinea pigs. Oral repeated-dose studies with CASRN 110-86-1 in rats showed systemic toxicity ranging from changes in body weights to histopathological changes in the liver at 33 mg/kg-bw/day; the NOAEL was 14 mg/kg-bw/day. In mice, repeated oral exposures showed effects on body weight gain and liver at 200 mg/kg-bw/day; the NOAEL for systemic toxicity was 100 mg/kg-bw/day. Repeated inhalation exposures of male rats to CASRN 108-99-6 showed no effects at the highest concentration tested; the NOAEC for systemic toxicity was 1.10 mg/L. Repeated inhalation exposures of rats to CASRN 109-06-8 showed no effects at the highest concentration tested; the NOAEC for systemic toxicity was 0.38 mg/L. Effects were observed on body weights and liver; the NOAEC for systemic toxicity was not established. No specific reproductive toxicity studies were available but effects on the male reproductive system were observed after repeated oral exposures to CASRN 110-86-1 in mice and rats. No developmental toxicity studies were available. Sub-category I did not induce gene mutations *in vitro*. CASRN 110-86-1 did not induce chromosomal aberrations *in vitro* or *in vivo*. In two-year bioassays in rats and mice exposed via drinking water, CASRN 110-86-1 increased the incidence of tumors.

The reproductive and developmental toxicity endpoints remain as data gaps under the HPV Challenge Program.

Sub-Category II: The acute toxicity of sub-category II is low via the oral (rats) and dermal (rabbits) routes of exposure. Repeated oral exposures with CASRN 100-54-9 in rats showed histopathological changes in the liver at 30 mg/kg-bw/day; the NOAEL for systemic toxicity was 5 mg/kg-bw/day. At higher doses, there was necrosis of spermatocytes and spermatids. No specific reproductive toxicity studies were available but effects on the male reproductive system were observed after repeated oral exposures to CASRN 100-54-9 in rats. No developmental toxicity studies were available. CASRN 100-54-9 did not induce gene mutations or chromosomal aberrations *in vitro*.

The reproductive and developmental toxicity endpoints remain as data gaps under the HPV Challenge Program.

Sub-Category III: The acute oral toxicity of CASRN 110-89-4 is moderate in rats and low in mice. Acute dermal toxicity in rabbits and inhalation toxicity in rats is moderate. CASRN 110-89-4 is corrosive to rabbit skin, severely irritating to rabbit eye and a skin sensitizer in guinea pigs. After repeated inhalation exposures, no adverse effects were observed in rats at the highest dose tested; the NOAEC for systemic toxicity was 0.348 mg/L. No data were available for the reproductive toxicity endpoint. In a prenatal developmental toxicity study in rats via the inhalation route, dams showed decreased weight gains at 0.015 mg/L; the NOAEC for maternal toxicity was 0.003 mg/L. Fetal body weights were decreased at 0.003 mg/L. The NOAEC for developmental toxicity was not established. CASRN 110-89-4 did not induce gene mutations *in vitro* and did not induce micronuclei *in vivo*. No data were available for the chromosomal aberrations endpoint. In a two-year bioassay in rats exposed via drinking water, CASRN

110-89-4 did not increase the incidence tumors.

The reproductive toxicity endpoint remains a data gap under the HPV Challenge Program.

Table 8. Summary of Human Health Data

Endpoints	Sub-Category I					Sub-Category II		Sub-Category III
	Pyridine **(CASRN 110-86-1)**	**4-Picoline** **(CASRN 108-89-4)**	**3-Picoline** **(CASRN 108-99-6)**	**2-Picoline** **(CASRN 109-06-8)**	**Pyridine, alkyl derivatives (CASRN 68391-11-7)**	**Nicotinonitrile** **(CASRN 100-54-9)**	**Picolinonitrile** **(CASRN 100-70-9)**	**Piperidine** **(CASRN 110-89-4)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**800-1600**	**700 to 841**	**630 to 710**	**810 to >950**	**2500**	**633 to 1455**	No Data 633-1455 (RA)	**337 to 740 (rats)** **536 to 633 (mice)**
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	**1000 to 2000**	**79.4 to 200**	**126 to 1000**	**200 to 500**	**>2.0 (mL/kg-bw)**	**2000 to 4000**	–**	**276**
Acute Inhalation Toxicity LC_{50} (mg/L)	**<12**	**3.8 to 9.2**	**5.0 to 11.8**	**7.6 to 13.2**	–**	–**	–**	**4.8**
Repeated-Dose Toxicity NOAEC/ LOAEC Inhalation (mg/L)	**NOAEC = NE** **LOAEC = 0.02**	–**	**NOAEC = 1.1 (highest concentration tested)**	**NOAEC~ 0.38 (highest concentration tested)**	–**	–**	–**	**NOAEC ~ 0.348 (highest concentration tested)**
Repeated-Dose Toxicity NOAEL/ LOAEL Oral (mg/kg-bw/day)	**(rat)** **NOAEL = 8** **LOAEL = 17** **(mice)** **NOAEL = 100** **LOAEL = 200**	No data (rat) NOAEL = 8 LOAEL = 17 (RA) (mice) NOAEL = 100 LOAEL = 200 (RA)	No data (rat) NOAEL = 8 LOAEL = 17 (RA) (mice) NOAEL = 100 LOAEL = 200 (RA)	No data (rat) NOAEL = 8 LOAEL = 17 (RA) (mice) NOAEL = 100 LOAEL = 200 (RA)	No data (rat) NOAEL = 8 LOAEL = 17 (RA) (mice) NOAEL = 100 LOAEL = 200 (RA)	**(rat)** **NOAEL = 5** **LOAEL = 30**	No Data (rat) NOAEL = 5 LOAEL = 30 (RA)	–**
Reproductive Toxicity NOAEL/ LOAEL Oral (mg/kg-bw/day)	Data Gap Data from repeated-dose study indicate effects on sperm motility in mice. Data from two-year study in rats show increased incidence of testicular adenoma.					Data Gap Data from repeated-dose study indicate effects on spermatocytes and spermatids in rats.		Data Gap
Developmental Toxicity NOAEC/ LOAEC Inhalation (mg/L) **Maternal Toxicity** **Developmental Toxicity**	Data Gap					Data Gap		**NOAEC = 0.003** **LOAEC = 0.015** **NOAEC = NE** **LOAEC = 0.003**

Table 8. Summary of Human Health Data

Endpoints	Sub-Category I					Sub-Category II		Sub-Category III
	Pyridine (CASRN 110-86-1)	**4-Picoline (CASRN 108-89-4)**	**3-Picoline (CASRN 108-99-6)**	**2-Picoline (CASRN 109-06-8)**	**Pyridine, alkyl derivatives (CASRN 68391-11-7)**	**Nicotinonitrile (CASRN 100-54-9)**	**Picolinonitrile (CASRN 100-70-9)**	**Piperidine (CASRN 110-89-4)**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**	**Negative**	**Negative**	**Negative**	No Data Negative (RA)	**Negative**	No Data Negative (RA)	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vitro*	**Negative**	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)	**Negative**	No Data Negative (RA)	–**
Genetic Toxicity – Chromosomal Aberrations *In vivo*	**Negative**	–**	–**	–**	–**	–**	–**	**Negative**
Genetic Toxicity – Other Effects *In vitro*		–**	–**	–**	–**	–**	–**	–**
Unscheduled DNA Synthesis	**Negative**							
Mouse Lymphoma	**Negative**							
SCE	**Negative**							
Skin Irritation	**Corrosive**	**Corrosive**	**Corrosive**	**Corrosive**	–**	–**	–**	**Corrosive**
Eye Irritation	**Severe**	**Severe**	**Severe**	**Severe**	–**	–**	–**	**Severe**
Skin Sensitization	**Negative**	–**	–**	–**	–**	–**	–**	**Positive**
Carcinogenicity	**Positive**	–**	–**	–**	–**	–**	–**	**Negative**

Measured data in bold text; (RA) = read across; −** endpoint not addressed for this chemical; NE = not established; m = male; f = female

4 Hazards to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 9. The table also indicates where data for tested category members are read across (RA) to untested members of the category.

Acute Toxicity to Fish

Sub-Category I
Pyridine (CASRN 110-86-1)
Fathead minnow (*Pimephales promelas*) were exposed to pyridine (concentrations not stated) under flow-through test conditions for 96 hours with analytical monitoring.
96-h LC_{50} = 99 mg/L

4-Picoline (CASRN 108-89-4)
Sheepshead minnow (*Cyprinodon variegatus*) were exposed to 4-picoline (concentrations not stated) under flow-through test conditions for 96 hours with analytical monitoring.
96-h LC_{50} = 400 mg/L

3-Picoline (CASRN 108-99-6)
Zebra fish (*Brachydanio rerio*) were exposed to 3-picoline at nominal concentrations of 0, 100, 180, 320, 560 and 1000 mg/L under static-renewal conditions for 96 hours with no analytical monitoring. Mortality was observed at concentrations greater than 560 mg/L.
96-h LC_{50} > 560 mg/L

2-Picoline (CASRN 109-06-8)
Fathead minnow (*Pimephales promelas*) were exposed to 2-picoline at measured concentrations of <15, 230, 333, 475, 718 or 1119 mg/L under flow-through conditions for 96 hours with analytical monitoring. Mortality was 100% at 1119 mg/L and occurred within 3 hours following exposure.
96-h LC_{50} = 897 mg/L

Pyridine, alkyl derivs (CASRN 68391-11-7)
Rainbow trout (*Oncorhynchus mykiss*) were exposed to pyridine, alkyl derivative at nominal concentrations of 0, 6.25, 12.5, 25, 50 and 100 mg/L under static conditions for 96 hours with no analytical monitoring. Mortality was 100% at 100 mg/L and 80% at 50 mg/L.
96-h LC_{50} = 40 mg/L

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)
Data for acute toxicity to fish were not provided for nicotinonitrile. A 96-hour EC_{50} for fish, estimated by ECOSAR (v. 1.00a), was provided to evaluate the acute toxicity of nicotinonitrile.
96-h EC_{50} = 2264 mg/L (ECOSAR v. 1.00a)

Picolinonitrile (CASRN 100-70-9)
Fathead minnow (*Pimephales promelas*) were exposed to picolinonitrile (concentrations not stated) under flow-through conditions for 96 hours with analytical monitoring.
96-h LC_{50} = 726 mg/L

Sub-Category III
Piperidine (CASRN 110-89-4)
A standard acute toxicity test for fish was not provided for piperidine. A 96-hour EC_{50} for fish, estimated by ECOSAR (v. 1.00a), was provided to evaluate the acute toxicity of piperidine.
96-h EC_{50} = 46 mg/L (ECOSAR v. 1.00a)

Acute Toxicity to Aquatic Invertebrates

Sub-Category I
Pyridine (CASRN 110-86-1)
Daphnia magna, pulex, and cucullata were exposed (concentrations not stated) to pyridine under static conditions for 48 hours with no analytical monitoring.
48-h EC_{50} = 1130-1755, 575 and 2470 mg/L for *magna, pulex* and *cucullata*, respectively.

4-Picoline (CASRN 108-89-4)
A standard acute toxicity test for invertebrates was not provided for 4-picoline. A 48-hour EC_{50} for invertebrates, estimated by ECOSAR (v. 1.00a), was provided to evaluate the acute toxicity of 4-picoline.
48-h EC_{50} = 137 mg/L (ECOSAR v. 1.00a)

3-Picoline (CASRN 108-99-6)
Water flea (*Daphnia magna*) were exposed to 3-picoline at nominal concentrations of 0, 100, 180, 320, 560 or 1000 mg/L under static conditions for 48 hours with no analytical monitoring.
48-h EC_{50} = 320 mg/L

2-Picoline (CASRN 109-06-8)
A standard acute toxicity test for invertebrates was not provided for 2-picoline. A 48-hour EC_{50} for invertebrates, estimated by ECOSAR (v. 1.00a), was provided to evaluate the acute toxicity of 2-picoline.
48-h EC_{50} = 137 mg/L (ECOSAR v. 1.00a)

Pyridine, alkyl derivs (CASRN 68391-11-7)
Waterflea (*Daphnia magna*) were exposed to pyridine alkyl derivatives at nominal concentrations of 0, 31.3, 62.5, 125, 250 and 500 mg/L under static conditions for 48 hours with no analytical monitoring. Mortality was 100% at 250 and 500 mg/L.
48-h EC_{50} = 69 mg/L

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)

A standard acute toxicity test for invertebrates was not provided for nicotinonitrile. A 48-hour EC_{50} for invertebrates, estimated by ECOSAR (v. 1.00a), was provided to evaluate the acute toxicity of nicotinonitrile.
48-h EC_{50} = 1000 mg/L (ECOSAR v. 1.00a)

Picolinonitrile (CASRN 100-70-9)
A standard acute toxicity test for invertebrates was not provided for picolinonitrile. A 48-hour EC_{50} for invertebrates, estimated by ECOSAR (v. 1.00a), was provided to evaluate the acute toxicity of picolinonitrile.
48-h EC_{50} = 1000 mg/L (ECOSAR v. 1.00a)

Sub-Category III
Piperidine (CASRN 110-89-4)
A standard acute toxicity test for invertebrates was not provided for piperidine. A 48-hour EC_{50} for invertebrates, estimated by ECOSAR (v. 1.00a), was provided to evaluate the acute toxicity of piperidine.
48-h EC_{50} = 4 mg/L (ECOSAR v. 1.00a)

Toxicity to Aquatic Plants

Sub-Category I
Pyridine (CASRN 110-86-1)
A standard toxicity test for aquatic plants was not provided for pyridine. A 96-hour EC_{50} for aquatic plants, estimated by ECOSAR (v. 1.00a), was provided to evaluate the toxicity to aquatic plants of pyridine.
96-h EC_{50} = 92 mg/L (ECOSAR v. 1.00a)

4-Picoline (CASRN 108-89-4)
A standard toxicity test for aquatic plants was not provided for 4-picoline. A 96-hour EC_{50} for aquatic plants, estimated by ECOSAR (v. 1.00a), was provided to evaluate the toxicity to aquatic plants of 4-picoline.
96-h EC_{50} = 49 mg/L (ECOSAR v. 1.00a)

3-Picoline (CASRN 108-99-6)
Green algae (*Pseudokirchneriella subcapitata)* were exposed to 3-picoline at nominal concentrations 0, 10, 32, 100, 320 or 1000 mg/L for 72 hours with no analytical monitoring. The reduction in the average specific growth rate began at 10 mg/L and continued till growth completely stopped at 1000 mg/L.
72-h EC_{50} (growth rate) = 320 mg/L

2-Picoline (CASRN 109-06-8)
A standard toxicity test for aquatic plants was not provided for 2-picoline. A 96-hour EC_{50} for aquatic plants, estimated by ECOSAR (v. 1.00a), was provided to evaluate the toxicity to aquatic plants of 2-picoline.
96-h EC_{50} = 49 mg/L (ECOSAR v. 1.00a)

Pyridine, alkyl derivatives (CASRN 68391-11-7)
A standard toxicity test for aquatic plants was not provided for pyridine, alkyl derivatives. A 96-hour EC_{50} for aquatic plants, estimated by ECOSAR (v. 1.00a), was provided to evaluate the toxicity to aquatic plants from pyridine, alkyl derivatives.
96-h EC_{50} = 14.2 mg/L (ECOSAR v. 1.00a)

Sub-Category II
Nicotinonitrile (CASRN 100-54-9)
A standard toxicity test for aquatic plants was not provided for nicotinonitrile. A 96-hour EC_{50} for aquatic plants, estimated by ECOSAR (v. 1.00a), was provided to evaluate the toxicity to aquatic plants of nicotinonitrile.
96-h EC_{50} = 232 mg/L (ECOSAR v. 1.00a)

Picolinonitrile (CASRN 100-70-9)
A standard toxicity test for aquatic plants was not provided for picolinonitrile. A 96-hour EC_{50} for aquatic plants, estimated by ECOSAR (v. 1.00a), was provided to evaluate the toxicity to aquatic plants of picolinonitrile.
96-h EC_{50} = 232 mg/L (ECOSAR v 1.00a)

Sub-Category III
Piperidine (CASRN 110-89-4)
A standard toxicity test for aquatic plants was not provided for piperidine. A 96-hour EC_{50} for aquatic plants, estimated by ECOSAR (v. 1.00a), was provided to evaluate the toxicity to aquatic plants of piperidine.
96-h EC_{50} = 1.2 mg/L (ECOSAR v. 1.00a)

Conclusion:
Sub-Category I**:** The acute hazard to fish is based on the toxicity values for CASRNs 108-89-4, 108-99-6, 109-06-8, 110-86-1 and 68391-11-7 ranging from 40 to 897 mg/L. The acute hazard to aquatic invertebrates is based on the toxicity values for CASRNs 108-99-6, 110-86-1 and 68391-11-7 ranging from 69 to 2470 mg/L. The acute hazard to aquatic plants is based on the toxicity value for CASRN 108-99-6 of 320 mg/L.

Sub-Category II**:** The acute hazard to fish is based on the toxicity value for CASRN 100-70-9 of 726 mg/L. The acute hazard to aquatic invertebrates is based on the estimated toxicity values for CASRNs 100-54-9 and 100-70-9 of 1000 mg/L. The acute hazard to aquatic plants is based on the estimated toxicity values for CASRNs 100-54-9 and 100-70-9 of 232 mg/L.

The acute toxicity to aquatic invertebrates and aquatic plants remain as data gaps under the HPV Challenge Program.

Sub-Category III**:** The acute hazard to fish is based on the estimated toxicity value for CASRN 110-89-4 of 46 mg/L. The acute hazard to aquatic invertebrates is based on the estimated toxicity value for CASRN 110-89-4 of 4 mg/L. The acute hazard to aquatic plants is based on the estimated toxicity values for CASRN 110-89-4 of 1.2 mg/L.

The acute toxicity to fish, aquatic invertebrates and aquatic plants remain as data gaps under the HPV Challenge Program.

Table 9. Summary of Environmental Effects – Aquatic Toxicity Data

Endpoints	Sub-Category I					Sub-Category II		Sub-Category III
	Pyridine (CASRN 110-86-1)	**4-Picoline (CASRN 108-89-4)**	**3-Picoline (CASRN 108-99-6)**	**2-Picoline (CASRN 109-06-8)**	**Pyridine, alkyl derivatives (CASRN 68391-11-7)**	**Nicotinonitrile (CASRN 100-54-9)**	**Picolinonitrile (CASRN 100-70-9)**	**Piperidine (CASRN 110-89-4)**
Fish 96-h LC_{50} (mg/L)	**99**	**400**	**>560**	**897**	**40**	No Data 726 (RA)	**726**	Data Gap 46 (e)
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**575-2470**	No Data 320 (RA)	**320**	No Data 320 (RA)	**69**	Data Gap 1000 (e)	Data Gap 1000 (e)	Data Gap 4 (e)
Aquatic Plants 72-h EC_{50} (mg/L)	No Data 320 (RA)	No Data 320 (RA)	**320**	No Data 320 (RA)	No Data 320 (RA)	Data Gap 232 (96-h) (e)	Data Gap 232 (96-h) (e)	Data Gap 1.2 (96-h) (e)

Measured data (i.e. derived from testing) are in bold; (e) = estimated data (i.e., derived from modeling); (RA) = read across