Screening Assessment for the Challenge

Pyridine, alkyl derivs.

Chemical Abstracts Service Registry Number
68391-11-7

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment on pyridine, alkyl derivs., Chemical Abstracts Service Registry Number* 68391-11-7. This substance was identified in the categorization of the Domestic Substances List as a high priority for action under the Challenge. Pyridine, alkyl derivs. was identified as a high priority as it was considered to pose the greatest potential for exposure of individuals in Canada and is classified by other agencies on the basis of carcinogenicity. The substance met the ecological categorization criteria for persistence but did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms.

According to information submitted under section 71 of CEPA 1999, pyridine, alkyl derivs. was not reported to be manufactured by any company in Canada during the calendar year of 2006 above the 100 kg reporting threshold. However, 1 000 000–10 000 000 kg of the substance were reported to be imported in 2006. The major use of pyridine, alkyl derivs. is corrosion inhibition of oil and gas wells and pipelines in Canada and this use is considered the principal source of potential releases to the environment through cleaning/washing of tanker trucks and periodic pipeline leaks under normal operating conditions. More minor uses of pyridine, alkyl derivs. include as: a formulant in one registered herbicide, a corrosion inhibitor in industrial cleaning and de-scaling products for closed water heat transfer systems, and an incidental additive in cleaning products for food contact surfaces.

As defined by the Chemical Abstracts Service, pyridine, alkyl derivs. is the complex combination of polyalkylated pyridines derived from coal-tar distillation or as high-boiling distillates approximately above 150°C from the reaction of ammonia with acetaldehyde, formaldehyde or paraformaldehyde. This is also the Domestic Substances List (DSL) definition. Therefore, this assessment only directly considers the polyalkylated components of the complex mixture. However, commercial versions of the substance in Canada may contain production by-products, such as non-alkylated pyridines, which are considered to be outside of the DSL definition.

Exposure of the general population to pyridine, alkyl derivs. via environmental media was estimated based upon the principal use in Canada, i.e., corrosion inhibition in the oil and gas extraction industry, which accounts for over 90% of the total use quantity in 2006. Conservatively estimated annual release quantities from process and occasional leaks are considered to be very low. While pyridine, alkyl derivs. is present in some cleaning products for food contact surfaces, dietary exposure for the general population from this source is not expected, as a potable water rinse is required after cleaner application. In addition, while various alkyl pyridines were identified in a variety of foods

and beverages, pyridine, alkyl derivs. as a complex mixture as defined by the Chemical Abstracts Service would not be expected in foods or beverages and, therefore, dietary exposure is not expected.

Based on the limited empirical health effects information available, it is considered that the major components of pyridine, alkyl derivs. within the Chemical Abstracts Service definition, i.e., discrete short chain alkylated pyridines, such as mono-, di-, tri-methylpyridines, ethylpyridines, methylethylpyridines and propylpyridines, are not highly hazardous. It is likely that the hazard potential of pyridine, alkyl derivs. is due to the presence of by-products in commercial versions of the substance, such as non-alkylated derivatives of pyridine.

As exposure of the general population through environmental media in Canada is expected to be negligible, and exposure is not expected from foods or beverages or consumer products, the risk to human health is considered to be low.

Based on the information available, it is concluded that pyridine, alkyl derivs. does not meet the criteria in paragraph 64*(c)* of CEPA 1999, as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Based mostly on empirical biodegradation data, the substance is not expected to degrade quickly in the environment. It is persistent in air, water, soil and sediments. This substance does not have the potential to accumulate in organisms or to biomagnify in trophic food chains. The substance has been determined to meet the persistence but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*. Empirical aquatic toxicity values indicate that the substance is not highly hazardous to aquatic organisms.

For this screening assessment, a realistic worst-case exposure scenario was selected in which an industrial operation discharges pyridine, alkyl derivs. into the aquatic environment. The conservative predicted environmental concentration in water (PEC) was less than the very conservative predicted no-effect concentration (PNEC) calculated based on effects data for green algae.

Based on the information available, it is concluded that pyridine, alkyl derivs. does not meet the criteria in paragraphs 64*(a)* and *(b)* as it is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

It is, therefore, concluded that pyridine, alkyl derivs. does not meet any of the criteria set out in section 64 of CEPA 1999.

This substance will be considered for inclusion in the Domestic Substances List inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or to human health.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce in Canada; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE) and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance, pyridine, alkyl derivs. was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by other agencies on the basis of carcinogenicity. The Challenge for this substance was published in the *Canada Gazette* on December 26, 2009 (Canada 2009a, 2009b). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information pertaining to the substance were received.

Although pyridine, alkyl derivs. was determined to be a high priority for assessment with respect to human health and did meet the ecological criteria for persistence, it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999. Screening assessments examine

scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution[†].

This final screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to October 2010 for human health and ecological sections of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions.

Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The final screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

This final screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from Dr. Susan Griffin (United States Environmental Protection Agency), Mr. Michael Jayjock (The Lifeline Group) and Dr. Bernard Gadagbui (Toxicology Excellence for Risk Assessment). Additionally, the draft of this screening assessment was subject to a 60-day public comment period.

Although external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment Canada. Approaches used in the screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel.

The critical information and considerations upon which the final assessment is based are summarized below.

[†] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) Challenge Batches 1-12 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of the regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being undertaken under other sections of CEPA or other Acts.

Substance Identity

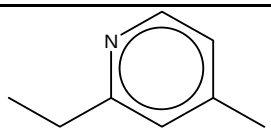
Substance name
For the purposes of this document, this substance will be referred to as pyridine, alkyl derivs., the name listed on the Domestic Substances List (DSL).

Pyridine, alkyl derivs. is a UVCB (**U**nknown or **V**ariable Composition, **C**omplex Reaction Products or **B**iological Materials) substance that, according to the DSL definition of a UVCB, cannot be represented by a single structural diagram and a single chemical formula. The Chemical Abstracts Service defines pyridine, alkyl derivs. as "the complex combination of polyalkylated pyridines derived from coal tar distillation or as high-boiling distillates approximately above 150°C from the reaction of ammonia with acetaldehyde, formaldehyde or paraformaldehyde" (NCI 2010). This is also the DSL definition. As a result, this assessment only directly considers the polyalkylated pyridines that are contained in the UVCB mixture. 2-ethyl-4-methyl pyridine (EPI Suite™'s default structure) and its isomeric structure 5-ethyl-2-methyl-pyridine (CAS RN 104-90-5) with boiling points > 170 ^{o}C were selected as discrete representative structures for pyridine, alkyl derivs.

However, commercial versions of the substance in Canada also contain production by-products, such as non-alkylated pyridines, which are considered to be outside of the DSL definition. The typical per weight concentration of alkylated pyridine constituents in commercial products is greater than 40 % (Environment Canada 2002; Vertellus 2010a, 2010b). Please refer to the Sources section below for further discussion of the identities of these potential by-products.

Table 1. Substance identity for pyridine, alkyl derivs.

Chemical Abstracts Service Registry Number (CAS RN)	68391-11-7
DSL name	Pyridine, alkyl derivs.
National Chemical Inventories (NCI) names[1]	*Pyridine, alkyl derivs. (TSCA, EINECS, ECL, PICCS, ASIA-PAC, NZIoC)* *Pyridine, alkyl derivatives (AICS, PICCS)*
Other names	*Paraldehyde and ammonia reaction product* *Pyridine bases* *Pyridines, polyalkylated, higher boiling fraction* *Pyridines, polyalkylated, lower boiling fraction* *Pyridines, polyalkylated: polyalkylated pyridines*
Chemical group (DSL Stream)	Organic UVCB
Major chemical class or use	Pyridines
Major chemical sub-class	Alkylated pyridines
Representative Chemical formula	$C_8H_{11}N_1$

Representative chemical structure (2-ethyl-4-methylpyridine) used to run the estimation model[2]	
Representative SMILES used to run the estimation model[3]	n1ccc(C)cc1CC
Molecular mass of representative chemical structure used to run the estimation model	121.18 g/mol

1 National Chemical Inventories (NCI). 2010: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); NZIoC (New Zealand Inventory of Chemicals), PICCS (Philippine Inventory of Chemicals and Chemical Substances); and TSCA (Toxic Substances Control Act Chemical Substance Inventory).

2 This substance is a UVCB (Unknown or Variable Composition, Complex Reaction Products, or Biological Materials); i.e., it is not a discrete chemical and thus may be characterized by a variety of structures. To assist with modelling, the structure and corresponding SMILES presented here were chosen to represent the substance. The representative structure chosen, 2-ethyl-4-methylpyridine, was selected from EPI Suite™ software (EPI Suite™ 2000-2008) and is considered to be an isomer of the representative structure of pyridine, alkyl derivs. used in a screening-level hazard characterization prepared by the United States Environmental Protection Agency, 5-ethyl-2-methylpyridine (US EPA 2009).

3 Simplified Molecular Line Input Entry System.

Physical and Chemical Properties

Few empirical data are available for pyridine, alkyl derivs. The programs, OECD Toolbox (OECD 2010) and ChemIDplus® (ChemIDplus Advanced 2010), did not identify any appropriate analogue data for pyridine, alkyl derivs. Therefore, analogue data were identified through the New Substances Notifications received by Environment Canada under the New Substances Notification Regulations of CEPA 1999. The names of the analogue substances may not be identified due to the confidentiality of these data and will be referred to as “Notified Substances A, B and C” (see Table 2a, 2b) (Environment Canada 2007a, 2007b, 2002). Two other analogues were identified through empirical studies submitted by industry. Information on the latter two analogues is presented in Table 2a.

Table 2a. Analogues selected to support the screening assessment

CAS RN	Substance name	Structure	Available empirical data
Confidential	Notified Substance A	n/a	Melting point, boiling point, density, vapour pressure, log K_{ow}, water solubility
Confidential	Notified Substance B	n/a	Melting point, boiling point, density, vapour pressure, log K_{ow}, water solubility
Confidential	Notified Substance C	n/a	Melting point, boiling point, density, vapour pressure, log K_{ow}, water solubility, pKa, persistence
168612-09-7	Pyridine, alkyl derivs., acetates	n/a	Persistence, aquatic toxicity
168612-10-0	Acetic acid mercapto-, compds with alkylpyridines	n/a	Persistence, aquatic toxicity

Table 2b below contains modelled physical and chemical properties of pyridine, alkyl derivs. that are relevant to its environmental fate. Models based on quantitative structure-activity relationships (QSAR) were used to generate data for some of the physical and chemical properties of pyridine alkyl derivs. using the EPI Suite™ representative structure 2-ethyl-4-methylpyridine. Empirical data from an isomer of this representative structure, 5-ethyl-2-methylpyridine, were also included. Since these models only accept the neutral form of a chemical as input (in SMILES form), the modelled values shown in Table 2b are for neutral forms.

Table 2b. Physical and chemical properties for pyridine, alkyl derivs., three analogue substances (Notified Substances A, B, C)[a], the neutral form of the representative structure 2-ethyl-4-methylpyridine (EPI Suite™) and 5-ethyl-2-methylpyridine, an isomer of the representative structure.

Property	Substance	Type	Value[b]	Reference
Physical state	Pyridine, alkyl derivs. (UVCB mixture)	Yellow to brown liquid		Vertellus 2008
Density (kg/m^3)	Pyridine, alkyl derivs. (UVCB mixture)	Experimental	970 - 1 000 [at 20ºC]	Vertellus 2008
		Experimental	1 020 [at 20ºC]	Lonza 2008b
		Experimental	995 – 1 102 (8.3 – 9.2 lb/gal)	Resonance Specialties Ltd. 2008
		Experimental	940	ChemicalLand21 2010
	Notified Substance A[a]	Experimental (OECD 109)	1 062 [at 20ºC]	Environment Canada 2007a

Property	Substance	Type	Value[b]	Reference
	Notified Substance B[a]	Experimental (OECD 109)	1 162 [at 20ºC]	Environment Canada 2007b
	Notified Substance C[a]	Experimental (OECD 109)	534 [at 20ºC]	Environment Canada 2002
	Isomer of representative structure (5-ethyl-2-methylpyridine)	N/A[c]	920.8	OECD 1995
Melting point (ºC)	Pyridine, alkyl derivs. (UVCB mixture)	Experimental	-17	Lonza 2008b
		Experimental	40	Chemical Book 2010
	Representative structure (2-ethyl-4-methylpyridine)	Modelled	4.29	MPBPWIN 2008
	Isomer of representative structure (5-ethyl-2-methylpyridine)	N/A[c]	-70.9	OECD 1995
	Notified Substance A[a]	Experimental (OECD 102)	-9.2	Environment Canada 2007a
	Notified Substance B[a]	Experimental (OECD 102)	3.85	Environment Canada 2007b
	Notified Substance C[a]	Experimental (OECD 102)	76 - 107	Environment Canada 2002
Boiling point (ºC)	Pyridine, alkyl derivs. (UVCB mixture)	Experimental	204 – 361	Resonance Specialties Ltd. 2008
		Experimental	210 – 340	Lonza 2008b
		Experimental	130 – 170	Chemical Book 2010
		Experimental	185 – 300	Vertellus 2008
	Representative structure (2-ethyl-4-methylpyridine)	Modelled	179.83	MPBPWIN 2008
	Isomer of representative structure (5-ethyl-2-methylpyridine)	N/A[c]	178.3	OECD 1995
	Notified Substance A[a]	Experimental (OECD 103)	171.85 [at 101.5 kPa]	Environment Canada 2007a
	Notified Substance B[a]	Experimental (OECD 103)	235.85 [at 101.4 kPa]	Environment Canada 2007b

Property	Substance	Type	Value[b]	Reference
	Notified Substance C[a]	Experimental (OECD 103)	214 - 220	Environment Canada 2002
Vapour pressure (Pa)	Pyridine, alkyl derivs. (UVCB mixture)	Experimental	<100 [at 50ºC]	Lonza 2008b
	Representative structure (2-ethyl-4-methylpyridine)	Modelled	130 (0.974 mm Hg) [at 25ºC]	MPBPWIN 2008
	Notified Substance A[a]	Experimental (OECD 104)	0.37 [at 25ºC]	Environment Canada 2007a
	Notified Substance B[a]	Experimental (OECD 104)	0.043 [at 25ºC]	Environment Canada 2007b
	Notified Substance C[a]	Experimental (OECD 104)	9.38×10^{-3} [at 21ºC]	Environment Canada 2002
Henry's Law constant ($Pa \cdot m^3/mol$)	Representative structure (2-ethyl-4-methylpyridine)	Modelled	1.16 (1.14×10^{-5} atm·m3/mol) [Bond method] 1.39 (1.38×10^{-5} atm·m3/mol) [Group method]	HENRYWIN 2008
	Notified Substance C[a]	Calculated	4.1×10^{-6}	Environment Canada 2002
Log K_{ow} (octanol-water partition coefficient) (dimensionless)	Representative structure (2-ethyl-4-methylpyridine)	Modelled	2.39	KOWWIN 2008
	Notified Substance A[a]	Experimental (OECD 117 HPLC)[d]	0.3 – 3.81	Environment Canada 2007a
	Notified Substance B[a]	Experimental (OECD 117 HPLC)[d]	0.3 – 6.5	Environment Canada 2007b
	Notified Substance C[a]	Experimental (OECD 117 HPLC)	-0.49 to -0.14	Environment Canada 2002
Log K_{oc} (organic carbon-water partition coefficient) (dimensionless)	Representative structure (2-ethyl-4-methylpyridine)	Modelled	2.55 [MCI method][e] 2.42 [K_{ow} method]	KOCWIN 2009
Water solubility (mg/L)	Pyridine, alkyl derivs. (UVCB mixture)	Experimental	Slightly soluble, <15% [at 20ºC]	Resonance Specialties Ltd. 2008

Property	Substance	Type	Value[b]	Reference
		Experimental	Slightly soluble	Vertellus 2008
		Experimental	Emulsifiable	Lonza 2008b
	Representative structure (2-ethyl-4-methylpyridine)	Modelled	18 030 [at 25ºC]	WSKOWWIN 2008
	Isomer of representative structure (5-ethyl-2-methylpyridine)	N/A[d]	12 000	OECD 1995
	Notified Substance A[a]	Experimental (OECD 105)[d]	123 - 7650	Environment Canada 2007a
	Notified Substance B[a]	Experimental (OECD 105)[d]	105 - 6290	Environment Canada 2007b
	Notified Substance C[a]	Experimental (OECD 105)	>54 700	Environment Canada 2002
pKa (acid dissociation constant) (dimensionless)	Isomer of representative structure (5-ethyl-2-methylpyridine)	Experimental	pKa = 6.6	OECD 1995
	Notified Substance C[a]	Experimental (OECD 112)	pKa_1 = 5.41 pKa_2 = 7.16	Environment Canada 2002

[a] As OECD Toolbox (OECD 2010) and ChemIDplus® (ChemIDplus Advanced 2010) did not identify appropriate analogue data for pyridine, alkyl derivs., analogues to assist in characterizing environmental fate, environmental persistence and ecotoxicity were selected from three New Substances Notification packages received by Environment Canada under the New Substances Notification Regulations of CEPA 1999. As the names of the analogues may not be identified due to the confidentiality of the data, they have been given the names "Notified Substance A" (Environment Canada 2007a), "Notified Substance B" (Environment Canada 2007b) and "Notified Substance C" (Environment Canada 2002).

[b] Values and units in parentheses ( ) represent those originally reported by the authors or estimated by the models.

[c] N/A: data not available.

[d] A large range of values is reported for $\log K_{ow}$ and water solubility for both Notified Substance A and B likely due to the wide variety of components present in the UVCB mixture.

[e] Molecular Connectivity Index method.

Sources

Pyridine, alkyl derivs. is a UVCB mixture of polyalkylated pyridines that, as defined by the Chemical Abstracts Service, may either be derived naturally through coal tar distillation or synthetically as the high-boiling distillates approximately above 150°C from the reaction of ammonia with acetaldehyde, formaldehyde or paraformaldehyde (NCI 2010). Pyridine, alkyl derivs. occurs only as a mixture, as no natural sources of

single pyridine compounds exist and few commercial synthetic methods produce a single pyridine compound (Scriven et al. 1996).

Natural production of pyridine, alkyl derivs. was the sole source of production until the early 1950s (Bizzari et al. 2007). Coal tar, containing roughly 0.01% by weight alkyl pyridines (Scriven et al. 1996), became insufficient to satisfy commercial demand for alkyl pyridines and, by 1988, less than 5% of alkyl pyridines were produced globally through natural production (Scriven et al. 1996). Natural production involves isolation of the alkyl pyridines from coal tar through solubilisation in acid to form organic salts, neutralization with base, then subsequent distillation at 115.5 – 146°C to isolate pyridine, alkyl derivs. (Scriven et al. 1996; Bizzari et al. 2007). Variations in composition are attributable to the nature of the distillation process and coal type (Johansen et al. 1997).

Synthetic production of pyridine, alkyl derivs., accounting for over 95% of current global production, involves the general reaction of aldehydes or ketones with ammonia in the presence of a fluidized solid-acid catalyst (Shinkichi et al. 1998; Bizzari et al. 2007; ATSDR 1992). This reaction, known as the Chichibabin reaction, may occur either in the gas phase at 350 – 550°C or in the liquid phase, using starting materials that are derived from petroleum (Scriven et al. 1996). A variety of alkyl pyridines will be produced with composition dependent upon the reactants chosen, additives, specialized technology and reaction conditions (Bizzari et al. 2007). As the reaction also co-produces many high boiling-point by-products, the total yield of commercially desired alkyl pyridines is not 100% in final commercial versions of the pyridine, alkyl derivs. mixture (Reddy et al. 2008; Shinkichi et al. 1998). These by-products may include various higher substituted alkyl pyridines with their isomers, alkylated benzenes, alkyl or unsaturated nitriles, alkanes and alkenes (Scriven et al. 2006) and large-size carbon-backbone linear and branched polymers with various double bonds, hydroxyl or amino groups (Vertellus 2010a). Various undefined amines, and the derivatives of quinoline, indole, naphthalene, pyrrole and pyrimidine may also be present in commercial versions of pyridine, alkyl derivs. (Vertellus 2008; Vertellus 2010a). The individual weight percentage of aniline (CAS RN 62-53-3) and quinoline (CAS RN 91-22-5) in commercial versions of pyridine, alkyl derivs. has been reported to be ≤0.5 % (Vertellus 2010a). Benzene is expected to be removed in the distillation process based on its low boiling point of 80^{o}C (Merck Index 1996) and is not present in commercial versions of pyridine, alkyl derivs. in Canada above the detection limit of 0.01 % by weight (Vertellus 2010a). By-products in commercial versions of pyridine, alkyl derivs., such as those mentioned above, are not directly considered in this assessment as they are outside of the DSL definition.

In response to a notice issued under section 71 of CEPA 1999, pyridine, alkyl derivs. was not reported to be manufactured at a quantity above the reporting threshold of 100 kg in 2006 (Environment Canada 2010a). Importation activities (whether alone, in a mixture, in a product or in manufactured items) were reported to be in the range of 1 000 000 – 10 000 000 kg in 2006 (Environment Canada 2010a).

The quantity reported to be manufactured in, imported into, or in commerce in Canada during the 1986 calendar year was 2 000 000 kg (Environment Canada 1988).

Uses

In response to a notice issued under section 71 of CEPA 1999, total use of pyridine, alkyl derivs. in Canada during the 2006 calendar year was reported to be in the range of 1 000 000 – 10 000 000 kg (Environment Canada 2010a).

The principal use of pyridine, alkyl derivs., accounting for over 90% of the total reported use quantity in 2006, was in the formulation of corrosion inhibitors used in oil and gas wells and pipelines at a concentration of 0.3-46% by weight (Environment Canada 2010a). The pyridine moiety of pyridine, alkyl derivs. contains a delocalized lone pair of electrons on the nitrogen atom that is not involved in the aromatic pi-bond of the six-membered ring (Bernthsen and Bansal 2003). The lone pair of electrons allows the pyridine moiety to act as a weak Lewis base by scavenging protons from acid molecules, in forming a pyridinium ion, to prevent acid attack of metal equipment such as gas and oil wells and pipelines (IARC 2000). In Canada, pyridine, alkyl derivs. may also be used as a corrosion inhibitor in an industrial chemical cleaner at unspecified concentration (Environment Canada 2010a) and in an acidic cleaning and de-scaling product for boilers and cooling towers at 0.1-1.0% by weight (Aquarian 2009).

Pyridine, alkyl derivs. was not notified as an ingredient in cosmetic products in Canada (CNS 2010) and does not appear on the Cosmetic Ingredient Hotlist, Health Canada's administrative list of ingredients that are intended to be prohibited or restricted for use in cosmetics in Canada (Health Canada 2010). Pyridine, alkyl derivs. is currently used as a formulant (non-active ingredient) in one registered herbicide product (PMRA 2010; July 2010 email from Pest Management Regulatory Agency, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Pyridine, alkyl derivs. is not listed as an approved food additive under Division 16 of the *Food and Drug Regulations* (Canada [1978]). Pyridine, alkyl derivs. was not identified in food packaging applications but was identified to be present and/or used in formulations of incidental additives that are used in two cleaning products for food contact surfaces and equipment and three de-scaling products, not for contact with foods, for use in boilers, condensers, chillers, evaporators and heat exchangers in food plants (July-August 2010 emails from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). As a potable water rinse is required after application of the two cleaning products, any exposure to the general population through food is anticipated to be incidental to non-existent (August 2010 email from Food Directorate, Health Canada to Risk Management Bureau, Health Canada; unreferenced).

Pyridine, alkyl derivs. is not listed in the Drug Product Database (DPD), the Therapeutic Products Directorate's internal Non-Medicinal Ingredient Database, the Natural Health Products Ingredients Database (NHPID) or the Licensed Natural Health Products Database (LNHPD) as a medicinal or a non-medicinal ingredient present in final pharmaceutical products, natural health products or veterinary drugs (DPD 2010; NHPID

2010; LNHPD 2010; May-June 2010 emails from Therapeutic Products Directorate, Health Canada to Risk Management Bureau, Health Canada; unreferenced).

Outside of Canada, other uses of pyridine, alkyl derivs. include manufacture of textiles, rubber, plastic, pulp and paper products (SPIN 2010), as a corrosion inhibitor in the integrated iron and steel manufacturing industry (Scorecard 2010) and as an active ingredient in eight pest control products registered for unrestricted use in repelling cats, dogs, rabbits and other wildlife (Scorecard 2010). Individual alkyl pyridines may be isolated by distillation from pyridine, alkyl derivs. for use as intermediates in the production of bioactive agents such as agricultural herbicides and insecticides, vitamin B_3, anti-ulcer and anti-arteriosclerotic drugs, flavouring agents, veterinary products, surfactants, catalysts and adhesives for textiles (Shinkichi et al. 1998; Peppard and Halsey 1980; Fetzner 1998; Tsukioka and Murakami 1987; Shimizu et al. 1993) in addition to functioning as solvents, due to their relative lack of reactivity, in organic chemistry (Scriven et al. 1996).

Releases to the Environment

In response to a notice issued under section 71 of CEPA 1999, 8 kg of pyridine, alkyl derivs. were reported to be released to air in the 2006 calendar year (Environment Canada 2010a). Section 71 data indicate that transfers of less than 100 kg of pyridine, alkyl derivs. to non-hazardous waste facilities and in the range of 1 000 to 10 000 kg of pyridine, alkyl derivs. to hazardous waste facilities occurred in the 2006 calendar year (Environment Canada 2010a). Pyridine, alkyl derivs. is not reportable to the National Pollutant Release Inventory (NPRI 2009) or to the United States Toxics Release Inventory Program (TRI 2009); therefore, no release information was available from these sources.

Section 71 data indicate that over 90% of the total use quantity of pyridine, alkyl derivs. in Canada for the 2006 calendar year is dedicated to corrosion inhibition of oil and gas wells and pipelines (Environment Canada 2010a). Natural reservoirs of oil and gas contain water with dissolved salts, minerals and gases such as CO_2, O_2 and H_2S that contribute to acid attack of metal equipment (United States Patent 4554090 [US Patent 1985]). As salt water will concomitantly be extracted with oil and gas, corrosion inhibitors are added so that a protective coating of pyridine, alkyl derivs. is formed on the interior surface of wells and pipelines through adsorption of the nitrogen to metal (Akzo Nobel 2006). Produced water containing pyridine, alkyl derivs. may be re-injected into oil and gas reservoirs to enhance extraction by increasing the pressure but ultimately will be disposed of either on-site or off-site through deep-well injection at licensed sites (i.e. disposal wells below groundwater aquifers) (PPRC 1993; Cheminfo 2011).

To estimate potential liquid losses of pyridine, alkyl derivs. to environmental media, five stages of the substance life-cycle were considered: (1) storage; (2) filling and emptying of tanker trucks; (3) cleaning and washing of returned trucks at sites of importation; (4) occasional leaks through corroded valves and seals of transport pipelines under normal operating conditions; (5) disposal. For vapour losses throughout the life cycle, limited

fugitive releases of pyridine, alkyl derivs. are anticipated due to the moderate to low vapour pressure.

Prior to use at oil and gas fields, importers may blend pyridine, alkyl derivs. into final corrosion inhibitor formulations containing 0.3-46% by weight of the substance (Environment Canada 2010a). Storage of pyridine, alkyl derivs. in the form of pure substance prior to mixing or in the form of blended corrosion inhibitor formulations may occur on-site in drums, bottles or intermediate bulk containers prior to shipping in tanker trucks (OECD 2009). Liquid losses during storage are not expected to be significant unless an accident occurs such as container breakage (OECD 2009).

For filling and emptying of tanker trucks, it is not considered currently possible to estimate any environmental liquid losses due to the variability of on-site liquid collection and secondary containment practices (e.g., bunded areas) in addition to uncertainty about whether the filling and emptying sites are dedicated (e.g., pre-designed fittings) (OECD 2009). However, it is considered likely that releases from cleaning and washing of residual corrosion inhibitor in tanker trucks may pose a greater source of potential liquid releases to the environment.

After tanker trucks are emptied, they may be sent back to the site of importation either for re-filling (i.e., dedicated process) or cleaning and washing (i.e., non-dedicated process) (OECD 2009). Assuming a worst-case non-dedicated process, the liquid loss of residue remaining in emptied tanker trucks per year is assumed as 1% of a full load for viscous liquids (OECD 2009). With the assumption that the 2006 maximum quantity of pyridine, alkyl derivs. in commerce, 10 000 000 kg, is used in blended corrosion inhibitors at a maximum concentration of 46% by weight (Environment Canada 2010a), the annual release quantity of pyridine, alkyl derivs. through tanker truck cleaning prior to waste water treatment is 100 000 kg/yr (see Equation 1).

Equation 1

$$E_{\text{road\_tanker\_cleaning\_water}} = M_s \times F_{\text{residue}} \times N \times F_{\text{pyridine, alkyl derivs.}}$$
$$= 25\,000 \text{ kg} \times 0.01 \times 869.57/\text{year} \times 0.46$$
$$= 100\,000 \text{ kg released per year}$$

Variable	Explanation
$E_{\text{road\_tanker\_cleaning\_water}}$	Total liquid loss of pyridine alkyl derivs. in the cleaning and washing of residual corrosion inhibitor in emptied tankers in Canada per year [kg/year]
M_s	Mass of corrosion inhibitor in a full tanker [kg] (OECD 2009)
$F_{residue}$	Fraction of corrosion inhibitor in a full tanker remaining as a residue after emptying (OECD 2009)[a]
N	Number of tankers containing corrosion inhibitor cleaned in Canada per year [N/year] Calculation: $N = \frac{\text{(maximum quantity of pyridine, alkyl derivs. imported in 2006)}}{(F_{\text{pyridine, alkyl derivs.}})(M_s)}$ = (10 000 000 kg/year) / (0.46 × 25 000 kg) = 869.57/year

$F_{\text{pyridine, alkyl derivs.}}$	Maximum weight fraction of pyridine, alkyl derivs. reported in blended corrosion inhibitor (Environment Canada 2010a)

[a] Based on the assumption that entire quantity of residue in the tanker is removed by the cleaning process (OECD 2009)

Depending upon whether the residue is considered to be hazardous waste, generated waste water from the cleaning and washing process may be either disposed of through incineration, landfills or designated holding ponds or be subjected to waste water treatment prior to release to sewers (OECD 2009). Assuming, as a realistic worst-case scenario, that all waste waters from tanker truck cleaning are not sent for disposal but are, instead, released to surface water sewers after an initial treatment step, the following treatment-related adjustment may be made to the 100 000 kg/year release estimate (see Equation 2). It is assumed, in this adjustment, that the pyridine, alkyl derivs. partially partitions into the organic phase of the corrosion inhibitor where it is removed by a Class 1 separator (OECD 2009). The quantity of pyridine, alkyl derivs. remaining in treated waste water that is released to sewers may then be calculated to be 3 160 kg/year.

Equation 2

$$
\begin{aligned}
E_{\text{sewer}} &= Q_{\text{s\_water}} + F_{\text{inhib}} \times Q_{\text{s\_inhib}} \\
&= \{E_{\text{water}} \div [1 + (V_{\text{inhib}}/V_{\text{water}} \times \text{K}_{\text{ow}})]\} + [(5\times10^{-6} \times V_{\text{water}} \times \text{RHO}_{\text{inhib}}) \div (V_{\text{inhib}} \times 1\,000)] \times [E_{\text{water}} - Q_{\text{s\_water}}] \\
&= \{100\,000 \text{ kg/year} \div \{1 + [(N \times F_{\text{water}} \times V_{\text{tanker}}) \div (N \times \text{Water})] \times 10^{2.39}\} + [(5\times10^{-6} \times V_{\text{water}} \times 900 \text{ kg/m}^3) \div (V_{\text{inhib}} \times 1\,000)] \times [100\,000 \text{ kg/year} - Q_{\text{s\_water}}] \\
&= [100\,000 \text{ kg/year} \div \{1 + [(2\,600/\text{year} \times 0.01 \times 25\,000 \text{ L}) \div (2\,600/\text{year} \times 2\,000 \text{ L})] \times 10^{2.39}\} + [(5\times10^{-6} \times V_{\text{water}} \times 900 \text{ kg/m}^3) \div (V_{\text{inhib}} \times 1\,000)] \times [100\,000 \text{ kg/year} - Q_{\text{s\_water}}] \\
&= [100\,000 \text{ kg/year} \div \{1 + [(650\,000 \text{ L/year}) \div (5\,200\,000 \text{ L/year})] \times 10^{2.39}\} + [(5\times10^{-6} \times 5\,200\,000 \text{ L/year} \times 900 \text{ kg/m}^3) \div (650\,000 \text{ L/year} \times 1\,000)] \times [100\,000 \text{ kg/year} - Q_{\text{s\_water}}] \\
&= 3\,156 \text{ kg/year} + [(3.6\times10^{-5}) \times (100\,000 \text{ kg/year} - 3\,156 \text{ kg/year})] \\
&= 3\,156 \text{ kg/year} + 3.5 \text{ kg/year} \\
&= 3\,160 \text{ kg of pyridine, alkyl derivs. released to sewer post-treatment per year}
\end{aligned}
$$

Variable	Explanation
$E_{\text{sewer}}^{\text{a,b,c}}$	Emission of pyridine, alkyl derivs. to surface water sewers per year [kg/year]
$Q_{\text{s\_water}}$	Quantity of pyridine, alkyl derivs. in water in equilibrium with insoluble organic phase [kg/year]
F_{inhib}	Fraction of insoluble organic phase in waste water emitted to surface water sewers after primary treatment [kg/year]
$Q_{\text{s\_inhib}}$	Quantity of pyridine, alkyl derivs. in insoluble organic phase in equilibrium with water phase [kg/year]
E_{water}	Emission of pyridine, alkyl derivs. to waste water from cleaning per year [kg/year]
V_{inhib}	Volume of corrosion inhibitor remaining as residues in all tanker trucks per year [L/year]
V_{water}	Volume of waste water emitted from all cleaning sites per year [L/year]
K_{ow}	Estimated octanol-water partition coefficient of representative structure of pyridine, alkyl derivs. from EPI Suite™ (2-ethyl-4-methylpyridine)
$\text{RHO}_{\text{inhib}}$	Density of insoluble organic phase [kg/m^3] (OECD 2009)
N	Total number of tankers cleaned in Canada per year [N/year]
F_{water}	Fraction of corrosion inhibitor released in water from the cleaning process (OECD 2009)
V_{tanker}	Volume of tanker [L] (OECD 2009)

Water	Total water consumption per tanker [L] (OECD 2009)

[1] An assumption made that the solubility of pyridine, alkyl derivs. in the organic phase of the corrosion inhibitor was comparable to solubility in n-octanol (OECD 2009).
[2] An assumption made that the partitioning of pyridine, alkyl derivs. between the insoluble organic phase of the corrosion inhibitor and the cleaning water is instantaneous and represented by K_{ow} (OECD 2009).
[3] An assumption made that a Class 1 separator was used so that the concentration of insoluble organic phase remaining after primary treatment is approximately 5 ppm (5 mg/L) (OECD 2009).

After addition of corrosion inhibitor to the oil and gas extraction systems, it may subsequently leak through the valves, seals and damaged cemented steel well casings of an otherwise closed system of transport pipelines (OECD 2009; Cheminfo 2011). The magnitude of pipeline emissions depends upon several site-specific factors including inspection and maintenance regimes, leak detection systems and the number of seals and valves in the system (OECD 2009). Without considering point releases from critical pipeline failures, such occasional leaks are assumed to occur to soil over a regional area (OECD 2009) and are best estimated as a percentage of the total use quantity in Canada for the 2006 calendar year (see Equation 3).

Equation 3

$$E_{\text{pipeline\_soil}} = M_s \times (3.5 \times 10^{-6})$$
$$= (10\ 000\ 000 \text{ kg/year}) \times (3.5 \times 10^{-6})$$
$$= 35 \text{ kg released to soil per year}$$

Variable	Explanation
$E_{\text{pipeline\_soil}}$	Total liquid loss of pyridine, alkyl derivs. to soil per year through occasional pipeline leakages [kg/year]
M_s	Maximum quantity of pyridine, alkyl derivs. used in Canada during the calendar year of 2006 [kg/year] (Environment Canada 2010a)

The 35 kg/year release estimate (see Equation 3) is considered to have relatively low reliability. The 0.00035% release percentage upon which the release estimate is based is derived from a compilation of spillage volumes in Europe caused by a variety of events that were not all due to normal operating conditions of a pipeline for the 2003 calendar year. Almost 90% was attributable to a single spillage event where a large proportion of the oil was recovered for recycling and disposal (OECD 2009). However, it is considered a reasonable worst-case estimate of pipeline releases for screening level purposes.

Finally, although releases through deep-well injection are possible, the ultimate disposal of produced waters through deep well injection would not be expected to result in exposure to the environment or to the general population as the deep reservoirs are situated several thousand feet below ground, in layers of impermeable strata below groundwater aquifers (PPRC 1993; Cheminfo 2011). For a summary of release estimates to environmental media, see Table 3.

Table 3: Annual release rates of pyridine, alkyl derivs. to environmental media from various life-cycle stages related to corrosion inhibition of oil and gas extraction wells and transport pipelines

Compartment	Annual release rate (kg/year)	Source

Air	8	Blending of pyridine, alkyl derivs. into corrosion inhibitor by importer (Environment Canada 2010a)
Water	3 160	Cleaning and washing of tanker trucks emptied of corrosion inhibitor (see Equation 1 and 2)
Soil	35	Occasional pipeline leaks (see Equation 3)

Environmental Fate

Pyridine, alkyl derivs. is a yellow to dark brown liquid with a density comparable to that of water (950 – 1160 kg/m^3) (see Table 2). Based on its physical chemical properties (Table 2) and potential uses, after being released into the environment, pyridine, alkyl derivs. would be expected to be found mostly in water, although some partitioning to solid phase materials (e.g., clay minerals) is also expected.

Pyridine compounds are weak bases that are expected to dissociate to some extent in the aquatic environment based on the dissociation constant (pK_a) (base) range (pK_a = 5.22 – 7.43) for various alkylated pyridine compounds (Andon et al 1954; OECD 1995; Scriven et al. 1996). A significant proportion of alkylated pyridines compounds released to water bodies with environmentally relevant pH (6-9) would thus be present in the cationic (pyridinium ion) form (ACD/pKaDB 2005). This is further confirmed by experimental pK_a1 (5.41) and pK_a2 (7.16) values measured for the UVCB analogue notified substance C (Table 2b)(Environment Canada 2002).

Calculated vapour pressure (130 Pa) and Henry's Law constant (1.13 – 1.39 Pa·m^3/mol) for the representative structure, and the experimental vapour pressure (9.38 x 10^{-3} –100 Pa) and Henry's Law constant (4.1 x 10^{-6} Pa·m^3/mol) values reported for both pyridine, alkyl derivs. and its analogues (see Table 2), indicate that pyridine, alkyl derivs. is slightly to moderately volatile. The lower experimental volatility of pyridine, alkyl derivs. compared to that of the representative structure is likely caused by the presence of less volatile larger molecular size alkylated pyridines and/or by the presence of non-volatile pyridinium cations in the experimental solutions.

The reported water solubility of pyridine, alkyl derivs. and its related compounds varies widely. For example empirical solubility data indicate that it is slightly soluble to completely emulsifiable (Lonza 2008a; Lonza 2008b; Lonza 2008c; Reilly Industries Inc 2000; Resonance Specialties Limited 2008; Vertellus 2008). The analogue data for Notified substance A, B and C, however suggest pyridine alkyl derivs. will be moderately to very highly soluble (water solubility = 105 - >54 700 mg/L) (Environment Canada 2002; Environment Canada 2007a; Environment Canada 2007b). The representative structure and its analogue, 5-ethyl-2-methyl-pyridine, are considered extremely soluble (water solubility: 12 000 - 18 000 mg/L) (OECD 1995) while most methylated and dimethylated pyridine compounds are miscible in water (Scriven et al 1996). The fact that a significant proportion of the substance is expected to be present in cationic form at ambient pH (6-9) also suggests that its solubility is relatively high. Therefore, while pyridine alkyl derivs is expected to be soluble and mobile in the aquatic environment, the

extent of solubility will likely depend on the pH of the water and the proportion and nature of the various alkylated pyridine constituents present.

Nitrogen-containing aromatic heterocycles such as pyridine compounds are pH-dependent organic cations which adsorb to clay minerals and other negatively charged surfaces in suspension (Ainsworth et al. 1987; Chattopadhyay and Traina 1999; Sims and O'Loughlin 1989). Pyridine and its derivatives often form complexes with metals in aqueous solutions (Yuen et al 1983; Sims and O'Loughlin 1989). Therefore, it is anticipated that the log K_{oc} value of 2.42 - 2.55 modelled for the neutral form of the representative alkylated pyridine structure underestimates its adsorption potential. Despite having relatively high water solubility, a portion of pyridine, alkyl derivs. and its alkylated pyridine constituents are expected to strongly bind to particulate matter and to settle down into sediments. The cationic nature of the alkylated pyridine constituents of pyridine, alkyl derivs. in surface waters at ambient pH range (6-9) may also be expected to attenuate its volatilization potential from water (US EPA 2009). If released to the aquatic environment, pyridine, alkyl derivs. is thus expected to reside in the aquatic and, to some extent, partition into sediment.

If released to soil, the high water solubilities and relatively low log K_{ow}s of pyridine, alkyl derivs. and its various alkylated pyridine components suggest that pyridine, alkyl derivs. has low adsorptivity to soil. On the other hand, adsorption to mineral surfaces via ionic mechanisms in soil, constitute an important fate process for these substances (Zachara et al 1987). Sorption to mineral surfaces is most likely when the soil solution pH is near or below the compound's pKa (Sims and O'Loughlin 1989). In a study of 28 pyridine derivatives in soil suspensions, volatilization of pyridines accounted for up to 57% of the loss from methyl and chloro-pyridine solutions in soil suspensions (Sims and O'Loughlin 1989, Sims and Sommers 1986), however in another experiment, the authors reported little volatilization loss (<5%) of 26 pyridine derivatives from whole soil (initial soil water pH = 6.7) (Sims and Sommers 1985).

Persistence and Bioaccumulation Potential

Environmental Persistence

Empirical data on the persistence of pyridine, alkyl derivs. and its analogues are presented in Table 4. Empirical biodegradation data were submitted by industry in response to the CEPA 1999 section 71 Notice for the 2006 calendar year (Environment Canada 2010a). Ready biodegradability studies evaluating the aerobic biodegradability in an aqueous medium of pyridine, alkyl derivs. acetates (CAS RN 168612-09-7) and acetic acid, mercapto-, compounds with alkylpyridines (CAS RN 168612-10-0) determined that neither compound was ready biodegradable (21 % biodegradation over 28 days) (SafePharm laboratories 2007a, 2007b). These tests were performed according to OECD Guidelines for Testing of Chemicals, Test No. 301B-1992, "Ready Biodegradability; CO_2 evolution Test". While this test method is normally recommended only for poorly

soluble, highly adsorbing and non-volatile compounds, Robust Study Summaries (RSS) for these two tests (see Appendix 1) determined that the studies were acceptable.

In addition, the extent of ultimate biodegradation in a 28-day biodegradation test for Notified Substance C was estimated to be 1.2% (Environmental Canada 2002). These experimental tests indicate that the ultimate degradation half-life in water is likely to be longer than 182 days (6 months) and that the substance will persist in water.

Table 4. Empirical data for degradation of pyridine, alkyl derivs. and its analogues

Substance	Medium	Fate process	Degradation value	Degradation endpoint / units	Reference
Pyridine, alkyl derivs., acetates (CAS RN 168612-09-7)	Water	Biodegradation	21 % BOD	28-day biodegradation / %	SafePharm Laboratories 2007a
Acetic acid mercapto-, compds with alkylpyridines (CAS RN 168612-10-0)	Water	Biodegradation	21 % BOD	28-day biodegradation / %	SafePharm Laboratories 2007b
Notified substance C	Water	Biodegradation	1.2 % BOD	28-day biodegradation / %	Environment Canada 2002
5-ethyl-2-methyl-pyridine	Water	Biodegradation	77 % BOD	28-day biodegradation / %	OECD 1995
			98.7 % BOD	21-day biodegradation / %	

An empirical 28-day ready biodegradation value of 77% obtained for the analogue 5-ethyl-2-methylpyridine found the substance to be inherently biodegradable but not ready biodegradable as the pass level of 60% biodegradation within 10 days of the beginning of the test was not reached (OECD 1995).

In addition to the empirical results described in Table 4 there are experimental data indicating that low-boiling point compounds such as pyridine (CAS RN 110-86-1) and 2-, 3- and 4-methyl pyridines (CAS RN 109-06-8, CAS RN 108-99-6 and CAS RN 108-89-4) have rapid to moderate biodegradation rates under aerobic and anaerobic conditions (US EPA 2009).While empirical data for low-boiling point alkylated pyridines indicate that they may not be persistent, according to its DSL definition, pyridine, alkyl derivs. is composed of compounds which have boiling points superior to pyridine and methyl pyridines (>150 ^{o}C).

It is acknowledged that the low biodegradation potential of the UVCB analogues presented in Table 4 may in part be explained by the presence of higher molecular weight alkylated pyridines or other compounds which are not ready or inherently biodegradable.

Nevertheless, based on empirical data for the UVCB substance, it is concluded that the ultimate biodegradation half-life of pyridine, alkyl derivs. in water is > 182 days

Using an extrapolation ratio of 1:1:4 for a water: soil: sediment biodegradation half-life (Boethling et al. 1995), the ultimate degradation half-life in soil is also >182 days and the half-life in sediments is >365 days. This indicates that pyridine, alkyl derivs. is expected to be persistent in soil and sediment.

As there are no empirical data regarding atmospheric degradation of pyridine, model values were generated using EPI Suite™ for the pyridine, alkyl derivs. representative structure. A predicted atmospheric oxidation half-life value of 2.9 days indicates that 2-ethyl-4-methyl-pyridine will be slowly oxidized (AOPWIN 2000-2008).

Based on the empirical and modelled data (see Table 4) pyridine, alkyl derivs. meets the persistence criteria in water, soil and sediment (half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days), and meets the criteria for air (half-life in air ≥ 2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

Since no experimental bioaccumulation factor (BAF) and/or bioconcentration factor (BCF) data for pyridine, alkyl derivs. were available, predictions were generated for the representative structure.

According to the *Persistence and Bioaccumulation Regulations* (Canada 2000) a substance is bioaccumulative if its BCF or BAF is ≥ 5000; however measures of BAF are the preferred metric for assessing bioaccumulation potential of substances. This is because BCF may not adequately account for the bioaccumulation potential of substances via the diet, which predominates for substances with log K_{ow} > ~4.0 (Arnot and Gobas 2003). Kinetic mass-balance modelling is in principle considered to provide the most reliable prediction method for determining the bioaccumulation potential because it allows for correction for metabolic transformation as long as the log K_{ow} of the substance is within the log K_{ow} domain of the model.

BCF and BAF estimates, corrected for potential biotransformation, were generated using the BCFBAF model (EPIsuite 2000–2008). Metabolic rate constants were derived using structure activity relationships described further in Arnot et al. (2008a; 2008b; 2009). Since metabolic potential can be related to body weight and temperature (Hu and Layton 2001, Nichols et al. 2006), the BCFBAFWIN model further normalizes the k_M for a 10g fish at 15°C to the body weight of the middle trophic level fish in the Arnot-Gobas model (184 g) (Arnot et al. 2008b). The middle trophic level fish was used to represent overall model output as suggested by the model developer and is most representative of fish weight likely to be consumed by an avian or terrestrial piscivore. After normalization routines, the median k_M is 3.66 (1/days) (for a 184 g fish at 15°C).

Table 5: Modelled data for bioaccumulation for the representative structure of pyridine, alkyl derivs.

Test organism	Model and model basis	Endpoint	Value wet weight (L/kg)	Reference
Fish	BCFBAF Sub-model 1: linear regression (not metabolism-corrected)	BCF	17.5	BCFBAF 2008
Fish	BCFBAF Sub-model 2: Gobas mass balance (metabolism-corrected)	BCF	12.6	BCFBAF 2008
Fish	BCFBAF Sub-model 3: Gobas-mass balance (metabolism-corrected)	BAF	12.6	BCFBAF 2008
Fish	OASIS Forecast 2005 (metabolism-corrected)	BCF	52	Dimitrov et al 2005
Fish	Baseline BCF Model (BCF Max)	BCF	69	Dimitrov et al 2005

The available evidence indicates that pyridine, alkyl derivs. is expected to have a low potential for bioaccumulation and for biomagnification due to its physical and chemical properties (low log K_{ow}, high water solubility, tendency to ionize), low modelled BAF and BCFs and its metabolism potential (see Table 5).

Based on the available empirical and kinetic-based modelled values corrected for metabolism for the representative structure of pyridine, alkyl derivs., the substance does not meet the bioaccumulation criteria (BCF or BAF $\geq$ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

The approach taken in this assessment was to examine the available scientific information and develop conclusions based on a weight-of-evidence approach and using precaution as required under CEPA 1999. Lines of evidence considered include results from a conservative risk quotient calculation, as well as information on the persistence, bioaccumulation, toxicity, sources and fate of the substance.

As described previously, based on empirical and model-generated data for the substance, pyridine, alkyl derivs. is persistent in all environmental compartments. It is expected, however, to have a low bioaccumulation potential.

Experimental ecological effects data for pyridine, alkyl derivs. (as a mixture of components) and its analogue compounds are summarized in Table 6a and Table 6b. Based on acute aquatic toxicity ranges for *Selenastrum capricornutum* (30.6 - 61.2 mg/L) *Daphnia magna* (8.8 – 68.8 mg/L) and fish (2.2 – 81.1 mg/L), pyridine, alkyl derivs. is not highly hazardous to aquatic organisms.

Table 6a. Empirical data for aquatic toxicity for pyridine, alkyl derivs. and its analogues

Substance	Test Organism	Test Type	Endpoint	Value (mg/L)	Reference
Pyridine, alkyl derivs.	*Daphnia magna*	Acute	48-hr EC_{50}[1]	68.8	Groetsch and Liu 1996
			NOEC[2]	< 31.3	
	Rainbow trout (*Oncorhynchus mykiss*)	Acute	96-hr LC_{50}[3]	40	Groetsch and Liu 1997
			NOEC[2]	25	
	Rainbow trout (*Oncorhynchus mykiss*)	Acute	96-hr LC_{50}[3]	3	Lonza 2008b
	Zebra fish (*Brachydanio rerio*)	Acute	96-hr LC_{50}[3]	6.1	
Pyridine, alkyl derivs., acetates	Fathead minnow (*Pimephales promelas*)	Acute	96-hr LC_{50}[3]	6.4	SafePharm Laboratories 2007c
			NOEC[2]	3.2	
Acetic acid mercapto-, compds with alkylpyridines	Fathead minnow (*Pimephles promelas*)	Acute	96-hr LC_{50}[3]	12	SafePharm Laboratories 2007d
			NOEC[2]	5.6	
Notified substance C	*Daphnia magna*	Acute	24-hr EC_{50}[1]	8.8	Environment Canada 2002
	Zebra fish (*Brachydanio rerio*)	Acute	96-hr LC_{50}[3]	2.2	

[1] EC_{50} – The concentration of a substance that is estimated to cause some effect on 50% of the test organisms
[2] NOEC – The No Observed Effect Concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.
[3] LC_{50} – Lethal concentration affecting 50% of the test population

Table 6b. Empirical aquatic toxicity data for 5-ethyl-2-methyl-pyridine, the isomer of the representative substance

Test Organism	Test Type	Endpoint	Value (mg/L)	Reference
Selenastrum capricornutum	Acute	72-hr EC_{50} (growth rate)	61.2	Pharmaco-LSR Ltd. 1994a
	Acute	72-hr EC_{50} (biomass)	30.6	
	Chronic	72-hr NOEC	0.689	
Daphnia magna	Chronic	48-hr EC_{50}	39.6	Pharmaco-LSR Ltd. 1994b
Fathead minnow	Acute	96-hr LC_{50}	81.1	Brooke et al. 1984

No suitable ecological effects studies were found for this compound in media other than water.

It is noted that while there is monitoring data for discrete alkylated pyridine substances (see the Exposure Assessment in Potential to Cause Harm to Human Health section), no data concerning concentrations of pyridine, alkyl derivs. (as defined in the DSL) in water in Canada have been identified; therefore, environmental concentrations are estimated from available information, including estimated substance quantities, release rates, and size of receiving water bodies.

Since a significant proportion of pyridine, alkyl derivs. is expected to be released to water, a risk quotient analysis, integrating conservative estimates of exposure with toxicity information, was performed for the aquatic medium to determine whether there is potential for ecological harm in Canada. A site-specific exposure analysis was conducted for a corrosion inhibitor formulations blending facility where cleaning and washing of tanker trucks occurs. The total quantity of pyridine, alkyl derivs. released to wastewater from this facility was assumed to be 3160 kg/yr, the total quantity estimated to be released in treated wastewater in Canada yearly (see Releases to the Environment section). Removal rate by the wastewater treatment plant receiving the substance was assumed to be zero. The site location was selected as its wastewater treatment facility receives effluent from the largest blending facilities who responded to the CEPA section 71 Notice (Environment Canada 2010a). The selection of this site represents a site-specific realistic worst case release scenario.

Using Environment Canada's Industrial Generic Exposure Tool – Aquatic (IGETA), a conservative predicted environmental concentration (PEC) of 3.38×10^{-2} mg/L in the receiving water was estimated based on the concentration in the wastewater treatment effluent and a dilution factor of 1 provided by the receiving water. Details regarding the inputs used to estimate this concentration and the output of the model are described in Environment Canada (2010b).

A very conservative predicted no-effect concentration (PNEC) was also derived from the lowest toxicity value identified - a chronic 72-hr NOEC for *Selenastrum capricornutum* of 0.69 mg/L for 5-ethyl-2-methyl-pyridine. This value was selected as the critical toxicity value, and divided by an assessment factor of 10 to account for uncertainties related to laboratory to field extrapolation, as well as intra- and inter-species variability.

The resulting very conservative risk quotient (PEC/PNEC) of 0.49 indicates that exposure values are unlikely to be high enough to cause harm to aquatic organisms. Since the majority of releases of this substance are likely to water at industrial sites, significant exposure of organisms at other types of locations is unlikely. Therefore, pyridine, alkyl derivs. is unlikely to be causing ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

It should be noted that this conclusion was reached despite the conservative assumptions that were made in response to uncertainties encountered in the assessment. A key uncertainty relates to the lack of empirical data on environmental concentrations in Canada, which was addressed by predicting a conservative concentration in water using an industrial exposure model. There is also uncertainty associated with the PNEC used in the risk quotient calculation, because of limited amount of empirical toxicity data available as well as the uncertainties regarding the nature of potential constituents of the UVCB. This uncertainty was addressed by dividing the critical toxicity value (already a conservative NOEC value) by an assessment factor of 10.

All modelling of a substance's physical and chemical properties and P, B and toxicity characteristics are based on chemical structures. Since this substance is an UVCB (**U**nknown or **V**ariable composition, **C**omplex reaction product or **B**iological material), it cannot be represented by a single, discrete chemical structure. Given that different representative structures may be derived for the same UVCB, it is recognized that structure-related uncertainties exist for this substance.

The bioaccumulation assessment is limited by the absence of bioaccumulation data; this necessitated use of model predictions for a representative structure using a model-calculated log K_{ow}. Although all predictions using models have some degree of error, both the metabolism-corrected and non-metabolism corrected mass balance model outputs confirmed that pyridine, alkyl derivs. (given its structural characteristics) can be expected to have a low bioaccumulative potential.

Also, regarding ecotoxicity, based on the predicted partitioning behaviour of these chemicals, the significance of air, soil and sediment as potential media of exposure is not well addressed by the effects data available. Indeed, although the water column may not be the medium of primary long-term concern, the only effects data identified apply primarily to pelagic aquatic exposures. Nevertheless, based on the relatively low aquatic toxicity of the substance, potential for harm to soil- or sediment-dwelling organisms is also expected to be low.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media and Diet

Empirical monitoring data for various alkyl pyridines were identified for a variety of environmental media: groundwater (Ronen and Bollag 1995; Ronen et al. 1996; Fetzner 1998; ATSDR 1995; Pereira et al. 1983; Turney and Goerlitz 1990; Riley et al. 1981; Johansen et al. 1997; Stuermer et al. 1982); subsurface soil (Ronen and Bollag 1995; Riley et al. 1981); air above shale oil wastewaters (Hawthorne and Slevers 1984); air inside metallurgical plants (Masek 1981); surface water (Kroner et al. 1952; ATSDR 1995; Riley et al. 1981); aquatic sediments (Tsukioka and Murakami 1987; Riley et al. 1981) and environmental tobacco smoke (ATSDR 1995; Kulshreshtha and Moldoveanu 2003). Overall, the environmental monitoring data centred on point source releases related to synthetic fuel production from shale oil or coal, coking operations for iron- and steel-works, or wood preservation using creosote, which is a coal condensate containing 4.4 – 8.2% by weight nitrogen-containing heteroaromatics including alkyl pyridines (Heikkilä 2001). The primary mechanism of alkyl pyridine transfer off-site from industrial locations, at least for sites producing alkyl pyridines through coal tar distillation or batch synthesis, is groundwater (ATSDR 1995).

Point source monitoring data indicated that contamination of environmental media was generally limited to the vicinity of industrial sites. Groundwater contamination of nitrogen-, sulphur- and oxygen-containing heteroaromatics at creosote-contaminated sites has been observed to be restricted to a vicinity of less than 100 – 160 m off-site due to dilution and degradation mechanisms in multiple studies (Johansen et al. 1997; Kiilerich and Arvin 1996; Pereira and Rostad 1986). Detectable air levels of alkyl pyridines emitted from shale oil wastewaters were projected to be localized to site areas and pose minimal danger to the surrounding environment (Hawthorne and Slevers 1984). Surface stream waters below a shale oil retort water discharge site contained only trace levels of alkyl pyridines at the 0.1-0.2 µg/mL level in comparison with the total concentration of alkyl pyridines in discharge water of 30.8 µg/mL (Riley et al. 1981); this indicated an off-site dilution mechanism was occurring (Sims and O'Loughlin 1989). In addition, alkyl pyridines were not detected in a sample of surface sediment from a stream located adjacent to the seep discharge at a detection limit of <0.1-0.2 µg/mL (Riley et al. 1981). Pyridine itself has rarely been detected in soil, air or water except in the vicinity of industrial sources such as steelworks or shale oil processing sites (ATSDR 1992).

Empirical monitoring data were also identified for various alkyl pyridines in a variety of foods and beverages (Sims and O'Loughlin 1989; Peppard and Halsey 1980; Nijssen et al. 2003; Harding et al. 1977, 1978; Vitzthum et al. 1975a, 1975b; Nunomura et al. 1978; Buttery et al. 1977; Golovnja et al. 1974; Yajima et al. 1978; Nishimura and Masuda

1971). The presence of alkyl pyridines in food is due to either addition as flavouring agents (Peppard and Halsey 1980; WHO 2005; Oser and Ford 1978) or the formation from natural precursors either upon microbial fermentation or cooking (Sims and O'Loughlin 1989). Cooking causes the *in situ* pyrolysis of proteins with subsequent formation of alkyl pyridines either through thermal decomposition of amino acids or the Maillard reaction of amino acids with D-glucose (Sims and O'Loughlin 1989). However, the presence of pyridine, alkyl derivs. as a UVCB mixture defined by the Chemical Abstracts Service would not be expected in foods and beverages. Residual levels of pyridine, alkyl derivs. in food are not currently monitored by the Canadian Food Inspection Agency (May 2010 email from Canadian Food Inspection Agency to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

While empirical monitoring data were available for a variety of alkyl pyridines, monitoring data specific to pyridine, alkyl derivs. as a UVCB mixture defined by the Chemical Abstracts Service could not be identified in Canada or elsewhere. To estimate environmental exposure to the general population, an alternative approach of modelling estimated environmental concentrations by means of estimated physicochemical properties of a representative structure, 2-ethyl-4-methylpyridine, from EPI Suite™ and annual release estimates of pyridine, alkyl derivs. from the largest source of commercial activity in Canada, corrosion inhibition in the oil and gas extraction industry, was used. As explained in the Releases to the Environment section, the annual release estimates were based upon several conservative assumptions that would lead to an overall protective approach to estimating environmental concentrations. While pyridine, alkyl derivs. may also be used as a corrosion inhibitor to a lesser extent in industrial cleaning and descaling products in Canada for boilers and cooling towers (Environment Canada 2010a; Aquarian 2009), these products are used in closed systems and at current use quantities in Canada would not be anticipated to lead to appreciable environmental releases beyond those estimated for corrosion inhibition in the oil and gas extraction industry.

Annual release estimates of pyridine, alkyl derivs. through use as a corrosion inhibitor in the oil and gas extraction industry were used as inputs in ChemCAN v6.00, a Canadian environmental exposure model, to provide estimated environmental concentrations (ChemCAN 2003) (see Appendix 2). The region of northern Alberta was selected as the representative region in this model due to the large number of oil and gas extraction sites present. The estimated environmental concentrations were then used as surrogates for empirical monitoring data in deriving intake estimates (see Appendix 3). Total multimedia exposure from all routes of environmental exposure was on the order of nanograms (10^{-9} g) per kilogram of body weight per day for all age groups and is considered negligible.

Consumer Products

In Canada, pyridine, alkyl derivs. has been identified for use only in industrial products, namely corrosion inhibitors for oil and gas extraction wells and transport pipelines, in cleaning and descaling products for closed water systems such as boilers and cooling

towers, and in one registered herbicide product (Environment Canada 2010a; Aquarian 2009; July 2010 email from Pest Management Regulatory Agency, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). As no product has been identified that is intended for consumer use, exposure to the general population through consumer products is not expected.

Confidence in the Exposure Assessment

Confidence in the assessment of total multimedia exposure from all routes of environmental exposure is moderate. As empirical monitoring data could not be identified for pyridine, alkyl derivs. as a UVCB mixture defined by the Chemical Abstracts Service, in Canada or elsewhere, modelling estimated environmental concentrations using ChemCAN v6.00 was required. As the region of northern Alberta was selected as the representative region in this model, the estimated environmental concentrations used to estimate general population exposure are considered protective of the populations most likely to be in the vicinity of a large number of oil and gas extraction sites. Confidence in the assessment of consumer products is high as no consumer uses were identified in Canada; therefore, exposure to the general population is not anticipated from consumer products.

Health Effects Assessment

The available empirical health effects information (Appendix 4) for pyridine, alkyl derivs. is very limited. Pyridine, alkyl derivs. products were mutagenic in bacteria (positive in Ames tests), but not clastogenic in mammalian cells (negative in chromosomal aberration tests in human lymphocytes) (Lonza 2008a, b, c). Oral LD_{50} values for this substance range from 169 to 2500 mg/kilogram of body weight (kg bw) in rats and dermal LD50 values in rabbits range from 1880 to > 2000 mg/kg bw (Reilly Industries Inc, 2000; US EPA 2003; Lonza 2008a, b, c; Vertellus. 2008, 2010b).

The European Commission has classified pyridine, alkyl derivs. as a category 2 carcinogen (*may cause cancer)* and a category 2 mutagen (*May cause heritable genetic damage*). This classification only applies to pyridine, alkyl derivs. products that contain benzene at concentrations above 0.1% by weight (European Commission 1994). Based on the results of a survey conducted under section 71 of CEPA 1999, the concentrations of benzene in pyridine, alkyl derivs. products in the current Canadian marketplace are below 0.1%.

There are some health effects data available for pyridine, alkyl derivs. products mixed with other organic acids. Overall, the data set showed these substances pose low to moderate oral acute toxicity (e.g., LD50 values in rats were between 300 to 2000 mg/kg bw for pyridine, alkyl derivs. mixed with acetic acid or with mercaptoacetic acid), low dermal acute toxicity, low to moderate oral short-term toxicity and low dermal short-term toxicity. Some, but not all, of these mixtures induced mutation in bacteria. For example, pyridine, alkyl derivs. mixed with acetic acid showed weak mutagenicity in Ames tests while mixed with mercaptoacetic acid showed negative results. The available *in vivo* and

in vitro clastogenicity tests were all negative. Except skin irritation and slight oedema, no other adverse effects, were observed in rats in short-term (28-days) repeated dose dermal studies, which were conducted according to OECD Guidelines for Testing of Chemicals, Section, No. 410 (OECD 1981) and the dermal no-observed-adverse-effect-level (NOAEL) were defined at 600 and 250 mg/kg bw per day (highest test doses in individual studies), respectively, for pyridine, alkyl derivs. mixed with acetic acid or with mercaptoacetic acid. In a short-term repeated dose oral study in rats that were administered with one of the pyridine, alkyl derivs. products mixed with organic acids, which was conducted according to OECD Guidelines for Testing of Chemicals, Section, No. 407 (OECD 2008), clinical signs and effects, such as piloerection, dyspnea, hunched back, reddening of fur, melaena, anorexia and pallor, changes in haematology that were associated with gastroenteritis, slightly reduced cortical area of the thymus, some mild adaptive changes in the liver, enlarged adrenals, decreased thymus weights, and reduced other organ weights that were associated with significantly decreased body weight gain, were observed at middle to high dose levels (confidential information) (Environment Canada 2002; SafePharm Laboratories. 2007e, 2007f, 2007g; Harlan Laboratories Ltd. 2009a, 2009b).

Pyridine, alkyl derivs. mainly contains mono-, di- or tri- methyl pyridines, methyl-ethyl-pyridines, ethyl- pyridines and propyl- pyridine. The available health effects information (Appendix 4) for the relevant compounds, based on the typical composition of pyridine alkyl derivs. products, is summarized below. Given the overall limited health effects information on alkylated pyridines, available toxicity data on some of the alkylated pyridine isomers that are not the typical constituents of pyridine alkyl derivs. products are also included in order to better assess the toxicity potential of this group compounds.

Mono-methylpyridines (also known as picoline) pose moderate acute toxicity. Oral LD_{50} of 2-, 3-, and 4- picolines in rats and mice range from 400 to 1600 mg/kg bw; dermal LD_{50} in rabbits range from 126 to 2000 mg/kg bw; inhalation lowest lethal concentrations (LCLo) in rats (4 h) range from 1300 to 4000 ppm (4952 – 15236 mg/m^3) (Patty's Toxicology 2001). 2-, 3-, and 4-picolines are severe eye and skin irritants and 4-picoline is the most potent one among the three compounds (Dutertre-Catella et al., 1989; Patty's Toxicology 2001). For the repeated dose toxicity, in a 2-week inhalation study conducted with 3-picoline, a short-term no-observed-adverse-effect-concentration (NOAEC) of 290 ppm (1105 mg/m^3) (the highest dose tested) was derived in rats. A sub-chronic NOAEC of 100 ppm (381 mg/m^3, the highest dose tested) was derived in a 6-month inhalation study with 2-picoline in rats and rabbits. Guinea pigs exhibited a slight-to-moderate increase in vacuolization of liver hepatocytes in the 6-month study, which was considered to be caused by fasting and judged as a reversible effect (Patty's Toxicology 2001). 2-, 3- and 4-picoline were negative in mutagenicity tests in bacteria (Ames test in *Salmonella typhimurium* and mutation in *Escherichia coli*) and in mammalian cells (V79 cells) (Patty's Toxicology 2001; Shoji and Kawakami, 2006; Eisentraeger et al., 2008; US EPA 2009). 3-picoline did not induce DNA single-strand breaks in Chinese hamster cells (NTP 2007), however, 2-picoline induced aneuploidy in yeast (Zimmermann et al., 1986). In addition, 2-picoline showed inhibition to mouse T and B cell mitogenesis *in vitro* (Sakazaki et al., 2001). Acute exposure to 2-, 3-, and 4-picolines, via either *in vivo*

intraperitoneal injection (Dyer et al. 1985) or *in vitro* tissue culture (Fountain and Teyler 2001), suppressed rat cerebral excitability. It has been noted, in an on-going study in rats that were administered 3-picoline (a mono-methylpyridine) in drinking water for two years, that the incidences of pituitary gland adenomas in males and lung alveolar and bronchiolar adenomas in both sexes were significantly increased at the highest dose level (625 mg/L), as indicated in the primary study reports, however, the conclusions of this study have not been finalized by the authors (NTP 2010).

Picolines are readily absorbed from the gastrointestinal tract, intraperitoneal cavity and lungs, and to a moderate extent through the skin. Cytochrome P450 system and glutathione transferase activity are involved in the metabolism of picolines (Dierickx 1994; Patty's Toxicology 2001).

Dimethylpyridines (also known as lutidine) pose moderate acute toxicity. Oral LD_{50} for 2,4- and 2,6-lutidines in rats and mice range from 200 to 800 mg/kg bw; dermal LD_{50} for 2,4- and 2,6-lutidines in guinea pigs range from 1000 to 5000 mg/kg bw; a concentration of 650 ppm (2849 mg/m^3) of 2,4-lutidine for 6 hours killed none of the three test rats and 7500 ppm (32871 mg/m^3) of 2,6-lutidine for 1.2 hours killed all three test rats (Patty's Toxicology 2001). Lutidines were negative in Ames tests (Florin et al., 1980; Ho et al., 1981; Aguayo et al., 2004), but 2,4- and 2,6- lutidines induced aneuploidy in yeast (Zimmermann et a., 1986).

Trimethylpyridines (also known as collidine) pose moderate oral acute toxicity. An oral LD_{50} for 2,4,6-collidine in rats was determined to be 400 mg/kg bw (Patty's Toxicology 2001). 2,3,5-, 2,3,6- and 2,4,6-collidine were negative in Ames tests (Aguayo et al., 2004; Eisentraeger et al., 2008).

The empirical health effects information for ethylpyridines is limited. 2-ethylpyridine was negative in Ames tests (Patty's Toxicology 2001). Inhalation studies showed that exposure to 5400 ppm (23667 mg/m^3) 2-ethylpyridine for 3 hours or to 2500 ppm (10957 mg/m^3) 4-ethylpyridine for 5 hours caused death of all test rats (Patty's Toxicology 2001).

No empirical health effects data for propylpyridines were identified.

The substance 2-methyl-5-ethylpyridine (MEP) has been assessed under Screening Information Data Sets (SIDS) for High Volume Chemicals (OECD, 1995), in which it stated that MEP is of moderate acute toxicity; it is not genotoxic; it has to be classified as corrosive; and it has no effects on the general reproductive performance of test animals. Oral LD_{50} of MEP range from 459 – 710 mg/kg bw; dermal LD_{50} of MEP range from 1000 - 2500 mg/kg bw; a concentration of 1000 ppm for 4 hours killed 5 of 6 test rats and a concentration of 1700 ppm for 3.7 hours killed all test rats (OECD, 1995). MEP is a severe eye and skin irritant, but did not induce sensitization in guinea pigs (Patty's Toxicology 2001). The potential reproductive and developmental effects of MEP exposure have been investigated in a one-generation study in rats dosed by gavage. No effects on the general reproductive performance were observed in the animals that were

administered MEP up to 300 mg/kg bw per day (the highest dose tested). The lowest-observed-adverse-effect-level (LOAEL) was defined to be 300 mg/kg bw per day, based on increased total litter loss, reduced offspring body weights by the birth, reduced pup body weight gain up to postnatal day 4 and decreased pup viability observed in the presence of maternal toxicity (statistic analysis was not provided). A no-observed effect level (NOEL) for developmental toxicity was defined to be 95 mg/kg bw per day (Pharmaco-LSR Ltd. 1994c). For the repeated dose toxicity, the lowest-observed-effect-level (LOEL) was defined to be 95 mg/kg bw per day, based on effects, such as slight deviations of clinical chemistry parameters and increased liver weights in both sexes of animals and hyaline droplets nephropathy in males, observed in a 28-day gavage study in rats (Biomedizinische Forschungsanstalt m.b.H. 1988). MEP did not induce mutation in bacteria (Ames tests) and yeast, or micronucleus in mice *in vivo* (Zimmermann et al., 1984; OECD, 1995), but it induced chromosome aberration in cultured mammalian cells with metabolic activation or at higher (near toxic) concentrations without metabolic activation (OECD, 1995). It also induced aneuploidy in yeast (Zimmermann et a., 1986). Health effects information on MEP isomers was not identified.

No epidemiological study data on human health effects for pyridine, alkyl derivs. or its major components were identified. Local irritation and central nervous system disturbance were the major effects reported in the cases of human accidentally or occupationally exposure to the short chain alkyl derivatives of pyridine (Patty's Toxicology 2001).

In the absence of chronic carcinogenicity data for pyridine, alkyl derivs. or its major components, several qualitative or quantitative structure activity relationship (Q)SAR models, including DEREK for Windows_12.0.0 (DEREK 2008), Leadscope FDA Model Applier version 1.3.2 (Model Applier 2008), TOPKAT version 6.2 (TOPKAT 2004) and CASETOX version 2.1 (CASETOX 2008), were applied in an attempt to predict the carcinogenicity potential of this substance. The structures of the main components of pyridine, alkyl derivs. (Vertullus 2010a), including several additional isomers of methyl-, ethyl-, propyl- or methyl-ethyl pyridines, were input in the models and the results are summarized in Appendix 5. The majority of the predictions were negative, while some were positive (20 positive versus 170 negative). The positive results were mainly predicted by the mouse models. It should be noted that, in some cases, the same (Q)SAR model predicted different carcinogenicity potential for different alkylated pyridine isomers, suggesting that the relative position(s) of alkyl group(s) in the N-heteroaromatic ring (pyridine ring) may influence the mode-of-action of the compounds.

It is recognized that pyridine, alkyl derivs. products in the Canadian marketplace also contain by-products, such as quinoline, aniline, amino- or vinyl- pyridines, and various alkylated pyridines at low concentrations (0.1 to 0.5%). Amongst these compounds, quinoline is one of the most potent toxicants. The Government of Canada has conducted a screening assessment for quinoline and proposed that quinoline meets the criteria set out in section 64(c) of CEPA 1999, based on its potential of tumour induction by directly interacting with genetic materials, which may cause harm at any level of exposure (Environment Canada, Health Canada 2010a). The Government of Canada has also

conducted a draft follow-up assessment report for aniline and proposed that aniline does not meet the criteria set out in section 64(c) of CEPA 1999, based on adequate margin of exposure (Environment Canada, Health Canada 2010b).

Overall, the weight of evidence indicates that the discrete short-chain alkylated pyridines are not mutagens. Some pyridine, alkyl derivs. products induced mutation in bacteria, which may be caused by the non-alkyl pyridine by-products, e.g., quinoline, in the products. Although there are some positive (Q)SAR-based carcinogenicity predictions for the discrete short-chain alkylated pyridines, it is unlikely that discrete short-chain alkylated pyridines could induce tumours by directly interacting with and irreversibly damaging genetic materials. However, pyridine, alkyl derivs. products may elicit both genotoxicity and carcinogenicity due to the presence of non-alkylated pyridine by-products within the substance mixture.

The confidence in health effects assessment is considered moderate to low owing to the lack of sufficient experimental data and the variation of the substance compositions, which limits the certainty in health effects identification and dose-response assessment for this compound.

Characterization of Risk to Human Health

Based on the limited data available, gene mutation as well as skin and eye irritation were observed to be associated with exposure to pyridine, alkyl derivs. Pyridine, alkyl derivs. products were mutagenic in bacteria, but not clastogenic in mammalian cells. However, the weight of evidence analysis indicates that the major components of pyridine, alkyl derivs. within the Chemical Abstracts Service definition, i.e., discrete short-chain alkylated pyridines, such as mono-, di-, tri-methylpyridines, ethylpyridines, methylethylpyridines and propylpyridines, are not mutagenic. Therefore, it is likely that the mutagenicity of pyridine, alkyl derivs. is due to the presence of by-products, such as non-alkylated derivatives of pyridine, in the UVCB substance.

Exposures of the general population to pyridine, alkyl derivs. through environmental media were estimated to be on the order of nanograms (10^{-9} g) per kilogram of body weight per day, and thus are expected to be negligible. Exposure of the general population to pyridine, alkyl derivs. in food and beverages as a complex mixture defined by the Chemical Abstracts Service is not anticipated. General population exposure to pyridine, alkyl derivs. from use of consumer products is not expected.

As exposure of the general population through environmental media in Canada is expected to be negligible, the risk to human health is considered to be low.

Uncertainties in Evaluation of Risk to Human Health

Owing to the paucity of the available health effects information for pyridine, alkyl derivs. and the variation in the compositions of this substance, there is uncertainty with respect to

other hazard potential of this substance, such as carcinogenicity, reproductive and developmental toxicity and repeated dose toxicity. Although it is unlikely that the major components of this substance, i.e., discrete short-chain alkylated pyridines, induce tumours by directly interacting with genetic materials, the by-products in this UVCB substance, such as the non-alkylated pyridine derivatives, may elicit additional adverse effects, including gene mutation and tumour occurrence. However, given the negligible exposure of the general Canadian population to this substance, it is unlikely that any effective doses of the by-products, at which any potential adverse effects could be induced, can be reached in the body from the exposure to this substance under current uses in Canada.

As environmental monitoring data specific to pyridine, alkyl derivs. as defined by the Chemical Abstracts Service could not be identified, environmental modelling using ChemCAN v6.00 was required based largely on estimated input parameters. In the case of the annual release estimates used in ChemCAN v6.00 modelling, several assumptions were applied in their derivation including: (1) all emptied tanker trucks are cleaned and washed prior to being refilled with corrosion inhibitor; (2) all residual corrosion inhibitor is removed during the cleaning process; (3) wastewater treatment post-cleaning involves instantaneous partitioning of pyridine, alkyl derivs. between the aqueous phase and insoluble organic phase of corrosion inhibitor based upon the log K_{ow} of a representative structure from EPI Suite™, i.e. 2-ethyl-4-methylpyridine; (4) occasional pipeline release percentages from Europe are applicable to Canada. In the case of physicochemical properties used for modelling, these were estimated using EPI Suite™ programs for a single representative structure of the complex UVCB mixture, 2-ethyl-4-methylpyridine. As pyridine, alkyl derivs. is a complex combination of alkyl pyridines and other by-products with variable composition, use of a single structure as being representative of the UVCB creates additional uncertainty in the modelling of estimated environmental concentrations.

Conclusion

Based on the information presented in this final screening assessment, it is concluded that pyridine, alkyl derivs. does not meet the criteria in paragraphs 64*(a)* and *(b)* of CEPA 1999, as it is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. Additionally, pyridine, alkyl derivs. meets the criteria for persistence, but not for bioaccumulation potential, as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based upon consideration of the available data, it is concluded that pyridine, alkyl derivs. does not meet the criteria in paragraph 64*(c)* of CEPA 1999, as it is not a substance entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that pyridine, alkyl derivs. does not meet the criteria as set out in section 64 of CEPA 1999.

This substance will be considered for inclusion in the Domestic Substances List inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during this screening assessment.

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SafePharm Laboratories 2007c Pyridine, alkyl derivs, acetates: Acute toxicity to fathead minnow; SPL Project Number: 2433/0005

SafePharm Laboratories 2007d Acetic acid, mercapto-, compounds with alkylpyridines: Acute toxicity to fathead minnow; SPL Project Number: 2433/0011

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Appendix 1 – Robust Study Summary

Robust Study Summary: Persistence in Water				
No	**Item**	**Weight**	**Yes/No**	**Specify**
1	Reference: Safepharm Laboratories. 2007a. Pyridine, alkyl derivs., acetates: Assessment of Ready Biodegradability; CO2 Evolution Test, SPL Project Number: 2433/0006.			
2	Substance identity: CAS RN	n/a	N	Sample from the supplier
3	Substance identity: chemical name(s)	n/a	Y	Pyridine, alkyl derivs, acetates
4	Chemical composition of the substance	2	N	The purity of the substance is not directly reported.
5	Chemical purity	1	N	Sample from the supplier
Method				
6	Reference	1	Y	OECD No 301B "Ready Biodegradability; CO_2 Evolution Test"
7	OECD, EU, national, or other standard method?	3	Y	
8	Justification of the method/protocol if not a standard method was used	2		n/a
9	GLP (Good Laboratory Practice)	3	Y	
Test design / conditions				
10	Test type (i.e. hydrolysis, biodegradation, etc.)	n/a	Y	Biodegradation
11	Test conditions type (aerobic or anaerobic)	n/a	Y	Aerobic
12	Test medium (water, sediment, or soil)	n/a	Y	Water
13	Test duration	n/a	Y	28 days
14	Negative or positive controls?	1	Y	Positive, sodium benzoate
15	Number of replicates (including controls)	1	Y	2 control of inoculated culture medium, 2 standard material (sodium benzoate), 2 test material, 1 test + standard material
16	Measured concentrations reported?	3	Y	Measured CO2 / DOC concentrations

17	Analytical method / instrument	1	Y	
Details on Biodegradation				
18	Type of biodegradation (ready or inherent) reported?	2	Y	Ready biodegradation
19	When type of biodegradation (ready or inherent) is not reported, if there is indirect information allowing to identify biodegradation type?	1		n/a
20	Inoculum source	1	Y	activated sewage sludge micro-organisms from the aeration stage of the Severn Trent Water Plc sewage treatment plant at Loughborough, Leicestershire, UK
21	Inoculum concentration or number of microorganisms	1	Y	Test vessel inoculated with prepared inoculum at a [ ] of 30 mg suspended solids / l
22	Were inoculum pre-conditioning and pre-adaptation reported?	1	Y	Inoculum not pre-conditioned or pre-adapted
23	Were inoculum pre-conditioning and pre-adaptation appropriate for the method used?	n/a		n/a
24	Temperature	1	Y	21 C in darkness
25	Has percentage degradation of the reference compound reached the pass levels by day 14?	n/a	Y	the toxicity control attained 42% degradation after 14 days and 46% degradation after 28 days, confirming that the test material was not toxic to sewage treatment micro-organisms
26	**Soil:** soil moisture reported?	1	n/a	n/a
27	**Soil and sediments**: background SOM (Soil Organic Matter) content reported?	1	n/a	n/a
28	**Soil and sediments**: clay content reported?	1	n/a	n/a
29	**Soil and sediments:** CEC (Cation Exchange Capacity) reported?	1	n/a	n/a
Details on Hydrolysis				
30	pH values reported?	1	n/a	n/a
31	Temperature	1	n/a	n/a

32	Were appropriate concentrations of the substance used?		n/a	n/a
33	If solvent was used, was it done appropriately?		n/a	n/a
	Details on Fhotodegradation			
34	Temperature	1	n/a	n/a
35	Light source	1	n/a	n/a
36	Light spectrum (nm)	1	n/a	n/a
37	Relative intensity based on sunlight intensity	1	n/a	n/a
38	Spectrum of a substance	1	n/a	n/a
39	**Indirect photolysis:** sensitizer (type)	1	n/a	n/a
40	**Indirect photolysis:** concentration of sensitizer	1	n/a	n/a
	Results			
41	Endpoint and value	n/a	n/a	28-d biodegradation = 21%
42	Breakdown products	n/a	N	
43	***Score*: ... %**		***86.4***	
44	***EC Reliability code*:**		***1***	
45	***Reliability category (high, satisfactory, low)*:**		***High Confidence***	
46	***Comments***			

Robust Study Summary: Persistence in Water

No	Item	Weight	Yes/No	Specify
1	Reference: Safepharm Laboratories. 2007b. Acetic acid, mercapto-, compounds with alkylpyridines: Assessment of Ready Biodegradability; CO2 Evolution Test, SPL Project Number: 2433/0012.			
2	Substance identity: CAS RN	n/a	N	
3	Substance identity: chemical name(s)	n/a	Y	Acetic acid, mercapto-, compds. with alkylpyridines
4	Chemical composition of the substance	2	N	The purity of the substance is not directly reported.
5	Chemical purity	1	N	Sample from the supplier
	Method			
6	Reference	1	Y	OECD No 301B "Ready Biodegradability; CO_2 Evolution Test"
7	OECD, EU, national, or other standard method?	3	Y	
8	Justification of the method/protocol if not a standard method was used	2		n/a
9	GLP (Good Laboratory Practice)	3	Y	
	Test design / conditions			
10	Test type (i.e. hydrolysis, biodegradation, etc.)	n/a	Y	Biodegradation

11	Test conditions type (aerobic or anaerobic)	n/a	Y	Aerobic
12	Test medium (water, sediment, or soil)	n/a	Y	Water
13	Test duration	n/a	Y	28 days
14	Negative or positive controls?	1	Y	Positive, sodium benzoate
15	Number of replicates (including controls)	1	Y	2 control of inoculated culture medium, 2 standard material (sodium benzoate), 2 test material, 1 test + standard material
16	Measured concentrations reported?	3	Y	Measured CO2 / DOC concentrations
17	Analytical method / instrument	1	Y	
Details on Biodegradation				
18	Type of biodegradation (ready or inherent) reported?	2	Y	Ready biodegradation
19	When type of biodegradation (ready or inherent) is not reported, if there is indirect information allowing to identify biodegradation type?	1		n/a
20	Inoculum source	1	Y	activated sewage sludge micro-organisms from the aeration stage of the Severn Trent Water Plc sewage treatment plant at Loughborough, Leicestershire, UK
21	Inoculum concentration or number of microorganisms	1	Y	Test vessel inoculated with prepared inoculum at a [ ] of 30 mg suspended solids / l
22	Were inoculum pre-conditioning and pre-adaptation reported?	1	Y	Inoculum not pre-conditioned or pre-adapted
23	Were inoculum pre-conditioning and pre-adaptation appropriate for the method used?	n/a		n/a
24	Temperature	1	Y	21 C in darkness
25	Has percentage degradation of the reference compound reached the pass levels by day 14?	n/a	Y	the toxicity control attained 53% degradation after 14 days and 53% degradation after 28 days, confirming that the test material was not toxic to sewage treatment micro-organisms

26	**Soil:** soil moisture reported?	1	n/a	n/a
27	**Soil and sediments**: background SOM (Soil Organic Matter) content reported?	1	n/a	n/a
28	**Soil and sediments**: clay content reported?	1	n/a	n/a
29	**Soil and sediments:** CEC (Cation Exchange Capacity) reported?	1	n/a	n/a
Details on Hydrolysis				
30	pH values reported?	1	n/a	n/a
31	Temperature	1	n/a	n/a
32	Were appropriate concentrations of the substance used?		n/a	n/a
33	If solvent was used, was it done appropriately?		n/a	n/a
Details on Fhotodegradation				
34	Temperature	1	n/a	n/a
35	Light source	1	n/a	n/a
36	Light spectrum (nm)	1	n/a	n/a
37	Relative intensity based on sunlight intensity	1	n/a	n/a
38	Spectrum of a substance	1	n/a	n/a
39	**Indirect photolysis:** sensitiser (type)	1	n/a	n/a
40	**Indirect photolysis:** concentration of sensitiser	1	n/a	n/a
Results				
41	Endpoint and value	n/a	n/a	28-d biodegradation = 21%
42	Breakdown products	n/a	N	
43	***Score*: ... %**		***86.4***	
44	***EC Reliability code*:**		***1***	
45	***Reliability category (high, satisfactory, low)*:**		***High Confidence***	
46	***Comments***			

Robust Study Summary: Aquatic iT				
No	**Item**	**Weight**	**Yes/No**	**Specify**
1	Reference: Safepharm Laboratories. 2007c. Pyridine, alkyl derivs, acetates: Acute toxicity to fathead minnow. SPL Project Number: 2433/0005.			
2	Substance identity: CAS RN	n/a	N	Sample from the supplier
3	Substance identity: chemical name(s)	n/a	Y	Pyridine, alkyl derivs, acetates
4	Chemical composition of the substance	2	N	The purity of the substance is not directly reported.
5	Chemical purity	1	N	Sample from the supplier
6	Persistence/stability of test substance in aquatic solution reported?	1	N	Discussed in a separate study

Method				
7	Reference	1	Y	OECD No 203 "Fish, Acute Toxicity Test"
8	OECD, EU, national, or other standard method?	3	Y	
9	Justification of the method/protocol if not a standard method was used	2		n/a
10	GLP (Good Laboratory Practice)	3	Y	
Test organism				
11	Organism identity: name	n/a	Y	Fat head minnow
12	Latin or both Latin & common names reported?	1	Y	*Pimephales promelas*
13	Life cycle age / stage of test organism	1	Y	juvenile fish
14	Length and/or weight	1	Y	mean standard length 4.9 cm; mean weight of 2.13 g
15	Sex	1	N	
16	Number of organisms per replicate	1	Y	7 fish per replicate
17	Organism loading rate	1	Y	0.75 g/L
18	Food type and feeding periods during the acclimation period	1	Y	
Test design / conditions				
19	Test type (acute or chronic	n/a	Y	acute
20	Experiment type (laboratory or field	n/a	Y	laboratory
21	Exposure pathways (food, water, both)	n/a	Y	water
22	Exposure duration	n/a	Y	96-hours
23	Negative or positive controls (specify)	1	Y	Negative
24	Number of replicates (including controls)	1	Y	6 replicates
25	Nominal concentrations reported?	1	Y	for 6 [ ]
26	Measured concentrations reported?	3	Y	Measured test concentrations ranged 60 - 81% of nominal concentrations
27	Food type and feeding periods during the long-term tests	1		n/a
28	Were concentrations measured periodically (especially in the chronic test)?	1	Y	concentrations measured at 0hr, 24hr and 96hr
29	Were the exposure media conditions relevant to the particular chemical reported? (e.g., for the metal toxicity - pH, DOC/TOC, water hardness, temperature)	3	Y	
30	Photoperiod and light intensity	1	Y	
31	Stock and test solution preparation	1	Y	
32	Was solubilizer/emulsifier used, if the chemical was poorly soluble or unstable?	1		n/a
33	If solubilizer/emulsifier was used, was its concentration reported?	1		n/a

34	If solubilizer/emulsifier was used, was its ecotoxicity reported?	1		n/a
35	Analytical monitoring intervals	1	Y	
36	Statistical methods used	1	Y	
Information relevant to the data quality				
37	Was the endpoint directly caused by the chemical's toxicity, not by organism's health (e.g. when mortality in the control >10%) or physical effects (e.g. 'shading effect')?	n/a	Y	no mortality in control
38	Was the test organism relevant to the Canadian environment?	3	Y	Fathead minnow is representative of a wide variety of natural habitats, and can be considered as an important non-target organism in the freshwater ecosystems
39	Were the test conditions (pH, temperature, DO, etc.) typical for the test organism?	1	Y	
40	Does system type and design (static, semi-static, flow-through; sealed or open; etc.) correspond to the substance's properties and organism's nature/habits?	2	Y	
41	Was pH of the test water within the range typical for the Canadian environment (6 to 9)?	1	Y	pH=7.2 - 7.9
42	Was temperature of the test water within the range typical for the Canadian environment (5 to 27°C)?	1	Y	21 C
43	Was toxicity value below the chemical's water solubility?	3	N	
Results				
44	Toxicity values (specify endpoint and value)	n/a	n/a	96-h LC50 = 4.5 mg/L (measured [ ])
45	Other endpoints reported - e.g. BCF/BAF, LOEC/NOEC (specify)?	n/a	Y	NOEC = 2.2 mg/L (measured [ ])
46	Other adverse effects (e.g. carcinogenicity, mutagenicity) reported?	n/a	Y	sub-lethal effects observed at nominal [ ] of 5.6 mg/L (measured [ ] of 3.75 - 4.54 mg/L)
47	***Score*: ... %**		***81.0***	
48	***EC Reliability code*:**		***1***	
49	***Reliability category (high, satisfactory, low)*:**		***High Confidence***	
50	***Comments***			

Robust Study Summary: Aquatic iT				
No	**Item**	**Weight**	**Yes/No**	**Specify**
1	Reference: Safepharm Laboratories. 2007d. Acetic acid, mercapto-, compounds with alkylpyridines : Acute toxicity to fathead minnow. SPL Project Number: 2433/0011.			
2	Substance identity: CAS RN	n/a	N	Sample from the supplier
3	Substance identity: chemical name(s)	n/a	Y	Acetic acid, mercapto-, compds. with alkylpyridines
4	Chemical composition of the substance	2	N	The purity of the substance is not directly reported.
5	Chemical purity	1	N	Sample from the supplier
6	Persistence/stability of test substance in aquatic solution reported?	1	N	Discussed in a separate study
Method				
7	Reference	1	Y	OECD No 203 "Fish, Acute Toxicity Test"
8	OECD, EU, national, or other standard method?	3	Y	
9	Justification of the method/protocol if not a standard method was used	2		n/a
10	GLP (Good Laboratory Practice)	3	Y	
Test organism				
11	Organism identity: name	n/a	Y	Fat head minnow
12	Latin or both Latin & common names reported?	1	Y	*Pimephales promelas*
13	Life cycle age / stage of test organism	1	Y	juvenile fish
14	Length and/or weight	1	Y	mean standard length 4.0 cm; mean weight of 1.24 g
15	Sex	1	N	
16	Number of organisms per replicate	1	Y	7 fish per replicate
17	Organism loading rate	1	Y	0.43 g/L
18	Food type and feeding periods during the acclimation period	1	Y	
Test design / conditions				
19	Test type (acute or chronic	n/a	Y	acute
20	Experiment type (laboratory or field	n/a	Y	laboratory
21	Exposure pathways (food, water, both)	n/a	Y	water
22	Exposure duration	n/a	Y	96-hours
23	Negative or positive controls (specify)	1	Y	Negative
24	Number of replicates (including controls)	1	Y	6 replicates
25	Nominal concentrations reported?	1	Y	for 6 [ ]

26	Measured concentrations reported?	3	Y	Measured test concentrations ranged 60 - 81% of nominal concentrations
27	Food type and feeding periods during the long-term tests	1		n/a
28	Were concentrations measured periodically (especially in the chronic test)?	1	Y	concentrations measured at 0hr, 24hr and 96hr
29	Were the exposure media conditions relevant to the particular chemical reported? (e.g., for the metal toxicity - pH, DOC/TOC, water hardness, temperature)	3	Y	
30	Photoperiod and light intensity	1	Y	
31	Stock and test solution preparation	1	Y	
32	Was solubilizer/emulsifier used, if the chemical was poorly soluble or unstable?	1		n/a
33	If solubilizer/emulsifier was used, was its concentration reported?	1		n/a
34	If solubilizer/emulsifier was used, was its ecotoxicity reported?	1		n/a
35	Analytical monitoring intervals	1	Y	
36	Statistical methods used	1	Y	
Information relevant to the data quality				
37	Was the endpoint directly caused by the chemical's toxicity, not by organism's health (e.g. when mortality in the control >10%) or physical effects (e.g. 'shading effect')?	n/a	Y	no mortality in control
38	Was the test organism relevant to the Canadian environment?	3	Y	Fathead minnow is representative of a wide variety of natural habitats, and can be considered as an important non-target organism in the freshwater ecosystems
39	Were the test conditions (pH, temperature, DO, etc.) typical for the test organism?	1	Y	
40	Does system type and design (static, semi-static, flow-through; sealed or open; etc.) correspond to the substance's properties and organism's nature/habits?	2	Y	
41	Was pH of the test water within the range typical for the Canadian environment (6 to 9)?	1	Y	pH=7.2 - 7.9
42	Was temperature of the test water within the range typical for the Canadian environment (5 to 27°C)?	1	Y	21 C
43	Was toxicity value below the chemical's water solubility?	3	N	
Results				

44	Toxicity values (specify endpoint and value)	n/a	n/a	96-h LC50 = 12 mg/L (nominal [ ])
45	Other endpoints reported - e.g. BCF/BAF, LOEC/NOEC (specify)?	n/a	Y	NOEC = 5.6 mg/L (measured [ ])
46	Other adverse effects (e.g. carcinogenicity, mutagenicity) reported?	n/a	Y	sub-lethal effects observed at nominal [ ] of 18 mg/L (measured [ ] of 3.75 - 4.54 mg/L)
47	***Score*: ... %**			***81.0***
48	***EC Reliability code*:**			***1***
49	***Reliability category (high, satisfactory, low)*:**			***High Confidence***
50	***Comments***			

Appendix 2: Estimated environmental concentrations of pyridine, alkyl derivs. in environmental media using ChemCAN v6.00 (ChemCAN 2003)

Compartment[a,b]	Estimated environmental concentration
Ambient air[c]	0.928 ng/m^3
Surface water[d]	59.7 ng/L
Soil[d]	0.101 ng/g solids
Sediment[d]	0.508 ng/g solids

[a] Default inflow concentrations of 2 ng/m^3 in air and 3 ng/L in water were specified by ChemCAN v6.00.
[b] Physicochemical properties selected for representative structure of pyridine, alkyl derivs., namely 2-ethyl-4-methylpyridine, from EPI Suite™ using EPI Suite™ programs (2000-2008).
[c] Atmospheric oxidation half-life of 35.286 hr specified for representative structure of pyridine, alkyl derivs. from EPI Suite™ using AOPWIN (2008).
[d] Degradation half-lives were assumed to be effectively infinite for surface water, soil and sediment.

Appendix 3: Upper-bounding estimates of daily intakes of pyridine, alkyl derivs. for various age groups in humans

Route of exposure	Estimated intake (µg/kg bw per day) of pyridine, alkyl derivs. by various age groups							
	0–0.5 years[a,b,c]			0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
	Breast milk fed	Formula fed	Not formula fed					
Air[i]	3.2×10^{-5}	3.2×10^{-5}	3.2×10^{-5}	7.0×10^{-4}	5.4×10^{-4}	3.1×10^{-5}	2.6×10^{-5}	2.3×10^{-5}
Drinking water[j]	N/A[k]	6.4×10^{-3}	2.4×10^{-3}	2.7×10^{-3}	2.1×10^{-3}	1.2×10^{-3}	1.3×10^{-3}	1.3×10^{-3}
Food and beverages[l]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Soil[m]	4.0×10^{-7}	4.0×10^{-7}	4.0×10^{-7}	6.5×10^{-7}	2.1×10^{-7}	5.1×10^{-8}	4.3×10^{-8}	4.2×10^{-8}
Total intake	2.6×10^{-4}	6.6×10^{-3}	2.6×10^{-3}	3.2×10^{-3}	2.6×10^{-3}	1.4×10^{-3}	1.5×10^{-3}	1.5×10^{-3}
Range of total intakes from all routes of exposure: 2.6×10^{-4} to 6.6×10^{-3} µg/kg bw per day								

a No quantitative data were identified for concentrations of pyridine, alkyl derivs. in breast milk.

b Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (Health Canada 1998).

c For exclusively formula-fed infants, intake from water is synonymous with intake from food. No quantitative data on concentrations of pyridine, alkyl derivs. in drinking water or formula were identified for Canada. The concentration of pyridine, alkyl derivs. in surface water, as a surrogate for drinking water, was estimated using ChemCAN v6.00 at 59.7 ng/L (ChemCAN 2003). For non-formula-fed infants, approximately 50% are introduced to solid foods by four months of age and 90% by six months of age (NHW 1990).

d Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (Health Canada 1998).

e Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (Health Canada 1998).

f Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

g Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

h Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

i No quantitative data were identified for concentrations of pyridine, alkyl derivs. in air. The concentration of pyridine, alkyl derivs. in air was estimated using ChemCAN v6.00 at 0.928 ng/m^3 (ChemCAN 2003).

j No quantitative data were identified for concentrations of pyridine, alkyl derivs. in drinking water. The concentration of pyridine, alkyl derivs. in surface water, as a surrogate for drinking water, was estimated using ChemCAN v6.00 at 59.7 ng/L (ChemCAN 2003).

k N/A: not available.

l No quantitative data were identified for concentrations of pyridine, alkyl derivs. in food or beverages.

m No quantitative data were identified for concentrations of pyridine, alkyl derivs. in soil. The concentration of pyridine, alkyl derivs. in soil was estimated using ChemCAN v6.00 at 0.101 ng/g solids (ChemCAN 2003).

Appendix 4. Summary of available toxicity data for pyridine, alkyl derivs. and its main components

Endpoint[a]	Pyridine, alkyl derivs.	Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	2-methyl-5-ethyl pyridine (MEP)
Acute toxicity	**Oral LD_{50}:** Pyridine, alkyl derivs.: 2500 mg/kg bw (rat) (US EPA 2009) Akolidine 10[b]: 1393 mg/kg bw (rat) (Lonza 2008a) Akolidine 11[b]: 1940 mg/kg bw (rat) (Lonza 2008b) Akolidine 12[b]: 3100 mg/kg bw (rat) (Lonza 2008c) PAP 220[b]: 737 - 760 mg/kg bw (rat) (Vertellus., 2008) HAP 310[b]: >1000 mg/kg bw (rat) (Vertellus., 2010b) Pyridine Bases[b]: 169 mg/kg bw (rat) (Reilly Industries	**Oral LD_{50}:** 2-,3-, and 4-picoline: 400 – 1600 mg/kg bw (rodents) (Patty's Toxicology 2001; US EPA 2009) **Dermal LD_{50}:** 2-picoline: 200 - 500 mg/kg bw (rabbit); 3-picoline: 126 - 2000 mg/kg bw (rabbit); 4-picoline: 270 mg/kg bw (rabbit) (Patty's Toxicology 2001; US EPA 2009) **Inhalation lowest lethal concentration (LCLo):** 2-picoline: 4000 ppm (15236 mg/m^3) (rat, 4 h); 3-picoline: 1300 - 3000 ppm (4952 – 11427 mg/m^3) (rat, 4h); 4-picoline: 4000 ppm (15236 mg/m^3) (rat, 4h) (Patty's Toxicology 2001; US EPA 2009)	**Oral LD_{50}:** 2,4- and 2,6-lutidine: 200 – 800 mg/kg bw (rodents) (Patty's Toxicology 2001) **Dermal LD_{50}:** 2,4- and 2,6-lutidine: 1000 - 5000 mg/kg bw (guinea pigs) (Patty's Toxicology 2001) **Inhalation LC_{50}:** 2,4- and 2,6-lutidine: 650 ppm (6h) - 7500 ppm (1.2h) 2849 – 32871 mg/m^3) (Patty's Toxicology 2001)	**Oral LD_{50}:** 2,4,6-collidine: 400 mg/kg bw (rat) (Patty's Toxicology 2001) **Dermal LD_{50}:** No data identified. **Inhalation LC_{50}:** No data identified.	**Oral LD_{50}:** No data identified. **Dermal LD_{50}:** No data identified. **Inhalation LC_{100}:** 2-ethylpyridine: 5400 ppm (23667 mg/m^3) (rat, 3h); 4-ethylpyridine: 2500 ppm (10957 mg/m^3) (rat, 5h) (Patty's Toxicology 2001)	**Oral LD_{50}:** No data identified. **Dermal LD_{50}:** No data identified. **Inhalation LC_{50}:** No data identified.	**Oral LD_{50}:** **Lowest LD_{50}** = 569 mg/kg bw (mouse) (OECD 1995) [Additional data in rats and rabbits, OECD 1995] **Dermal LD_{50}:** Lowest LD_{50} = 1000 mg/kg bw (rabbit) (OECD 1995) [Additional data in guinea pigs, OECD 1995] **Inhalation** LC_{50}: < 1000 ppm (4956 mg/m^3) (rats, 4 h) (OECD 1995) [Additional data in rats, OECD 1995]

Endpoint[a]	Pyridine, alkyl derivs.	Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	2-methyl-5-ethyl pyridine (MEP)
	Inc, 2000) KW48[b]: 2500 mg/kg bw (rat) (US EPA 2003) **Dermal LD_{50}:** Pyridine, alkyl derivs.: > 2.0 mL/kg bw (rabbit, about 2000 mg/kg bw) (US EPA 2009) PAP 220[b] and HAP 310[b]: > 2000 mg/kg bw (rabbit) (Vertellus., 2008, 2010b; US EPA 2003) Pyridine Bases[b]: 1880 mg/kg bw (rabbit) (Reilly Industries Inc., 2000) **Inhalation LC_{50}:** No data identified.						
Short-term toxicity	No data identified.	3-picoline: short-term inhalation NOAEC = 290 ppm (1105 mg/m^3) (rats, 2 weeks). In this study, rats were	No data identified.	No data identified.	No data identified.	No data identified.	**The lowest LOEL** (rat) = 95 mg/kg bw per day, based slight deviations of clinical chemistry parameters and increased liver weights.

Endpoint[a]	Pyridine, alkyl derivs.	Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	2-methyl-5-ethyl pyridine (MEP)
		exposed to 290 ppm 3-picoline for 6 h a day, 5 days a week for 2 weeks. There were no adverse effects observed with respect to body weights, clinical signs, clinical laboratory measurements or histopathological examination. After the last exposure, rats showed slight liver weight increases, which returned to normal 13 days after exposure (Patty's Toxicology 2001; US EPA 2009).					Hyaline droplets nephropathy were observed in males at 95 and 300 mg/kg bw per day. In this study Sprague-Dawley rats (males and females, presumably 5/sex/group as this study followed OECD 407, no further experimental details were provided) were administered 30, 95 or 300 mg MEP/kg bw per day by gavage for 28 days (statistical analysis was not provided) (Biomedizinische Forschungsanstalt m.b.H. 1988) [additional data: Biomedizinische Forschungsanstalt m.b.H. 1987; Pharmaco-LSR Ltd. 1994c]
Sub-chronic toxicity	No data identified.	2-picoline subchronic inhalation NOAEC = 100 ppm (381 mg/m^3) (rats and rabbits, 6 months). In this study, rats, rabbits and guinea pigs were exposed to 2-picoline by inhalation for 7 h a day for 6 months, rats and rabbits showed no compound-related effects at 25, 50 or 100 ppm (95, 191 or	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.

Endpoint[a]	**Pyridine, alkyl derivs.**	**Picolines**	**Lutidines**	**Collidines**	**Ethylpyridines**	**Propylpyridines**	**2-methyl-5-ethyl pyridine (MEP)**
		381 mg/m^3). Guinea pigs exhibited a slight to moderate increase in vacuolization of liver hepatocytes, an effect also caused by fasting and judged reversible (Patty's Toxicology 2001). [Additional data: 13 week drinking water studies with 3-picoline in rats and mice are in the process, NTP 2010]					
Chronic toxicity/carcinogenicity	No data identified.	No data identified. [Additional data: two year drinking water studies with 3-picoline in rats and mice are in the process. It has been noted that the incidences of pituitary gland adenomas in male rats and lung alveolar and bronchiolar adenomas in both male and female rats were significantly increased at the highest dose level (625 mg/L, however, the study report has not been finalized. NTP 2010]	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.
Genotoxicity – *in vitro*	**Mutagenicity Ames tests:**	**Mutagenicity Ames tests:**	**Mutagenicity Ames tests:**	**Mutagenicity Ames tests:**	**Mutagenicity Ames tests:**	No data identified.	**Mutagenicity Ames tests:**

Endpoint[a]	Pyridine, alkyl derivs.	Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	2-methyl-5-ethyl pyridine (MEP)
	Akolidine 10[b] and Akolidine 11[b]: Positive (followed OECD 471, no further details) (Lonza. 2008a, b) Akolidine 12[b]: Negative (Lonza. 2008c) **Chromosome aberration** Akolidine 10[b] and Akolidine 11[b]: human lymphocytes (*in vitro*): Negative (followed OECD 473, no further details) (Lonza 2008a, b)	2-, 3-, and 4-picolines: Negative in *Salmonella typhimurium* TA1535, TA1537, TA1538, TA 97, TA98, TA100 and TA 102, with and without metabolic activation (Ho et al., 1981; Patty's Toxicology 2001; Shoji and Kawakami, 2006; Eisentraeger et al., 2008; US EPA 2009). **Mutation in mammalian cells:** 2-, 3- and 4-picolines: Negative in Chinese hamster lung cells (V79) without metabolic activation (US EPA 2009). **DNA single-strand breaks:** 3-picolines: Negative in Chinese hamster lung cells (V79) without metabolic activation (NTP 2007). **Aneuploidy induction:** 2-picoline: Positive in *Saccharomyces cerevisiae* D61.M	2,6- and 3,5-lutidines: Negative in *Salmonella typhimurium* TA 100, with and without metabolic activation (Florin et al., 1980); 2,3-, 2,5-, 3,5-, 3,4-, 2,4- and 2,6-lutidines: Negative in *Salmonella typhimurium* TA1535, TA1537, TA1538 TA98 and TA100 with metabolic activation (Ho et al., 1981); 2,3-lutidine: Negative in *Salmonella typhimurium* TA 98, TA 100, with and without metabolic activation (Aguayo et al., 2004) **Aneuploidy**	2,3,5-, 2,3,6- and 2,4,6-collidines: Negative in *Salmonella typhimurium* TA 98, TA 100, with and without metabolic activation (Aguayo et al., 2004; Eisentraeger et al., 2008); 2,4,6-collidine: Negative in *Salmonella typhimurium* TA1535, TA1537, TA1538 TA98 and TA100 with metabolic activation (Ho et al., 1981)	2- and 3-ethylpyridine : Negative in *Salmonella typhimurium* TA1535, TA1537, TA1538 TA98 and TA100 with metabolic activation (Ho et al., 1981)		Negative in *Salmonella typhimurium* TA1535, TA1537, TA1538 TA98 and TA100 with metabolic activation (OECD 1995) **Gene conversion:** Negative in *Saccharomyces cerevisiae* (Zimmermann et al., 1984). **Chromosome aberration:** Positive in cultured human lymphocytes with metabolic activation, and positive at near toxic concentrations without metabolic activation (but negative at lower concentrations without activation) (OECD 1995) **Aneuploidy induction:** Positive in *Saccharornyces cerevisiae* D61.M (Zimmermann et al., 1986)

Endpoint[a]	**Pyridine, alkyl derivs.**	**Picolines**	**Lutidines**	**Collidines**	**Ethylpyridines**	**Propylpyridines**	**2-methyl-5-ethyl pyridine (MEP)**
		(Zimmermann et al., 1986).	**induction:** 2,4- and 2,6-lutidines: Positive in *Saccharomyces cerevisiae* D61.M (Zimmermann et al., 1986)				
Genotoxicity – *in vivo*	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.	**Micronucleus assay** Negative in mouse, CD-1 strain (followed OECD guideline 474) (OECD 1995)
Developmental toxicity	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.	**LOAEL** for developmental toxicity (rat) = 300 mg/kg bw per day, based on increased total litter loss, reduced offspring body weights by the birth, reduced pup bodyweight gain to day 4 and decreased pup viability in the above described study (statistical analysis was not provided). NOEL = 95 mg/kg bw per day. In this one generation study, Sprague-Dawley rats (males and females, presumably 10/sex/group as this study followed OECD guideline 421, no further experimental details were provided) were administered 30, 95 or 300 mg MEP/kg

Endpoint[a]	Pyridine, alkyl derivs.	Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	2-methyl-5-ethyl pyridine (MEP)
							bw per day by gavage, 15 days before pairing and during mating, gestation and lactation until day 4 post partum. LOEL for parental toxicity = 95 mg/kg bw per day, based increased salivation in both males and females and reduced bodyweight gain during lactation in females. At 300 mg/kg bw per day dose level, reduced bodyweight gain were observed in both sex of animals. Two males treated with 300 mg/kg per day developed accentuated lobular liver patterns, reduced or dehydrated gastro-intestinal contents, reduced testes, epididymides, prostate glands and seminal vesicles and a small mass on one spermatozoal granuloma and clinical symptoms, such as ataxia, partially closed eyes, prostrate posture and under activity. Three females at this dose level lost total litter and developed inactive mammary tissues, two of them showed liver changes, smaller spleens, and pale

Endpoint[a]	**Pyridine, alkyl derivs.**	**Picolines**	**Lutidines**	**Collidines**	**Ethylpyridines**	**Propylpyridines**	**2-methyl-5-ethyl pyridine (MEP)**
							areas in the kidneys (Pharmaco-LSR Ltd. 1994c)
Reproductive toxicity	No data identified.	No data identified.	No data identified.	No data identified.			NOAEL = 300 mg/kg bw per day, based on no effects on the general reproductive performance were observed in treated animals in the above described one generation study (Pharmaco-LSR Ltd. 1994c)
Irritation	**Skin irritation:** Akolidine 10[b]: Moderate irritant (rabbit) (Lonza 2008a) Akolidine 11[b] and Akolidine 12[b]: Mild irritant (rabbit) (Lonza 2008b;c) PAP 220[b]: Corrosive to skin (Vertellus, 2008) **Eye irritation:** PAP 220[b]: Corrosive to eyes (Vertellus, 2008) Pyridine Bases[b]: Corrosive/severe eye irritant (Reilly Industries Inc.,	**Skin irritation:** 2-, 3-, and 4-picolines are severe skin irritants; 4-picoline is the most potent (Dutertre-Catella et al., 1989; Patty's Toxicology 2001). **Eye irritation:** 2-, 3-, and 4-picolines are severe eye irritants; 4-picoline is the most potent (Dutertre-Catella et al., 1989; Patty's Toxicology 2001).	No data identified.	No data identified.	No data identified.	No data identified.	**Skin irritation:** Severe skin irritant, corrosive (OECD 1995; Patty's Toxicology 2001). **Eye irritation:** Severe eye irritant (Patty's Toxicology 2001).

Endpoint[a]	**Pyridine, alkyl derivs.**	**Picolines**	**Lutidines**	**Collidines**	**Ethylpyridines**	**Propylpyridines**	**2-methyl-5-ethyl pyridine (MEP)**
	2000)						
Sensitization	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.	Negative in guinea pigs (Patty's Toxicology 2001).
Human	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.	No data identified.

[a] Definitions: LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level.
[b] Underscored terms are the trade names or common names of mixtures containing pyridine, alkyl derivs.

Appendix 5. Summary of (Q)SAR results[i] on carcinogenicity prediction for the main components of pyridine, alkyl derivs.

Model/Substance			Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	Methyl-,ethyl-pyridines
Model Applier	Mouse	Mouse	2-picoline: ND 3-picoline: **P** 4-picoline: ND	2,3-lutidine: ND 2,4-lutidine: ND 2,5-lutidine: **P** 2,6-lutidine: ND 3,4-lutidine: ND 3,5-lutidine: **P**	2,3,5-collidine: ND 2,4,6-collidine: ND 2,3,6-collidine: ND	2-ethylpyridine: N 3-ethylpyridine: **P** 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: **P** 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: ND 4-methyl-2-ethyl-pyridine: N
		Female	2-picoline: ND 3-picoline: **P** 4-picoline: ND	2,3-lutidine: ND 2,4-lutidine: ND 2,5-lutidine: **P** 2,6-lutidine: ND 3,4-lutidine: ND 3,5-lutidine: **P**	2,3,5-collidine: ND 2,4,6-collidine: ND 2,3,6-collidine: ND	2-ethylpyridine: N 3-ethylpyridine: N 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: N 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: ND 4-methyl-2-ethyl-pyridine: N
		Male	2-picoline: N 3-picoline: **P** 4-picoline: N	2,3-lutidine: ND 2,4-lutidine: ND 2,5-lutidine: **P** 2,6-lutidine: N 3,4-lutidine: ND 3,5-lutidine: **P**	2,3,5-collidine: ND 2,4,6-collidine: ND 2,3,6-collidine: ND	2-ethylpyridine: N 3-ethylpyridine: **P** 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: **P** 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: ND 4-methyl-2-ethyl-pyridine: ND
	Rat	Rat	2-picoline: ND 3-picoline: ND	2,3-lutidine: ND 2,4-lutidine: ND	2,3,5-collidine: ND 2,4,6-collidine: ND	2-ethylpyridine: N 3-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: N	2-methyl-5-ethyl-pyridine:

Model/Substance			Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	Methyl-,ethyl-pyridines
			4-picoline: ND	2,5-lutidine: ND 2,6-lutidine: ND 3,4-lutidine: ND 3,5-lutidine: ND	2,3,6-collidine: ND	4-ethylpyridine: N	4-propylpyridine: N	ND 4-methyl-2-ethyl-pyridine: ND
		Female	2-picoline: N 3-picoline: N 4-picoline: N	2,3-lutidine: ND 2,4-lutidine: ND 2,5-lutidine: N 2,6-lutidine: N 3,4-lutidine: ND 3,5-lutidine: N	2,3,5-collidine: ND 2,4,6-collidine: ND 2,3,6-collidine: ND	2-ethylpyridine: N 3-ethylpyridine: N 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: N 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: ND 4-methyl-2-ethyl-pyridine: ND
		Male	2-picoline: N 3-picoline: ND 4-picoline: ND	2,3-lutidine: ND 2,4-lutidine: ND 2,5-lutidine: ND 2,6-lutidine: N 3,4-lutidine: ND 3,5-lutidine: ND	2,3,5-collidine: ND 2,4,6-collidine: ND 2,3,6-collidine: ND	2-ethylpyridine: N 3-ethylpyridine: N 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: N 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: ND 4-methyl-2-ethyl-pyridine: ND
	Rodent		2-picoline: N 3-picoline: ND 4-picoline: ND	2,3-lutidine: ND 2,4-lutidine: ND 2,5-lutidine: ND 2,6-lutidine: N 3,4-lutidine: ND 3,5-lutidine: ND	2,3,5-collidine: ND 2,4,6-collidine: ND 2,3,6-collidine: ND	2-ethylpyridine: N 3-ethylpyridine: N 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: N 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: ND 4-methyl-2-ethyl-pyridine: N
Multicase Casetox	Rodent		2-picoline: N 3-picoline: N 4-picoline: IC	2,3-lutidine: N 2,4-lutidine: N 2,5-lutidine: N 2,6-lutidine: N 3,4-lutidine: N 3,5-lutidine: IC	2,4,6-collidine: N 2,3,5-collidine: N 2,3,6-collidine: N	2-ethylpyridine: N 3-ethylpyridine: IC 4-ethylpyridine: IC	2-propylpyridine: N 3-propylpyridine: IC 4-propylpyridine: IC	2-methyl-5-ethyl-pyridine: N 4-methyl-2-ethyl-pyridine: N
	Mouse	Male	2-picoline: N 3-picoline: N 4-picoline: IC	2,3-lutidine: N 2,4-lutidine: N 2,5-lutidine: N 2,6-lutidine: N 3,4-lutidine: N 3,5-lutidine: N	2,4,6-collidine: N 2,3,5-collidine: IC 2,3,6-collidine: N	2-ethylpyridine: N 3-ethylpyridine: IC 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: N 4-propylpyridine: IC	2-methyl-5-ethyl-pyridine: N 4-methyl-2-ethyl-pyridine: IC
		Female	2-picoline: N	2,3-lutidine: N	2,4,6-collidine: N	2-ethylpyridine: N	2-propylpyridine: N	2-methyl-5-

Model/Substance			Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	Methyl-,ethyl-pyridines
			3-picoline: N 4-picoline: IC	2,4-lutidine: N 2,5-lutidine: N 2,6-lutidine: N 3,4-lutidine: N 3,5-lutidine: N	2,3,5-collidine: N 2,3,6-collidine: N	3-ethylpyridine: IC 4-ethylpyridine: N	3-propylpyridine: N 4-propylpyridine: IC	ethyl-pyridine: N 4-methyl-2-ethyl-pyridine: N
	Rat	Male	2-picoline: N 3-picoline: N 4-picoline: N	2,3-lutidine: N 2,4-lutidine: N 2,5-lutidine: N 2,6-lutidine: N 3,4-lutidine: N 3,5-lutidine: N	2,4,6-collidine: N 2,3,5-collidine: N 2,3,6-collidine: N	2-ethylpyridine: N 3-ethylpyridine: N 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: N 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: N 4-methyl-2-ethyl-pyridine: N
		Female	2-picoline: N 3-picoline: N 4-picoline: N	2,3-lutidine: N 2,4-lutidine: IC 2,5-lutidine: N 2,6-lutidine: N 3,4-lutidine: N 3,5-lutidine: N	2,4,6-collidine: N 2,3,5-collidine: N 2,3,6-collidine: N	2-ethylpyridine: N 3-ethylpyridine: N 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: N 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: N 4-methyl-2-ethyl-pyridine: IC
Topkat	Rat	Male	2-picoline: N 3-picoline: N 4-picoline: N	2,3-lutidine: N 2,4-lutidine: N 2,5-lutidine: N 2,6-lutidine: N 3,4-lutidine: N 3,5-lutidine: N	2,4,6-collidine: N 2,3,5-collidine: N 2,3,6-collidine: N	2-ethylpyridine: N 3-ethylpyridine: N 4-ethylpyridine: N	2-propylpyridine: IC 3-propylpyridine: N 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: N 4-methyl-2-ethyl-pyridine: N
		Female	2-picoline: IC 3-picoline: IC 4-picoline: **P**	2,3-lutidine: IC 2,4-lutidine: IC 2,5-lutidine: IC 2,6-lutidine: IC 3,4-lutidine: IC 3,5-lutidine: IC	2,4,6-collidine: **P** 2,3,5-collidine: **P** 2,3,6-collidine: IC	2-ethylpyridine: IC 3-ethylpyridine: IC 4-ethylpyridine: IC	2-propylpyridine: IC 3-propylpyridine: IC 4-propylpyridine: IC	2-methyl-5-ethyl-pyridine: IC 4-methyl-2-ethyl-pyridine: IC
	Mouse	Male	2-picoline: IC 3-picoline: IC 4-picoline: IC	2,3-lutidine: IC 2,4-lutidine: IC 2,5-lutidine: IC 2,6-lutidine: N 3,4-lutidine: IC 3,5-lutidine: IC	2,4,6-collidine: IC 2,3,5-collidine: IC 2,3,6-collidine: IC	2-ethylpyridine: IC 3-ethylpyridine: IC 4-ethylpyridine: IC	2-propylpyridine: IC 3-propylpyridine: IC 4-propylpyridine: IC	2-methyl-5-ethyl-pyridine: N 4-methyl-2-ethyl-pyridine: IC

Model/Substance			Picolines	Lutidines	Collidines	Ethylpyridines	Propylpyridines	Methyl-,ethyl-pyridines
		Female	2-picoline: N 3-picoline: **P** 4-picoline: **P**	2,3-lutidine: IC 2,4-lutidine: N 2,5-lutidine: N 2,6-lutidine: N 3,4-lutidine: IC 3,5-lutidine: **P**	2,4,6-collidine: N 2,3,5-collidine: IC 2,3,6-collidine: **P**	2-ethylpyridine: N 3-ethylpyridine: N 4-ethylpyridine: N	2-propylpyridine: N 3-propylpyridine: IC 4-propylpyridine: N	2-methyl-5-ethyl-pyridine: IC 4-methyl-2-ethyl-pyridine: N
Derek		Mammal	No carcinogenicity alert for any of the substances					

[i] N: negative; P: positive; ND: not in domain; IC: inconclusive