Draft Screening Assessment

2-Pyrrolidinone, 1-methyl- (NMP)
and
2-Pyrrolidinone, 1-ethyl- (NEP)

Chemical Abstracts Service Registry Numbers
(872-50-4 and 2687-91-4)

Environment Canada
Health Canada

February 2017

Synopsis

Pursuant to sections 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Ministers of Environment and of Health have conducted a screening assessment of two substances referred to collectively herein as the NMP/NEP group. 2-Pyrrolidinone, 1-methyl- (NMP) was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA, whereas 2-pyrrolidinone, 1-ethyl (NEP) was considered a priority as a result of the process identified in the approach for identification of risk assessment priorities. The Chemical Abstracts Service Registry Numbers (CAS RNs[1]), their Domestic Substances List (DSL) names and their acronyms are listed in the table below.

Substances in the NMP/NEP group

CAS RN	DSL name	Acronyms
872-50-4	2-Pyrrolidinone, 1-methyl-	NMP
2687-91-4	2-Pyrrolidinone, 1-ethyl-	NEP

NMP and NEP are solvents that are miscible with water. Depending on the application, NMP is used generally as an organic solvent, intermediate or surfactant in a range of industrial and consumer applications. Products in Canada that contain NMP and that may be available to the general population include paint strippers. As a replacement for NMP, NEP may be used in similar products as those identified for NMP. Both substances are used in Canada in cosmetics and in certain food packaging materials.

With respect to volumes, in 2011, NMP was imported into Canada in quantities ranging from 100 000 to 1 000 000 kg, and NEP was imported in quantities ranging from 1 000 to 10 000 kg. In the United States, NMP is a high production volume (HPV) chemical.

The ecological risk of substances in the NMP/NEP group was characterized using the ecological risk classification of organic substances (ERC). The ERC is a risk-based approach that uses multiple metrics for both hazard and exposure based on weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are established based principally on metrics regarding mode of toxic action, chemical reactivity, food-web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include potential emission rate, overall persistence and long-range-transport potential. A risk

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matrix is used to assign a low, moderate or high level of potential concern for substances based on their hazard and exposure profiles. The ERC identified NMP and NEP as having low potential to cause ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from NMP and NEP. It is proposed to conclude that NMP and NEP do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as NMP and NEP are 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.

With respect to human health, NMP was assessed by the United States Environmental Protection Agency (US EPA) in 2015, and NEP was assessed by the European Chemicals Agency (ECHA) in 2011. In these assessments, developmental toxicity was identified as the critical effect for both NMP and NEP.

Potential exposure of the general population to NMP and NEP from use of products was characterized for select uses, namely paint strippers, nail polish remover and body lotion.

Consistent with the US EPA assessment, a comparison of estimated levels of exposure to NMP and critical effect levels results in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure databases. A comparison of estimated levels of exposure to NEP and critical effect levels results in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure databases.

Based on the information presented in this draft screening assessment, it is proposed to conclude that NMP and NEP do not meet the criteria under paragraph 64(*c*) of CEPA as NMP and NEP are 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.

It is proposed to conclude that NMP and NEP do not meet any of the criteria set out in section 64 of CEPA.

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1. Introduction

Pursuant to section 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of Environment and Climate Change and the Minister of Health have conducted screening assessments of two substances referred to as the NMP/NEP group to determine whether these substances present or may present a risk to the environment or to human health.

The substances in this group include N-methyl-2-pyrrolidone (NMP), which was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA, while N-ethyl-2-pyrrolidone (NEP) was considered a priority as a result of the process identified in the approach for identification of risk assessment priorities (ECCC and Health Canada 2015, ECCC 2016a). Given the potential for these two substances to be used in similar ways and applications, potential risk is assessed using similar exposure and hazard considerations across the group.

The ecological risk of substances in the NMP/NEP group was characterized using the Ecological Risk Classification of organic substances (ERC) (ECCC 2016b). The ERC describes the hazard of a substance using key metrics including mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity and considers the possible exposure of organisms in the aquatic and terrestrial environments based on factors including potential emission rates, overall persistence and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

The NMP/NEP group has been assessed by US EPA and ECHA. NMP was assessed by US EPA as part of the work plan of chemicals for further assessment under *the Toxic Substance Control Act* (TSCA)(US EPA 2015). A risk assessment of NEP has been conducted by ECHA (ECHA 2011). These assessments undergo rigorous review and approval processes and these assessments inform this assessment. In addition exposure estimates for paint stripper containing NMP presented in the US EPA report inform this assessment as it was determined that use patterns are similar between the US and Canada.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposure, including additional information submitted by stakeholders. Relevant data were identified up to October 2015. Empirical data from key studies as well as some results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Programs at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. Comments on the ERC approach and results were received from Dr. Jon Arnot (ARC Arnot Research and Consulting) and Mr. Geoff Granville (GCGranville Consulting Corp.). Additionally, the ERC document was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Environment and Climate Change Canada and Health Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA, by examining scientific information, and incorporating a weight-of-evidence approach and precaution[2]. The draft screening assessment presents the critical information and considerations upon which the proposed conclusion is made.

2. Identity of Substances

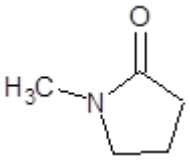
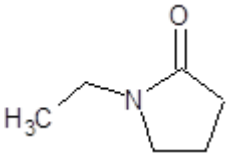
The Chemical Abstracts Service Registry Numbers (CAS RN[3]), Domestic Substances List (DSL) names, acronyms for the individual substances in the NMP/NEP group are presented in Table 2-1

Table 2-1 Substance identity

CAS RN (acronym)	DSL name	Chemical structure and molecular formula	Molecular weight (g/mole)

[2] 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 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations* and the *Controlled Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

[3] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

CAS RN (acronym)	DSL name	Chemical structure and molecular formula	Molecular weight (g/mole)
872-50-4 **(NMP)**	**2-Pyrrolidinone, 1-methyl-**	 **C5H9NO**	**99.13**
2687-91-4 **(NEP)**	**2-Pyrrolidinone, 1-ethyl-**	 **C6H11NO**	**113.16**

3. Physical and Chemical Properties

A summary of physical and chemical properties of the substances NMP and NEP are presented in Table 3-1 and Table 3-2 respectively. Additional physical and chemical properties are presented in ECCC 2016b. NMP and NEP are highly polar aprotic solvents that are soluble in both water and organic solvents (EPA 2015; FMI 2015). Additional physical and chemical properties are presented in ECCC (2016c).

Table 3-1 Physical and chemical property values for NMP (at standard temperatures and pressures)

Property	Value	Type of data	Key reference(s)
Physical state	Liquid	[4]	Ullmann's, 2000 cited in OECD SIDS 2007

[4] Type of data were not available for these properties.

Property	Value	Type of data	Key reference(s)
Melting point (°C)	-23.5	Measured	Domanska & Lachwa, 2002 cited in OECD SIDS 2007
Boiling point (°C)	204.1-204.4 (at 1013 hPa)	Extrapolation based on measured values	BASF AG, 1985 cited in OECD SIDS 2007
Density (g/cm^3)	1.029	Measured at 25°C	Maloka & Ibrahim, 2004 cited in OECD SIDS 2007
Vapor pressure	0.190 mmHg	Measured at 25°C	BASF AG, 1989a cited in OECD SIDS 2007
Henry's law constant ($Pa \cdot m^3/mol$)	0.00032	Measured at 20°C	Kim et al., 2000 cited in OECD SIDS 2007
Water solubility (mg/L)	$1x10^6$	Measured at 25°C	Riddick JA et al., 1986 cited in OECD SIDS Dossier 2007
Partitioning coefficient n-octanol/water, K_{ow} (dimensionless)	-0.46	Measured at 25°C	BASF AG, 1988a cited in OECD SIDS 2007
Log K_{ow} (dimensionless)	-0.727	Measured at 25°C	US EPA 2015
Dissociation constant pK_a, (dimensionless)	0.93	Calculated	BASF AG, 2007 cited in OECD SIDS 2007
Flash point (°C)	95		

Abbreviations: K_{ow}, octanol–water partition coefficient; K_{oc}, organic carbon–water partition coefficient; pK_a, acid dissociation constant

Table 3-2 Physical and chemical property values for NEP (at standard temperatures and pressures)

Property	Value	Type of data	Key reference(s)

Property	Value	Type of data	Key reference(s)
Physical state	Clear colourless to pale yellow liquid with a characteristic amine odour	X	INRS 2008 cited in ECHA 2011
Melting point (°C)	< -75	X	INRS 2008 cited in ECHA 2011
Boiling point (°C)	212-213	X	INRS 2008 cited in ECHA 2011
Density	0.998 (at 20°C)	X	INRS 2008 cited in ECHA 2011
Vapour pressure (Pa)	50 (at 32°C)	X	INRS 2008 cited in ECHA 2011
Henry's law constant ($Pa \cdot m^3/mol$)	NA	X	X

4. Sources and Uses

NMP and NEP do not occur naturally in the environment and are anthropogenic substances used primarily as solvents.

Based on information submitted pursuant to section 71 of CEPA (Canada 2012), between 100 000 and 1 000 000 kg of NMP and 1 000 and 10 000 kg of NEP were reported to be imported into Canada during 2011 (Environment Canada 2012)[5].

In the US, NMP is classified as a high production volume (HPV) chemical (US EPA 2015) and the national aggregated production volumes of NMP and NEP were reported to be between 4.5 to 45 million kg (10 to 100 million pounds) and 0.45 to 4.5 million kg (1 to 10 million pounds), respectively, for the 2012 calendar year (CDAT 2015).

NMP has been reported to Environment and Climate Change Canada's National Pollutant Release Inventory (NPRI), where 42 000 kg (42 tonnes) were released on-site to air from various Canadian companies during the 2014 reporting year (NPRI 2016).

[5] Values reflect quantities reported in response to a survey conducted under section 71 of CEPA (Canada 2012). See survey for specific inclusions and exclusions (schedules 2 and 3).

In Canada, based on survey results for the 2011 calendar year, uses for both substances include paints and coatings, adhesives and sealants, plastic and rubber materials. Additional uses reported for NMP in Canada included electrical and electronics, agricultural products, chemical manufacturing, metal and mining products, pharmaceuticals, paper and wood products, and it was reported to have a role in the manufacturing of automotive and transportation products. No consumer product applications were identified for NEP (Environment Canada 2013).

Several of the above Canadian NMP uses were confirmed, based on publically available product material safety data sheets (MSDSs), to be available to the general population in Canada, such as paint strippers, graffiti removers, coatings, and cosmetics (e.g., MSDS 2005; MSDS 2009a, b; MSDS 2011; MSDS 2013; MSDS 2015).

In Canada, neither NMP nor NEP are included on the List of Prohibited and Restricted Cosmetic Ingredients (Health Canada 2015). Based on notifications submitted to Health Canada under the *Cosmetic Regulations*, both substances are present in cosmetic products. NMP is present in adhesives for eyelashes and nails, and NEP is present in body lotion, face moisturizer and nail polish (personal communication, email from Consumer Product Safety Directorate (CPSD) to Existing Substance Risk Assessment Bureau (ESRAB), dated October 2015; unreferenced). In Canada, NMP and NEP are used in certain inks and coatings in food packaging materials, including some with direct food contact (personal communication, email from Food Directorate, HC, to ESRAB, HC; dated October 2015; unreferenced). Furthermore, concentration limits for NMP, in pharmaceutical products, have been adopted in Canada (Health Canada 2016). Finally, NMP has been identified to be used in pest control products as a formulant (personal communication, email from Pest Management Regulatory Agency, HC to Risk Management Bureau (RMB), HC; dated October 2015; unreferenced).

Globally, NMP is used as a solvent, intermediate, and formulating agent in various applications in industrial and consumer products (US EPA 2015; WHO 2001). NMP solvent applications include the petroleum industry, engineering plastics, coatings (i.e., resins, paint), agricultural chemicals, electronic cleaning and industrial/domestic cleaning, paint stripping, and as a potential substitute for dichloromethane (DCM) in paint stripping applications (US EPA 2015). Applications as a formulating agent include pesticides, pigments, dyes and ink, and intermediates in pharmaceuticals (WHO 2001; OECD 2007; ECHA 2015). NMP is found in various products available to consumers including paint strippers, paints, automotive products, adhesives and sealants, cleaners and cosmetics (US EPA 2015). NMP is used in cosmetics as a solvent, surfactant (SCCS 2011) and vehicle (WHO 2001). It is also used to enhance the dermal absorption of other ingredients in cosmetics (SCCS 2011) and in topically applied drugs (WHO 2001; NICNAS 2013). In general, less information on uses was identified for NEP; however, given its marketed use as a substitute for NMP, NEP often has similar applications as NMP (BASF 2010; ECHA 2011; Silberzahn 2013; FMI 2015). Furthermore, due to their similar physical-chemical properties, both substances are often used interchangeably (FMI 2015).

5. Potential to Cause Ecological Harm

5.1 Characterization of Ecological Risk

The ecological risk of substances in the NMP/NEP group was characterized using the Ecological Risk Classification of organic substances (ERC) (ECCC 2016b). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure based on weighted consideration of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., LC_{50}) for characterization. Section 5 summarizes the approach, which is described in detail in ECCC (2016b).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox), and in response to surveys under section 71 of CEPA, or they were generated using selected Quantitative Structure-Activity Relationship (QSAR) or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

Hazard profiles were established based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were also composed of multiple metrics including potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low, moderate, or high. . Additional rules were applied (e.g. classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

A risk matrix was used to assign a low, moderate or high classification of potential risk for each substance based on its hazard and exposure classifications. ERC classifications of potential risk were verified using a two-step approach. The first step adjusted the risk classification outcomes from moderate or high to low for substances which had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point-source of discharge) risk scenarios designed to be

protective of the environment, to determine whether classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over and under classification of hazard and exposure and subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC 2016b. The following describes two of the more substantial areas of uncertainty. Error with empirical or modeled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from QSAR models. However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue used for critical body residue (CBR) analysis. Error with underestimation of acute toxicity will be mitigated through the use of other hazard metrics such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus reflect exposure and risk in Canada based on what is believed to be the current use quantity, and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for NMP and NEP, and the hazard, exposure and risk classification results are presented in ECCC (2016c).

The hazard and exposure classifications for the NMP/NEP group are summarized in Table 6.1.

Table 5-1 Ecological risk classification results for NMP and NEP

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
NMP	**Low**	**Low**	**low**
NEP	**Low**	**Low**	**low**

Based on low hazard and low exposure classifications according to ERC for NMP and NEP, these substances were classified as having a low potential for ecological risk. It is therefore unlikely that these substances result in concerns for organisms or the broader integrity of the environment in Canada.

6. Potential to Cause Harm to Human Health

6.1 Exposure Assessment

Environmental Media

Limited environmental monitoring data relevant to current exposures in Canada have been identified for NMP and none have been identified for NEP. NMP has been monitored in indoor air samples (n > 3000) collected within the Canadian Health Measures Survey (CHMS) Cycle 2 (2009-2011), where concentrations ranged from <0.15 µg/m^3 (detection limit in field blanks) to 1.18 µg/m^3 ("upper mean" metric reported) with a detection frequency of 37% (personal communication, Zhu 2012 raw data; unreferenced; Patry-Parisien et al. 2013). NMP was also included in a study by the National Research Council (NRC) of Canada on chemicals released to indoor air of residences from building materials and furnishings (Won and Lusztyk 2011). NMP was not frequently detected; NMP was released from 2 out of 66 materials in total, where chamber air concentrations ranged from 0.84 to1.54 µg/m^3 and were associated to carpet and rubber-based flooring (Won and Lusztyk 2011). In the same report, concentrations of NMP in air and dust collected from homes in the Quebec City field study were also reported. Concentrations in air ranged from 0.39 to 6.26 µg/m^3 (detection frequency of 9%) and concentrations in dust ranged from 0.21 to 47.42 µg/g (detection frequency of 15%) (Won and Lusztyk 2011). While no ambient air monitoring has been identified in the literature, NMP has been reported to be released to air from point sources (NPRI 2016). However, indoor air is expected to be a more relevant source of environmental media exposure (e.g.,from the use of products available to consumers).

No Canadian data on levels of NMP and NEP, if any, in food are available. In Canada, NMP and NEP have been identified to be used in certain inks and coatings used in food packaging materials, including some with direct food contact, however dietary exposure from these uses are estimated to be low (email from Food Directorate, HC, to ESRAB, HC; dated October 2015; unreferenced).

Exposure to NMP and NEP from environmental media or food is expected to be low compared to exposure through certain products available to consumers.

Products Available to Consumers

Paint Stripper

NMP is used in a variety of products available to consumers that may result in exposure. Based on a review of available MSDSs, paint stripping products were found to contain the highest concentrations of NMP ("range of 30–60%", products may be accessible to Canadian consumers) although only a very limited number of these products were identified (MSDS 2009a; MSDS 2009b). The majority of products identified typically contained concentrations of NMP below 10%. No information on NEP-containing consumer paints and coatings were identified; however, NEP may be used in these applications given its use as a replacement for NMP (BASF 2010; Silberzahn 2013; FMI 2015).

Paint stripper, relative to other products, was identified as the product used by consumers that would be expected to result in the highest exposures to the general population of Canada given the combination of high concentrations and factors that influence exposure related to paint stripping. In the US EPA assessment of NMP, paint stripper was identified as the product likely resulting in the highest exposures (US EPA 2015). As such, the estimates of exposure derived by the US EPA, for acute exposures for consumers, are used in this assessment.

Several paint stripper consumer scenarios were developed by the US EPA in order to obtain a range of potential estimates of exposure (Table 7-1), and these scenarios were deemed relevant in the Canadian context. A detailed overview of US EPA exposure characterization is provided in US EPA (2015).

Briefly, various consumer scenarios were developed by the US EPA that were considered applicable to the Canadian general population where an adult consumer, specifically a woman of childbearing age, undertook a paint stripping project (i.e., table, chest of drawers or bathtub) for less than 4 hours. The scenarios varied based on several parameters including NMP concentration (25 and 50%), product type (brush-on and spray products), product amount depending on the surface area of objects treated (e.g., table vs. bathtub), and the optional use of gloves. To estimate exposure for consumers for each scenario, chamber test study emission profiles and conservative emissions factors were incorporated into the Multi-Chamber Concentration and Exposure Model (MCCEM) to estimate air concentrations in both the room of use and the rest of the house. It was assumed that users would be exposed to NMP via inhalation and dermal (both direct liquid contact and vapour-through-skin) routes while nearby non-users (e.g., a child in an adjacent room) would only be exposed via inhalation and vapour-through skin, and would have negligible dermal liquid contact.

In the US EPA assessment, predicted dermal and inhalation estimates were subsequently integrated in a physiologically-based pharmacokinetic (PBPK) model to derive peak, or maximum, blood concentrations of NMP (denoted as Cmax), for a woman of childbearing age, for the various consumer scenarios with and without the use of gloves (US EPA 2015, see table 7-1). The PBPK model was based on a human model published by Poet et al. that was further assessed and validated by the US EPA.

To note, the PBPK model was calibrated and validated based on several human toxicokinetic studies (Poet et al. 2010 as cited in US EPA 2015).

Table 6-1 Estimates of exposure to the general population to NMP from use of paint strippers [a]

Scenario	Treated Product	Application Type	Conc. (%)	TWA 4-hr (mg/m^3)[b]	ED[c] (h/d)	Cmax[d] (µg/L) (without gloves[e])
Typical/Average	Coffee Table	Brush-on	25	1.8	0.5	0.65
Upper bounding	Coffee Table	Brush-on	50	8.3	1.5	1.36
Upper bounding (higher Csat[e])	Bathtub	Brush-on	50	136	2	7.32
Upper bounding (lower Csat)	Bathtub	Brush-on	50	133.2	2	6.98
Upper bounding (lower spray volatility)	Coffee Table	Spray-on	53	6.5	1.41	0.18
Upper bounding (higher spray volatility)	Coffee Table	Spray-on	53	53.3	1.41	1.55

[a] Estimates are based on US EPA (2015) for users. Exposures derived for non-users were found to be lower.
[b] Four-hour (4-hr) time-weighted averages (TWAs) as predicted by MCCEM for personal exposure for users (e.g., exposure from the zone of use and the rest of house)
[c] ED, exposure duration
[d] Cmax, maximum (peak) blood concentration for women of childbearing age.
[e] Exposure estimates were also derived for users wearing gloves, where exposure estimates were found to be lower. It was assumed that wearing gloves reduced the exposed skin surface area by 10% relative to the area exposed without gloves.
[f] Csat: saturation concentration

The results of the exposure assessment indicated that the scenario for stripping a bathtub resulted in the highest exposure (Cmax: 4.42 – 7.32 µg/L) for the general population. This scenario represented an upper bound exposure for a woman of childbearing age based on conservative factors such as the use of a large amount of a high concentration (50%) product, a large surface area treated within a bathroom over a 2-hour exposure duration with limited ventilation, and the formation of a “source cloud” consisting of high NMP concentrations driven by a high NMP saturation concentration (Csat). Furthermore, as with all consumer scenarios, a conservative emission factor (i.e., 86% of applied NMP released to air) derived from a product containing 65-70%

NMP were also integrated in this scenario. This exposure scenario is considered representative of exposures for the general population of Canada.

No MSDSs for products available to the general population of Canada were identified for NEP. Given the marketed use of NEP as a replacement for NMP (BASF 2010; Silberzahn 2013; FMI 2015), similar uses may be expected, and as such, exposure estimates for NMP, for paint stripper use, are expected to represent potential exposures for NEP.

Cosmetics

Based on notifications submitted to Health Canada under the *Cosmetic Regulations*, NMP is present in adhesives for synthetic eyelashes and nails in concentrations ranging from 0.001 to 1%, while NEP is used in face cream, eye shadow, face cleanser, body lotion at concentrations ranging from 0.002 to 0.3 % (email from CPSD to RMB, dated Oct. 2015; unreferenced). NMP is also present in nail polish remover in Canada at a concentration of 3% (MSDS 2005). Cosmetic uses of NMP in Canada also correspond to uses in the US (nail polish remover and mascara) (US EPA 2015; concentrations unspecified).

Nail polish remover is considered to represent an intermittent exposure whereas body lotion is considered to represent a daily exposure. These products were selected as representative products given their higher exposure potential. Exposure estimates were generated using ConsExpo 4.1 (RIVM 2006).

Table 6-2 Estimates of exposure to the general population from use of cosmetics containing NMP and NEP

Substance	Product	Route	Conc. (%)	Frequency (×/day)	Exposed Area (cm^2)	Product Amount Applied (g)	Exposure Estimates
NMP	Nail polish remover	Dermal	3 [a]	0.19	11	1.3 [b]	0.55 mg/kg/event [c]
NMP	Nail polish remover	Inhalation	3	0.19	26	3.06 [b]	0.0315 mg/m^3 mean event concentration [d]
NEP	Body lotion	Dermal	0.1 [e]	1.1	16 925	4.4	0.0683 mg/kg/d
NEP	Body lotion	Inhalation	0.1	1.1	16 925	4.4	0.0098 mg/m^3 on day of exposure

[a] Based on MSDS (2005)

[b] Assuming total nail polish remover exposure area is 26 cm^2 (i.e., 15 cm^2 for the finger nail area + 11 cm^2 for the skin on the sides of the nail area), the total amount of product used is 3.06 g (CTFA 1983) which is available for inhalation exposure. Assuming dermal nail polish remover exposure occurs through the sides of the nails only, then the amount of product available for dermal exposure is 1.3 g (i.e., 3.06 g (CTFA 1983) x (11 cm^2/26 cm^2) (RIVM 2006)).

[c] Note "per event" estimates

[d] Modelled exposure estimates based on the Thibodeaux model for evaporation

[e] Email from CPSD to ESRAB, dated October 2015; unreferenced

6.2 Health Effects Assessment

US EPA (2015) and ECHA (2011) summarized the health effects information and characterized hazard related to NMP and NEP respectively, therefore, these two assessments inform the health effects assessment for the respective substances, including selection of critical effects and points of departure. A literature search was conducted for the period from November 2010 to October 2015 for NEP, and from March 2014 to October 2015 for NMP and no studies which could result in a different health effects characterization from those of the US EPA (2015) and ECHA (2011) were identified.

NMP

This section summarizes critical effects and corresponding points of departure identified by the US EPA (2015)

US EPA (2015) selected developmental toxicity (i.e., reduced fetal body weight and fetal resorption) as the most appropriate critical effect for health effect and risk characterization. Reduced fetal body weight is considered a marker for fetal growth restriction and may be most relevant to repeated rather than acute exposures. However, developmental effects could also occur after single exposures as some developmental effects, such as fetal resorptions and mortality, may result from a single exposure at a developmentally critical period (Davis et al., 2009; EPA, 1991b; Van Raaij et al., 2003). Therefore, US EPA (2015) specifically selected increased fetal resorptions and fetal death to assess risks from acute exposures and reduced fetal body weight to evaluate risks from repeated exposures.

Oral and inhalation developmental studies (Saillenfait et. al in 2002 and 2003) were used to derive points of departure for acute exposure. In the oral study, rats (Sprague-Dawley) were administered, via gavage at 0, 125, 250, 500 or 750 mg/kg bw per day from gestational day (GD) 6 to 20. A NOAEL was identified at 125 mg/bw per day based on reduced fetal body weight. Fetal resorption was observed at 500 and 750 mg/kg bw per day in a dose dependent manner (Saillenfait et. al 2002). In the inhalation study, rats (Sprague-Dawley) were exposed whole body to NMP vapors at 0, 30, 60 or 120 ppm (approximately equivalent to 0, 122, 243 or 486 mg/m^3), 6 hours per day, from GD 6 to 20. A NOAEL was identified at 243 mg/m^3 based on reduced fetal body weight (Saillenfait et. al 2003). Although fetal absorption was not observed in this inhalation study (Saillenfait et. al 2003) increased fetal resorption and fetal mortality were observed in an earlier NMP inhalation study (Du Pont 1990).

US EPA (2015) used PBPK models to convert exposure concentrations of NMP, used in the above oral and inhalation animal studies, to internal doses and then applied

benchmark dose (BMD) modeling to the internal doses to generate the appropriate point of departure (POD) for acute consumer exposure scenarios. The POD (internal dose) for acute exposure is 216 mg/L (blood) which is the BMDL for 1% increased fetal resorptions and fetal mortality.

In addition, a NOAEL was identified at 237 mg per kg bw per day, from a dermal developmental study, based on reduced fetal body weight and increased fetal resorptions and mortality. In this study, rats (Sprague-Dawley) were dosed, at 0, 75, 237 and 750 mg/kg/day from GD 6 to15. The application site was the clipped back of each animal; and the test materials were spread on the site and rubbed in. NMP was applied for 8 hours per day and at the end of each daily exposure period, the back of each animal was thoroughly washed with water to remove any residual material (Becci et al 1982).

NEP

This section summarizes critical effects and corresponding points of departure identified by ECHA (2011). ECHA identified developmental toxicity as the critical effect for the risk characterization of NEP. Since the predominant route of exposure is dermal, a point of departure was identified from a dermal study in rats.

In this study, Wistar rats were administered 0, 200, 400 and 800 mg/kg bw per day from GD 6 to 19. The dosing solution was a 33.3% aqueous solution of NEP. Deionized water or ascending volumes of NEP dosing solution were administered onto an intact shaven dorsal skin, covered by semi-occlusion gauze patch for six hours and subsequently washed off and dried. A NOAEL was identified at 400 mg/kg bw per day based on reduced fetal body weight (BASF 2005 cited in ECHA 2011).

NMP and NEP are structurally similar with a one methyl group difference on the side chain (i.e. NMP has a methyl group while NEP has an ethyl group attached to the heterocyclic nitrogen). The similarity of these two substances is also reflected in their activity in different toxicological studies. For example, both NMP and NEP produced negative results in several genotoxicity tests (e.g. Ames test, in vitro mammalian gene mutation) while showing similar developmental effects (i.e. increased fetal resorptions and reduced body weight) in rats via the oral route (ECHA 2011, EPA 2015). Based on these similarities, ECHA (2011) considered health effects information of NMP to be applicable to the evaluation of NEP health effects.

6.3 Characterization of Risk to Human Health

NMP

Margins of exposure for NMP are presented in Table 6-3

Table 6-3 Margins of Exposure for NMP

Exposure Scenario	Exposure Estimate	Critical Effect Level	Critical effect	MOE
Acute consumer exposure to NMP-based paint stripping products	0.18 – 7.32 mg/L (modelled peak blood exposure, Cmax)	POD (acute, internal dose) = 216 mg/L	Increased fetal resorptions and fetal mortality	29.5 – 1203.8
Intermittent consumer exposure via cosmetic products (nail polish remover)	Dermal: 0.55 mg/kg/event	NOAEL (dermal) = 237 mg/kg-bw/day	Reduced fetal body weight and increased fetal resorptions and mortality	431
	Inhalation: 0.032 mg/m^3	NOAEC (inhalation) = 243 mg/m^3	Reduced fetal body weight	7594

The US EPA identified paint stripper as the representative product for the assessment of consumer exposure to NMP because of high content of NMP in products and high potential exposure to consumers. Paint stripper was also identified as the product type containing the highest concentration of NMP accessible for consumers use in Canada, although a limited number of such products were identified in Canada (MSDS 2009a,b). Therefore, given the similarities of the higher concentration products in Canada ("range of 30–60 %") to the paint stripper products assessed by the US EPA, the US EPA's quantitative assessment on paint stripper use was used to inform the exposure assessment on this use, and relative to other scenarios, represented upper bound estimates of exposure.

Increased fetal resorptions were identified as the critical effect for evaluation of acute exposure to NMP in paint stripping products. Conservative assumptions were used to derive a variety of potential exposure scenarios, for consumers, based on combined inhalation, dermal and vapor-through-skin exposures. Exposure values were converted to estimates of systemic exposure using PBPK modeling (see Exposure section and US EPA 2015). The margin of exposure was derived based on the ratio of the internal acute POD of 216 mg/L to the estimated peak exposure (Cmax, mg/L) for the sensitive life-stage. The MOEs were compared to a target MOE of 30. The target MOE value derived by the US EPA accounted for intra-species (10X for humans) and inter-species (3X for

rat to human toxicodynamics as the use of PBPK model accounted for toxicokinetic differences between laboratory animals and humans) uncertainty factors.

The US EPA margins of exposure for the paint stripper scenarios ranged from 29.5 to 1203.8. The lowest MOE (29.5) was calculated based on a conservative scenario of brush application of paint stripper containing 50% of NMP (see exposure section for scenario parameters). EPA considered this value to be equivalent to the benchmark MOE of 30, indicating low risk. Given the considerations outlined in the assessment (i.e. conservativeness of upper-bound exposure scenario, limited number of high concentration products on the Canadian market), these MOE's are considered adequate to account for uncertainties in the health effects and exposure databases.

Consumer exposure to NMP through use of nail polish remover was identified as an intermittent exposure scenario. Comparison of a NOAEC (243 mg/m^3) identified from a developmental inhalation study in rats with the highest derived upper-bounding estimate of intermittent inhalation exposure (0.032 mg/m^3) results in a margin of exposure of approximately 7600; whereas comparison of a NOAEL (237 mg/kg-bw/day) identified from a developmental dermal study in rats with the highest derived upper-bounding estimate of intermittent dermal exposure (0.55 mg/kg/event) results in a margin of exposure of approximately 430. These margins are considered adequate to address uncertainties in the health effects and exposure databases.

NEP

Margins of exposure for NEP are presented in Table 6-4

Table 6-4Margins of Exposure for NEP

Exposure Scenario	Exposure Estimate	Critical Effect Level	Critical effect	MOE
Daily exposure via cosmetics (body lotion)	0.0683 mg/kg bw/day (modelled dermal exposure output)	NOAEL(dermal) = 400 mg/kg bw/day	Reduced fetal body weight	5856

Body lotion was identified as the consumer exposure scenario which would be associated with the highest potential for exposure to NEP. Comparison of the NOAEL (400 mg/kg-bw/day) identified from a developmental dermal study in rats to the highest derived upper-bounding estimate of daily dermal exposure (0.0683 mg/kg-bw/day) results in a margin of exposure of approximately 5860. This margin is considered to be adequate to address uncertainties in the health effects and exposure databases.

Inhalation exposure to NEP in body lotion was significantly lower than the dermal route and the risk is considered to be low.

While exposure of the general population to NMP and NEP are not of concern at current levels, these substances are considered to have a health effect of concern based on their potential developmental effects. Therefore, there may be a concern for human health if exposure were to increase.

6.4 Uncertainties in Evaluation of Risk to Human Health

There are a number of uncertainties associated with the consumer exposure assessment. Limited data were available on consumer use exposure patterns (e.g. duration of exposure) associated with paint stripping projects. There are uncertainties associated with the market share and prevalence of high concentration NMP- and NEP-containing paint stripping products in Canada.

In addition, for acute consumer exposures, the peak blood concentration of NMP (Cmax) was calculated over a single day, in which the use occurs, and the risk was evaluated by comparing this value to the POD associated with increased fetal resorptions from short term developmental studies (Saillenfait et al. 2002, 2003). Therefore, there is uncertainty related to this comparison as the relationship between time at which peak blood concentration occurs and induction of post implantation fetal resorption, and the specific time point that this effect occurs, are not fully understood.

7. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from NMP and NEP. It is proposed to conclude that NMP and NEP do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA 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.

Based on the information presented in this screening assessment, it is proposed to conclude that NMP and NEP do not meet the criteria under paragraph 64(*c*) of CEPA as it is not entering or may enter 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 proposed to conclude that NMP and NEP do not meet any of the criteria set out in section 64 of CEPA.

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