Screening Assessment for the Challenge

2-Pyrrolidinone, 1-ethenyl-
(1-Vinyl-2-pyrrolidone)

Chemical Abstracts Service Registry Number
88-12-0

Environment Canada
Health Canada

September 2010

Synopsis

The Ministers of the Environment and of Health have conducted a screening assessment of 2-pyrrolidinone, 1-ethenyl- (1-vinyl-2-pyrrolidone, abbreviated as NVP), Chemical Abstracts Service Registry Number 88-12-0. This substance was identified as a high priority for screening assessment and included in the Challenge. NVP was identified as a high priority as it was classified by the European Commission on the basis of carcinogenicity. The substance did not meet the ecological categorization criteria for persistence, bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, the focus of this assessment of NVP relates primarily to human health risks.

According to information submitted under section 71 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), NVP was not manufactured above the 100 kg reporting threshold by any company in Canada in the calendar year 2006. However, approximately 10 000–100 000 kg of the substance was imported in 2006. The major use of NVP is in the industrial manufacturing of NVP-derived polymers, which are used in the personal care products industry. The polymers function as thickeners, dispersing agents and binders in cosmetics and as stiffeners in hair grooming products. Polymerized NVP has many uses in the pharmaceutical industry. It is used as a binding agent for tablets and in film coatings of capsules to aid ingestion. NVP-derived polymers function as stabilizers for enzymes and heat-sensitive drugs as well as crystallization inhibitors in liquid medications. Industrial uses of NVP include the manufacturing of ultraviolet curable inks and coatings. NVP is used as a formulant in 11 pesticides registered for commercial use in Canada.

The principal source of exposure of the general population in Canada is thought to be through personal care products (cosmetics). Chronic exposure to NVP from pharmaceuticals is lower than exposure from personal care products.

As NVP was classified on the basis of carcinogenicity by other national and international agencies, carcinogenicity was a key focus for this screening assessment. In a chronic/carcinogenicity study, rats exposed to NVP by inhalation showed dose-related increased incidences of hepatocellular carcinomas and nasal cavity adenomas and adenocarcinomas as well as increased incidences of squamous carcinomas of the larynx at the highest dose tested. Neoplastic changes were also seen in female rats exposed to NVP by inhalation for 3 months followed by 21 months of recovery. However, no long-term study investigating exposure to NVP in other species or via the oral or dermal route of exposure was identified. Consideration of the available information regarding genotoxicity and the conclusions of other agencies indicates that NVP is not likely to be mutagenic. Accordingly, a threshold approach is used to assess risk to human health.

Non-neoplastic effects based on inhalation exposure in repeated-dose studies were observed at the same critical effect level as the neoplastic effects, and the liver and respiratory tract of rats and mice were identified as the target organs. The margins between upper-bounding estimates of exposure from acute and chronic exposure to

personal care products and the critical effect level are considered to be adequately protective to account for data gaps and uncertainties in the human health assessment for both cancer and non-cancer effects.

Based on the available information on the potential to cause harm to human health and the resulting margins of exposure, it is concluded that NVP is a substance that 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.

On the basis of its low ecological hazard and reported releases of NVP to the environment, it is concluded that the substance 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. NVP does not meet the criteria for persistence or bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* of CEPA 1999.

Based on the information available, it is concluded that NVP does not meet any of the criteria set out in section 64 of CEPA 1999.

This substance will be considered for inclusion in the DSL 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), which 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 1-ethenyl-2-pyrrolidinone (1-vinyl-2-pyrrolidone, abbreviated as NVP) was identified as a high priority for assessment of human health risk because it was considered to present IPE and had been classified by other agencies on the basis of carcinogenicity. The Challenge for this substance was published in the *Canada Gazette* on March 14, 2009 (Canada 2009). 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 NVP was determined to be a high priority for assessment with respect to human health, it did not meet the ecological criteria for persistence, 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[1].

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 and stakeholder research reports and from recent literature searches, up to July 2009 for the 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 (non-occupational) exposure 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. Bernard Gadagbui, Toxicology Excellence for Risk Assessment; Dr. Michael Jayjock, The LifeLine Group; and Dr. Bob Benson, US Environmental Protection Agency.

Additionally, the draft of this screening assessment 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 Health Canada and Environment Canada. Approaches used in the screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel.

[1] 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 regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use.

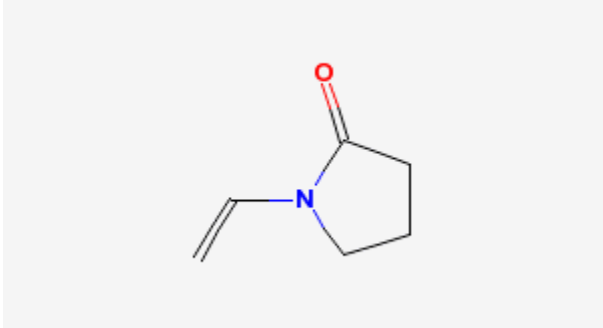
The critical information and considerations upon which the final assessment is based are summarized below.

Substance Identity

For the purposes of this document, this substance will be referred to as 1-vinyl-2-pyrrolidone (NVP), based on the European Inventory of Existing Commercial Chemical Substances name and as listed on the Domestic Substances List (DSL). NVP is a monomer and therefore may be present at residual levels when polymerized to polyvinyl pyrrolidone (PVP or povidone) or other NVP-derived polymers. Information on the identity of the monomer, NVP, is summarized in Table 1.

Table 1. Substance identity

CAS RN	88-12-0
DSL name	2-Pyrrolidone, 1-vinyl-
NCI names	1-Ethenyl-2-pyrrolidinone (ECL) 2-Pyrrolidinone, 1-ethenyl (PICCS) 2-Pyrrolidinone, 1-ethenyl- (AICS, ASIA-PAC, NZIoC, PICCS, SWISS, TSCA) Pyrrolid-2-one, 1-vinyl- (PICCS) *N*-Vinyl-2-pyrrolidine (PICCS) *N*-Vinyl-2-pyrrolidon (SWISS) 1-Vinyl-2-pyrrolidone (EINECS) *N*-Vinyl-2-pyrrolidone (ENCS) Vinylpyrrolidone (PICCS)
Other names	Aronix M 150 NSC 10222 NSC 683040 N-V 2RC N-VP NVP 300 V-Pyrol V-Pyrol RC 1-Vinyl-2-pyrrolidinone *N*-Vinyl-2-pyrrolidinone Vinylbutyrolactam *N*-Vinylpyrrolin-2-one
Chemical group (DSL stream)	Discrete organics
Major chemical class or use	Aliphatic amines; tertiary amines
Major chemical subclass	Not available
Chemical formula	C_6H_9NO

Chemical structure	
SMILES	O=C(N(C=C)CC1)C1
Molecular mass	111.14 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; NCI, National Chemical Inventories; NZIoC, New Zealand Inventory of Chemicals; PICCS, Philippine Inventory of Chemicals and Chemical Substances; SMILES, simplified molecular input line entry specification; SWISS, Swiss Giftliste 1 and Inventory of Notified New Substances; TSCA, *Toxic Substances Control Act* Chemical Substance Inventory.
Source: NCI 2006

Physical and Chemical Properties

A summary of key physical and chemical properties of NVP that are relevant to its environmental fate is presented in Table 2.

Table 2. Physical and chemical properties of NVP

Property	Type	Value[1]	Temperature (°C)	Reference
Melting point (°C)	Experimental	13.50[2]		Richardson and Gangolli 1994
	Modelled	28.82		MPBPWIN 2008
Boiling point (°C)	Experimental	218		Kroschwitz 1991
	Modelled	219.88		MPBPWIN 2008
Density (kg/m^3)	Experimental	1045	20	Frank 1954
Vapour pressure (Pa)	Experimental	13.3[2] (0.1 mmHg)	24	Aldrich 1995
	Modelled	17.6 (0.132 mmHg)	25	MPBPWIN 2008
Henry's Law constant (Pa·m^3/mol)	Modelled	5.6×10^{-3} (5.53×10^{-8} atm·m^3/mol)	25	HENRYWIN 2008
Log K_{ow} (dimensionless)	Experimental	0.37–0.40[2]		BASF 1988a; Hansch et al. 1995

Property	Type	Value[1]	Temperature (°C)	Reference
	Modelled	0.25		KOWWIN 2008
Log K_{oc} (dimensionless)	Modelled	1.08		PCKOCWIN 2008
Water solubility (mg/L)	Modelled	1.08×10^5	25	WSKOWWIN 2008

Abbreviations: K_{oc}, organic carbon–water partition coefficient; K_{ow}, octanol–water partition coefficient.
[1] Values and units in parentheses represent those originally reported by the authors or estimated by the models.
[2] Value used for fate modelling. Experimentally obtained values were chosen over modelled estimates.

Sources

NVP is not known to occur as a natural product. NVP is a monomer used alone or in combination with other monomers to produce a number of polymers (EURAR 2003).

Global production of NVP has been identified in Germany and the United States (Chemical Information Services 1995; NICNAS 2000; EURAR 2003).

NVP was not manufactured in Canada in 2006 above the reporting threshold of 100 kg (Environment Canada 2009a). However, the reported aggregate quantity of NVP imported into Canada in 2006 was 10 000–100 000 kg, based on data submitted under section 71 of CEPA 1999 (Environment Canada 2009a).

International trade data from Statistics Canada (CIMT 2009) reveal that NVP importation into Canada has been in decline since 1988, when 228 445 kg was imported. From 1995 to 2006, the average amount of NVP imported into Canada was 23 449 kg annually (CIMT 2009). However, NVP may be entering Canada in the form of a residual monomer or co-monomer in formulated consumer products that may not be captured in section 71 submissions or international trade data from Statistics Canada.

Uses

NVP is used for the industrial synthesis of the homopolymer, polyvinyl pyrrolidone (PVP), or with other monomers to produce copolymers for use in formulations of industrial or consumer products. There are no direct consumer end use products containing NVP itself, but NVP may be found in consumer products as a residual monomer from the polymerization process (NICNAS 2000; EURAR 2003).

Major global uses of NVP include its use in formulants for personal care products (PCPs), pharmaceuticals, ultraviolet (UV) curable printing inks and UV stain topcoats (Moore 1983; ECB 2000; NICNAS 2000; Kricheldorf et al. 2005; HSDB 2009).

Internationally, PVP and its copolymers are widely used in the personal care products industry (Moore 1983; Gmahl and Ruess 1993; Hössel et al. 2000; EURAR 2003). PVP functions as a thickener, dispersing agent and binder in cosmetics and as a stiffener in hair grooming products (EURAR 2003). In Canada, PVP and its copolymers are reported in formulations of more than 1500 PCPs, of which 85% are composed of hair care products (2009 personal communication from Risk Management Bureau, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced).

PVP has a wide range of applications in the pharmaceutical industry. The polymer becomes sticky when wetted and is used as a binder for tablets. It is also used in film coatings to aid oral ingestion of tablets, vitamins and minerals, and it functions as a stabilizer for enzymes and heat-sensitive drugs as well as a crystallization inhibitor in liquid medicines (EURAR 2003).

In Canada, PVP is listed in the Health Canada Drug Product Database (DPD) as a non-medicinal ingredient present in final pharmaceutical products (DPD 2009). Although NVP does not appear in the DPD, it may be present in pharmaceutical products as an impurity (2009 personal communication from Therapeutic Products Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). PVP has similar use in veterinary drugs available in Canada (2009 personal communication from Veterinary Drugs Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

PVP is listed in the Natural Health Products Ingredients Database (NHPID) as an acceptable non-medicinal ingredient in natural health products, with an acceptable daily intake of 50.0 mg/kg body weight (kg-bw) (adopted from FAO/WHO 1986) (NHPID 2009). PVP is listed in the Licensed Natural Health Products Database (LNHPD); thus, it is used in current licensed natural health products available in Canada (LNHPD 2009). Therefore, NVP may be present in licensed natural health products at residual levels (2009 personal communication from Natural Health Products Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

In Canada and elsewhere, NVP is used as a reactive diluent in UV curable inks and coatings (BASF 1997; Environment Canada 2009a). Global demand for NVP for use in UV curable products has been in decline (Henriks-Eckerman and Kanerva 1997; NICNAS 2000; EURAR 2003), which may account for the significant decrease in NVP importation into Canada over the past 20 years. In Canada, it was reported that 78% of NVP was used in the formulation of UV stains, whereas 21% was utilized in the manufacturing of UV curable inks (Environment Canada 2009a). In response to a section 71 notice, UV curable stain and ink products were identified as industrial products that were not intended for sale to the general public (Environment Canada 2009a).

In Europe, PVP may have limited use in the brewing industry as a clarifier in processing bottled or canned beer and wine (EURAR 2003; Kricheldorf et al. 2005). In Canada, there are two known uses of PVP in food product packaging (2009 personal

communication from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

In Canada, NVP was also identified as an unintended residual in the manufacturing of polyurethane spray foam insulation (Environment Canada 2009a) and as a formulant in 11 commercial pesticides with food uses at a maximum concentration of 50 ppm (2009 personal communication from Pest Management Regulatory Agency, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced).

As NVP is on the Ingredient Disclosure List (concentration, 1% by weight) of the *Hazardous Products Act* (Canada 1988), there may be a number of products containing residual levels of NVP that have not been identified as being in commerce in Canada.

Products identified elsewhere, but not confirmed in Canada, include gas-permeable contact lenses (Bohnert et al. 1988; Garrett and Milthorpe 1996; Cai and Gupta 2005), powders for clothes washing, adhesive glue sticks, denture fixatives to anchor false teeth and wettable gums for postage stamps and envelopes (EURAR 2003).

Historically, PVP was used as a blood plasma substitute, but this use is no longer apparent (Wood 1970; Lorenz 1971; Kricheldorf et al. 2005), although PVP continues to be used as an ingredient in cryo-protectants for organ transplantation (O'Neil et al. 2001). A copolymer composed of NVP and polymethacrylates has a historical use as a viscosity improver in automobile crankcase oils; however, this application was identified as being very limited and not considered in the risk characterization of NVP by the European Union (EURAR 2003). Recent information to support the risk characterization for this application was not found during the preparation of this assessment.

Releases to the Environment

In response to a notice issued under section 71 of CEPA 1999, one release of less than 100 kg of NVP to the atmosphere was reported in the 2006 calendar year (Environment Canada 2009a). In the same calendar year, it was reported that less than 100 kg of NVP was transferred to hazardous waste facilities (Environment Canada 2009a). NVP does not appear on either the National Pollutant Release Inventory substance list (NPRI 2006) or the US Toxics Release Inventory Program list of reportable substances (TRI 2009).

Environmental Fate

Based on its physical and chemical properties (see Table 2 above), the results of Level III fugacity modelling (Table 3) suggest that NVP will reside predominantly in water or soil, depending on the compartment of release.

Table 3. Results of Level III fugacity modelling of NVP (EQC 2003)

Substance released to:	Fraction of substance partitioning to each medium (%)			
	Air	Water	Soil	Sediment
Air	17	23	60	0
Water	0	99.8	0	0.2
Soil	0	21	79	0

Persistence and Bioaccumulation Potential

Environmental Persistence

Table 4a presents empirical biodegradation data for NVP. In one study by BASF (1979a), 100% biodegradation of NVP was observed over 14 days using the Zahn-Wellens test. In another study (BASF 1995), the biodegradability in active sludge from laboratory sewage plants was measured using the reduction in dissolved organic carbon (DOC), as described in Organisation for Economic Co-operation and Development (OECD) Guideline 301 A (BASF 1995) for ready biodegradability. The substance was found to be readily biodegradable, with >70% degraded within 10 days and 100% decomposed after 28 days. These tests indicate that the ultimate degradation half-life in water is likely to be much shorter than 182 days (6 months) and that the substance is therefore likely to not persist in that environmental compartment.

Table 4a. Empirical data for degradation of NVP

Medium	Fate process	Degradation value	Degradation endpoint / units	Reference
Water	Biodegradation (Zahn-Wellens test)	100% decomposed after 14 days	Ready biodegradability / %	BASF 1979a
Water	Biodegradation (OECD Guideline 301 A, ready biodegradability: DOC die-away test)	>70% decomposed after 10 days; 100% decomposed after 28 days	Ready biodegradability / %	BASF 1995

Since few experimental data on the degradation of NVP are available, a quantitative structure–activity relationship (QSAR)–based weight of evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 4b. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that NVP is expected to be released to this compartment, primarily biodegradation in water was examined. NVP does not contain functional groups expected to undergo hydrolysis (no results were generated from HYDROWIN (2008). Table 4b summarizes the results of available QSAR models for degradation in water and air..

Table 4b. Modelled data for degradation of NVP

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Air			
Atmospheric oxidation	AOPWIN 2008[1]	$t_{½}$ = 0.29 day (12 h day)	<2
Ozone reaction	AOPWIN 2008[1]	$t_{½}$ = 6.55 days	≥2
Water			
Hydrolysis	HYDROWIN 2008[1]	$t_{½}$ = n/a (pH 7)[2] $t_{½}$ = n/a (pH 8)[2]	n/a
Primary biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[1] Submodel 4: Expert Survey (qualitative results)	4.0[3] "biodegrades fast – days"	<182
Ultimate biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[1] Submodel 3: Expert Survey (qualitative results)	2.9[3] "biodegrades fast – weeks"	<182
Biodegradation (aerobic)	BIOWIN 2008[1] Submodel 5: MITI linear probability	0.58[4] "biodegrades fast"	<182
Biodegradation (aerobic)	BIOWIN 2008[1] Submodel 6: MITI non-linear probability	0.73[4] "biodegrades fast"	<182
Biodegradation (aerobic)	TOPKAT 2004 Probability	0[4] "biodegrades slowly"	≥182
Biodegradation (aerobic)	CATABOL ©2004–2008 % BOD	% BOD = 27.1 "may biodegrade fast"	≥182

Abbreviations: BOD, biological oxygen demand; MITI, Ministry of International Trade & Industry, Japan; $t_{½}$, half-life.

[1] EPIsuite 2008

[2] Model does not provide an estimate for this type of structure.

[3] Output is a numerical score from 0 to 5.

[4] Output is a probability score.

In air, a predicted atmospheric oxidation half-life of 0.29 day (see Table 4b) demonstrates that this substance is likely to be rapidly oxidized. The substance is expected to react with other photo-oxidative species in the atmosphere, such as ozone, but at a much slower rate. It is unlikely to degrade via direct photolysis. Therefore, it is expected that reactions with hydroxyl radicals will be the most important fate process in the atmosphere for NVP. With an estimated half-life of 0.29 day via reactions with hydroxyl radicals, NVP is considered not to be persistent in air.

In water, a predicted hydrolysis half-life for NVP could not be calculated by EPIsuite, as no hydrolysable groups are present. Other fate processes in water therefore need to be considered to determine the persistence in this medium.

There are conflicting model results for biodegradation. All BIOWIN (2008) primary and ultimate biodegradation models suggest that biodegradation may be fast and that the half-

life in water would be <182 days, whereas the predictions for TOPKAT (2004) and CATABOL (©2004–2008) suggest a half-life of ≥182 days. The predictions for CATABOL (©2004–2008) and TOPKAT (2004) are in the domains of both models, and both are in principle considered reliable. CATABOL (©2004–2008) is close to the threshold and suggests a slow rate of biodegradation (a result of <20% suggests relatively low ultimate biodegradation potential), and TOPKAT (2004) indicates that biodegradation may be very slow or non-existent (≤0.3 suggests low ultimate biodegradation potential.

Although the model results are conflicting, both empirical results indicate that NVP degrades rapidly in water (Table 4a). Considering the empirical data, although highly variable are the most reliable, and taking into consideration the fact that the substance has structural features that are associated with chemicals that are easily biodegraded. i.e., amides, cyclic chemicals consisting only of carbon, oxygen, nitrogen and hydrogen), it is concluded that the biodegradation half-life of NVP is likely to be no more than a few weeks, and certainly much less than 182 days, in water.

Using an extrapolation ratio of 1:1:4 for water:soil:sediment biodegradation half-lives (Boethling et al. 1995), the half-life in soil is also <182 days and the half-life in sediments is <365 days. This indicates that NVP is not expected to be persistent in soil or sediment.

Based on the empirical and modelled data (see Tables 4a and 4b), NVP does not meet the persistence criteria for air, water, soil or sediment (half-life in air ≥2 days, half-lives in soil and water ≥182 days and half-life in sediment ≥365 days) as set out in the *Persistence and Bioaccumulation Regulations* of CEPA 1999 (Canada 2000).

Potential for Bioaccumulation

Experimental and modelled octanol–water partition coefficients (log K_{ow} values) for NVP suggest that this chemical has low potential to bioaccumulate in biota (see Table 2).

Since no experimental bioaccumulation factor (BAF) or bioconcentration factor (BCF) data for NVP were available, a predictive approach was applied using available BAF and BCF models, as shown in Table 5. The results of these models are expected to be reliable, as this substance is within the domains of their training sets.

Table 5. Modelled data for bioaccumulation of NVP

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Fish	BAF	1.03	Arnot and Gobas 2003 (Gobas BAF middle trophic level model)
Fish	BCF	1.03	Arnot and Gobas 2003 (Gobas BCF middle trophic level model)
Fish	BCF	2.68	Dimitrov et al. 2005 (Dimitrov mitigating factors model)
Fish	BCF	3.16	BCFBAFWIN 2008

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 the 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 be the most reliable prediction method for determining the bioaccumulation potential, because it can allow for competing rates of uptake and elimination, such as metabolic biotransformation.

Metabolic biotransformation information for this substance was not available, nor was it necessary to consider it in the Arnot and Gobas (2003) BAF and BCF models, because, based on the log K_{ow} of 0.40, gill elimination is expected to be a much greater loss process than biotransformation for the bioaccumulation of NVP in aquatic organisms.

The available evidence (Table 5) suggests that NVP will have low bioaccumulation potential due to its physical and chemical properties (i.e., very high water solubility and low log K_{ow}). The Arnot and Gobas (2003) BAF middle trophic level model for fish predicted a BAF of 1.03 L/kg, indicating that NVP does not have the potential to bioaccumulate in fish and biomagnify in food webs. The results of BCF model calculations provide additional evidence to support the low bioconcentration potential of this substance. Based on the available empirical log K_{ow} and kinetic-based bioaccumulation model values, NVP does not meet the bioaccumulation criteria (BAF or BCF ≥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, NVP is not expected to be persistent in air, water, soil or sediment. It is also expected to have a low bioaccumulation potential. However, the importation volumes of NVP into Canada, along with information on its uses, indicate potential for widespread release into the Canadian environment. Experimental and modelled effects data are summarized in Tables 6a and 6b, respectively.

Table 6a. Empirical data for aquatic toxicity of NVP

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Alga (*Scenedesmus subspicatus*)	Acute (72 h)	EC_{50}	780	BASF 1988a
Alga	Acute (96 h)	EC_{50}	>1000	BASF 1988a

(*Scenedesmus subspicatus*)				
Daphnia magna	Acute (48 h)	EC_{50}	45	BASF 1988a
Fish (*Oncorhynchus mykiss*)	Acute (96 h)	LC_{50}	913	BASF 1987a
Fish (*Oncorhynchus mykiss*)	Acute (72 h)	LC_{50}	976	BASF 1987a

Abbreviations: EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms.

Table 6b. Modelled data for aquatic toxicity of NVP

Test organism	Test type	Endpoint	Value (mg/L)	Reference
Fish	Acute	LC_{50}	348	ECOSAR 2008 (amides)
Fish	Chronic	ChV	2.05	
Green alga	Acute	EC_{50}	0.75	
Green alga	Chronic	ChV	0.18	
Daphnid	Acute	LC_{50}	107	
Daphnid	Chronic	ChV	1.4	
Fish	Acute	LC_{50}	1 888	OASIS Forecast 2005
Fish	Acute	LC_{50}	27 047	AIES 2003–2005
Daphnid	Acute	LC_{50}	145	AIES 2003–2005
Alga	Acute	EC_{50}	26.1	AIES 2003–2005
Fish	Acute	LC_{50}	1 400	TOPKAT 2004

Abbreviations: ChV, chronic toxicity value; EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms.

Empirical acute ecotoxicity studies are available for fish, *Daphnia*, and algae, the results are from unpublished studies documented in the European Union risk assessment report (EURAR 2003; see Table 6a). Ecotoxicity values reported were 45 mg/L for a 48-hour *Daphnia* immobilization study and 913 mg/L for a 96-hour LC_{50} and 976 mg/L for a 72-hour LC_{50} for *Oncorhynchus mykiss*. The effect of NVP on reproduction and growth rate for *Scenedesmus subspicatus* was investigated, and the 72- to 96-hour EC_{50}s for inhibition of reproduction and inhibition of growth rate were 770 mg/L and >1000 mg/L, respectively. EC_{10} values for *Scenedesmus subspicatus*, which correspond to No-Observed-Effect Concentrations (NOEC), range from 115 to 125 mg/L for 72 and 96 hours, respectively, and indicate that algae are likely not sensitive to NVP

Modelled results for acute effects for fish, daphnids and algae (Table 6a) are consistent with empirical results, although one of two models appear to overestimate toxicity to green algae (EC_{50} = 0.75 mg/L) (ECOSAR 2008). Chronic modelled values indicate a higher toxicity than the acute modelled results and are suspect.

The experimental toxicity values are considered to indicate a low to moderate level of acute toxicity; thus, NVP is generally not expected to cause acute harm to aquatic

organisms at low concentrations (<1 mg/L). However, some model results (excluding ECOSAR estimates in algae) suggest the possibility of chronic effects at relatively low exposure concentrations. These data suggest that NVP has the potential to be moderately to highly hazardous to more sensitive aquatic organisms exposed for long periods of time.

A conservative predicted no-effect concentration (PNEC) was derived from the lowest empirical toxicity value identified: an acute EC_{50} for *Daphnia magna* of 45 mg/L. This value was selected as the critical toxicity value and divided by an assessment factor of 100 to account for uncertainties related to interspecies and intraspecies variabilities in sensitivity, and extrapolation from a laboratory EC_{50} to a no-effect value in the field. This calculation resulted in a conservative PNEC of 0.45 mg/L.

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

A – Industrial Release

The aquatic exposure of NVP is expected if the substance is released from industrial use to a wastewater treatment plant and the treatment plant discharges its effluent to a receiving water body. The concentration of the substance in the receiving water near the discharge point of the wastewater treatment plant is used as the predicted environmental concentration (PEC) in evaluating the aquatic risk of the substance. It can be calculated using the equation

$$C_{water-ind} = \frac{1000 \times Q \times L \times (1 - R)}{N \times F \times D}$$

where

$C_{water-ind}$:	aquatic concentration resulting from industrial releases, mg/L
Q:	total substance quantity used annually at an industrial site, kg/yr
L:	loss to wastewater, fraction
R:	wastewater treatment plant removal rate, fraction
N:	number of annual release days, d/yr
F:	wastewater treatment plant effluent flow, m^3/d
D:	receiving water dilution factor, dimensionless

A site-specific exposure analysis was conducted for the aquatic compartment at a total of three sites where NVP was used in high quantities. The quantity of the substance used at each site (Q) was in the range of 10 000 to 100 000 kg/yr. The fraction lost to wastewater (L) from the facility at each site was conservatively estimated at 5% resulting from the cleaning of chemical containers and process treatment. It was also conservatively assumed that there was no on-site wastewater treatment. The wastewater containing the substance was further assumed to be released to sewer and subsequently treated by the local sewage treatment plant (STP). The STP at each site was identified as a secondary system and its removal rate was predicted as 62% (R) by a computer model ASTreat system (ASTreat 2006). For the three sites, the STP effluent flow was found in the range of 10 000 to 400 000 m^3/d (F) and the receiving water dilution factor was estimated as

10(D). Finally, the release was assumed to occur 250 days per year (N) which is typical for small and medium-sized facilities. Based on the above assumptions and site-specific data, the predicted environmental concentrations (PECs) estimated for the three sites are in the range of 0.0003 to 0.03 mg/L (Environment Canada 2010). These PEC values represent the level of exposure in the receiving water near the point of the discharge from the municipal sewage treatment plant at each site.

B – Consumer Products Release

As NVP is found in consumer products and can be released to water, Mega Flush, Environment Canada's spreadsheet tool was employed to estimate the substance concentration in multiple water bodies receiving sewage treatment plant effluents to which consumer products containing the substance may have been released (Environment Canada 2009c). The spreadsheet tool provides these estimates for approximately 1000 release sites across Canada based on realistic assumptions.

The equation and inputs used in this scenario are described in Environment Canada (2009d).The maximum PEC of 0.15 mg/L was derived based on a conservative scenario. This conservative scenario assumes that the total release across the about 1000 sites from consumer products is at the maximum quantity of 100 000 kg/yr imported in Canada and the STP removal rate is zero. In addition, standard input values such as the 10^{th} percentile flow for watercourses and 365 days/yr for release frequency were used in the estimation.

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine the supporting 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 persistence, bioaccumulation, toxicity, sources and fate of the substance.

Based on the available empirical log K_{ow} and kinetic-based bioaccumulation model values, NVP does not meet the bioaccumulation criteria (BAF or BCF are ≥ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based on the empirical and modelled data (see Tables 4a and 4b), NVP does not meet the persistence criteria for air, water, soil or sediment (half-life in air ≥ 2 days, half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* of CEPA 1999 (Canada 2000).

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. With PEC in the range of 0.0003 to 0.03 mg/L and PNEC of 0.45 mg/L, the resulting risk quotients (PEC/PNEC) estimated for industrial releases ranged from 0.0007 to 0.07, which indicates that exposure values are unlikely to be high enough to cause harm to aquatic organisms.

For exposure resulting from down-the-drain releases through consumer products, the maximum PEC is 0.15 mg/L under a conservative scenario and the maximum risk quotient (PEC/PNEC) is 0.3. This indicates that down-the-drain consumer and industrial releases of NVP are unlikely to harm aquatic organisms.

Overall, the results of the assessment suggest that NVP does not have the potential to cause ecological harm in Canada. This conclusion was made despite the uncertainties from lack of empirical data on environmental concentrations in Canada. Concentrations in water were modelled based on conservative assumptions.

Although there were empirical data for physical-chemical properties, biodegradation and acute ecological effects of NVP, no chronic experimental effects data were available. Modelled data were also used to supplement and confirm the validity of the experimental data. The application factor of 100 was used, in part, to account for the fact that acute toxicity results are available for three trophic levels. In addition, there was no information on bioaccumulation of NVP. The log K_{ow} of 0.40 suggests that bioaccumulation is not likely to occur to a significant extent, and the modelled bioaccumulation data available for NVP confirm this.

There is some uncertainty in the estimation of the potential for NVP to cause ecological harm using the industrial release and down-the-drain scenarios; however, the conservative assumptions that are made when using the models are intended to ensure that exposure concentrations are not underestimated.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media and Food

Upper-bounding estimates of NVP intake from environmental media for each age group in the general population of Canada are presented in Appendix 1a. These upper-bounding estimates of intake range from 2×10^{-6} µg/kg-bw per day (12–19, 20–59, and 60+ years old) to 5×10^{-6} µg/kg-bw per day (0.5–4 years old). For all age groups, indoor air, based on NVP levels predicted in ambient air, was estimated to be the major contributor to NVP exposure, albeit at very low levels.

Information on the concentration of NVP in the Canadian environment was not found during the preparation of this report, and less than 100 kg of NVP was released to the environment in 2006 (Environment Canada 2009a). Therefore, NVP concentrations in air, water and soil were predicted based on environmental modelling estimates (ChemCAN 2003) using a worst-case scenario derived from Canadian import quantities (Environment Canada 2009a) and an estimated emissions release rate of 5%. Based on this scenario, predicted concentrations of NVP in air, water and soil would be very low—

8.64×10^{-6} µg/m^3, 3.57×10^{-6} µg/L and 4.37×10^{-4} µg/kg, respectively (ChemCAN 2003).

While NVP itself is not a permitted food additive, there are a few food uses of PVP (in which NVP may be present as a residual) for which there are food additive provisions, namely as a fining agent in various alcoholic beverages at a maximum level of 2 ppm in the finished product, as a tablet binder in tabletop sweetener tablets containing aspartame at a maximum use level of 0.3% and as a viscosity reduction agent and stabilizer in colour lake dispersions at a maximum use level consistent with Good Manufacturing Practice (residues of PVP not to exceed 100 ppm in the finished foods) as per Division 16 of the *Food and Drug Regulations* (Canada [1978]). PVP must meet the specifications of the Food Chemicals Codex (FCC) when used in these food additive applications (Canada [1978]). The FCC monograph for PVP specifies an acceptance criterion for unsaturation (as vinylpyrrolidone) of not more than 0.001% (FCC 2008). Similarly, polyvinylpolypyrrolidone (PVPP) could be used as a fining agent in the manufacture of some alcoholic beverages that are sold in Canada. For PVPP, the FCC has the same acceptance criterion for unsaturation (as vinylpyrrolidone) as it does for PVP (i.e., not more than 0.001%). Although the *Food and Drug Regulations* do not regulate PVPP as a food additive when used in this manner, PVPP is a powder that is insoluble in water, so it is expected that filtering of the beverage would remove PVPP. Consequently, negligible consumer exposure to NVP is expected to occur as a result of the use of PVPP as a fining agent in the manufacture of alcoholic beverages.

In Canada, NVP may be a residual impurity in an ingredient present in adhesives for paper or polyethylene bags with glued ends used to package dry foods. It may also be present in a UV curable ink used on the outside of plastic bottles. Since the adhesive is not in contact with the dry food and the ink is applied to the outside surface, there would be no direct contact with food; thus, exposure is expected to be negligible (2009 personal communication from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

Based on the absence of environmental data and insignificant releases of NVP to the Canadian environment (Environment Canada 2009a), it is unlikely that Canadians are exposed to significant concentrations of NVP from the environment. This finding is supported by estimated upper-bounding daily intakes of NVP, assuming that 5% of NVP imported into Canada (Environment Canada 2009a) are released to the atmosphere (Appendix 1a).

In spite of the uncertainty regarding NVP levels in environmental media and food, confidence in the assessment of environmental exposure is moderate, based on the limited uses of NVP in Canada and the low exposure levels estimated from a scenario in which all NVP imported into Canada is released to the atmosphere.

Consumer Products

NVP-derived polymers are found in a wide range of PCPs, which include hair products, skin moisturizers and cleansers, deodorant, nail polish, shaving cream and makeup. Owing to the widespread use of NVP-derived polymers in PCPs, PCPs are considered the primary source of exposure of Canadian consumers to NVP, even though NVP concentrations are present at trace, residual levels only.

BASF Corporation has identified several polymers—and their corresponding maximum NVP residual levels—that are available in Canada: notably, the homopolymer PVP (100 ppm) and two quaternized NVP copolymers—polyquaternium-16 (100 ppm) and polyquaternium-11 (50 ppm) (BASF 2006). In Europe, the maximum allowable NVP concentration in cosmetic-grade PVP is 1000 ppm, but the analytically determined concentration is consistently found to be no greater than 100 ppm (EURAR 2003). In Australia, the copolymer polyquaternium-44 has a maximum NVP residual of 50 ppm (NICNAS 2001). The level of 100 ppm was chosen as the maximum NVP residual level in Canadian cosmetic-grade polymers, as it was the highest known concentration in Canada.

NVP levels in Canadian PCPs were estimated by assuming a residual NVP concentration of 100 ppm in NVP-derived polymers found in PCPs (Table 7). PCPs and polymer concentrations shown in Table 7 were provided by the Risk Management Bureau, Health Canada (2009 personal communication to Risk Assessment Bureau, Health Canada; unreferenced).

Table 7. Concentration range of NVP in personal care products

Personal care product category	Concentration range of NVP[1] (ppm)	95th-percentile concentration of NVP (ppm)
Products used to derive an exposure assessment		
Antiwrinkle cream	1–3	3
Baby cream	0.1–3	3
Bath foam[2]	≤1	1
Deodorant	≤1	1
Hair bleach	0.3–1	1
Hair conditioner	≤30	10
Hair dye	≤10	3
Hair grooming (gel)[3]	<100	10
Hair shampoo	≤10	10
Hair wave permanent[4]	≤10	10
Makeup (eyeliner)	0.3–3	3
Makeup (eye mascara)	≤30	10
Makeup (eyeshadow)	≤30	30
Makeup (face)	0.1–10	10
Moisturizer (body)	≤10	3
Moisturizer (face)	0.1–30	30
Nail polish	3–30	30
Shaving cream	≤3	3
Skin cleanser	≤3	1

Personal care product category	Concentration range of NVP[1] (ppm)	95th-percentile concentration of NVP (ppm)
Products excluded from exposure assessment		
Bath salts[2]	0.3–1	1
Hair grooming (cream)[3]	0.1–30	10
Hair grooming (mousse)[3]	≤30	10
Hair grooming (spray)[3]	≤30	10
Hair straightener[4]	≤10	3
Tanning preparation[5]	Unknown	Unknown
Teeth whitening strips[6]	10–30	30

[1] Based on a maximum NVP residual level in polymer of 100 ppm (BASF 2006). Results can also be expressed as concentration range of NVP-derived polymer in personal care product (% by weight).
[2] Bath foam assumed to have the same frequency of use as bath salts (RIVM 2006), but used by a greater age demographic (0.5–60+ years) compared with bath salts (20–60+ years).
[3] Hair gel, cream, mousse and spray assumed to have the same frequency of use (RIVM 2006). NVP exposure from hair gel is greater than exposure from other hair grooming products based on maximum NVP concentrations.
[4] Hair wave permanent and hair straightener have identical use modelling scenarios and NVP concentration ranges (RIVM 2006).
[5] Insufficient information to assess exposure.
[6] Exposure considered negligible based on amount of product applied per use.

Source: 2009 communication of data from Health Canada's Cosmetic Notification System from Risk Management Bureau, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced.

Concentrations of NVP-derived polymers found in PCPs are grouped by category (e.g. face makeup, nail polish, etc.) and reported as ranges (footnote 1 in Table 7). For 10 of 25 categories presented in Table 7, the upper-limit of the polymer concentration range is 30% or more. However, the polymer concentrations of PCPs comprising the ranges are not equally distributed: 60% of the PCPs in the 10 categories have NVP-derived polymer concentrations at the lower end of the range (≤1% concentration, by weight). In Canada less than 3% of PCPs have NVP-derived polymer concentrations above 10%. (2009 communication from Risk Management Bureau, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced). Therefore, to be protective of the general population of Canada, NVP intake estimates in this report are based on the 95th percentile of NVP residual levels in PCPs.

Chronic and acute estimates of upper-bounding NVP intake were predicted using consumer product modelling software and are presented in Appendix 1b (ConsExpo 2006). Exposure modelling parameters used to estimate NVP exposure from PCPs are presented in Appendix 1c. PCPs considered to be applied biweekly or more frequently were categorized as chronic NVP exposure sources, while acute exposure sources were defined as PCPs used on a monthly or less frequent basis.

The maximum chronic NVP intake from PCPs ranged from 1.1 to 2.2 µg/kg-bw per day. Adolescents aged 12–19 years had the greatest estimated chronic intake (2.2 µg/kg-bw per day), followed by adults aged 20–59 years and seniors aged 60+ years, with identical intakes of 1.9 µg/kg-bw per day. Children aged 0.5–4 years had the lowest maximal estimates of NVP intake, at 1.1 µg/kg-bw per day.

Acute NVP exposure intakes were 22 and 18 µg/kg-bw per event for adolescents and the remaining adult population, respectively. Acute exposure intakes for infants and toddlers aged 4 years and younger were not determined, as the scenarios involved the application of hair bleach, hair dye or hair wave permanent.

For all age categories, the major route of exposure from PCPs is dermal, although inhalation and oral routes of exposure do exist. Hair spray has an inhalation component but was not considered for this assessment, as hair gel is used for a similar purpose and had a higher predicted total intake estimate. The calculated acute inhalation exposure from hair spray was considered to be negligible at 7.5×10^{-5} µg/kg-bw per event. Oral exposure to NVP from teeth whitening strips was not considered to be a significant exposure source based on the amount of product applied per use.

When considering NVP intake from PCPs, it is unlikely that a significant part of the population would use every type of PCP that contains PVP on a regular basis. Therefore, some PCPs were excluded from the exposure assessment presented in Appendix 1b. There are several reasons to exclude certain PCPs when determining a maximal daily intake of NVP. When more than one PCP could reasonably be expected to be used for the same or similar function, the product with the greatest NVP concentration (e.g., hair gel vs. hair mousse/spray) or use by the largest percentage of the general population (e.g., bath foam vs. bath salt) was selected to derive an exposure estimate. For tanning preparations insufficient information was available to conduct an exposure assessment. In general, the major source of NVP exposure from PCPs was from leave-on products with high NVP residual levels, such as moisturizers (body and face) and hair gel. Rinse-off products (hair shampoo and conditioner, shaving cream and body wash) had a 10% retention factor applied to exposure assessments.

Information obtained from Canadian businesses reported that 99% of NVP in Canada was used in the formulation of UV stains and curable inks (Environment Canada 2009a). The UV coatings and inks are cured *in situ* and used to coat rigid or semi-rigid surfaces, such as metal, wood or plastic (EURAR 2003). UV curable stains and ink are not intended for sale to the general public, and, once cured, NVP residual levels for this type of use are below detectable limits (EURAR 2003; Environment Canada 2009a). As discussed previously, UV curable inks in food packaging do not come in contact with food; therefore, consumer exposure to NVP from UV curable inks and coatings is considered to be negligible.

In Canada, PVP is listed on the Health Canada DPD (2009) as a non-medicinal ingredient present in final pharmaceutical products. Thus, NVP may be present in pharmaceutical products as an impurity (2009 personal communication from Therapeutic Products Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). The European Union, in EURAR (2003), described "a reasonable worst-case scenario" that involved the daily consumption of as many as 30 tablets. Based on this scenario, NVP exposure from pharmaceuticals in Canada would be lower than NVP exposure from PCPs. It should also be noted that the potential risks associated with taking any excipient

in medication, including NVP, must be considered against the underlying ailment being treated. Therefore, an NVP intake from pharmaceuticals was not estimated.

Confidence in the assessment of NVP exposure from consumer products is moderate, based on the limited amount of Canadian exposure and use data available. Exposure to NVP from PCPs was established using exposure modelling software, but confidence is moderate in the results obtained, because residual NVP levels in polymers were based on recent information from the manufacturer and applied to highly conservative polymer concentrations.

Health Effects Assessment

An overview of key toxicological studies is presented in Appendix 2.

The European Commission has classified NVP as Category 3 for carcinogenicity (causes concern for humans owing to possible carcinogenic effects) with risk phrase R40 (limited evidence of carcinogenic effect), but it is also stated that the available information was not adequate for making a satisfactory assessment (EURAR 2003). A similar classification with respect to carcinogenicity was given by Australia: Category 3 carcinogen (NICNAS 2000). These classifications were based on clear evidence of carcinogenicity in rats exposed by inhalation, the absence of studies investigating the carcinogenic potential of NVP in other experimental animals and humans and the lack of genotoxic activity in a wide range of *in vitro* and a few *in vivo* assays. A classification of Group 3 (not classifiable as to its carcinogenicity to humans) was given by the International Agency for Research on Cancer (IARC 1999) based on the same carcinogenicity database, but in the absence of the genotoxicity studies that were not made available to the working group.

Male and female Sprague-Dawley rats were exposed to NVP concentrations of 0, 23, 46 or 92 mg/m^3 (0, 7.1, 14.3 and 28.5 mg/kg-bw per day; dose conversion according to Health Canada 1994) stabilized with 3 ppm Kerobit for 24 months. In both sexes, there was a clear dose-related increased incidence of hepatocellular carcinomas and nasal cavity adenomas at all doses, a dose-related increased incidence of nasal cavity adenocarcinomas at the middle and highest doses, as well as a higher incidence of squamous carcinomas of the larynx in the highest-dose group. The nasal cavity adenomas and adenocarcinomas were considered to be different tumours, as they arose from different regions (BASF 1992a; Klimisch et al. 1997a).[2] The carcinogenicity of NVP was also examined in a study in which investigations were confined to the liver. Neoplastic changes were seen in female rats exposed to unstabilized NVP at 207 mg/m^3 (64.2 mg/kg-bw per day; Health Canada 1994) for 3 months followed by a 21-month recovery period; no liver tumours were detected in control animals (BASF 1987b; Klimisch et al.

[2] IARC (1999) described a separate 1-year study (Klimisch et al. 1997b) in which nasal cavity adenomas were observed, but that study appears to be a satellite group of the 2-year study, based on the same experimental conditions, the presence of a 3-month satellite group and the similarity in the described neoplastic and non-neoplastic effects.

1997a). This study supported the conclusion that liver tumours observed in the 2-year study were due to NVP and not to the small quantities of Kerobit present.

Several *in vitro* and a limited number of *in vivo* genotoxicity studies on NVP were identified. There was no indication of genotoxicity in a wide variety of *in vitro* tests in both bacterial and mammalian cell systems (BASF 1978a, 1987c; HRC 1978a; Litton Bionetics 1980a, b, c; Simmon and Baden 1980; Knaap et al. 1985), with the exception of a poorly reported study that found slight increases in sister chromatid exchanges in human lymphocyte cultures (Norppa and Tursi 1984). *In vivo* studies were limited; there was no increase in micronuclei induction in the bone marrow of mice given a gavage dose of up to 600 mg/kg-bw (BASF 1993). In addition, there was no increase in the frequency of lethal heritable mutations in male *Drosophila melanogaster* (Knaap et al. 1985), and there was no evidence of protein, deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) binding in the liver of male rats following intraperitoneal injection (IRI 1985). Based on the largely negative genotoxicity results, it is likely that non-genotoxic mechanisms were involved in the development of tumours in the liver, nasal cavity and larynx in the *in vivo* carcinogenicity studies. The undetermined mode of action underlying the development of NVP vapour–induced tumours necessitates that these tumours be considered relevant for human health (EURAR 2003). NVP carcinogenicity studies investigated by the oral and dermal routes were not identified.

Acute exposure of NVP has been studied in a wide range of species (BASF 1953, 1955, 1963a, b, 1964, 1979b, c, 1996; Kvasov 1972; FDRL 1975; Burnette 1978; HRC 1978b; Schwach and Hofer 1978). The lowest median lethal dose/concentration (LD_{50}/LC_{50}) values identified were the following: 834–1314 mg/kg-bw in rat (oral), 3070 mg/m^3 (952 mg/kg-bw per day) in rat (inhalation) and 560 mg/kg-bw in rabbits (dermal). A no-observed-adverse-effect level (NOAEL) of 200 mg/kg-bw and a lowest-observed-adverse-effect level (LOAEL) of 375 mg/kg-bw based on mortality for acute exposure by the dermal route were also identified in a study conducted in rabbits (FDRL 1975; Burnette 1978). However, in another study conducted in the same species, no mortality, local irritation or abnormalities were observed at doses of 400 mg/kg-bw (BASF 1979c).

Extensive repeated-dose studies by the inhalation route have been carried out in rodents at doses ranging from 4.6 to 553 mg/m^3 using exposure durations up to 2 years (BASF 1986a, b, 1988b, c, d, e, 1992a; Klimisch et al. 1997a, b). NVP doses of 207 and 553 mg/m^3 (275.3 and 171.4 mg/kg-bw per day; Health Canada 1994) resulted in mortality in mice and rats, respectively (BASF 1986a, 1988e; Klimisch et al. 1997b). Dysproteinemia, increased levels of enzyme markers of liver toxicity and hematological changes suggestive of anemia were consistently observed, and the liver and the respiratory tract were identified as the major target tissues. The severity of the pathological changes depended on both dose and duration of the exposure. In a 3-month study in rats, nasal cavity toxicity, including inflammation, atrophy of olfactory epithelium and basal cell hyperplasia, as well as slight dysproteinemia, were observed at the lowest-observed-adverse-effect concentration (LOAEC) of 23 mg/m^3 (7.1 mg/kg-bw per day; Health Canada 1994) (BASF 1986a, b; Klimisch et al. 1997b).

The same LOAEC of 23 mg/m^3 was determined for shorter exposures of 7 weeks in mice and rats, at which inflammation, atrophy of the olfactory epithelium and cell hyperplasia in the respiratory epithelium were observed in mice and atrophy of the olfactory epithelium and hepatic centrilobular necrobiosis were observed in one rat (BASF 1988d, e; Klimisch et al. 1997b). This LOAEC was also determined for longer exposures of up to 2 years, at which hepatotoxicity (focal hepatocyte hyperplasia, eosinophilic foci and foci of spongiosis hepatis) and upper respiratory tract irritancy (focal metaplasia of respiratory epithelium, inflammation, atrophy of olfactory epithelium, focal hyperplasia of submucosal glands and focal mucopurulent inflammation in larynx) were detected (BASF 1992a; Klimisch et al. 1997a). At higher doses, degenerative changes in the nucleus, fatty infiltration and glycogen accumulation within hepatocytes and necrobiosis were found in the centrilobular region of the liver (EURAR 2003). The concentration of 23 mg/m^3 was the lowest concentration tested in all the inhalation studies identified, with the exception of a 3-month study in rats; no effect was observed at the lowest dose of 4.6 mg/m^3 (1.4 mg/kg-bw per day; Health Canada 1994) (BASF 1986a, b; Klimisch et al. 1997b).

In contrast, when NVP was administered repeatedly by the oral route, the respiratory tract was no longer a target tissue, and higher doses (equivalent to inhalation concentrations) were required to elicit liver toxicity. A LOAEL of 40 mg/kg-bw per day was identified in a 3-month gavage study in rats; at this dose, increased water consumption, γ-glutamyltransferase activity (significant only in females) and relative liver weight in females were observed. Foci in the liver morphologically similar to those observed in inhalation studies, however, were evident only at 100 mg/kg-bw per day (BASF 1986c; Klimisch et al. 1997b). Hydrolysis and/or spontaneous polymerization of NVP under the acidic conditions of the stomach prior to absorption have been suggested to reduce oral bioavailability and therefore toxicity of NVP (EURAR 2003). A LOAEL of 4.1–8.3 mg/kg-bw per day (range accounts for decreased dose with time) was established for rats exposed to NVP for 3 months through their drinking water, based on slight reductions in water consumption, dysproteinemia and decreased levels of total proteins, globulins and, in females, albumin (BASF 1986d; Klimisch et al. 1997b). A LOAEL of 5 mg/kg-bw per day was identified when rats were exposed to NVP in their drinking water for a shorter exposure duration of 21 days. At this dose, a dose-dependent decrease in water consumption and reduced body weight gain in females were observed. Repeated-dose dermal toxicity studies for NVP were not identified.

Female Wistar rats were exposed to NVP at 0, 4.6, 23 or 92 mg/m^3 (0, 1.4, 7.1 and 28.5 mg/kg-bw per day; Health Canada 1994) during gestational days 6–19 to determine the developmental toxicity of NVP. A LOAEC of 92 mg/m^3 for fetotoxicity was determined based on reduced fetal body weight, incomplete ossification and wavy ribs, while a LOAEC of 23 mg/m^3 was observed for pregnant dams based on decreased body weight gain. The investigators further concluded, according to the European Union risk assessment report (EURAR 2003), that there was some evidence that pregnant rats may be more susceptible than non-pregnant rats to the toxicity of NVP based on the magnitude of reductions in body weight gain (BASF 2001).

Although the potential for NVP to adversely affect fertility has not been specifically investigated in experimental animals, no adverse effects on reproductive organs have been reported in repeated-dose studies. These studies have examined reproductive organs from rats inhaling aerosols of up to 300 mg/m^3 (93 mg/kg-bw per day; Health Canada 1994) for 4 weeks (FDRL 1976), in rats and mice inhaling up to 207 mg/m^3 (64.2 and 275.3 mg/kg-bw per day in rats and mice, respectively; Health Canada 1994) for 7 weeks (BASF 1988d, e), in rats inhaling NVP at 207 or 553 mg/m^3 (64.2 and 171.4 mg/kg-bw per day; Health Canada 1994) for 3 months (BASF 1986a), in rats inhaling NVP at 92 mg/m^3 (28.5 mg/kg-bw per day; Health Canada 1994) for 2 years (BASF 1992a) and in rats given NVP at 4.1–8.3 mg/kg-bw per day in drinking water for 3 months (BASF 1986d; Klimisch et al. 1997b).

NVP was not found to be a skin irritant in studies conducted in experimental animals (BASF 1963a, b, 1978b, 1979c), nor was it found to be a skin sensitizer (BASF 1996), but, in its liquid form, it caused irreversible corneal opacity, conjunctival chemosis and iris lesions when directly applied to the eyes of rabbits (BASF 1978b; Burnette 1978). The European Union (EURAR 2003) also suggested that NVP would most likely cause respiratory tract irritation based on increased respiration rates and nasal secretions seen in acute inhalation studies and on its ability to severely irritate eyes.

The toxicokinetics of NVP have been extensively characterized in the rat and to a lesser extent in the dog (Digenis and McClanahan 1982; McClanahan et al. 1983, 1984, 1987; Digenis 1990; BASF 1992b). NVP is rapidly absorbed by both the oral and inhalation routes and is expected to have good dermal absorption, according to EURAR (2003), based on its physicochemical characteristics and its structural similarity to *N*-methyl-2-pyrrolidone. Quantitative absorption data, however, were not available for the inhalation or dermal route of exposure. NVP has a plasma half-life of 3–4 hours in rats but only 20–40 minutes in dogs, the reason for which is unclear. It is widely distributed within the body, with the highest levels in the liver, small intestines and kidneys. Metabolic studies in the rat have found NVP to be extensively metabolized to highly polar compounds; the two major ones were not identified. It is rapidly eliminated in the urine, with much smaller amounts in the feces through the bile and in exhaled air as carbon dioxide.

Only one epidemiological study was identified, but, given the uncertainty about the actual levels of NVP inhaled or the possibility of co-exposure of the workers in a German manufacturing plant to other chemicals, it was not further considered (Zober et al. 1992).

The confidence in the toxicity database in experimental animals is considered to be moderate, as there was some information to address effects that may be of concern based on inhalation and, to some extent, oral exposures. However, there was no chronic/carcinogenic study conducted for the oral route, and the ones conducted by the inhalation route were only in one species, with the mode of action remaining uncharacterized. There was also a lack of dermal studies and human data for most endpoints.

Characterization of Risk to Human Health

Based on a weight of evidence approach, NVP exposure via inhalation leads to carcinogenicity and to toxicity in the liver and respiratory tract. NVP vapour was carcinogenic in rats, resulting in tumours in the liver, nasal cavity and larynx (BASF 1987b, 1992a; Klimisch et al. 1997a). The carcinogenic potential of NVP has, however, not been tested in other experimental animals or by other routes of exposure. The genotoxicity data for NVP appear to indicate a lack of genotoxicity, including mutagenicity, but there were few *in vivo* studies. Also, hepatocellular tumours have developed after only 3 months of exposure to NVP at 207 mg/m^3 (64.2 mg/kg-bw per day) in rats, suggesting that there is early initiation of irreversible changes with high exposure concentrations (BASF 1987b; Klimisch et al. 1997a). Some uncertainties also exist with respect to the mechanisms responsible for the development of nasal and laryngeal tumours. Consequently, in the absence of evidence to the contrary, it must be assumed that these tumours are relevant to human health. Such a conclusion was also reached by the European Union (EURAR 2003). Given that NVP is unlikely to be mutagenic, it is considered a threshold carcinogen with a LOAEC of 23 mg/m^3 (7.1 mg/kg-bw per day), based on an increased incidence of hepatocellular carcinomas and nasal cavity adenomas in male and female rats (BASF 1992a; Klimisch et al. 1997a). These tumours were observed at the lowest dose tested in a chronic toxicity/carcinogenicity study. The same critical effect level based on non-neoplastic effects was determined in repeated-dose studies ranging from 7 weeks to 2 years (BASF 1986a, b, 1988d, e, 1992a; Klimisch et al. 1997a, b).

Comparison of the LOAEC for chronic exposure via inhalation (i.e., 7.1 mg/kg-bw per day) with the upper-bounding estimate of daily intake of NVP by the most highly exposed group (12–19 years) via frequently used PCPs in Canada (2.2×10^{-3} mg/kg-bw per day) results in a margin of exposure (MOE) of approximately 3200. This MOE value is also retained for short-term and subchronic exposures to PCPs, and it is considered adequate given the conservatisms used in the upper-bounding estimates of exposure and the use of a dermal absorption rate of 100%.

A LOAEL based on a route of exposure other than inhalation was also considered for repeated-dose studies. In the absence of repeated-dose dermal toxicity studies, a LOAEL range of 4.1–8.3 mg/kg-bw per day (the range accounts for decreased dose with time) was established for rats exposed to NVP for 3 months through their drinking water. This range was based on the level at which slight reductions in water consumption, dysproteinemia and decreased levels of total proteins and globulins in both sexes and decreased levels of albumin in females were observed (BASF 1986d; Klimisch et al. 1997b). The toxicity noted in this study was indicative of dehydration following reduced water consumption (possible due to palatability), and the use of these endpoints for toxicological reference values is considered to be a conservative interpretation of the study. Based on the LOAEL range and the upper-bounding estimate of daily NVP intake from frequently used PCPs in Canada (2.2×10^{-3} mg/kg-bw per day), the MOE has an estimated range of 1900–3800. This MOE range is considered adequately protective of human health, as the exposure assessment of NVP from PCPs assumed conservative upper-bounding estimates and the use of a dermal absorption rate of 100%.

In the absence of adequate acute dermal toxicity endpoints, a MOE was calculated for the highest no-adverse-effect level in the acute toxicity database. A NOAEL of 200 mg/kg-bw was therefore used for the calculation of an MOE, since the LOAEL of 375 mg/kg-bw was based on mortality (FDRL 1975; Burnette 1978). Confidence in the use of this NOAEL is further strengthened by the absence of local irritation, apparent abnormalities at necropsy and mortality at a dose of 400 mg/kg-bw in another dermal study conducted in the same species (BASF 1979c). Comparison of this critical effect dose level with the upper-bounding estimate of total acute NVP intake from PCPs (0.022 mg/kg per event for the 12–19 years age group) results in an MOE of approximately 9100 and is considered adequately protective of human health.

Uncertainties in Evaluation of Risk to Human Health

There is uncertainty associated with the cancer endpoint, given that the mode of tumour induction has not been analysed or fully elucidated, carcinogenicity studies were done in one species only via one route of exposure and a NOAEL was not identified in the carcinogenicity/chronic studies. To address these uncertainties, it is assumed that the tumours observed in rats are relevant to humans. In addition, there is uncertainty associated with a lack of oral and dermal studies as well as human data for most endpoints. In the majority of studies conducted, a NOAEL was not identified, and the lowest dose tested was the LOAEL. However, the MOE between the critical effect level and the highest estimated intake of NVP is considered adequately protective to address deficiencies in the data set. An experimentally determined dermal absorption value was not available, which would have been particularly relevant given the prevalence of the dermal route of exposure of humans to NVP. In the absence of an experimentally derived dermal absorption value, a value of 100% dermal absorption was used. While this assumption entails a great deal of uncertainty, the use of a 100% dermal absorption value greatly increases the conservatism inherent in the risk characterization.

Lack of recent Canadian data on levels of NVP in environmental media, food and consumer products is a source of uncertainty in the upper-bounding exposure estimates for the general population of Canada. However, concern about this uncertainty is reduced by taking into account the MOE between the critical effect level and the highest estimated intake of NVP. Confidence is moderate that the derived multimedia and consumer product exposure estimates are adequately protective of the general population of Canada, as highly conservative estimates and upper-bounding scenarios were used when recent Canadian data were unavailable.

Conclusions

Based on the information presented in this screening assessment, it is concluded that NVP 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, NVP does not meet the criteria for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based on comparison of the upper-bounding estimated exposures to NVP in Canada with the critical effect levels, it is concluded that the resulting MOEs are adequately protective of human health and that NVP 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.

It is therefore concluded that NVP does not meet any of the criteria under 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.

References

[AIES] Artificial Intelligence Expert System. 2003–2005. Version 1.25. Ottawa (ON): Environment Canada. Model developed by Stephen Niculescu. Available from: Environment Canada, Ecological Assessment Division.

Aldrich. 1995. Aldrich catalogue handbook of fine chemicals. Milwaukee (WI): Sigma-Aldrich Co., USA.

[AOPWIN] Atmospheric Oxidation Program for Windows [Estimation Model]. 2008. Version 1.92a. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. QSAR Comb Sci [Internet] 22(3):337–345. Available from: http://www3.interscience.wiley.com/journal/104557877/home [restricted access]

ASTreat Model [sewage treatment plant removal model]. 2006. Versioon 1.0. Cincinnati (US): Procter and Gamble Company [cited 2010 08 03]. Available Procter and Gamble Company, P.O. Box 538707, Cincinnati, OH 45253-8707, US.

BASF. 1953. Report on the orientating biological testing of a-pyrrolidone and N-vinyl-a-pyrrolidone. Unpublished data. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Report Nos.: III/50, III/51 (12.12.53). [cited in EURAR 2003].

BASF. 1955. Report on the testing of N-vinyl-a-pyrrolidone for antineoplastic effects. Unpublished data. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Report Nos.: V/103, 176, 233 (13.10.55). [cited in EURAR 2003].

BASF. 1963a. Study of acute toxicity and skin and eye irritation. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Report No.: XIII/37 (2.5.63). [cited in EURAR 2003].

BASF. 1963b. Study of acute toxicity and skin and eye irritation. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Report No.: XIII/38 (2.5.63). [cited in EURAR 2003].

BASF. 1964. Report on the acute and sub-acute peroral toxicity of vinylpyrrolidone for guinea pigs, rabbits and cats. Unpublished results. Ludwigshafen/Rhein (DE): BASF AG, Department of Toxicology. Report No.: XIII/38 (28.2.64). [cited in EURAR 2003].

BASF. 1978a. Ames test for vinylpyrrolidone. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Report No.: 77/241 (30.5.78). [cited in EURAR 2003].

BASF. 1978b. Primary skin and eye irritation tests with N-vinylpyrrolidone in albino rabbits. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. TNO Report No. B77/907-30 (August 1978). [cited in EURAR 2003].

BASF. 1979a. Unpublished study. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Ecological Laboratory. [cited in EURAR 2003].

BASF. 1979b. Report on the determination of the acute inhalation toxicity, LC_{50} of vinylpyrrolidone in a 4 hour exposure period on Sprague-Dawley rats. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Report No.: 77/753 (22.1.79). [cited in EURAR 2003].

BASF. 1979c. Bericht über die Prüfung der akuten dermalen Toxizität von Vinylpyrrolidon Dest. (mit 10 ppm Kerobit BDP stabilisiert) an der Rückenhaut weißer Kaninchen (8.1.79). Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. [cited in EURAR 2003].

BASF. 1986a. Study of the sub-chronic inhalation toxicity of N-vinyl-2-pyrrolidone in Sprague-Dawley rats (3-month study). Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 42J0165/8005 (12.3.86). [cited in EURAR 2003].

BASF. 1986b. Study of the sub-chronic inhalation toxicity of N-vinyl-2-pyrrolidone as a vapour in Sprague-Dawley rats after 3-month inhalation (supplementary study). Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 42I0186/8233 (12.3.86). [cited in EURAR 2003].

BASF. 1986c. Report on the pilot studies of the toxicity of N-vinyl-2-pyrrolidone in Wistar rats after administration in the drinking water for 3 and 4 weeks and after administration by gavage for 13 weeks. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 12C0053/8404 (21.2.86). [cited in EURAR 2003].

BASF. 1986d. Report on the study of the toxicity of N-vinyl-2-pyrrolidone in rats after 3-months administration in the drinking water. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 32C0250/8417 (21.2.86). [cited in EURAR 2003].

BASF. 1987a. Unpublished studies. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 12F161/86 (23.03.87). [cited in EURAR 2003].

BASF. 1987b. Preliminary study on the reversibility of the sub-chronic inhalation toxicity of N-vinylpyrrolidone-2 in female Sprague-Dawley rats (3-month exposure and subsequent recovery periods of 9 and 21 months). Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 51I0186/8234 (8.12.87). [cited in EURAR 2003].

BASF. 1987c. In-vitro cytogenetic investigations of N-vinylpyrrolidone-2 in human lymphocytes. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 30M0161/8616 (26.11.87). [cited in EURAR 2003].

BASF. 1987d. Preliminary study on the sub-chronic inhalation toxicity of N-vinylpyrrolidone-2 in Syrian hamsters (3-month study). Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 52I0186/8235 (8.12.87). [cited in EURAR 2003].

BASF. 1988a. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Ecological Laboratory (0703/88, Fraunhofer Society). [cited in EURAR 2003].

BASF. 1988b. The inhalation toxicity of N-vinylpyrrolidone (extra pure) as vapour on Fischer 344 rats after 2 or 5 exposures or combination exposure. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 43I0459/8470S (16/12/88). [cited in EURAR 2003].

BASF. 1988c. The inhalation toxicity of N-vinylpyrrolidone (extra pure) as vapour on female C57 black mice after 2 or 5 exposures or combination exposure. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 44I0459/8471S (16.12.88). [cited in EURAR 2003].

BASF. 1988d. The inhalation toxicity of N-vinylpyrrolidone (extra pure) as vapour on Fischer 344 rats (7-week test). Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 43I0459/8470 (16.12.88). [cited in EURAR 2003].

BASF. 1988e. The inhalation toxicity of N-vinylpyrrolidone (extra pure) as vapour on C 57 black mice (7-week test). Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 44I0459/8471 (16.12.88). [cited in EURAR 2003].

BASF. 1992a. Two year inhalation study on N-vinylpyrrolidone-2 (NVP) as a vapour in Sprague-Dawley rats with interim kills of satellite subgroups after 3 month and 12 month exposure periods and a third satellite subgroup that was exposed for 18 months and killed at 2 years. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 71I0459/8478 (14.8.92). [cited in EURAR 2003].

BASF. 1992b. Study of the quantitative correlation of the serum concentration after exposure to defined concentrations of N-vinylpyrrolidone-2 as vapour as well as single oral or dermal applications of 5 mg/kg body weight to dogs. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 25I0242/91010 (29.10.92). [cited in EURAR 2003].

BASF. 1993. Cytogenetic study in vivo of N-vinylpyrrolidone-2 (N-VP) in mice, micronucleus test, single oral administration. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology. Project No. 26M0133/924090 (26.1.93). [cited in EURAR 2003].

BASF. 1995. Safety data sheet N-vinyl-2-pyrrolidone dist. (28.11.1995). Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft. [cited in EURAR 2003].

BASF. 1996. Buehler test in guinea pigs. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft. Project No. 32H0084/962038 (20.9.96). [cited in EURAR 2003].

BASF. 1997. N-Vinyl-2-pyrrolidone. Technical data sheet [Internet]. Mount Olive (NJ): BASF Corporation, Chemicals Division. [cited 2010 Jan 7]. Available from: http://www2.basf.us/diols/pdfs/n-vinyl2.pdf

BASF. 2001. N-Vinyl pyrrolidone—Prenatal development inhalation toxicity study in Wistar rats vapour exposure. Unpublished results. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Experimental Toxicology and Ecology. Project No. 31R0050/00003. [cited in EURAR 2003].

BASF. 2006. BASF polymers [Internet]. Florham Park (NJ): BASF Corporation. [cited 2009 Oct 29]. Available from: http://www.cosmetics.basf.de/pdf/Documents/EMC/Brochure/EN/Polymer%20Pamphlet_nafta.pdf

[BCFBAFWIN] BioConcentration Factor Program for Windows [Estimation Model]. 2008. Version 3.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

BIBRA. 1989. Toxicity profile: N-vinylpyrrolidone. Surrey (GB): TNO BIBRA International Ltd.

[BIOWIN] Biodegradation Probability Program for Windows [Estimation Model]. 2008. Version 4.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Boethling RS, Howard PH, Beauman JA, Larosche ME. 1995. Factors for intermedia extrapolations in biodegradability assessment. Chemosphere 30(4):741–752.

Bohnert JL, Horbett TA, Ratner BD, Royce FH. 1988. Adsorption of proteins from artificial tear solutions to contact lens materials. Invest Ophthalmol Vis Sci 29(3):362–373.

Burnette LW. 1978. Personal communication from Mr. L.W. Burnette, GAF Corporation, Wayne, New Jersey, to Dr. A. Friedman, Tractor Jitco Inc., November 2, 1978. [cited in NIOSH 1981].

Cai W, Gupta RB. 2005. Hydrogels. In: Kroschwitz JI, editor. Kirk-Othmer encyclopedia of chemical technology, vol. 13. 5th ed. New York (NY): Wiley and Sons. p. 729–759.

Canada. [1978]. Food and Drug Regulations, C.R.C., c. 870, s. B.16.100, Table VIII. Available from: http://laws.justice.gc.ca/PDF/Regulation/C/C.R.C.,_c._870.pdf

Canada. 1988. Ingredient Disclosure List [Internet]. SOR/88-64. [cited 2009 Aug 4]. Available from: http://www.canlii.org/ca/regu/sor88-64/part274942.html

Canada. 1999. Canadian Environmental Protection Act, 1999. S.C., 1999, c. 33. Available from: http://www.gazette.gc.ca/archives/p3/1999/g3-02203.pdf

Canada. 2000. Canadian Environmental Protection Act, 1999: Persistence and Bioaccumulation Regulations, P.C. 2000-348, 23 March 2000, SOR/2000-107. Available from: http://www.gazette.gc.ca/archives/p2/2000/2000-03-29/pdf/g2-13407.pdf

Canada, Dept. of the Environment, Dept. of Health. 2006. Canadian Environmental Protection Act, 1999: Notice of intent to develop and implement measures to assess and manage the risks posed by certain substances to the health of Canadians and their environment. Canada Gazette, Part I, vol. 140, no. 49, p. 4109–4117. Available from: http://www.gazette.gc.ca/archives/p1/2006/2006-12-09/pdf/g1-14049.pdf

Canada, Dept. of the Environment, Dept. of Health. 2009. Canadian Environmental Protection Act, 1999: Notice with respect to Batch 9 Challenge substances. Canada Gazette, Part I, vol. 143, no. 11. Available from: http://canadagazette.gc.ca/rp-pr/p1/2009/2009-03-14/pdf/g1-14311.pdf#page=4

[CIMT] Canadian International Merchandise Trade [database on the Internet]. 2009. Result for HS Code 2914290010. Ottawa (ON): Statistics Canada. Available from: http://www.statcan.gc.ca/trade/scripts7/trade_search.cgi

CATABOL [Computer Model]. ©2004–2008. Version 5.10.2. Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. Available from: http://oasis-lmc.org/?section=software&swid=1

ChemCAN [Level III fugacity model of 24 regions of Canada]. 2003. Version 6.00. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. Available from: http://www.trentu.ca/academic/aminss/envmodel/models/CC600.html

Chemical Information Services. 1995. Directory of world chemical producers. 1995/96 edition. Dallas (TX): Chemical Information Services. [cited in IARC 1999].

[ConsExpo] Consumer Exposure Model [Internet]. 2006. Version 4.1. Bilthoven (NL): Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment). Available from: http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp#tcm:13-42840

Digenis GA. 1990. Disposition and pharmacokinetics of N-VP. Unpublished report. Ludwigshafen/Rhein (DE): BASF Aktiengesellschaft, Department of Toxicology.

Digenis GA, McClanahan JS. 1982. N-Vinyl-2-pyrrolidone: disposition and metabolism studies. Toxicologist 2(1):165–166.

Dimitrov S, Dimitrova N, Parkerton T, Comber M, Bonnell M, Mekenyan O. 2005. Base-line model for identifying the bioaccumulation potential of chemicals. SAR QSAR Environ Res 16(6):531–554.

[DPD] Drug Product Database [database on the Internet]. 2009. Povidone-iodine. Ottawa (ON): Health Canada. [cited on 2009 Oct 16]. Available from: http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

[ECB] European Chemicals Bureau. 2000. IUCLID dataset for 1-vinyl-2-pyrrolidone (CAS No. 88-12-0). Available from: http://ecb.jrc.ec.europa.eu/IUCLID-DataSheets/88120.pdf

[ECOSAR] Ecological Structure Activity Relationships [Internet]. 2008. Version 1.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Environment Canada. 2007. Guidance for conducting ecological assessments under CEPA, 1999: science resource technical series, technical guidance module: QSARs. Reviewed draft working document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2009a. Data for Batch 9 substances collected under Canadian Environmental Protection Act, 1999, section 71: Notice with respect to Batch 9 Challenge substances. Data prepared by: Environment Canada, Existing Substances Program.

Environment Canada. 2009b. Guidance for conducting ecological assessments under CEPA, 1999: science resource technical series, technical guidance module: the Industrial Generic Exposure Tool – Aquatic (IGETA). Working document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2009c. IGETA report: CAS RN 88-12-0, 2009-11-04. Unpublished report. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2009d. Guidance for conducting ecological assessments under CEPA 1999: science resource technical series, technical guidance module: Mega Flush consumer release scenario. Working document. Gatineau (QC): Environment Canada, Ecological Assessment Division. Available on request.

Environment Canada. 2009e. Mega Flush report. CAS RN 88-12-0, 2009-11-16. Internal draft document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

[EPIsuite] Estimation Programs Interface Suite for Microsoft Windows [Estimation Model]. 2008. Version 4.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/eqisuitedl.htm

[EQC] Equilibrium Criterion Model. 2003. Version 2.02. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry. Available from: http://www.trentu.ca/academic/aminss/envmodel/models/EQC2.html

[EURAR] European Union Risk Assessment Report: CAS: 88-12-0: 1-vinyl-2-pyrrolidone [Internet]. 2003. Luxembourg: Office for Official Publications of the European Communities. Report No.: EUR 20763 EN. Available from: http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/vinylpyrrolidonereport040.pdf

[FAO/WHO]. Joint FAO/WHO Expert Committee on Food Additives. 2007. Summary of evaluations performed by the Joint FAO/WHO expert committee on food additives. Polyvinylpyrrolidone. Joint FAO/WHO expert committee on food additives. Geneva (CH): World Health Organization. [2007 Mar 1; cited 2009 Oct 30]. Available from: http://jecfa.ilsi.org/evaluation.cfm?chemical=POLYVINYLPYRROLIDONE&keyword=PYRROLIDONE

[FCC] Food Chemicals Codex. 6th ed. 2008. Baltimore (MD): The United States Pharmacopeial Convention, United Book Press, Inc.

[FDRL] Food and Drug Research Laboratories Inc. 1975. Acute dermal toxicity study in rabbits. Unpublished results (22.7.75). New York (NY): GAF Inc. [cited in EURAR 2003].

[FDRL] Food and Drug Research Laboratories Inc. 1976. 30-day inhalation study with vinylpyrrolidone in the rat. Unpublished results (16.7.76). New York (NY): GAF Inc. [cited in EURAR 2003].

Frank HP. 1954. The lactam-amino acid equilibria for ethylpyrrolidone and polyvinylpyrrolidone. J Polym Sci 12:565–576.

Garrett Q, Milthorpe BK. 1996. Human serum albumin adsorption on hydrogel contact lenses in vitro. Invest Ophthalmol Vis Sci 37(13):2594–2602.

Gmahl E, Ruess W. 1993. Identification and characterization of vinylpyrrolidone–vinylimidazolium chloride copolymers in cosmetic products by pyrolysis–gas chromatography–mass spectrometry method. Int J Cosmet Sci 15:77–81.

Hansch, C, Leo A, Hoekman D. 1995. Exploring QSAR—hydrophobic, electronic, and steric constants. Washington (DC): American Chemical Society. [cited in HSDB 2009].

[HSDB] Hazardous Substances Data Bank [database on the Internet]. 1983– . Bethesda (MD): National Library of Medicine (US). [revised 2006 Dec 20; cited 2009 Jul 31]. Available from: http://toxnet.nlm.nih.gov

Health Canada. 1994. Human health risk assessment for priority substances. Ottawa (ON): Health Canada, Environmental Health Directorate. Available from: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/approach/approach-eng.pdf

Health Canada. 1998. Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate.

Henriks-Eckerman M-L, Kanerva L. 1997. Product analysis of acrylic resins compared to information given in material safety data sheets. Contact Dermatitis 36:164–166.

[HENRYWIN] Henry's Law Constant Program for Microsoft Windows [Estimation Model]. 2008. Version 3.20. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Hössel R, Dieing R, Nörenberg R, Pfau A, Sander R. 2000. Conditioning polymers in today's shampoo formulations—efficacy, mechanism and test methods. Int J Cosmet Sci 22:1–10.

[HRC] Huntington Research Centre. 1978a. Ames metabolic activation test to assess the potential mutagenic effect of N-vinyl pyrrolidone. Unpublished results (6.4.78). Huntingdon, Cambridgeshire (GB): Huntingdon Research Centre. [cited in EURAR 2003].

[HRC] Huntington Research Centre. 1978b. Acute oral toxicity to rats of N-vinyl pyrrolidone. Unpublished results (3.3.78). Huntingdon, Cambridgeshire (GB): Huntingdon Research Centre. [cited in EURAR 2003].

[HYDROWIN] Hydrolysis Rates Program for Microsoft Windows [Estimation Model]. 2008. Version 2.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

[IARC] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 1979. N-vinyl-2-pyrrolidone and polyvinyl pyrrolidone. IARC Monogr Eval Carcinog Risks Hum 19:461–477.

[IARC] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 1999. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC Monogr Eval Carcinog Risks Hum 71:1181–1187.

[IRI] Inveresk Research International. 1985. N-Vinyl-2-pyrrolidone: association of ^{14}C-labelled chemical with rat liver DNA. Unpublished results. Musselburgh (GB): Inveresk Research International. IRI Project No. 732496. [cited in EURAR 2003].

Klimisch H-J, Deckardt K, Gembardt C, Hildebrand B, Küttler K, Roe FJC. 1997a. Long-term inhalation toxicity of N-vinylpyrrolidone-2 vapours. Studies in rats. Food Chem Toxicol 35:1041–1060.

Klimisch H-J, Deckardt K, Gembardt C, Hildebrand B, Küttler K, Roe FJC. 1997b. Subchronic inhalation and oral toxicity of N-vinylpyrrolidone-2. Studies in rodents. Food Chem Toxicol 35:1061–1074.

Knaap AGA, Voogd CE, Kramers PGN. 1985. Mutagenicity of vinyl compounds. Mutat Res 147:303.

[KOWWIN] Octanol–Water Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2008. Version 1.67. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Kricheldorf HR, Nuyken O, Swift G, editors. 2005. Handbook of polymer synthesis. 2nd ed. New York (NY): Marcel Dekker.

Kroschwitz JI, editor. 1991. Kirk-Othmer encyclopaedia of chemical technology. 4th ed. New York (NY): John Wiley & Sons.

Kvasov AG. 1972. Gidrokhim. Issled. (Chem. Abstr. 79, 964y). p. 88. [cited in BIBRA 1989].

Litton Bionetics. 1980a. Mutagenicity evaluation of V-Pyrol (N-vinyl-2-pyrrolidone) in the mouse lymphoma forward mutation assay. Unpublished results. Wayne (NJ): GAF Corporation. LBI Project No. 20989 (February 1980). [cited in EURAR 2003].

Litton Bionetics. 1980b. Evaluation of V-Pyrol (N-vinyl-2-pyrrolidone) in the primary rat hepatocyte unscheduled DNA synthesis assay. Unpublished results. Wayne (NJ): GAF Corporation. LBI Project No. 20991 (April 1980). [cited in EURAR 2003].

Litton Bionetics. 1980c. Evaluation of V-Pyrol (N-vinyl-2-pyrrolidone) in the in vitro transformation of BALB/3T3 cells assay. Unpublished results. LBI Project No. 20992 (April 1980). Wayne (NJ): GAF Corporation. [cited in EURAR 2003].

[LNHPD] Licensed Natural Health Products Database [database on the Internet]. 2009. Ottawa (ON): Health Canada. [cited 2009 Dec 29]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/lnhpd-bdpsnh-eng.php

Lorenz DH. 1971. N-Vinyl amide polymers. In: Bikales NM, editor. Encyclopedia of polymer science and technology; plastics, resins, rubbers, fibers, vol. 14. New York (NY): Interscience. p. 239–251. [cited in IARC 1979].

McClanahan J, Chaney J, Blecher L, Digenis GA. 1983. Disposition of N-vinylpyrrolidone in the rat. In: Digenis GA, Ansell J, editors. Proceedings of the 1st International Symposium on Povidone, April 17–20, 1983 (Supplement). Lexington (KY): University of Kentucky Press. p. 250–268.

McClanahan JS, Lin YC, Digenis GA. 1984. Disposition of N-vinyl-2-pyrrolidinone in the rat. Drug Chem Toxicol 7:129–148.

McClanahan J, Hawi AA, Digenis GA. 1987. Disposition and metabolism of N-vinyl-2-pyrrolidone in the rat. In: Digenis GA, editor. Proceedings of the 2nd International Symposium on Povidone, April 12–15, 1987. Lexington (KY): University of Kentucky Press. p. 318–329.

Moore A. 1983. Final report on the safety assessment of polyvinylpyrrolidone/vinyl acetate copolymer. Int J Toxicol 2(5):141–159.

[MPBPWIN] Melting Point Boiling Point Program for Microsoft Windows [Estimation Model]. 2008. Version 1.43. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

[NCI] National Chemical Inventories [database on a CD-ROM]. 2006. Columbus (OH): American Chemical Society, Chemical Abstracts Service. [cited 2006 Dec 11]. Available from: http://www.cas.org/products/cd/nci/index.html

[NHPID] Natural Health Products Ingredients Database [database on the Internet]. 2009. PVP; NHPID approved name povidone. Ottawa (ON): Health Canada. [revised 2007 Apr 18; cited 2009 Dec 29]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/online-enligne/nhpid-bipsn-eng.php

[NHW] Dept. of National Health and Welfare (CA). 1990. Present patterns and trends in infant feeding in Canada. Ottawa (ON): Department of National Health and Welfare. NHW Cat. No. H39-199/1990E. [cited in Health Canada 1998].

[NICNAS] National Industrial Chemicals Notification and Assessment Scheme (AU). 2000. 1-Vinyl-2-pyrrolidone. Priority Existing Chemical Report No. 11 [Internet]. Commonwealth of Australia. Available from: http://nicnas.gov.au/Publications/CAR/PEC/PEC11/PEC_11_Full_Report_PDF.pdf

[NICNAS] National Industrial Chemicals Notification and Assessment Scheme (AU). 2001. Luviquat Care (polyquaternium 44). Full public report [Internet]. Commonwealth of Australia. Available from: http://www.nicnas.gov.au/publications/CAR/new/NA/NAFULLR/NA0900FR/NA961FR.pdf

[NIOSH] National Institute for Occupational Safety and Health. 1981. Registry of toxic effects of chemical substances. 1981-1982 edition. DHHS (NIOSH) Pub No 83-107, Cincinnati (OH) 1983. [cited in BIBBRA 1989].

Norppa H, Tursi F (1984). Erythrocyte-mediated metabolic activation detected by SCE. In: Tice RR, Hollaender A, editors. Sister chromatid exchanges. 25 years of experimental research. Part B. Genetic toxicology and human studies. New York (NY): Plenum Press.

[NPRI] National Pollutant Release Inventory [database on the Internet]. 2006. Gatineau (QC): Environment Canada. [cited 2009 Jul 31]. Available from: http://www.ec.gc.ca/inrp-npri/

[OASIS Forecast] Optimized Approach based on Structural Indices Set [Internet]. 2005. Version 1.20. Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. Available from: http://oasis-lmc.org/?section=software

O'Neil MJ, Smith A, Heckelman PE, Budavari S, editors. 2001. Merck index. 13th ed. Whitehouse Station (NJ): Merck & Co. p. 1374.

[PCKOCWIN] Organic Carbon Partition Coefficient Program for Windows [Estimation Model]. 2008. Version 2.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Richardson ML, Gangolli S, editors. 1994. Dictionary of substances and their effects, vol. 7. Cambridge (GB): Royal Society of Chemistry.

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu. 2006. Cosmetics fact sheet: to assess the risks for the consumer. Updated version for ConsExpo 4 [Internet]. Bilthoven (NL): RIVM (National Institute for Public Health and the Environment). Report No.: 320104001/2006. [cited 2009 Oct 23]. Available from: http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf

Schwach GW, Hofer H. 1978. Ber. Oesterr. Studienges. Atomenerg, SGAE Ber. No. 3004 (Chem. Abstr. 90, 133656Y). [cited in EURAR 2003].

Simmon VF, Baden JM. 1980. Mutagenic activity of vinyl compounds and derived epoxides. Mutat Res 78:227–231.

[TOPKAT] TOxicity Prediction by Komputer Assisted Technology [Internet]. 2004. Version 6.2. San Diego (CA): Accelrys Software Inc. Available from: http://accelrys.com/mini/toxicology/predictive-functionality.html

[TRI] Toxics Release Inventory Program [database on the Internet]. 2009. TRI Explorer 4.8. Washington (DC): US Environmental Protection Agency. [cited 2009 Jul 31]. Available from: http://www.epa.gov/tri/index.htm

Wood AS. 1970. Vinyl polymers (pyrrolidone). In: Kirk RE, Othmer DF, editors. Kirk-Othmer encyclopedia of chemical technology, vol. 21. 2nd ed. New York (NY): Wiley and Sons. p. 427–440. [cited in IARC 1979].

[WSKOWWIN] Water Solubility for Organic Compounds Program for Microsoft Windows [Estimation Model]. 2008. Version 1.41. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Zober MA, Hoffmann G, Pluto RP, Ott MG. 1992. Morbidity study of N-vinylpyrrolidone production workers. In: Occupational health in the chemical industry: selected papers from the 23rd ICOH Congress on Occupational Health, 22–28 September 1990, Montreal, Quebec, and the XIX Medichem Congress, 17–20 September 1991, Basel, Switzerland. Geneva (CH): World Health Organization.

Appendix 1a: Upper-bounding estimates of daily intake of NVP by the general population in Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of NVP by various age groups							
	0–6 months[1]			0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	Breast fed[2]	Formula fed[3]	Not formula fed					
Ambient air[9]	$<1\times10^{-6}$			$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$
Indoor air[10]	2×10^{-6}			5×10^{-6}	4×10^{-6}	2×10^{-6}	2×10^{-6}	2×10^{-6}
Drinking water[11]	N/A	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$
Food and beverages[12]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Soil[13]	$<1\times10^{-6}$			$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$	$<1\times10^{-6}$
Total intake	**N/A**	**3×10^{-6}**	**3×10^{-6}**	**5×10^{-6}**	**4×10^{-6}**	**2×10^{-6}**	**2×10^{-6}**	**2×10^{-6}**

Abbreviation: N/A, not applicable.

[1] 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).

[2] No data on detectable levels of NVP in breast milk were located.

[3] For exclusively formula-fed infants, intake from water is that amount required to reconstitute formula. No data on NVP levels in formula were found; however, concentrations of NVP in drinking water were used in this model (see footnote 11). Approximately 50% of non-formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990).

[4] 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).

[5] 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).

[6] 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).

[7] 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).

[8] 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).

[9] In the absence of experimental data from Canada, a modelled estimate of an NVP concentration of 8.64×10^{-6} µg/m^3 was used to calculate the upper-bounding estimates for ambient air exposure (ChemCAN 2003). Canadians are assumed to spend 3 h per day outside (Health Canada 1998).

[10] In the absence of experimental data from Canada, the modelled estimate of 8.64×10^{-6} µg/m^3 of NVP in ambient air (see footnote 9) was used to calculate maximal daily exposure from indoor air. Canadians are assumed to spend 21 h indoors each day (Health Canada 1998).

[11] In the absence of experimental data from Canada, a modelled estimate of an NVP concentration of 3.57×10^{-6} µg/L was used to calculate the upper-bounding estimates for drinking water exposure (ChemCAN 2003).

[12] No data were identified for the concentration of NVP in foods in Canada or elsewhere.

[13] In the absence of experimental data from Canada, a modelled estimate of an NVP concentration of 4.37×10^{-4} µg/kg was used to calculate the upper-bounding estimates for soil exposure (ChemCAN 2003).

Appendix 1b: Upper-bounding estimates of chronic and acute intake of NVP from personal care products[1,2]

Product	NVP concentration (ppm)	Estimated intake of 1-vinyl-2-pyrrolidone by various age groups					
		0–6 months[3]	0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
Chronic exposure (µg/kg-bw per day)							
Antiwrinkle cream	3					0.067	0.067
Baby cream	3	0.22					
Bath foam	1		0.031	0.016	0.0082	0.0068	0.0067
Deodorant	1			0.032	0.017	0.014	0.014
Hair conditioner	10		0.37	0.18	0.096	0.081	0.079
Hair grooming (gel)	10			0.095	0.050	0.042	0.042
Hair shampoo	10	1.3	0.65	0.32	0.17	0.14	0.14
Makeup (eyeliner)	3			0.48	0.025	0.021	0.021
Makeup (eye mascara)	10			0.0081	0.0042	0.0035	0.0035
Makeup (eyeshadow)	30			0.019	0.011	0.0085	0.0083
Makeup (face)	10			0.26	0.14	0.11	0.11
Moisturizer (body)	3				0.81	0.67	0.67
Moisturizer (face)	30				0.81	0.68	0.67
Nail polish	30			0.014	0.0072	0.0060	0.0059
Shaving cream	3				0.010	0.0085	0.0083
Skin care, body wash	1			0.077	0.040	0.033	0.033
Acute exposure (µg/kg-bw per event)							
Hair bleach	1				3.0	3.0	3.0
Hair dye	3				5.0	4.0	4.0
Hair wave permanent	10				14.	11.	11.
Total chronic		**1.5**	**1.1**	**1.1**	**2.2**	**1.9**	**1.9**
Total acute					**22.**	**18.**	**18.**

Abbreviation: N/A, not applicable.

[1] NVP concentrations based on the 95th percentile of NVP-derived polymer concentrations in personal care products and a maximum NVP residual level in polymer of 100 ppm (BASF 2006).

[2] Dermal absorption assumed to be 100%. All scenarios are based on ConsExpo 4.1 and assume dermal route of exposure (RIVM 2006).

[3] Assumed to weigh 7.5 kg (Health Canada 1998).

[4] Assumed to weigh 15.5 kg (Health Canada 1998).

[5] Assumed to weigh 31.0 kg (Health Canada 1998).

[6] Assumed to weigh 59.4 kg and to breathe 15.8 m^3 of air per day (Health Canada 1998).
[7] Assumed to weigh 70.9 kg and to breathe 16.2 m^3 of air per day (Health Canada 1998).
[8] Assumed to weigh 72.0 kg and to breathe 14.3 m^3 of air per day (Health Canada 1998).

Appendix 1c: Parameters used to predict exposure to NVP from personal care products

Type of product	Consumer product scenario in ConsExpo	Assumptions from RIVM (2006), unless otherwise specified[1]
Antiwrinkle cream	Face cream	Exposure frequency: twice daily Applied amount: 0.8 g
Baby cream	Baby cream	Exposure frequency: twice daily Applied amount: 0.27 g
Bath foam	Bath foam	Exposure frequency: twice weekly Applied amount: 17 g 10% retention factor applied
Deodorant	Deodorant stick	Exposure frequency: twice daily Applied amount: 0.5 g
Hair conditioner	Hair conditioner	Exposure frequency: twice weekly Applied amount: 20 g 10% retention factor applied
Hair grooming (gel)	Hair gel	Exposure frequency: once daily Applied amount: 0.3 g
Hair shampoo	Hair shampoo	Exposure frequency: once every 2 days Applied amount: 20 g 10% retention factor applied
Makeup (eyeliner)	Eyeliner	Exposure frequency: once daily Applied amount: 0.005 g
Makeup (eye mascara)	Mascara	Exposure frequency: once daily Applied amount: 0.025 g
Makeup (eyeshadow)	Eyeshadow	Exposure frequency: twice daily Applied amount: 0.01 g
Makeup (face)	Facial makeup	Exposure frequency: once daily Applied amount: 0.8 g
Moisturizer (body)	Body lotion	Exposure frequency: twice daily Applied amount: 8 g
Moisturizer (face)	Face cream	Exposure frequency: twice daily Applied amount: 0.8 g
Nail polish	Nail polish	Exposure frequency: twice weekly Applied amount: 0.05 g
Shaving cream	Shaving cream	Exposure frequency: once daily Applied amount: 0.2 g 10% retention factor applied
Skin care, body wash	Liquid soap (showering)	Exposure frequency: 329 times/year Applied amount: 26.1 g 10% retention factor applied
Hair bleach	Hair bleach	Exposure frequency: 10 times/year Applied amount: 200 g
Hair dye	Hair dye	Exposure frequency: 10 times/year Applied amount: 100 g
Hair wave permanent	Hair perm	Exposure frequency: 4 times/year Applied amount: 80 g

[1] All scenarios assume a first-tier (instant application; direct dermal contact with product) dermal route of exposure and a 100% dermal uptake of product remaining after use.

Appendix 2: Summary of health effects information for NVP

Endpoint	Lowest effect levels[1]/results
Laboratory animals and *in vitro* studies	
Acute toxicity	**Lowest inhalation LC_{50} (4 h)** = 3070 mg/m^3 (667 ppm) in male and female Sprague-Dawley rats (BASF 1979b). [Additional acute inhalation studies: Burnette 1978] **Lowest oral LD_{50}** = 834–1314 mg/kg-bw in CFY rats, two per sex per group (HRC 1978b). **Other oral LD_{50}** = 940 mg/kg-bw in Swiss mice, 10 per sex per group (Schwach and Hofer 1978) [Additional acute oral studies: BASF 1953, 1955, 1963a, b, 1964; Kvasov 1972; Burnette 1978] **Lowest dermal LD_{50}** = 560 mg/kg-bw in rabbits, five per group, exposed to NVP at doses of 200, 375, 800, 1000 or 2000 mg/kg-bw through intact skin. At ≥375 mg/kg-bw, mortality was seen within 5 days of dosing; at ≥1000 mg/kg-bw, mortality was 100% (FDRL 1975; Burnette 1978). **NOAEL in another acute dermal study** = 400 mg/kg-bw in rabbits exposed to 400 mg/kg-bw (undiluted, stabilized with 10 ppm Kerobit) occluded for 24 h. No mortality, local irritation or apparent abnormalities at necropsy; slight apathy was only reported sign of toxicity (BASF 1979c). [Additional acute dermal studies: HRC 1978a; BASF 1996]
Short-term repeated-dose toxicity	**Lowest inhalation LOAEC** = 23 mg/m^3 (5 ppm) based on catarrhal-purulent rhinitis in nasal cavities, atrophy of the nasal olfactory epithelium and hyperplasia of submucous glandular cells and of the nasal respiratory epithelium in C57BL mice, 10 per sex per group, exposed to 0, 23, 69 or 207 mg/m^3, 6 h/day, 5 days/week, for 7 weeks. Liver toxicity and dysproteinemia were observed at the next dose level. Outward signs of toxicity decreased as the study progressed (BASF 1988e; Klimisch et al. 1997b). **Lowest inhalation LOAEC** = 23 mg/m^3 (5 ppm) based on centrilobular necrobiosis in liver and focal atrophy of olfactory epithelium (one male rat) in F344 rats, 10 per sex per group, exposed to 0, 23, 69 or 207 mg/m^3, 6 h/day, 5 days/week, for 7 weeks. Liver toxicity, dysproteinemia and anemia were observed at the next dose level (BASF 1988d; Klimisch et al. 1997b). [Additional inhalation studies: FDRL 1976; BASF 1988b, c] **Lowest oral LOAEL** = 5 mg/kg-bw per day based on dose-dependent decrease in water consumption and reduced body weight gain in females in a study in Wistar rats, five per sex per dose, exposed to 0, 5.5, 11 or 21 mg/kg-bw per day (0, 50, 100 or 200 mg/L) in drinking water, 7 days/week for 21 days. The actual dose ingested, however, was 0, 5, 10 or 20 mg/kg-bw per day,

Endpoint	Lowest effect levels[1]/results
	according to EURAR (2003). Dysproteinemia (females), decreased glucose levels and a dose-dependent increase in creatine (males) were observed at the next dose level (BASF 1986c; Klimisch et al. 1997b) [Additional oral studies: BASF 1986c; Klimisch et al. 1997b] No dermal study was identified.
Subchronic toxicity	**Lowest inhalation LOAEC** = 23 mg/m^3 (5 ppm) based on nasal cavity inflammation, atrophy of olfactory epithelium, hyperplasia of basal cells of respiratory and olfactory epithelium and dysproteinemia in Sprague-Dawley rats, 10 per sex per group, exposed to 0, 4.6, 23, 69, 207 or 553 mg/m^3 vapour, 6 h/day, 5 days/week, for 3 months. Increased liver weight, foci of cellular alterations in the liver and anemia were observed at the next dose level (BASF 1986a, b; Klimisch et al. 1997b). [Additional inhalation studies: in hamsters: BASF 1987d; Klimisch et al. 1997b; in rats and mice with a 6-month exposure: Klimisch et al. 1997b] **Lowest oral LOAEL** = 4.1–8.3 mg/kg-bw per day (range accounts for a decrease in actual dose by end of study) based on dysproteinemia and decreased levels of total proteins, globulins and, in females, albumin in Wistar rats, 10 per sex per group, exposed to 0, 0.5, 1.3, 3.6 or 8.3 mg/kg-bw per day (0, 5, 12, 30 or 75 mg/L) in drinking water for 3 months. There were no other treatment-related gross or microscopic structural changes in a wide variety of organs, including the liver and reproductive organs (BASF 1986d; Klimisch et al. 1997b). **Other oral LOAEL** = 40 mg/kg-bw per day based on increased water consumption, γ-glutamyltransferase activity (significant only in females) and relative liver weight (females) in Wistar rats, five per sex per group, exposed to 0, 40, 60 or 100 mg/kg-bw per day by gavage, 5 days/week, for 3 months. A significant increase in platelet counts and male liver weight was observed at the next dose level. Dysproteinemia was not observed at any dose level (BASF 1986c; Klimisch et al. 1997b). No dermal study was identified.
Chronic toxicity/ carcinogenicity	**Inhalation study in rats:** Groups of male and female Sprague-Dawley rats (60 per sex per dose and 70 per sex for controls) were exposed to 0, 23, 46 or 92 mg/m^3 (0, 5, 10 or 20 ppm) (vapour stabilized with 3 ppm Kerobit), 6 h/day, 5 days/week, for 24 months. Results reported occurred in animals surviving until study termination (males, 39, 38, 30, 34; females, 29, 25, 26, 26) and in those dying prematurely. **Neoplastic changes:** Hepatocellular carcinomas (males, 1, 6, 5, 17**; females, 1, 3, 6, 26**); nasal cavity adenomas (males, 0, 8, 9, 10*; females, 0, 2, 8, 12*) and adenocarcinomas (males, 0, 0, 4, 6**; females, 0, 0, 0, 4*); squamous carcinomas of larynx (males, 0, 0, 0, 4; females, 0, 0, 0, 4); * $p < 0.001$, ** $p < 0.0001$. Most nasal cavity adenomas were located in anterior part of nose (source: respiratory epithelium or submucosal glands in areas lined by respiratory epithelium), while adenocarcinomas were found in areas lined with olfactory epithelium and were poorly differentiated (source: olfactory

Endpoint	Lowest effect levels[1]/results
	epithelium or submucosal glands). **Non-neoplastic LOAEC =** 23 mg/m^3 (5 ppm) based on dose-related increase in anisocytosis of erythrocytes in females, liver toxicity (decreased lymphoid infiltration in males, focal hepatocyte hyperplasia and eosinophilic foci and foci of spongiosis hepatis), nasal cavity toxicity (focal metaplasia of respiratory epithelium into squamous epithelium in septum and lateral wall, inflammation, atrophy of olfactory epithelium, dose-related incidence of hyperplasia of goblet cells and minimal to marked focal hyperplasia of submucosal glands) and focal mucopurulent inflammation of the larynx (dose related in females). In addition to these effects, centrilobular fatty infiltration in the liver (males) and minimal to moderate focal epithelial hyperplasia in the larynx were observed at the next dose level (BASF 1992a; Klimisch et al. 1997a). **Other inhalation study in rats:** Female Sprague-Dawley rats (15 per group) were exposed to 0 or 207 mg/m^3 (0 or 45 ppm) (vapour, unstabilized), 6 h/day, 5 days/week, for 3 months followed by 21 months of recovery. Investigations were confined to the liver. Six treated and four control rats survived to study termination. **Neoplastic changes:** Seen only in treated rats: 2/6 had benign neoplastic nodes and another 2/6 had hepatocellular carcinomas. Cells taken from three of the four rats with tumours contained elevated levels of glycogen. **Non-neoplastic changes:** Increased liver γ-glutamyltransferase and reduced glutathione levels, liver cell enlargement (cloudy, hydropic, vacuolar, hypertrophy) and foci of cellular proliferation with glycogen accumulation (BASF 1987d; Klimisch et al. 1997a). No oral or dermal chronic toxicity/carcinogenicity study was identified.
Reproductive toxicity	No inhalation, oral or dermal reproduction study was identified.
Developmental toxicity	**LOAEC for developmental toxicity = 92 mg/m^3** based on decrease in fetal weight (9% below control) and developmental delay (incomplete ossification of supraoccipital (6.3, 11.5, 11.8, 22.4; historical control range 4.0–9.7) or hyoid bones (0.7, 1.4, 0.6, 5.8; historical control range 0–0.8) and wavy ribs (0.8, 4.2, 4.2, 15.4; historical control range 1.4–5.5) in mated female Wistar rats, 25 per group, exposed to 0, 4.6, 23 or 92 mg/m^3 (0, 1, 5 or 20 ppm, respectively) vapour by whole-body exposure, 6 h/day on gestational days 6–19 (BASF 2001). **LOAEC for maternal toxicity = 23 mg/m^3 (5 ppm)** based on treatment-related reductions in net maternal body weight (terminal body weight on day 20 minus weight of unopened uterus minus body weight on day 6) at next dose level (magnitudes exceed those reported at comparable exposure concentrations in repeated inhalation exposure studies in non-pregnant rats). [No additional inhalation study was identified.] No oral or dermal developmental study was identified.
Genotoxicity and related endpoints:	**Chromosome damage (micronuclei) in bone marrow** **Negative:** In NMRI mice (five per sex per group; positive control, five

Endpoint	Lowest effect levels[1]/results
in vivo	animals) orally administered 0, 150, 300 or 600 mg/kg-bw by gavage (BASF 1993). **DNA binding in liver** **Negative:** In three male CD mice, single or repeated intraperitoneal injections for 5 consecutive days of *N*-vinyl[α,β-^{14}C]-2-pyrrolidone (label on vinyl group) or *N*-vinyl-2-pyrrolidone[5-^{14}C] (ring labelled) at 150 or 300 mg/kg-bw in aqueous solution. NVP and its metabolites did not bind to liver DNA, RNA or proteins (IRI 1985). **Gene mutation (sex-linked recessive lethal)** **Negative:** In male *Drosophila melanogaster* (fruit flies) administered by injection up to toxic concentrations. No concentrations or details on experimental conditions are provided (Knaap et al. 1985).
Genotoxicity and related endpoints: *in vitro*	**Bacterial tests:** ***Ames test (mutagenicity)*** **Negative:** *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537 strains (10, 100, 1000 or 10 000 µg/plate in dimethyl sulphoxide) with and without rat liver S9 (HRC 1978a). **Negative:** *S. typhimurium* TA98, TA100 and TA1537 strains (3.15, 10, 31.5, 100, 315, 1000 or 3000 µg/plate) with and without rat liver S9 (BASF 1978a). **Negative:** *S. typhimurium* TA98 strain (up to 3 mg/plate) with S9 to which epoxide hydrolase inhibitor and glutathione depletor 1,1,1-trichloro-propene-2,3-oxide were added (BASF 1978a). **Negative:** *S. typhimurium* TA98, TA100 and TA1535 strains with and without rat liver S9 (Simmon and Baden 1980). **Negative:** *S. typhimurium* TA98 and TA100 strains (closed system, up to toxic concentrations) with and without S9; no further details on experimental conditions provided (Knaap et al. 1985). ***Fluctuation test (mutagenicity)*** **Negative:** *Klebsiella pneumoniae* with and without activation; very few experimental details provided (Knaap et al. 1985). **Mammalian cell tests:** ***Mutagenicity in mouse lymphoma cells*** **Negative:** In mouse lymphoma cells L5178Y ($TK^{+/-}$), 0.39–10 µL/mL for 4 h, with and without rat liver S9 (Litton Bionetics 1980a). **Negative:** In mouse lymphoma cells L5178Y (HPRT and TK loci), up to 5 µL/mL (toxic concentrations) with and without metabolic activation (Knaap et al. 1985). ***Chromosomal aberration*** **Negative:** In human peripheral blood lymphocytes exposed to 0, 20, 40 or 60 µg/mL without metabolic activation or to 0, 300, 600 or 900 µg/mL with rat liver S9 (BASF 1987c). ***Sister chromatid exchange*** **Positive (slight increase):** In human, whole blood lymphocyte cultures and isolated peripheral lymphocytes exposed to 0.1, 1.0, 10.4, 104 or 520 µg/mL

Endpoint	Lowest effect levels[1]/results
	without activation. No details reported, poorly reported study (Norppa and Tursi 1984). ***Unscheduled DNA synthesis (UDS)*** **Negative:** In primary rat hepatocytes exposed to 0.30, 0.59, 1.19, 2.36, 4.73 or 9.45 mg/mL for 1 h followed by 3 h labelling; 18.93 mg/mL was lethal (Litton Bionetics 1980b). ***Cell transformation assay*** **Negative:** In BALB/3T3 cells exposed to 0.1, 1.0, 10.4, 104 or 520 µg/mL without activation (Litton Bionetics 1980c).
Irritation	**Skin irritation** **Irritating:** In rabbits following ear exposure (BASF 1953). **Slight to no irritation:** In rabbits (BASF 1963a, b, 1978b, 1979c). **Eye irritation** **Irritating:** In rabbits (Draize test and in two brief studies) (BASF 1963a, b, 1978b; Burnette 1978).
Sensitization	**Not sensitizing:** In 20 female guinea pigs (10 untreated), Buehler test (BASF 1996).
Human studies	
Epidemiological studies	**Cross-sectional morbidity study** on production workers in a German manufacturing plant; comprehensive medical examinations for 94 workers (representing 96% of the workforce assigned to NVP operations, average of 12.7 years in plant), of which 89 also participated in biomonitoring program. Controls: 95 from ammonia production department (where process materials handled in totally enclosed systems and facility is of open-air construction). Actual levels of exposure unclear, and possible exposure to other chemicals not stated. Occupational exposure: 59 air monitoring samples (personal and general) collected from 1980 to 1990: >80% samples contained NVP at ≤0.45 mg/m^3 (0.1 ppm), and five samples contained NVP at >0.68 mg/m^3 (0.15 ppm). Biomonitoring data showed three people with a serum NVP concentration ≤0.3 mg/L (detection limit = 0.1 mg/L). No exposure-related signs of ill health identified (no tumour of upper respiratory tract or of liver and no laboratory findings suggesting subclinical effects on target organs). However, air-fed respirators were provided to workers during operations likely to involve exposure, and source of the hygiene data provided in report was unclear (Zober et al. 1992). No other study was identified.

[1] LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level.