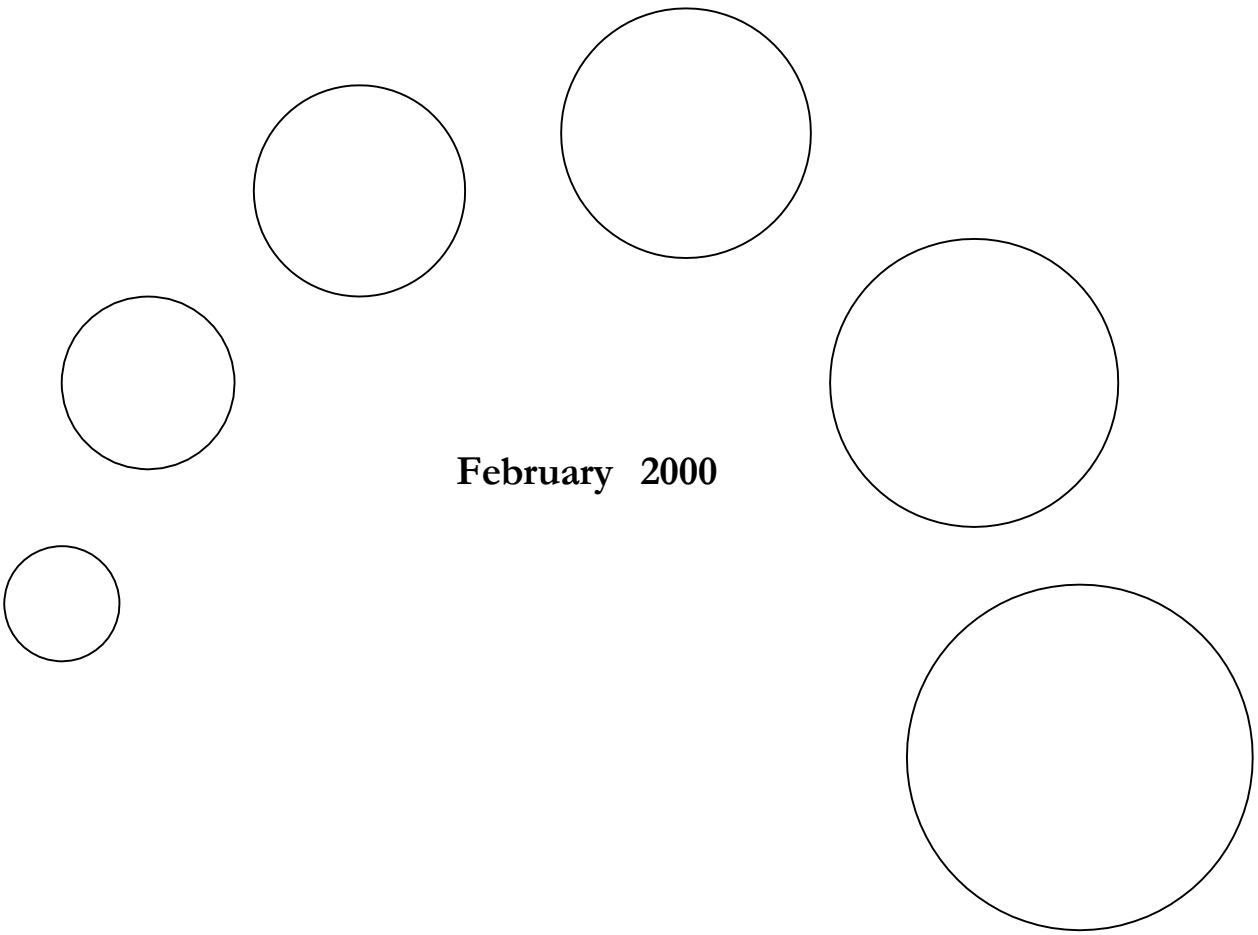
NICNAS

National Industrial Chemicals Notification and Assessment Scheme

1-Vinyl-2-pyrrolidone

Priority Existing Chemical Report No.11



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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with Environment Australia and the Therapeutic Goods Administration, which carry out the environmental and public health assessments, respectively.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia. Chemicals selected for assessment are referred to as Priority Existing Chemicals.

This Priority Existing Chemical report has been prepared by the Director (Chemicals Notification and Assessment) in accordance with the Act. Under the Act manufacturers and importers of Priority Existing Chemicals are required to apply for assessment. Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made appear in the *Commonwealth Chemical Gazette.*

In accordance with the Act, publication of this report revokes the declaration of this chemical as a Priority Existing Chemical, therefore manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty to provide any new information to NICNAS, as required under section 64 of the Act.

For the purposes of Section 78(1) of the Act, copies of Assessment Reports for New and Existing Chemical assessments may be inspected by the public at the Library, NOHSC, 92-94 Parramatta Road, Camperdown, Sydney, NSW 2050 (between 10 am and 12 noon and 2 pm and 4 pm each weekday). Summary Reports are published in the *Commonwealth Chemical Gazette*, which are also available to the public at the above address.

Copies of this and other Priority Existing Chemical reports are available from NICNAS either by using the prescribed application form at the back of this report, or directly from the following address:

GPO Box 58

Sydney

NSW 2001

AUSTRALIA

Tel: +61 (02) 9577 9437

Fax: +61 (02) 9577 9465 or +61 (02) 9577 9465 9244

Other information about NICNAS (also available on request) includes:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on Priority Existing Chemical and New Chemical assessment programs;
- subscription details for the NICNAS Handbook for Notifiers; and
- subscription details for the Commonwealth Chemical Gazette.

Information on NICNAS, together with other information on the management of workplace chemicals can be found on the NOHSC Web site:

http://www.nohsc.gov.au/nicnas

Overview

N-vinyl-2-pyrrolidone (NVP), Chemical Abstracts Service (CAS) number 88-12-0, was declared a Priority Existing Chemical on 7th April 1998 due to the potential for high occupational and environmental exposure and potential adverse health effects such as severe eye irritation and in particular, possible carcinogenic effects.

In Australia, NVP is mainly used in manufacturing of ultraviolet (UV) curing inks and paper coating products. Small amounts of NVP are also used in laboratories for research purposes. A NVP containing polymer, polyvinyl pyrrolidone (PVP) is used widely in industries such as cosmetics, pharmaceuticals, and agricultural formulations.

Occupational and environmental exposures may occur from any of the above uses and also during transportation and disposal. Exposure to the general public may occur from use of PVP products.

Adverse health effects following short-term or prolonged exposure to NVP in humans have not been reported.

NVP exhibits acute toxicity by oral, dermal and inhalational routes in animals. Liquid NVP has been shown to cause severe eye irritation in animals. Signs of respiratory tract irritation were observed in a range of animal species following a single exposure to NVP aerosol and repeated inhalation of NVP vapour.

The target organs after repeated inhalational exposure to NVP in animal studies were the liver and nasal cavity. Liver effects included enlarged hepatocytes with clear cell areas, degenerative changes of the nucleus, centrilobular necrobiosis, fatty infiltration, cellular proliferation, cirrhosis-like metaplasia and glycogen accumulation within centrilobular hepatocytes in the liver. Cell hyperplasia and inflammatory changes in the olfactory and respiratory epithelia in the nasal cavity were observed. A no observed adverse effect level (NOAEL) of 1 ppm (1mg/kg) has been identified in a 3 month study in rats. However, it is not certain whether the NOAEL is applicable to longer or lifetime exposures as there are indications that at 5 ppm (5 mg/kg), the lowest observed adverse effect level (LOAEL), hepatotoxicity takes longer than 3 months to develop in rats. Administration of NVP by the oral route results in damage only to the liver and the dose required to produce histopathological changes is much higher than that required by inhalation. A NOAEL of 3.6 mg/kg has been identified in a drinking water study in rats. There are no data relating to the effects of repeated dermal exposure to NVP.

Carcinogenicity studies in rats by the inhalation route indicate the principal tumour sites are the liver, nasal cavity and larynx. A NOAEL could not be identified from these studies as tumours occurred at 5 ppm (5 mg/kg) which was the lowest dose tested. NVP is not a mutagen and the exact mechanism of tumour formation in animals is not known.

Currently NVP is not listed on the National Occupational Health and Safety Commission (NOHSC) *List of Designated Hazardous Substances* (NOHSC, 1999b).

The occupational risk assessment concluded that a risk of acute eye effects is likely during formulation of NVP products due to accidental contact with liquid NVP. In the absence of monitoring data for workers involved in formulation of NVP products and use of UV curing inks containing NVP, estimates for NVP exposure were obtained using

modelling. Results from this modelling indicate that the atmospheric levels of NVP likely during these operations are of concern.

Environmental risk assessment indicates that NVP does not cause adverse effects on the aquatic compartment. Adverse effects on aquatic organisms or on microbial activity during formulation or end use of NVP is not likely in Australia.

The public health risk assessment concluded that laboratory use of NVP in small quantities and industrial use in UV curing inks and paper coating are not considered to present a significant hazard to public health. The highest consumer exposure is likely to be associated with cosmetics containing PVP with high levels of NVP (more than 200 ppm). It is therefore prudent to limit the allowable contamination of PVP to 200 ppm NVP, in order to provide an adequate margin of exposure for the general public using such products.

Based on the assessment of health effects and in accordance with the NOHSC *Approved Criteria for Classifying Workplace Hazardous Substances* (NOHSC, 1999a), it is recommended that NVP be classified as 'Harmful by inhalation, in contact with skin and if swallowed' [risk phrase (R) 20/21/22], 'Irritating to respiratory system' (R37), 'Possible risk of irreversible effects, Carcinogen Category 3' (R40), 'Risk of serious damage to eyes' (R41), 'Harmful: danger of serious damage to health by prolonged exposure through inhalation' (R48/20).

Suppliers of NVP and products containing NVP for workplace uses should review their MSDS and labels in accordance with NOHSC requirements. It is recommended that employers implement specific workplace control measures for uses identified in Australia where necessary. In addition, atmospheric monitoring should be conducted, in conjunction with engineering controls, to ensure that the levels of NVP are low, as a safe level has not been identified.

In the absence of analytical data on the level of NVP in cosmetic products and reliable dermal absorption data, it is recommended that the Department of Health and Age Care establish a maximum level of 200 ppm NVP present in PVP for cosmetic use.

It is recommended that the final Priority Existing Chemical report on NVP be forwarded to relevant authorities for consideration of the public health impact of NVP in pharmaceuticals, food and agricultural formulations respectively.

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Abbreviations and Acronyms

ACTS	Advisory Committee on Toxic Substances
ADG CODE and	Australian Code for the Transport of Dangerous Goods by Road and Rail
AICS	Australian Inventory of Chemical Substances
ALAT	alanine aminotransferase
ANZFA	Australian New Zealand Food Authority
ASTER	Assessment Tools for the Evaluation of Risk database (US EPA)
BCF	bioconcentration factor
BOD	biochemical oxygen demand
CAS	Chemical Abstract Service
CO	carbon monoxide
EA	Environment Australia
EASE	Estimation and Assessment of Substance Exposure
EC	European Commission
EHD	estimated human dose
EINECS	European Inventory of Existing Commercial Chemical Substances
EU	European Union
FID	flame ionisation detector
FORS	Federal Office of Road Safety
GC	gas chromatography
HPLC	high performance liquid chromatography
HPV	High Production Volume
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
ILO	International Labour Organisation
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union for Pure and Applied Chemistry
LEV	local exhaust ventilation
LOAEL	Lowest Observed Adverse Effect Level
MAK	"Maximale Arbeitsplatz-Konzentration" (Germany) (maximum workplace concentration)
MCH	Mean corpuscular haemoglobin
MDHS	Methods for the Determination of Hazardous Substances

MEL	Maximum Exposure Limit
MOE	margin of exposure
MSDS	Material Safety Data Sheet
NDPSC	National Drugs and Poisons Schedule Committee
NICNAS	National Industrial Chemical Notification and Assessment Scheme
NIOSH	National Institute of Occupational Safety and Health
NMP	N-methyl-2-pyrrolidone
NOx	nitrogen oxides
NOAEL	No Observed Adverse Effect Level
NOHSC	National Occupational Health and Safety Commission
NRA	National Registration Authority
NVP	N-vinyl-2-pyrrolidone
OECD	Organization for Economic Cooperation and Development
PEC	Predicted Environmental Concentration
PNEC	Predicted no effect concentration
PPE	personal protective equipment
PVP	polyvinyl pyrrolidone
QSAR	Quantitative Structure Activity Relationship
SAGE	Solvent Alternatives Guide
SIAM	SIDS Initial Assessment Meeting
SIAR	SIDS Initial Assessment Report
SIDS	Screening Information Data Set
SRC	Syracuse Research Corporation
STEL	short-term exposure limit
STP	sewage treatment plant
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Good Administration
TOC	total organic carbon
TSCA	Toxic Substances Control Act
TWA	time weighted average
US EPA	Environmental Protection Agency of the USA
UV	Ultraviolet

1. Introduction

1.1 Declaration

N-vinyl-2-pyrrolidone (NVP), Chemical Abstracts Service (CAS) number 88-12-0, was declared a Priority Existing Chemical for full assessment by the Minister for Employment, Workplace Relations and Small Business under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), as amended, by notice in the *Chemical Gazette* on 7 April 1998.

The declaration was made on the basis that there were reasonable grounds for believing that the formulation, handling and use of NVP may give rise to a risk of adverse health effects. In summary, these grounds were:

- the potential for high occupational and environmental exposure and potential adverse health effects such as severe irritation and in particular, possible carcinogenic effects;
- lack of information on the health and environmental effects of NVP which is of concern in view of the high volumes used and potential exposure; and
- a need for characterization of exposure and associated health and environmental risks.

In accordance with section 56 of the Act, those introducing NVP into Australia applied for assessment of the chemical. As NVP is not manufactured in Australia, applications were limited to importers.

1.2 Purpose of assessment

The purpose of the assessment is to:

- critically review the acute and chronic animal data, particularly data of relevance to carcinogenicity;
- characterize the potential hazards of NVP to human health and the environment;
- identify use patterns and potential exposure in Australia;
- characterize the risk of adverse effects resulting from exposure to workers, the general public, and the environment; and
- make appropriate recommendations to control exposures and/or reduce potential health and environmental risks.

1.3 Data collection

In accordance with the Act, importers of NVP who wished to continue importing NVP, whilst it was a Priority Existing Chemical were required to apply for assessment and supply information. Data supplied by applicants included:

- quantity of NVP imported;
- uses of the chemical and products containing the chemical;
- Material Safety Data Sheet (MSDS) and labels; and

- a list of end users.

No unpublished data on health or environmental effects of NVP were provided by applicants. Information for the assessment was also received from end users, formulators, and from a comprehensive database and literature search.

Concurrent with this report has been the preparation of a Screening Information Data Set (SIDS) Initial Assessment Report (SIAR) by the United Kingdom (UK) Health and Safety Executive (HSE) (UK draft report). The UK draft report (1998) was briefly discussed at the 8th Organization for Economic Cooperation and Development (OECD) SIDS Initial Assessment Meeting (SIAM) in October 1998 and will be discussed at a future SIAM. As a joint sponsor for this chemical under the SIDS Program, Australia had the opportunity to review the report before the 8th SIAM. To enhance the efficiency of the National Industrial Chemical Notification and Assessment Scheme (NICNAS) assessment, the review of health effects on experimental animals and humans has been based on the UK draft report (1998). The primary studies from the UK draft report (1998) were not sighted and were indicated with an asterisk (*) in this report. The system used is to provide transparency. Recent data (post 1996) were identified from on-line searches of a number of databases. The UK draft report (1998) was also used as the basis of the environmental fate and toxicity review.

Surveys

The applicants for the assessment on-sell the imported NVP and were unable to provide any data on occupational exposure during use of the chemical. NICNAS therefore conducted a survey in October 1998 to investigate the use patterns, occupational exposure levels, control technologies and environmental exposure to NVP in Australia (NICNAS industry survey). Formulators and end users of NVP products participated in the survey by completing a questionnaire.

Site Visits

Information on mode of use and exposure was also obtained through a number of site visits to screen printing ink formulators, paper coating formulators and end users of NVP products (screen printing and paper coating industries).

1.4 Peer review

During all stages of preparation, the report has been subject to internal peer review by NICNAS, Environment Australia (EA) and Therapeutic Good Administration (TGA). The hazard assessment and classification sections of this report were also peer reviewed by the UK HSE.

2. Background

2.1 History

NVP was first prepared from butyrolactone during World War II. It is manufactured commercially by the vinylation of 2-pyrrolidone with acetylene.

NVP has been produced commercially in the United State (US) since 1955. There is understood to be only two producers of NVP world wide, one in Germany and one in the US. In the past, as is today, NVP has mainly been used to manufacture its homopolymer, polyvinyl pyrrolidone (PVP), to make copolymers with other monomers, and as a chemical intermediate.

2.2 International perspective

NVP is widely used in the world for its film-forming and adhesive properties. As a monomer, it is mainly used as a reactive diluent for radiation-cured inks and/or lacquers in screen printing industry. The use of NVP polymers is diverse, with the major uses being pharmaceuticals, adhesives and washing additives. Other uses of the polymers include food additives, cosmetics, contact lens manufacturing, and paint dispersions. NVP is listed on the OECD Representative List of High Production Volume (HPV) chemicals.

Reviews of the health effects of NVP have been carried out by the International Agency for Research on Cancer (IARC) (IARC, 1979), BIBRA International (BIBRA, 1989), Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of Maximale Arbeitsplatz-Konzentration (MAK) (MAK, 1993) and is underway in the OECD SIDS Program by the UK HSE (see section 1.3).

International and national concern about the health and environmental safety implications of NVP has resulted in a number of regulations and controls that have impacted on the use of NVP.

United States

NVP was listed on the US Environmental Protection Agency (US EPA) Toxic Substances Control Act (TSCA) Inventory in 1993. NVP has been notified under Section 8(e) of TSCA, indicating that information exists which supports the conclusion that the chemical presents a substantial risk of injury to health or to the environment.

European Union

The European Union (EU), under Council Regulation No. 793/93 lists NVP as a high production volume chemical, indicating that manufacture or importation volume within the EU exceeds 1000 tonnes per year.

Industry

An International Uniform Chemical Information Database (IUCLID) data sheet on NVP issued by BASF (International) Pty Ltd. (European Commission, 1996a) classifies NVP as a hazardous substance on the basis of available data. The data sheet contains relevant risk and safety phrases.

In 1991, International Specialty Products (ISP) Pty Ltd. (International) chose to classify the chemical as an animal carcinogen, and lowered its recommended workplace exposure limit from 1 ppm to 0.1 ppm in response to the preliminary results of an animal carcinogenicity study.

2.3 Australian perspective

In Australia, NVP is mainly used in Ultraviolet (UV) screen printing inks and paper coatings. Concern by public interest organizations has been expressed over its adverse health effects, including its carcinogenic potential and the limited availability of toxicological data.

NVP is not listed in the *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP) or the National Occupational Health and Safety Commission (NOHSC) *List of Designated Hazardous Substances*, and no Australian exposure standard has been established.

As part of its contribution to the OECD Existing Chemicals Program, Australia, in conjunction with the UK, has sponsored NVP under the SIDS program. The NICNAS assessment report will be forwarded to the OECD as part of the SIDS requirement of the program.

3. Applicants

Following the declaration of NVP as a Priority Existing Chemical, six companies applied for assessment of the chemical. The applicants supplied information on the properties, import quantities, MSDS and uses of the chemical. In accordance with the *Industrial Chemicals (Notification and Assessment) Act 1989*, NICNAS provided the applicants with a draft copy of the report for comments during the corrections/variation phase of the assessment. Data for the assessment were also provided by 5 notifiers, that is, companies which purchase NVP in Australia and formulate it into various products.

The applicants were, as follows:

BASF Australia Ltd
PO Box 84
ALTONA
VIC 3018

Bio-Scientific Pty Ltd
PO Box 78
GYMEA
NSW 2227

Crown Scientific Pty Ltd
144 Moorebank Ave
MOOREBANK
NSW 2170

ISP (Australasia) Pty Ltd
PO Box 6564
SILVERWATER
NSW 2128

3M Australia Pty Ltd
PO Box 144
St MARYS
NSW 2760

Sigma Aldrich Pty Ltd
PO Box 970
CASTLE HILL
NSW 2154

4. Chemical Identity and Composition

4.1 Chemical name (International Union for Pure and Applied Chemistry, IUPAC)

1-vinyl-2-pyrrolidone

4.2 Registry numbers

NVP is listed on the Australian Inventory of Chemical Substances (AICS)

CAS Number: 88-12-0

EINECS Number: 201-800-4

4.3 Other names:

1-Ethenylpyrrolidin-2-one 1-Vinyl-2-pyrrolidinone

1-Vinyl-2-pyrrolidone

2-Pyrrolidinone, 1-ethenyl- 2-Pyrrolidinone, 1-vinyl- N-Vinyl-2-pyrrolidinone

N-Vinyl-2-pyrrolidone N-Vinylpyrrolidinone N-Vinylpyrrolidone

Vinylbutyrolactam

Vinylpyrrolidon

Vinylpyrrolidone

1-Ethenyl-2-pyrrolidone

Vinyl butylolactam

V-Pyrol

4.4 Trade names

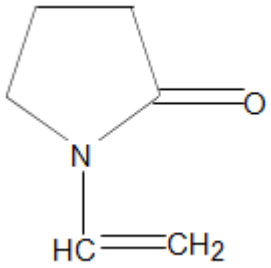
V-Pyrol

1-Vinyl-2-pyrrolidinone

4.5 Molecular formula

$C_6H_9N_1O_1$

4.6 Structural formula



4.7 Molecular weight

111 $g.mol^{-1}$

4.8 Composition of commercial grade product

No impurities/additives are listed in IUCLID (EC, 1996a) but it is stated that the product is stabilised against spontaneous polymerisation before delivery because heat is developed during polymerisation.

Preparations are inhibited with potassium hydroxide or N-N'-di-sec-butyl-p-phenylenediamine (UK draft Report, 1998).

5. Physical and Chemical Properties

5.1 Physical state

NVP is an organic liquid. It is colourless to light yellow, although the liquid darkens in the absence of stabilisers (UK draft Report, 1998).

Table 1: Physico-Chemical properties of NVP (UK draft Report, 1998)

Property	Value	Comments
Melting point	13-14°C; 14°C; 13.5°C	
Boiling point	90-92°C at 13 hPa; 148°C; 90-93°C	
Density	1.043 g/cm^3 at 20°C	
Vapour pressure	0.12 hPa at 20°C; 0.29 hPa at 30°C; 0.1 mmHg at 24°C (= 0.13 hPa)	
Vapour density	3.8	
Partition coefficient	-0.37 (calc.); 0.4 at 25°C (measured)	Flask shaking method (EC, 1996a)
Solubility	miscible with water at 20°C	soluble in acetone, diethyl ether, ethanol, toluene and benzene.
Flash point	95°C; 93°C	
Auto-flammability	240°C	
Explosive properties	Explosive limits in air: 1.4-10% by volume	
Oxidising properties	Not an oxidising agent	
Other hazardous reactions	Can polymerise exothermically in the absence of stabilisers particularly in acid conditions or if shelf life exceeded	

6. Methods of Detection and Analysis

6.1 Identification

There is no specific recognized methodology to identify NVP. Gas chromatography (GC) has been used to identify NVP in a mixture obtained during its synthesis in a study by Arakelyan et al. cited in a review by IARC (1979),

6.2 Atmospheric monitoring

Atmospheric monitoring of NVP is not done routinely in Australia. There is no specific method for detection and analysis of NVP. However, the described methods for organic vapours in the US National Institute of Occupational Safety and Health (NIOSH)'s Manual of Analytical Methods (1994) can be used for NVP.

GC methods involving pumped sampling on charcoal sorbent tubes for pyridine are feasible. Solvent desorption of charcoal with dichloromethane has been found suitable for pyridine (NIOSH, 1994) and can be used for measurement of NVP using a specific nitrogen detector. A dimethylformamide/water mixture has also been used to desorb the analogue N-methyl-2-pyrrolidone (NMP) from charcoal (Beaulieu & Schmerber, 1991) using GC with a flame ionisation detector (FID). Desorption behavior of NVP and NMP from charcoal are expected to be similar. Alternatively, pumped air samples may be taken on Tenax TA, followed by thermal desorption and GC, using a general thermal desorption method based on the Methods for the Determination of Hazardous Substances (MDHS) MDHS 72 (HSE, 1993). The limit of detection using all above pumped methods is better than 0.01 ppm for a 20 liter sample. Diffusive sampling on Tenax (MDHS 80) is also feasible for NVP vapour (HSE, 1995) with a detection limit of 0.1 ppm for 8-hour sampling.

Information on methods for determination of NVP in air was submitted by ISP (Australasia) Pty Ltd. The methods are similar with the standard NIOSH method and are included in Appendix 1. A limit of detection of 1 μg per sample was recommended in this submission.

6.3 Biological monitoring

There is no recognized biological monitoring methodology to determine the level of NVP in the human body. However, high performance liquid chromatography (HPLC) with UV method has been used to quantify NVP in serum with the limit of detection of 0.05 mg/L and the limit of quantitation 0.2 mg/L (Digenis*, 1990).

7. Use, Manufacture and Importation

7.1 Manufacture and importation

NVP is not manufactured in Australia. The chemical is imported into Australia mainly from the USA in quantities up to 30 tonnes/year. It is imported in 209 litre drums. NVP is also imported in 5 g, 250 g and 1 kg glass bottles for laboratory uses. From the information provided for assessment, it appears that NVP is not imported as an ingredient in formulated products. However, it is possible that some products containing NVP are imported into Australia as it is not certain that all importers of NVP products were identified. NVP products containing varying concentrations of the chemical are formulated in Australia.

7.2 Uses

There are no published data on the use patterns of NVP and NVP products in Australia. During the NICNAS industry survey, a total of 128 questionnaires were sent to companies identified as users of NVP and NVP products. The same questionnaire (Appendix 2) was also sent to formulators of NVP products. Information on MSDS, labels, workplace exposure, waste management and disposal were also sought. Forty-five responses were received, representing a response rate of 35%. The information below is based on data gathered from this survey and is considered representative but not complete.

The major use of NVP in Australia is in the manufacturing of UV curing inks. Four companies producing UV curing inks have been identified in Australia. Concentrations of NVP in the ink range from 4 to 20%. Other constituents of the ink are pigments, flow additives, a photo-initiator and some pre-polymers. The UV curing inks are used in screen printing. During printing, the ink is first applied to a printing screen. Following this the screen is passed through UV lights when the NVP polymerises and cross-links with the pre-polymers to produce a firm and shining print. The inks are used in printing on a variety of surfaces such as paper, plastic bottles, vinyl, rubber, particle-board, wood and metals.

NVP is also used as a component of a coating which is formulated to bond with aluminum for paper coating in Australia. Paper is coated with the NVP product and cured via an electron beam. The coated paper is then metallised in a vacuum and again coated for print receptibility via an electron beam curing process which gives the coating a 100% solid physical nature. The coated paper is sold to printers who supply the cold beverage market.

Small amounts of NVP are used in the laboratory for research purposes. Information provided to NICNAS indicates that NVP is polymerised to form a slow release coating for fertilizers and also used as a dipolarophile in cycloaddition reactions.

NVP and products containing NVP are not available to the general public. However, a NVP containing polymer, PVP is imported into Australia and used widely in industries such as pharmaceuticals, adhesives, agriculture, surface coating and cosmetics. The NICNAS industry survey did not collect information on the industrial uses of PVP from end users. However, the residual NVP monomer levels in PVP were obtained from a few major importers of PVP. It appears that there are different grades of PVP imported into Australia depending on the end use such as pharmaceutical, cosmetic or industrial grade. The residual NVP monomer content in the PVP imported into Australia varies and ranges from 10 ppm to 2000 ppm.

7.3 Trends

Data supplied during assessment indicate that importation of NVP has fallen significantly since 1994. Suppliers and end users of NVP products reported that the use of NVP or NVP containing products is declining. Alternatives have been developed for some of the products in Australia. However, NVP continues to be used in certain select products because of its specific properties. According to the UK draft report (1998), the decline in its use in UV curing inks in the EU was attributed to human health concerns highlighted by suppliers of NVP.

7.4 Other uses

There are several uses reported for NVP in the literature, however, not all reported uses occur in Australia. Uses reported in literature, other than those identified above, include:

- PVP manufacture;
- as a reactive diluent in the manufacture of UV curing lacquers;
- as a co-monomer (water soluble and hydrophilic polymers);
- as a grafting reagent (ashless lubricant dispersants);
- making vinylpyrrolidone-vinylacetate copolymers;
- manufacture of copolymers with a wide range of other comonomers such as acrylic acid, esters, vinyl acetate and acrylonitrile;
- as an intermediate in the manufacture of modified phenolic resins that are used as plasticizers and of dyes and textile assistants;
- may be used in adhesives for use in contact with food at a extremely low level;
- manufacture of contact lenses where it is polymerised with co-monomers.

Contact lenses manufacture using NVP does not occur in Australia but a semi-finished form (button) contact lenses are imported.

8. Exposure

8.1 Occupational exposure

8.1.1 Routes of exposure

Occupational exposure to NVP in Australia may result from direct use of NVP in laboratories, during formulation of NVP products or during use of products containing NVP. Other potential sources of exposure are during transport and storage of NVP or NVP products and during disposal of the contaminated solvent.

In the assessment of occupational exposure to chemicals, it is generally necessary to evaluate intake from all potential routes of exposure i.e. ingestion, inhalation and dermal exposure. For NVP, ingestion is unlikely during occupational use. Workers may be exposed to NVP by the inhalation and dermal routes. Inhalation of NVP may occur through exposure to vapour emitted from liquid NVP or mixtures containing NVP. Activities such as heating of the liquid and stirring at high speed will increase the emission of vapours and the likelihood of exposure. Dermal absorption of NVP may occur through contact with liquid NVP or products containing NVP.

An evaluation of available information on use profiles obtained from suppliers and users and from site visits indicates that for Australian occupational exposure scenarios, inhalation is likely to be the major route of exposure.

8.1.2 Methodology for assessing exposure

Good quality measured data for various work scenarios is preferable in the assessment of occupational exposure. When such data is not available or inadequate, then mathematical modelling can be used. Due to a lack of monitoring data for NVP, the EASE (Estimation and Assessment of Substance Exposure) model developed by the UK HSE (EC, 1996b) was used to estimate exposure.

EASE is a knowledge-based electronic data system designed to facilitate the assessment of workplace exposure. It is a general-purpose predictive model for workplace exposure assessments and is used where measured exposure data is limited or not available. EASE predicts exposure as ranges in the form of conventional 8-hour time weighted average (TWA). Dermal exposure is assessed by EASE as potential exposure rate predominately to the hands and forearms (approximately 2,000 cm^2).

Exposure is determined by the EASE model at the high-end or maximum concentrations (ie. worst case estimates) in feasible but not unrealistic situations (ie reasonable worst case situation). The estimates are not intended to be representative of extreme or unusual use scenarios which are unlikely to occur in the workplace. Modelling by definition takes a conservative approach and is likely to overestimate exposure. The majority of occupational exposures will be below these estimates.

Occupational exposure to NVP is discussed for each major activity with likely workplace exposure, namely:

- Importation;
- Formulation;
- Use of NVP in the laboratory; and
- Use of products containing NVP.

The EASE model estimation printout for the various scenarios are in Appendix 3.

8.1.3 Importation

NVP is imported in 209 L sealed steel drums and is transported by road, unopened, to formulators of NVP products. Information from laboratory suppliers indicates that NVP is imported in 1 kg, 250 g and 5 g glass bottles and usually transported by road to either distributors or directly to end users. Exposure during importation, transportation and storage of drums and glass bottles is unlikely except in cases of accidental spills or leaks of products.

Information provided for assessment indicates that NVP and NVP products are not repacked in Australia.

8.1.4 Formulation

The NICNAS industry survey revealed that in Australia, NVP is used mainly to formulate UV curing inks. An additional product is also formulated for paper coating.

Process

Formulation of UV curing inks

Processes commonly involved in the manufacture of UV curing inks include charging NVP liquid to mixing vessels and subsequent mixing, filling product containers and cleaning empty mixing vessels.

Nineteen individual UV ink products containing NVP were reported to be formulated in Australia by four formulators (Appendix 4). Information on the formulation process, including engineering controls was provided and is summarised in Table 2. The number of workers directly handling NVP during formulation was estimated to be 16. However, some of the processes such as mixing were undertaken in a large area jointly with other operations at some of sites visited. There may be more workers potentially exposed to NVP during formulation. Formulation of NVP products is a batch process and the time spent in formulating products varies and ranges from 3 to 8 hours a day for 90 to 200 days per year.

Table 2: Details of exposure information provided to NICNAS industry survey by UV screen ink formulators

Worksite	Activity	No. of workers	Duration (h/d)	Frequency (d/year)	Ventilation
1	Manufacturing including mixing, blending and cleaning	6	varies	varies	Reducer formulation – enclosed process after charging NVP; Ink formulation - Exhaust ventilation.
	Quality control	2	varies	varies	No information given.
2	Mixing	1	5	30	Exhaust ventilation and fans.
	Blending	1	8	75	Exhaust ventilation and fans.
3	Mixing	1	1	200	Exhaust ventilation above mixing tank; industrial fans near by.
	Blending	1	2	200	Exhaust ventilation.
	Cleaning	1	2	200	Exhaust ventilation above cleaning area.
4	Weighing and blending	3	3	90	Exhaust ventilation.
Total		**16**			

According to data provided and information gained over site visits, the formulation process is similar at various sites and is conducted at room temperature. During formulation, NVP drums are moved to a mixing area by forklift. A drum lift is used to charge NVP into a mixing vessel. Batches tend to be designed to take a full drum of NVP. If additional NVP is required it is taken from an open bucket in the mixing area and manually added to the mixing vessel. After adding other ingredients, the mixtures are dissolved by mixing at most of the formulating worksites and by heating at one company. Mixing is done with a high-speed mechanical stirrer (about 900 to 1400 rpm) for about 3 to 6 hours depending on room temperature. The mixing vessel is covered at most sites during mixing, however, it is open at some sites. By heating, the vessel is sealed with a lid fitted with a filtered vent and put on hot plates (temperatures not known but lower than 100 ^{0}C) for about 8 hours for a 40 kg batch. During mixing or heating, the dissolution status and temperature of the mixture are checked manually. The resulting product, which contains about 40 - 60% NVP, is called "varnish" or "reducer" and is decanted either to drums for storage or into containers for sale. The "reducer" is used for diluting the colours of finished inks.

The make printing inks, the "reducer" is charged into smaller mixing vessels and blended with colours by a mechanical stirrer for around half an hour. The concentration of NVP in the final blend is between 4 to 20%. Heavy pigments absorb more NVP and contain a higher concentration. The resultant blend is decanted into containers (5 or 20 kg cans) with lever lids ready for sale.

The empty mixing vessels are cleaned with solvents either manually or mechanically. Manual cleaning involves use of hand held brushes of different sizes for cleaning the bottom and top of the mixing vessels. In mechanical cleaning, the empty mixing vessel is cleaned by a machine with brushes which rotate to clean the inside of the vessel. Cleaning is either done by a single individual for a full shift or by workers involved in the formulation process.

Information obtained from the NICNAS industry survey indicates that all worksites are equipped with an exhaust ventilation system above the mixing vessel and in the blending area. In addition to exhaust ventilation, industrial fans are also used at some sites. Use of the personal protective equipment (PPE) varies, with all the workplaces using gloves and most using safety glasses and overalls. Where specified, gloves are described as PVC, solvent resistant, Latex or neoprene. A dust/gas cartridge mask is used at two workplaces.

Empty NVP drums are disposed of mainly through sale to drum recyclers.

Formulation of paper coating

Information obtained from the NICNAS industry survey indicates that one formulator produces paper coating products containing NVP in Australia. Formulation of product for paper coating is similar to formulation of UV curing inks. After NVP is charged into a mixing vessel, it is mixed with other ingredients with a slow speed mechanical stirrer for about 45 to 60 minutes. The final coating liquid contains 2% NVP and is transported manually to a tank for coating paper.

Formulation of paper coating products is also a batch process and occurs about once a week. The total quantity required for each batch is calculated according to

customer orders and is used up entirely in the process. Coating products are not stored at the worksite. A number of different formulations are prepared for the coating process depending on customer requirements. Two workers are involved in the mixing process at the site visited. No extraction ventilation is present in the mixing area. Rubber gloves and apron are used by workers.

The mixing tank does not require cleaning very often as there are no residues.

In summary, during the manufacture of products containing NVP, operators are likely to be exposed to NVP by inhalation and skin contact during the charging of mixing vessels, mixing and sampling, filling of product containers and cleaning. However, since formulation is a batch process, exposure to NVP will only occur on the days when NVP based products are formulated. The potential exposure of workers to NVP during formulation is likely to be higher at worksites with an open mixing process.

Australian occupational exposure data

Atmospheric monitoring data

The NICNAS industry survey indicated that air monitoring had been conducted at only two of the four UV printing ink formulation worksites identified. One of these was conducted for general chemicals in the workplace and not specifically for NVP. No monitoring results were provided for assessment although this was asked for during the NICNAS industry survey. No air monitoring data was available from the paper coating formulator.

No information on skin permeability in humans and animals is available.

Estimated data

Levels of exposure to NVP by inhalation and skin during formulation of NVP products were estimated using the EASE model.

Exposure by inhalation

Formulators of UV curing inks reported use of a local exhaust ventilation (LEV) system above the mixing vessel, but no LEV is used during formulation of paper coating products. For the purposes of modelling occupational exposure to NVP, two scenarios were considered:

- plants operating with LEV;
- plants operating without LEV.

The EASE scenario that best describes the formulation process is non-dispersive use as it refers to processes in which substances are used in such a way that only certain groups of workers, with the knowledge of the processes, come into contact with these substances (EC, 1996b). It is possible that exposure to NVP vapour may be higher at higher temperatures as in summer.

For plants operating with LEV

Inhalation exposure to NVP vapour by the EASE model is estimated as 0.5 to 3 ppm 8-hour TWA at a temperature of 20°C (Appendix 3, log file 1). This scenario assumes that the operator spends the full shift working on a batch and is exposed to pure NVP alone. However, as stated above the operator is likely to be

exposed to pure NVP only during charging of NVP into the mixing vessel, during high-speed stirring and sampling. During subsequent work such as blending NVP with colours and filling of product containers, the NVP concentration ranges 4 to 20% in the product. Therefore, for the rest of the shift the operator will only be exposed to very low levels of NVP from fugitive emissions which are assumed to be negligible for the purpose of modelling exposure to NVP. It is therefore reasonable to assume that the operator is only exposed to NVP for half the shift as the information obtained from the NICNAS industry survey and site visits indicates that the whole process of mixing takes about 4 hours. The EASE prediction can therefore be adjusted for the period of no exposure and this results in an 8-hour TWA of 0.25 to 1.5 ppm.

For plants operating without LEV

The EASE model that best describes this scenario is non-dispersive use with direct handling and dilution ventilation. Dilution ventilation means general ventilation which is the minimal control in workplaces and was observed at one of the paper coating sites visited by NICNAS. The exposure level predicted by the EASE model for this scenario was 10 to 50 ppm (Appendix 3, log file 2). Paper coating formulation, as with formulation of UV inks, is a batch process and takes about 1 hour. Adjustment for the period of no exposure results in an 8-hour TWA of 1.25 to 6.25 ppm.

Dermal exposure

Surfaces of equipment may remain contaminated with NVP and/or NVP products as NVP has low volatility resulting in dermal contact during handling of equipment. The EASE model that best describes this scenario is non-dispersive use with intermittent contact. According to the EASE model, intermittent contact is assumed to be 2 to 10 events per day involving exposure as part of a process. This results in an exposure of 0.1 to 1 mg/cm^2/d (Appendix 3, log file 3). As stated above, the operator comes into contact with 100% NVP only during charging and sampling and then for the rest of the shift with blends which contain about 4 to 20% NVP. In addition, all companies responding to the NICNAS industry survey reported using gloves and other types of PPE. It is therefore reasonable to assume that the exposure is at the lower level of the above range.

Overseas atmospheric monitoring data

Atmospheric monitoring data was available from an UK manufacturer of UV inks containing NVP (UK draft report, 1998). The personal samples were collected using charcoal tubes in one operator during the whole process of manufacturing for a total duration of 7 hours. Ventilation used in this site is not known. The average level of NVP measured was 0.1 ppm with the highest level of 0.17 ppm obtained during charging of the mixing vessel and the lowest level measured was 0.05 ppm. Static air sampling using charcoal tubes was also conducted at the same site during formulation of two batches, resulting in exposure levels of 0.001 ppm and 0.012 ppm (8-hour TWA).

Another UK manufacturer of UV inks conducted air sampling from their plant (UK draft report, 1998). Sixty-nine static air samples were collected using charcoal tubes, solvent desorption and GC from nine separate surveys in a 3-year period. Sampling equipment was located at a few places near the operators with the sampling head at the level of the operator's breathing zone. Local exhaust

ventilation (LEV) was used in all surveys. It was reported that the exposure level ranged from less than 0.037 ppm to 0.56 ppm. No details were provided for the locations at which the higher result of 0.56 ppm was obtained.

No air monitoring had been conducted overseas for paper coating formulation. No skin permeability data is available.

Summary of exposure data during formulation

Levels of exposure to NVP during formulation of NVP products are summarised in Table 3.

Table 3: Exposure data during formulation of NVP products

	Personal Monitoring	Static Monitoring
Australian monitoring data	No data	No data
Overseas monitoring data	1.5 – 0.17 ppm (7 h, 1 operator)	1) 0.001 ppm and 0.012 ppm (2 samples, 8-hour TWA) (engineering control not stated) 2) 0.037 – 0.56 ppm (69 samples, duration not stated) (with LEV)
	With LEV	**Without LEV**
EASE model estimation	0.25 – 1.5 ppm (8-hour TWA)	1.25 – 6.25 ppm (8-hour TWA)

Dermal exposure of 0.1 mg/cm^2/d was estimated using the EASE model.

8.1.5 Use of NVP in laboratories

During the NICNAS industry survey, sixteen questionnaires were sent to laboratories using NVP. Four laboratories responded, of which only two stated that NVP was used. Of the remaining two, one used PVP and the other had used NVP in the past to produce a copolymer for use in electrostatic large format printing inks/toners but the product is currently out of production.

Information from the NICNAS industry survey indicates that use of NVP in laboratories is very limited. In one laboratory, NVP was polymerised to form a slow release coating for fertilizer as part of a 'one-off' activity for the purpose of research and development. NVP was also purchased for use as a dipolarophile in cycloaddition reactions in another laboratory. It was reported that the process is partially closed by use of a fume hood. The time spent is approximately 1 to 2 hours per day and 1 to 2 days per year. Test equipment is cleaned using chemicals or hot water and then rinsed with water. Gloves (Latex or surgical), safety glasses and laboratory coat were worn while handling NVP.

As NVP is polymerised immediately in reactions, the potential exposure of workers to NVP during use in laboratories is likely to be low except during accidental spills.

Atmospheric monitoring data is not available for use in Australia or overseas.

Exposure prediction for NVP using EASE model was not conducted due to one-off use in the laboratory and immediate polymerisation of NVP in reactions.

8.1.6 Use of products containing NVP

In Australia NVP products are used for screen printing and paper coating.

Process

UV screen printing

Approximately 100 screen printing companies in Australia use UV inks containing NVP. Thirty-seven companies responded to the NICNAS industry survey. Of these 23 current users were identified. These companies range from small workshops with 1 printing line to large companies operating about 8 printing lines. Different types of printing techniques such as letterpress, lithographic printing and silkscreen printing are used for different scales of production. For example, letterpress and lithographic printing are used for large-scale production of stickers or roll labels for bottles whereas silkscreen printing is carried out for large advertising banners, posters and placards.

Approximately 110 workers at the 23 current sites are potentially exposed to NVP during the use of UV inks containing NVP. This figure may not be representative due to the low response rate to the NICNAS industry survey. Exposure time to NVP inks during screen printing varies as some small workshops do not operate daily and printing occurs according to market demands. The time ranges from 1 to 8 hours a day for 10 to 260 days per year. Exposure information obtained from the NICNAS industry survey are provided in Table 4.

Table 4: Details of exposure information provided to NICNAS industry survey by NVP products users

Worksite	Activity	No. of workers	Duration (h/d)	Frequency (d/year)	Ventilation
1	printing	6	8	[did not answer]	air conditioning, exhaust/extraction on machine drier and print shop area.
2	printing	6-8	8	[did not answer]	[did not answer]
3	printing	4	2	25	general dilute ventilation
4	printing	20	8	240	extra exhaust fans and redesigned ducting
	mixing	1	8	240	exhaust fan
	screen & washing	3	8	240	exhaust ventilation updated
5	printing	5	[did not answer]	[did not answer]	motorized extraction to above outdoor roof level.
	cleaning	2	[did not answer]	[did not answer]	[did not answer]
6	printing	4	7	30	[did not answer]
7	printing	2	4	200	4 exhaust ventilation on the roof over the print area.
	cleaning	[did not answer]	[did not answer]	[did not answer]	local exhaust ventilation
8	printing	3	4	50	mechanical exhausting above machine and pedestal fans.
9	printing	Varies	[did not answer]	[did not answer]	[did not answer]
10	printing	[did not answer]	[did not answer]	[did not answer]	exhaust ventilation; general dilute ventilation.

Table 4: Details of exposure information provided to NICNAS industry survey by NVP products users (cont.)

Worksite	Activity	No. of workers	Duration (h/d)	Frequency (d/year)	Ventilation
11	printing	3	4	10	fans and exhaust.
12	printing	6	[did not answer]	26	high volume extraction units on all machinery.
13	printing	2	8	200	exhaust fan and exhaust ventilator
14	mixing & printing	3	8	240	exhaust fan from curer and extractor fan in roof
15	mixing & printing	1	[did not answer]	[did not answer]	natural ventilation
16	printing	10-14	5	220	air conditioned and ventilated factory
	mixing	5-7	3	75	air conditioned and ventilated factory
17	printing	3	4	220	fans
18	printing	3	1	25	exhaust ventilation
19	printing	8	8	260	exhaust fans fitted to all UV curing dryers
20	printing & cleaning	4	6	200	exhaust ventilation
21	printing	3	[did not answer]	36	open windows, doors etc.
22	printing	2	1	12	UV dryer exhausted through roof
23	printing	2	4	180	ventilation

Processes generally involved in screen printing include colour mixing, printing and cleaning of the equipment.

Mixing operations may be conducted on site if pre-mixed inks are not used. Inks are mixed according to standard formulations and occur in small containers using hand held mixers. Mechanical stirrers are used for mixing larger quantities. Lacquer thinners and rags are used to clean ink affected surfaces and to remove ink from hands. The viscous nature of the ink is likely to limit accidental spillage or splashing. A large number of open ink containers were observed at one site visited.

Letterpress and lithographic printing is largely automated as a result of the need for large-scale production and the printing heads on the machines are small and partially enclosed. Silkscreen printing is also carried out mechanically, but the printing heads are larger and open. The inks are poured or applied by spatulas manually onto the ink trays of the machine or silkscreen. When a colour is changed, the leftover ink is scraped off the trays or silkscreen manually using spatulas and returned to the ink storage area.

The printing heads of letterpress and lithographic printing machines are cleaned periodically during printing by using solvents and rags. At one of the silkscreen printing sites visited, cleaning of the silkscreens was done manually using solvents in a separate room for a full shift.

Twenty screen printing companies provided information on engineering controls during use of NVP products. Various types of engineering controls including local or general exhaust ventilation and industrial fans were reported to be used in sixteen workplaces. Four worksites had general ventilation only. PPE is used in most of the workplaces. Gloves are the most commonly used PPE at the various worksites. Types of gloves used vary and include PVC, neoprene, rubber, polyethylene, maresa polythene, Solvex, Latex, solvent resistant, or nitrile. Other PPE such as safety glasses, overalls and disposable masks are also used at some of the sites. Three of the workplaces indicated that they do not use any PPE.

Paper coating

The NICNAS industry survey indicated that in addition to printing inks a coating product containing NVP is formulated in Australia. The product is used to coat materials such as paper, films and plastics that are used mainly for food and beer labels.

The coating process is fully automated. The coating machine consists of a slot for the NVP coating liquid and coating heads. The coating liquid is mechanically pumped into the slot through an enclosed system and applied to the coating heads. Paper passes through the coating heads continuously and then through an electron beam for immediate drying and firm attachment of the coating to the paper.

The coating slot on the machine is cleaned manually with rags using acetone. This is done after the machine stops only if coating residues are observed.

In summary, during use of NVP inks, occupational exposure may occur during the addition of ink to the printing head, from emission during application and printing and during cleaning of printing heads or screens. Exposure is likely to be higher at workplaces having an open printing process such as silkscreen

printing with no mechanical ventilation. Occupational exposure of workers to NVP during paper coating is limited as the process is enclosed and may only occur during cleaning of equipment.

Australian occupational exposure data

Atmospheric monitoring data

Air monitoring data during use of inks containing NVP for screen printing were provided to NICNAS by one company. Personal sampling representative of the workers breathing zone for NVP vapour was carried out in 1991 on one operator in each of the silkscreen printing, colour matching and screen cleaning areas. The concentrations of NVP in the products used was not stated. Sampling was carried out according to Australian Standard AS 2986 (1987) *Workplace Atmospheres – Organic Vapours – Sampling by Solid Absorption Techniques*. Samples were collected in activated charcoal tubes approximately over a five and a half hour work period. The samples were analysed by GC technique. Five of the seven printing machines in the workplace have exhaust ventilation over the UV drying area and the efficiency of the exhaust ventilation system for the print machines was assessed using a smoke tube and appeared to be adequate. Airflow across the face was measured to be 0.2 m/s in the cleaning area.

The concentration of NVP in air was 0.5 ppm in the colour matching area, 0.7 ppm around the screen printer and 0.1 ppm in the screen cleaning area. These results can be regarded as 8-hour TWA as operators work for a full shift in these areas.

Air monitoring for solvents including NVP was carried out in 1995 and 1996 at a paper coating site. Both personal and static samples were collected using activated charcoal tubes and analysed by GC technique. The paper coating process is fully enclosed. Duration of testing, concentration of NVP in coating products and number of samples were not stated. Sampling methodology for solvents was in accordance with Australian Standard AS 2986 (1987) *Workplace Atmospheres – Organic Vapours – Sampling by Solid Absorption Techniques*. The results from both personal and static samples showed that NVP levels were undetectable.

No data on skin permeability in human and animals is available in Australia.

Estimated data

Exposure to NVP by inhalation and through the skin during use of NVP products were estimated using the EASE model.

Exposure by inhalation

In order to cover the range of processes in the industries using NVP products, following EASE scenarios were assumed:

- enclosed use system with full containment;
- non-dispersive use for UV screen printing:
  a) UV screen printing with LEV;
  b) UV screen printing without LEV (direct handling).

Information provided during the NICNAS industry survey indicates that the concentration of NVP in the UV inks ranges from 4% to 20% and the paper coating products contain 2% NVP. The EASE model allows adjustment of the exposure estimate for the concentrations of 5%, 10% and 20% NVP in the products.

Enclosed use system with full containment

This scenario closely describes the process during use of the paper coating product. The EASE model predicted an exposure level of 0 to 0.1 ppm (Appendix 3, log file 4). This exposure is during use of 100% NVP. The paper coating product contains only 2% NVP and exposure can therefore be regarded as negligible during use of this product.

UV screen printing lines with LEV

This scenario applies to workplaces operating letterpress and lithographic printing. LEV was selected as control pattern in the EASE model as the process is largely automated and the printing heads are partially enclosed. An exposure level of 0.5 to 3 ppm 8-hour TWA was estimated using the model (Appendix 3, log file 5). With adjustment for NVP concentrations, the estimation gives an 8-hour TWA exposure level of 0.025 to 0.15 ppm for 5% NVP, 0.05 to 0.3 ppm for 10% NVP and 0.1 to 0.6 ppm for 20% NVP inks respectively.

UV screen printing lines without LEV

The EASE model that best approximates silkscreen printing process is direct handling with dilute ventilation as the processes are open and the printing heads are larger than the other printing techniques. Exposure was estimated to be 10 to 50 ppm of NVP at 20°C (Appendix 3, log file 6). The adjusted 8-hour TWA for NVP concentrations is 0.5 to 2.5 ppm for 5% NVP, 1 to 5 ppm for 10% NVP and 2 to 10 ppm for 20% NVP respectively.

Dermal exposure

Dermal exposure of workers to NVP during paper coating is limited, however dermal exposure is likely during use of UV inks. The EASE model predicted an exposure of 0.1 to 1 mg/cm^2/d assuming non-dispersive use with intermittent contact (Appendix 3, log file 7). With adjustment for concentration of NVP in the printing inks, exposure levels of 0.05 to 0.25 mg/cm^2/d for 5% NVP inks, 0.1 to 0.5 mg/cm^2/d for 10% NVP inks and 0.2 to 1 mg/cm^2/d for 20% NVP inks were obtained.

Overseas atmospheric monitoring data

Atmospheric monitoring data during use of NVP inks for screen printing were available from Germany and the UK.

Personal sampling results at a screen printing site in Germany ranged from 0.53 ppm to 0.9 ppm and static samples ranged from 0.66 to 1.94 ppm. Details on testing methods and duration were not provided.

Static sampling data from the UK, using charcoal tubes, solvent desorption and GC techniques, were available. Sampling was carried out around the printer and the sampling head was at the operator's breathing zone. Six samples were

collected over periods of 1 to 4 hours. The airborne concentration of NVP ranged from none detected to 0.05 ppm. No details about the process or methods of control were available. In another factory with no local exhaust ventilation, twelve samples were collected from 3 separate surveys. The level of NVP varied from less than 0.05 ppm to 3.07 ppm. It was reported that the higher result detected in one of the 3 surveys was due to the use of a "squeegee" during printing. Details on duration of sampling were not reported.

No skin permeability data is available.

Summary of exposure data during use of NVP products

Levels of exposure to NVP during use of NVP products are summarised in Table 5.

Table 5: Exposure data during use of NVP products

	Personal Monitoring	Static Monitoring
Australian monitoring data	1) 0.5 ppm (mixing) 0.7 ppm (printing) 0.1 ppm (cleaning) (with LEV, 5.5 h) (3 samples) 2) ND (paper coating) (enclosed process, duration and number of samples not stated)	No data
Overseas monitoring data	0.53 – 0.9 ppm (no details)	1) 0.66 – 1.94 ppm (no details) 2) ND - 0.05 ppm (1 - 4 h, 6 samples) (ventilation not stated) 3) 0.05 – 3.07 ppm (without LEV, 12 samples) (duration not stated)
	With LEV	**Without LEV**
EASE model estimation (8-hour TWA)	5% 0.025 – 0.15 ppm 10% 0.05 – 0.3 ppm 20% 0.1 – 0.6 ppm	5% 0.5 – 2.5 ppm 10% 1 – 5 ppm 20% 2 –10 ppm

ND; not detectable.

Dermal exposure of 0.2 to 1 mg/cm^2/d was estimated during use of 20% NVP inks (worst case estimation).

8.2 Environmental exposure

8.2.1 Environmental release

Releases may be expected through formulation processes and end use of formulated products.

Formulation

Import volume is expected to be in excess of 20 tonnes per annum. Information from the NICNAS industry survey indicated that this material is sold to five main customers for reformulation.

Formulation of UV curing inks

The processes commonly involved in the manufacture of UV curing inks are described in section 8.1.4 While the potential exists for release through accidental spillage during mixing and decanting operations, reports of spillage are not common. The reducers containing NVP is relatively viscous which lowers the likelihood of release through splashing.

During blending the viscosity of the end products suggests release through splash will not be significant. In the event of spills, rags may be used to clean up. These will be disposed of through normal waste and end up in landfill.

Cleaning solvent waste is collected through a tap and disposed of to a licensed contractor. Empty NVP drums are collected by recyclers or reconditioners, and release through this route is expected to be low. As described below, it is assumed a release of 2% to water occurs.

Formulation of paper coating products

Description of the formulating process was provided by formulators and summarised in section 8.1.4

Vessels are cleaned by acetone which is pumped into a drum for disposal by a registered waste disposal authority. Original drums are sent to a drum reconditioning plant. Environmental releases through these routes are expected to be low (assumed 2% release to water, see section 8.2.3).

When formulating NVP based polymers for hair and skin care products, PVP is cold blended at low concentrations with surfactants in aqueous solutions.

Use of products containing NVP

UV screen printing

The viscous nature of the ink is likely to limit accidental spillage, or releases through splashing during ink mixing operation.

NVP may be emitted to the atmosphere during the UV curing process. Substrates (eg. labels, plastic surfaces, boards etc.) are passed through an UV curing dryer where fumes are exhausted to the external environment.

Wastes generated by companies in the screen printing industry include ink residue from mixing bowls and screens, old inks, contaminated inks from workshops and empty containers. Cleaning tends to involve the use of solvents, either as a wash process, or with rags or brushes. A minority of companies appear to conduct cleaning in separate rooms under local exhaust. Sometimes, screens are washed or pressure cleaned in wet areas.

It is expected that cleaning rags contaminated with NVP will be disposed of to landfill. It may be expected that smaller operators will discharge liquids used for cleaning to the sewer. Otherwise, solids from cleaning operations may be screened out and disposed of with solid waste. Where solvent washes are used,

this may drain into a holding tank for recycling. Spent solvent is expected to be collected and disposed of by licensed waste management collectors.

Empty containers with uncured residues are likely to end up in landfill as general waste. Similarly, contaminated and old inks may end up in landfill, or consigned to liquid waste as it will be in an uncured state.

Paper coating

Additional information provided indicate that there is no chance of release from dripping between the coating head and electron beam curer as absorption of the substrate will not release the coating and the amount applied is carefully monitored via production routings. The distance between coating head and curer is approximately 25 metres. However, the paper is running at around 400 metres per minute, so the time between leaving the coating head until entering the curing stage is less than 4 seconds. After curing, the chemical is locked in a 100% solid matrix.

Environmental release through end use

Respondents to the NICNAS industry survey provided estimates of releases to the atmosphere with responses ranging from 0 - 10%. Most respondents did not know. Of those who did estimate, most thought between 0.01 - 1% was released to the atmosphere. However, these estimates are largely unverified from any monitoring data. Due to the wide variability in responses, and the number of respondents not providing an estimate, the release of NVP from the use in inks and coatings has been estimated using the default values for Industry Category 14 (Paints, lacquers and varnishes industry) in the Technical Guidance Document (EC, 1996b). This indicates for a chemical of this solubility and vapour pressure, 0.5% will be released to air, and 2% to water. The five companies involved in reformulation will also be assumed to have the same release estimates.

It is assumed that reformulation procedures will be conducted on 100 days of the year, and screen-printing operations will be conducted on 240 days of the year.

Table 6 shows the estimated release of NVP during formulation and use of NVP products to the Australian environment.

Table 6: Release estimates to the Australian environment.

	Quantity (kg per annum)	Days per annum	Release to Air (kg/d)	Release to Water (kg/d)
Formulation	20430	100	1.02	4.1
End use				
Screen Printing	19840	240	0.41	1.65
Other[a]	190.4[a]	300	0.00	0.63
TOTAL			**1.43**	**6.38**

a) Includes all NVP used in hair and skin care and in laboratories. Assumes residual monomer of 1000 ppm in PVP (0.4 kg NVP total). Assumes 100% release to water.

End products containing NVP in the cured ink are likely to end up in landfill or incinerated. In landfill, the NVP will be present in the cured ink, so further release to the environment will be unlikely.

8.2.2 Environmental fate

The level 1 MacKay fugacity model, as modelled by US EPA's Assessment Tools for the Evaluation of Risk (ASTER) (USEPA, 1998), indicates that at equilibrium, 7.4% will partition to air, 92.6% will partition to water, and 0.02% will partition to soil. This is based on an estimated water solubility of 216 g/L, Henry's Constant of $2.27X10^{-6}$ atm/m^3/mole and LogPow of 0.408.

No new studies have been received by EA for NVP.

Aquatic fate

It is stated in the IUCLID data sheet (EC, 1996a) that NVP is stable towards alkalis at room temperature. Above 0 ^{0}C, the chemical is cleaved by aqueous mineral acids into acetaldehyde and 2-pyrrolidone; the latter reacts with an excess of NVP to give 1,1'-ethylidene-bis-2-pyrrolidone.

ASTER (USEPA, 1998) has calculated the hydrolysis half life of this chemical to be 190 days.

The IUCLID data sheet (EC, 1996a) provides the rate constant for reaction of NVP with OH radicals in a water solution as 7.3×10^9 L/mol/sec (average of two values). No other experimental information on abiotic degradation is available.

No estimations or experiments on half life in surface or ground water are available.

The vapour pressure of NVP puts it in the category of volatile (Mensink et al, 1995). However, the water solubility is also high. The Henry's Law constant can provide an indication of the volatility characteristics of compounds (Lyman et al, 1982). Based on the calculated Henry's law constant of 0.0056, (UK draft report, 1998), NVP is expected to volatilise slowly.

Atmospheric fate

The UK draft report (1998) for NVP provides a calculated half life in air of NVP as determined by the Syracuse Research Corporation's (SRC) atmospheric oxidant program (AOP). No measured results were available. The gas-phase reaction rate for the most prevalent atmospheric oxidant, hydroxyl radicals, with chemical compounds is estimated by AOP. Gas-phase ozone and nitrate radical reaction rates are also estimated, as appropriate. Atmospheric half-lives for each reaction are automatically determined. The calculated atmospheric half life using this model was 3.6 hours, indicating rapid degradation in the atmosphere.

Terrestrial fate

The level 1 MacKay fugacity model, as modelled by ASTER (USEPA, 1998), indicates that at equilibrium, only 0.01% will partition to soil, and based on the low LogPow, NVP would not be expected to adsorb to soil, sediment or suspended matter to a significant extent.

This would be the case for free NVP released through reformulation or end use procedures. The main use of NVP in Australia is in UV cured screen printing inks. Once incorporated and cured in the final ink, the majority of NVP imported into Australia will eventually become associated with soils as the substrates on which the inks are printed are landfilled in a diffuse manner.

Once incorporated into end articles, the NVP is not expected to leach out, and therefore, not to be bioavailable.

Biodegradation and bioaccumulation

The biodegradation of NVP by bacteria in active sludge was measured and results provided in the UK draft report (1998). The experiment was performed using total organic carbon (TOC) and the concentration of NVP used was 400 mg/L. NVP was 100% degraded after 14 days. It was remarked that the substance is easily eliminated from water and biologically degradable.

Further testing was summarised in the IUCLID data sheet (EC, 1996a). These data are supplied by industry and not validated by the EU. Where IUCLID results do not appear in the UK draft report (1998), they are assumed by EA to be invalid tests. They are reported here nonetheless due to the lack of information available. Activated sludge of municipal/synthetic effluent was used with the test substance at a concentration of 29.4 mg/L. The test was conducted following OECD guideline 301 A "Ready Biodegradability: DOC Die Away Test". Again, NVP was rapidly biodegraded, with 98% eliminated after 24 days, and 100% after 28 days. The 70% within 10 days requirement was also met.

ASTER (USEPA, 1998) has provided a biochemical oxygen demand (BOD) half-life estimation of between 2 and 15 days.

No information is available on bioaccumulation of NVP. However, the log Pow value is 0.4, which suggests that bioaccumulation of NVP is not likely to occur to a significant extent. The Technical Guidance Document (EC, 1996b) provides a Quantitative Structure Activity Relationship (QSAR) for bioconcentration factor (BCF) for substances with logPow <6:

$$\text{LogBCF} = 0.85 \log\text{Pow} - 0.7$$

This equation provides a BCF of 0.46, further suggesting only slight concentration.

8.2.3 Predicted Environmental Concentrations (PECs)

The PECs of NVP in water has been calculated according to the methods in the Technical Guidance Document (EC, 1996b). Releases have been outlined above in Table 6.

PEC_{local}

The PEClocal for water can be calculated using the equation in the Technical Guidance Document where full details on the calculation can be found (EC, 1996b). For the Australian case, all discharge to water will be assumed to occur in one city, where the sewage treatment plant (STP) is assumed to carry a daily output of 250 megalitre. The daily discharge to water has been estimated following assumptions outlined in Section 8.2.1, and a daily discharge rate of 10.45 kg determined.

$$\mathbf{PEC_{local(water)} = C_{eff}/(1+Kp_{(susp)}.c_{susp}.10^{-6}).D}$$

Where:

$PEC_{local(water)}$ = predicted environmental concentration (mg/L)
C_{eff} = concentration of the chemical in the STP (mg/L)
$K_{p(susp)}$ = Suspended matter-water adsorption coefficient (L/kg)
C_{susp} = Concentration of suspended matter in receiving waters (mg/L)
D = Dilution factor

$$\mathbf{C_{eff} = W.(100-P)/100.Q}$$

Where:

W = emission rate (kg/d)
Q = volume of wastewater (megalitre/d)
P = percentage removal in the sewage treatment plant

$$\mathbf{K_{p(susp)} = Foc_{susp}.Koc}$$

Where:

Foc_{susp} = Fraction organic carbon in suspended matter
Koc = Organic carbon adsorption coefficient. [Determined by QSAR from LogPow as per the Technical Guidance Document (EC, 1996b)]

Values:

C_{susp} = 15 mg/L (Default)
D = 10
W = please refer to Table 6
Q = 250 megalitre
P = 76%
Foc_{susp} = 0.1
Koc = 2.65

Assuming NVP is classified as readily biodegradable, with a LogH –2.5, and Log Pow 0.4, the SIMPLETREAT model estimates that 0% will partition to air, 9% will partition to water, 0% will partition to sludge, and 91% will be degraded over the retention period in the STP (EC, 1996b). This gives total removal in the STP of 91%.

These equations have been used to calculate PEC_{local} for the surface water compartment based on release of NVP when processed from a raw material in Australia, either for formulation or end use of NVP products. The PECs calculated are given in Table 7.

The $PEC_{effluent}$ is equivalent to the $PEC_{local(surface\ water)}$ before dilution. A dilution rate of 10 is used so values for $PEC_{effluent}$ have also been calculated and are in Table 7.

Table 7: Local PECs calculated for the aquatic environment

Process	Annual release to sewer (kg)	Release (days per annum)	Emission to sewer (kg/d)	$PEC_{effluent}$ (µg/L)	PEC_{local} (µg/L)
Formulation	408.5	100	4.1	1.48	0.15
End Use					
Screen Printing	396	240	1.65	0.59	0.06
Other[a]	189	300	0.63	0.23	0.02
TOTAL	**993.5**		**6.38**	**2.3**	**0.23**

a) Includes all NVP used in hair and skin care and in laboratories. Assumes residual monomer of 1000 ppm in PVP (0.4 kg NVP total) and 100% is released to water.

Comparison with measured values

EA has been unable to locate any monitoring information or literature on this chemical in sewage discharge or groundwater to enable verification of the predicted environmental concentrations determined above.

Atmosphere

Table 6 indicates that 1.43 kg NVP per day are estimated to be released to air during formulation and end use processes.

A PEC_{local} for air via point source emissions from processing raw NVP can be calculated, again using the methodology from the Technical Guidance Document (EC, 1996b). As a worst case, it will be assumed that all emissions occur from a single point source.

C_{air} =Emission.$Cstd_{air}$

where:

C_{air} =concentration in air at 100 m from a point source (kg/m^3)
Emission =emission rate to air (kg/s)
$Cstd_{air}$ =Standard concentration in air at source strength of 1 kg/s
= 24 x 10^{-6} kg/m^3.

A daily release of 1.43 kg per day to the atmosphere equates to $1.66X10^{-5}$ kg/s. This gives an NVP concentration at 100 m from the STP of 0.4 µg/m^3.

There is currently no exposure limit for this chemical set by NOHSC. However, the major importer of NVP to Australia recommends an exposure limit of 0.1 ppm, which is several orders of magnitude higher than the predicted environmental concentration in air determined above.

8.3 Public Exposure

8.3.1 Laboratory and industrial uses

The NICNAS industry survey showed that NVP is mainly used for manufacturing UV curing inks and paper coating products with small quantities for laboratory use. The processes involved in these uses are described in section 8.1 and indicate minimal public exposure.

Printed materials are for use in a number of applications including labels for the snack food industry. Once the ink is applied to the printing medium and UV cured, NVP is bound in an insoluble polymeric matrix with other substances. The potential for public exposure to NVP from the printed material is considered to be negligible.

Disposal of wastes arising from industrial uses of NVP is described in section 8.1 and 8.2. NVP is easily eliminated from water and biologically degradable. The half life in air is 3.6 h and in sludge 14 days. Public exposure from disposal is considered negligible.

There is low potential for public exposure from laboratory use of small quantities of NVP.

8.3.2 Consumer products

Some disposable contact lenses are made from NVP in UK (UK draft report, 1998). NVP is polymerised in contact lens moulds, and only residual monomer at the level of around 250 ppm is present in the lens. Such lenses may be marketed in Australia. Given the low level of NVP and the small size of contact lenses, exposure should be very low.

Two PVP importers indicated that the imported PVP might contain a maximum of 1000 or 2000 ppm NVP (USP23 grade), and another PVP importer stated that the level of NVP in PVP is below 10 ppm. In Europe, NVP residues in PVP are generally below 100 ppm (UK draft report, 1998). PVP is used in foods, pharmaceuticals, cosmetics/toiletry products and adhesives (adhesive tapes, glue sticks, and possibly wettable gum on postage stamps).

Chemicals used in foods are regulated by the Australian New Zealand Food Authority (ANZFA), and pharmaceutical drugs are regulated by the Drug Safety and Evaluation Branch of the TGA. PVP is used in pharmaceutical drugs as a suspending agent or tablet binder at the level of up to 25% (Wade and Weller, 1994). The maximum allowable level of NVP present in PVP for use in pharmaceutical products is specified to be 10 ppm in the British Pharmacopoeia (Medicines Commission, 1998) and European Pharmacopoeia (European Council, 1998). The level of NVP present in the final pharmaceutical products should not exceed 2.5 ppm.

PVP has a limited use in food such as artificial sweeteners or as a clarifying agent in wine and beer brewery (insoluble PVP) (UK draft report, 1998; National Food Authority, 1995). According to the US Food Chemicals Codex specifications (National Academy Press, 1981), which are adopted by the ANZFA for PVP, the maximum level of NVP may be present in PVP for food use is 0.2% (ie. 2000 ppm). Although the maximum level of NVP in PVP used in food is significantly higher than that for pharmaceutical use, the limited use of PVP in food indicates low public exposure.

PVP is used in cosmetic products as a thickener, dispersing agent and binder. One PVP user in Australia indicated the use of PVP in hair treatment products, facial creams and bath gels. PVP is used in mousses at up to 9.7%, in shampoos at up to 1.4%, in hair treatment conditioners at up to 1%, in bath gels at 0.1%, and in facial creams at 0.2%. Assuming NVP is present in PVP at the maximum specification level of 2000 ppm, the NVP level in final consumer products would be 200 ppm in mousses, 30 ppm in shampoos, 20 ppm in hair treatment conditioners, 2 ppm in bath gels and 4 ppm facial creams. PVP may also be used in other cosmetic products, but the above should represent typical uses of PVP in the cosmetic industry. The main route of exposure through the use of above products is by dermal contact, and possibly by inhalation.

PVP or other NVP polymers are also used in adhesives such as glue sticks, adhesive tapes and possibly wettable gums on postage stamps. These products are widely used by consumers. However, given that the exposure is infrequent and any residual NVP present in PVP is embedded in the adhesives, public exposure through the use of glue sticks, adhesive tapes or postage stamps is considered negligible.

9. Toxicokinetics and Metabolism

This section of the report is based on the UK draft report (1998) and the studies in this section are cited.

Very little data is available on the toxicokinetics of NVP in humans. The toxicokinetics of NVP has been extensively characterised in the rat. Some data in dogs is also available.

9.1 Absorption

NVP is a low molecular weight compound and is readily soluble in water. NVP is hydrolysed in acidic conditions. A study by Hawi* et al, (1987) found that the rate of hydrolysis is inversely related to pH. The half life of NVP in aqueous solution was 1.5 minutes at a pH of 1.2, 20 - 40 minutes at pH 2.2 - 2.5, 380 minutes at pH 3.5 and at least 24 hours at pH 7.2. NVP also undergoes spontaneous polymerisation in acidic conditions. The rate of hydrolysis of NVP observed in the rat stomach (pH 4) was much slower than that seen at more acidic pHs. It is therefore likely that polymerisation also plays a role in lowering the bioavailability in the rat when the residing time of NVP in the stomach is increased by, for example, feeding.

Data on the absorption of NVP are available in rats (oral) and in dogs (inhalation, oral, dermal).

In dogs, following whole body exposure to NVP vapour at concentrations of 0.69, 5.5, 24 and 62 mg/m^3 for 6 hours (BASF*, 1992a), plasma concentrations of NVP rose with ascending exposure concentrations indicating that NVP is absorbed from the respiratory tract.

Following administration of single gavage doses of 0.5 or 5 mg/kg of NVP liquid (purity unstated) in fasted rats, the bioavailability of NVP from the gastrointestinal tract was approximately 80%. A half life of 3 to 4 hours following a linear pattern of elimination from plasma was found in fasted rats for both doses (Digenis*, 1990). In non-fasted rats given 5 mg/kg, the plasma concentration was half that in fasted rats and the bioavailability was 26%. The authors relate the reduction in bioavailability to increased gastric emptying time due to the food in the stomach, allowing more time for hydrolysis and polymerisation reactions to occur. Similar results were obtained in non-fasted rats given repeated doses 0.5 mg/kg NVP for 6 days, to those results in non-fasted rats given single doses of NVP, indicating that NVP does not bioaccumulate or produce enzyme induction.

In the same study, oral absorption was also investigated in fasted dogs at successive dose levels of 5, 10 and 20 mg/kg. The absolute bioavailability was determined to be around 29, 69 and 89% respectively. According to the authors, decrease in bioavailability at lower doses is due to hydrolysis of a major part of the dose before absorption. Elimination from plasma followed an exponential pattern, with a half life of 20 to 40 minutes which is significantly shorter than in rats. In fed dogs given 20 mg/kg NVP, bioavailability was about 92% indicating

that the presence of food did not affect uptake or plasma elimination. The reason for the species differences is not clear.

Dermal application of 5 mg/kg of undiluted NVP to 25 cm^2 area of shaved skin for 6 hours resulted in absorption of less than 2% of the applied dose in dogs (BASF*, 1992a), indicating that dermal absorption was relatively low in this experimental situation. However, the physicochemical properties of NVP (ready solubility in water and most organic solvents and a Log Partition coefficient of around 0.4) suggest significant dermal absorption could be predicted for this substance. This is supported by the findings of the acute dermal toxicity studies in other species (see section 10. 2.1).

9.2 Distribution

Following oral administration in rats, absorbed NVP is distributed widely throughout the body, with high levels in the liver (Digenis*, 1990). High levels were also found in whole blood, plasma, kidneys, small intestine and pancreas. The testes also contained small amounts of NVP. In the same study, in dogs given 5 or 20 mg/kg NVP, approximately 13% and 10% of the doses respectively were bound to plasma proteins.

Another study in rats was conducted to investigate the distribution of radiolabeled NVP by intravenous injection (Digenis & McClanahan*, 1982). Satellite groups of one or 3 rats were given 1.1 mg/kg radiolabeled NVP and sacrificed after 15, 30 and 90 minutes. The levels of total radioactivity were measured in a range of tissues. It was found that NVP, as in the oral study, is distributed to all the major organs. Elimination of NVP from blood was biphasic with a half life of 1.5 to 1.9 hours for the slow phase.

9.3 Metabolism

A number of experiments have been carried out in male rats to investigate the metabolism of NVP following intravenous dosing (McClanahan* et al., 1983; 1984; 1987). All the studies showed that NVP is extensively metabolised and the metabolites rapidly eliminated.

Groups of 2 or 4 rats were given doses of 0.3, 0.5, 0.8 or 1.3 mg/kg and urine, feaces and expired air samples collected (McClanahan* et al., 1983). It was found that less than 1% of the dose was eliminated as intact NVP in any subsequent sample of urine, feaces or exhaled air. Chemical analysis showed that the urinary metabolites of NVP are highly polar. The majority of urinary metabolites are acidic species (89%), of which 12% was acetic acid. The remaining metabolites were mostly neutral with a small proportion of basic species (1.7%).

A more detailed analysis of urine samples (McClanahan* et al., 1987) was conducted by coadministering N-[^{14}C-vinyl]-2-pyrrolidone (^{14}C) and [4-^{3}H]-N-vinyl-2-pyrrolidone (^{3}H) intravenously in male rats. All samples were analysed for total ^{14}C and ^{3}H activity. This study revealed the presence of two major metabolites containing both ^{14}C and ^{3}H and accounting for 50% and 33% of the dose. However, the structures of either major metabolite could not be identified. Three minor metabolites were identified as N-vinylsuccinimide, 2-pyrrolidone, and N-acetyl-γ-aminobutyric acid, which accounted for around 5, 6 and 5.6% of the dose respectively.

The potential for NVP and its metabolites to bind to DNA and proteins have been investigated both in male Sprague-Dawley rats (IRI*, 1985) and *in vitro* (Yamakita* et al., 1992; McClanahan* et al., 1983). The studies in rats concluded that NVP and its metabolites do not bind to DNA, RNA or protein. The *in vitro* studies investigating binding to plasma proteins and microsomal proteins have shown that about 12 % of NVP or metabolites bind to plasma proteins concluding that it is not metabolised to an alkylating species.

9.4 Elimination and excretion

Animal studies indicate that NVP and its metabolites are rapidly eliminated, predominantly by the urinary route.

McClanahan* et al. (1983) reported that in rats approximately 60% of an intravenously administered dose was eliminated in urine in the first 6 hours and a further 10 to 30% of the dose was eliminated within the first 18 hours. Between 1 and 8% of the administered dose was eliminated via the faecal route over the first day and between 1 to 3% as $^{14}CO_2$ via the lungs.

NVP excretion through bile was investigated in rats following administration of 1.1 mg/kg NVP (McClanahan* et al., 1984). Bile samples were collected up to 6 hours after dosing. Analysis of bile revealed that 19% of the administered radioactivity was excreted by this route. Comparing with faecal excretion (0.4%), the authors concluded that biliary metabolites of NVP undergo extensive enterohepatic recirculation.

10. Effects on Laboratory Mammals and Other Test Systems

A number of reviews of the health effects of NVP were conducted in the late '80s and early '90s with the UK draft report (1998) being the most recent review. This section of the report is based on the UK draft report (1998) and the studies in this section are cited. No additional data was provided during the assessment by applicants. A literature search identified two articles published by Kilmisch et al (1997a, b). These articles summarise the earlier unpublished studies described in the UK draft report (1998). Additional information provided in the published articles for the studies has been included in Table 9.

10.1 Acute toxicity

A number of acute lethality studies have been conducted with NVP using different routes of administration. The LD_{50} and LC_{50} from these studies are noted in Table 8.

Table 8: Lethal dose studies for NVP

Route	Species	Results	Reference
Inhalation			
	rat	LC_{50} = 3070 mg/m^3 (3.07 mg/l) (4 h)	(BASF*, 1979)
Oral			
	rat	LD_{50} = 834 - 1314 mg/kg	(HRC*, 1978a)
	rat	LD_{50} = 1043 mg/kg	(BASF*, 1963a)
	rat	LD_{50} = 1022 mg/kg	(BASF*, 1963b)
	rat	LD_{50} = 1700 mg/kg	(BASF*, 1953)
	rat	LD_{50} = 2500 mg/kg	(BASF*, 1955)
	mice	LD_{50} = 940 mg/kg	(Schwach & Hofer*, 1978)
Dermal			
	rat	LD_{50} = 1043 - 4127 mg/kg (occluded for 24 h)	(HRC*, 1978b)
	Rabbit	LD_{50} = 560 mg/kg (exposure conditions unknown)	(FDRL*, 1975)
	Guinea pigs	LD_{50} = 3000 - 5000 mg/kg (occluded for 6 h)	(BASF*, 1996)

The main acute toxic effects observed in a range of species (rats, mice, rabbits, guinea pigs, cats) were respiratory distress, increased salivation and nasal secretion, ataxia, narcosis and lack of appetite. In addition, at high doses by the

oral route lachrymation, ptosis, diuresis, and loss of righting reflex were observed.

Autopsy of decedents revealed that the liver, lungs and kidneys are the major target organs by all three routes of exposure. Effects on the liver including centrilobular necrobiosis, isolated necrotic cells, and changes in cell nuclei (mitosis, polymorphism, pale karyoplasm) were found in rats after 2 days exposure to 69 mg/kg NVP vapour (BASF*, 1988b). Discoloration of the kidneys and congestion of the lungs were observed in rats. Irritation of the mucous membrane lining of the gastrointestinal tract was also reported following oral or inhalation exposure. Blood changes noted were increases in alkaline phosphatase and reductions in total protein levels.

None of the above changes were apparent in animals surviving single high doses, indicating that these pathological changes are reversible.

10.2 Irritation and corrosivity

10.2.1 Skin

Several studies in rabbits (BASF*, 1978a; CPT*, 1978) at doses varying from 400 mg/kg to 2500 mg/kg using occluded dressing for 24 hours reported slight erythema. In a dermal toxicity study in rats no skin irritation was reported at doses up to 10430 mg/kg for 24 hours (HRC*, 1978b). No skin irritation was observed in a recent skin sensitisation study in guinea pigs (BASF*, 1996) following an occlusive dressing of diluted and undiluted NVP for 6 hours.

However, severe skin irritation was observed in earlier studies in rabbits (BASF*, 1941; 1953) and in rats (BASF*, 1953). It is unclear why this effect was produced in the earlier studies. Differences in the grade of NVP used or the purity of the preparation may account for these effects.

10.2.2 Eye

Corneal opacity, conjunctival chemosis, and iris lesions were observed in a study following instillation of 0.1 mL liquid NVP (purity and use of stabilisers unknown) to the eyes of 6 rabbits (BASF*, 1978a). According to the UK draft report scoring for eye irritation included conjunctival chemosis grade 2.2, conjunctival redness grade 1.9, iris lesions grade 1 and corneal opacity grade 1.8 at 24 to 72 hours. These lesions became worse with time and there were no signs of recovery. Grade 3 opacities covering half of the entire cornea were observed in 5 rabbits by day 7 indicating that liquid NVP is severely irritant to the eye.

Following application of undiluted NVP (dose and purity not stated) to the eyes of rabbits, chemosis, oedema and corneal clouding followed by scarring were noted during the 8 days observation period in two briefly reported studies (BASF*, 1963a,b).

No studies have been undertaken specifically to investigate eye irritation caused by NVP vapour. Repeated inhalation studies in rats did not report eye irritation following 12 months exposure to NVP vapour, however, the highest dose level was only 20 ppm (BASF*, 1992b).

10.2.3 Respiratory tract

Increased respiratory rate and nasal secretions were observed in a rat study following a single inhalational exposure to NVP aerosol (purity >99%, stabilised with 10 ppm Kerobit, particle size not stated) at concentration ranges from 0.8 mg/L to 5.6 mg/L (BASF*, 1979). Increased nasal secretion was also found in a few earlier studies in which a range of animal species (rats, mice, cats, rabbits and guinea pigs) were exposed to NVP vapour for 6 or 8 hours (BASF* 1964; 1963a; 1941). These studies were conducted using air saturated with NVP vapour.

10.3 Sensitisation

A skin sensitisation study (Buehler test) was conducted (BASF*, 1996) by applying 0.25 mL of 99.7% pure NVP to the flanks of 20 guinea pigs under an occlusive dressing for 6 hours. No skin reactions were observed during both induction and testing phases, indicating that NVP did not induce skin sensitisation. According to the UK draft report (1998), the study was conducted to contemporary regulatory protocols.

No studies have been undertaken to specifically investigate the respiratory tract sensitisation potential of NVP.

10.4 Immunotoxicity

The immunotoxicity of NVP has not been investigated in animals.

10.5 Repeated dose toxicity (other than carcinogenicity)

Repeated dose studies (other than carcinogenic toxicity) by inhalation and oral routes have been conducted in a range of species, with varying doses and exposure durations. The majority of these studies were carried out in the 1980's and conducted according to GLP and contemporary regulatory protocols. These studies have been reviewed in the UK draft report (1998). The results of the major studies are summarised in Table 9.

The main target organs for toxicity following repeated exposure of animals to NVP by the inhalation and oral routes are in the liver and nasal cavity. Other adverse effects reported include haematological changes indicative of anaemia, dysproteinaemia, increased levels of γ-GT and enzyme markers of liver toxicity and histopathological lesions of the stomach. Histopathological lesions in respiratory tract and lungs were also noted in inhalation studies. Treatment related deaths were reported in mice exposed to 45 ppm NVP vapour for 10 days (BASF*, 1988d). A level of 120 ppm was lethal to rats within the first week (BASF*, 1986a).

Adverse effects on the liver were noted within one week following inhalation exposure to 15 ppm NVP vapour in rats and mice (BASF*, 1988 c, d). Toxic effects reported in the rat liver after exposure to 10 ppm NVP for 3 months in the 2 year study include enlarged hepatocytes with clear cell areas and degenerative changes of the nucleus (BASF* 1992b, see section 10.8, Table 11). Other liver effects such as centrilobular necrobiosis, fatty infiltration and glycogen accumulation within centrilobular hepatocytes were observed at higher doses. The severity of the pathological changes was related to both dose and duration of

exposure. In addition, there were indications that these changes were not reversible (BASF*, 1987a, see section 10.8).

Signs of respiratory tract irritation such as catarrhal-purulent rhinitis were seen in mice after repeated inhalation of 5 ppm NVP, which is the Lowest Observed Adverse Effect Level (LOAEL), for one week (BASF*, 1988d). Other adverse effects include cell hyperplasia and inflammatory changes in the olfactory and respiratory epithelia in rats and mice. These changes were observed in rats following exposure to 5 ppm NVP vapour for 3 months (BASF* 1986a, 1992b).

A No Observed Adverse Effect Level (NOAEL) of 1 ppm was identified in a 3 month inhalation study in rats with no treatment related effects observed in the liver or nasal cavity (BASF*, 1986b). Exposure to 5 ppm for 3 months resulted in changes in the nasal cavity and minimal effects such as slight dysproteinaemia in the liver. However, marked adverse effects on the liver were seen in rats exposed to 5 ppm for 12 months or longer (BASF*, 1992b). This indicates that at 5 ppm hepatotoxicity takes longer than 3 months to develop. It is possible that hepatotoxicity may develop in rats at 1 ppm if exposed to longer durations. The NOAEL of 1 ppm observed in a 3 months study may therefore not be applicable to exposures of longer duration.

Unlike effects due to inhalation exposure to NVP vapours, no liver damage was observed in rats exposed to NVP aerosols. In addition, signs of nasal cavity and trachea irritation were observed at a much higher aerosol dose than NVP vapour (FDRL*, 1976). These differences may be due to an intrinsic difference in the way that vapours and aerosols are handled in the upper respiratory tract and lungs.

Species differences in liver toxicity of NVP have been noted. In contrast to findings in rats and mice, very few toxic effects were seen in hamsters exposed to 45 ppm NVP vapour for 3 months (BASF*, 1987b). The reason underlying this apparent species difference is not known.

Administration of NVP by the oral route results in damage to the liver, however, the dose required to produce histopathological changes is much higher than that required by inhalation. This is probably due to some of the NVP undergoing hydrolysis and polymerisation in the acidic environment of the stomach prior to absorption. Dysproteinaemia was observed in a 3 month drinking water study (BASF*, 1986d) but was not observed at much higher concentrations in the 3 month gavage study (BASF*, 1986c). This suggests that there may be differences in the way the body responds to a bolus gavage dose compared with the gradual intake of NVP via drinking water. The deaths in the pilot drinking water study (BASF*, 1986c) are likely to be the result of unpalatability which leads to severely restricted food and water consumption as only mild effects were observed in rats given gavage doses of up to 100 mg/kg/d. A NOAEL of 3.6 mg/kg has been identified in a drinking water study (BASF*, 1986d).

No studies have been conducted to investigate the effects of repeated dermal exposure to NVP.

Table 9: Repeated dose toxicity (other than carcinogenic)

Species	Exposure*	NOAEL	LOAEL	Results	Reference
Sub-acute toxicity (up to 14 days)					
Inhalation					
Rats (F344, 2 males/group)	0, 5, 15, 45 ppm (purity 99.94%, stabilised with 3 ppm Kerobit) whole body exposure for 2 and 5 consecutive days		5 ppm	Outward signs of toxicity at 15 or 45 ppm similar to 7 weeks study in rats (BASF*, 1988c) observed after 2 days; no signs observed at 5 ppm, however, histopathological examinations were undertaken only in the liver.	(BASF*, 1988a)
Mice (C57, 5 females/group)	0, 5, 15, 45 ppm (purity 99.94%, stabilised with 3 ppm Kerobit) whole body exposure for 2 and 5 consecutive days		5 ppm	Similar results as in rat study above (BASF*, 1988a).	(BASF*, 1988b)
Sub-chronic toxicity (>14days <3 months)					
Inhalation					
Rats (FDRL Wistar, 15 males and 15 females/ group)	0, 75 mg/m^3 in water, 300 mg/m^3 undiluted NVP whole body exposure for 4h/d, 5 d/week for 4 weeks. Exposure was to NVP aerosols (generated by atomisation, undiluted, particle size unstated).			No treatment related mortality occurred; no abnormal findings in hematology, ophthalmoscopy and urinalysis; microscopically peribronchial lymphoid hyperplasia in males at 16 and 65 ppm and interstitial inflammation in top dose females observed; dose related inflammation indicated by increased number of leukocytes and leucocytic exudate observed in mucosal surfaces; no indication of liver damage.	(FDRL*, 1976)
Mice (C57, 20 males, 20 females/group)	0, 5, 15, 45 ppm (purity 99.94%, stabilised with 3 ppm Kerobit) for 7 weeks 5/sex/group were sacrificed after 1, 3, and 10/sex/group at 7 weeks.		5 ppm	Treatment related death at 45 ppm; in contrast to rat study (BASF*, 1988c), biochemical and haematological changes less marked than in rats; liver toxicity only seen at 45 ppm; inflammatory changes in the bronchial epithelium observed in all top dose females after 1 week; dose related bronchial epithelium disarrangement in all top dose animals and in one 15 ppm female; catarrhal-purulent rhinitis and atrophied nasal olfactory epithelium observed at all dose levels and all time points; hyperplasia of the submucous glandular cell in treated animals after 7 weeks and slight hyperplasia of nasal respiratory epithelium at all dose levels at all time points. No histopathological changes were observed in the lungs and kidneys.	(BASF*, 1988d)

* inhalation studies were carried out with NVP vapour and animals were exposed whole body for 6 hours per day, 5 days per week unless otherwise stated.

Species	Exposure*	NOAEL	LOAEL	Results	Reference
Rats (F344, 20 males, 20 females/group)	0, 5, 15, 45 ppm (purity 99.94%, stabilised with 3 ppm Kerobit) for 7 weeks 5/sex/group were sacrificed after 1, 3, and 10/sex/group at 7 weeks.		5 ppm	Apathy, poor general state, altered breathing behavior at 45 ppm but not present after 2 weeks. *Biochemical changes*: dysproteinaemia mainly due to reduced globulin levels at 15 or 45 ppm after 1 and 3 weeks; initial increases in a few enzyme markers of liver toxicity observed; statistically significant increase in serum cholesterol levels at 15 or 45 ppm at study termination. *Haematological changes:* signs of anaemia, increase in γ-GT and glutathione levels and increased platelet counts at top two doses in both sexes at all time points. *Liver:* increased absolute liver weights in females at 45 ppm at all time points; macroscopic changes seen in the liver at 45 ppm; hepatic centrilobular necrobiosis and fatty infiltration in all top dose rats after 1 week and progressed with increasing duration of exposure; no liver damage at 15 ppm after 7 weeks, but hepatic centrilobular necrobiosis found in one male at 5 ppm. *Nasal cavity:* olfactory epithelium atrophy in the nasal mucosa at 45 ppm at all time points in all animals, at 15 ppm after 3 weeks and at 5 ppm in one male after 7 weeks. No histopathological changes were observed in other tissues examined microscopically (the lungs, heart, spleen, kidneys, adrenals and testes).	(BASF*, 1988c)
Rats (Sprague-Dawley, 10 males, and 10 females/group)	0, 5, 15, 45, 120 ppm (purity >99%, unstabilised) for 3 months		5 ppm	At 120 ppm, most animals died in the first few days; apathy, atonia, ptosis, dyspnoea, haematuria and histopathological changes of stomach mucosal ulceration, centrilobular hepatocyte hypertrophy, respiratory tract epithelium inflammation and necrosis observed before death; at 5, 15, 45 ppm treatment related biochemical, haematological changes and toxic effects in the liver and nasal cavity were as described in rat studies (BASF*, 1988a,c; 1992b); glycogen accumulation also evident in the liver foci.	(BASF*, 1986a)
Rats (Sprague-Dawley, 10 males, and 10 females/group)	0, 1 ppm (purity 99.7-99.9%, stability not stated) for 3 months	1 ppm		No treatment related effects were observed in the liver or nasal cavities.	(BASF*, 1986b)
Hamsters (Syrian golden)	0, 45 ppm (purity 99.7-99.9%, unstabilised) for 3 months			Ataxia, apathy, salivation and nasal discharge observed on the first and disappeared by the second day; body weight gain reduced during the exposure period. No pathological changes found in the liver (only the liver was examined).	(BASF*, 1987b)

* inhalation studies were carried out with NVP vapour and animals were exposed whole body for 6 hours per day, 5 days per week unless otherwise stated.

Species	Exposure*	NOAEL	LOAEL	Results	Reference
Oral					
Rats (Wistar, 5 males and 5 females/group)	0, 5, 10, 20, 25, 30, 25, 40 mg/kg (purity>96.5%) in drinking water, 5 d/week for 3-4 weeks		5 mg/kg	Significantly reduced water and food consumption and deaths occurred at doses ≥30 mg/kg; slight decrease in bodyweight gain in females at ≥5 mg/kg; dysproteinaemia in females (≥10 mg/kg) and males (≥20 mg/kg). Ulcerative gastritis observed in 3 males at the top dose; fatty infiltration seen at 30 mg/kg in 2 females.	(BASF*, 1986c)
Rats (Wistar, 5 males and 5 females/group)	0, 40, 60, 100 mg/kg (purity>96.5%) by gavage, 5 d/week for 3 months		40 mg/kg	Dose related increase in water consumption in all treated rats; slight increase in liver weight in females at all doses and in males at the top two doses; significant increase in γ-GT activity in females at all dose levels; increased platelet counts in both sexes at top two doses; minor microscopic changes (small foci of cellular alterations) observed in the liver at 100 mg/kg in both sexes, but more pronounced in females.	(BASF*, 1986c)
Rats (Wistar, 10 males and 10 females/group)	0, 0.5, 1.3, 3.6, 8.3 mg/kg/d (purity>99.48%) in drinking water for 3 months	3.6 mg/kg		No clinical signs of toxicity; dysproteinaemia in both sexes at the top dose only; slight increase in kidney weights in males at top two doses with no pathological changes.	(BASF*, 1986d)
Chronic toxicity (>3 months)					
Inhalation					
Rats (F344, 10 males and 10 females/group)	0, 10 ppm (purity >99.9%, stabilised with 3 ppm Kerobit) for 6 months			Biochemical, haematological changes and toxic effects in the liver and nasal cavity were the same as described in other BASF studies.	(Klimisch et al, 1997)
Mice (10 males and 10 females/group)	0, 10 ppm (purity >99.9%, stabilised with 3 ppm Kerobit) for 6 months			Biochemical, haematological changes and toxic effects in the liver and nasal cavity were the same as described in other BASF studies.	(Klimisch et al, 1997)

* inhalation studies were carried out with NVP vapour and animals were exposed whole body for 6 hours per day, 5 days per week unless otherwise stated.

10.6 Reproductive toxicity

No studies have been conducted to specifically investigate reproductive or developmental toxicity of NVP. However, reproductive organs such as testes, epididymides, prostate glands, seminal vesicles, ovaries and uterus from rats and mice were specifically examined microscopically in repeated dose toxicity studies following inhalation of NVP vapour (BASF*, 1992b; 1988c,d; 1986a) and aerosols (FDRL*, 1976). Reproductive organs of rats were also examined following oral administration of up to 8.3 mg/kg/d NVP for 3 months (BASF*, 1986d). The results did not indicate any NVP induced adverse effects on the reproductive organs. No conclusions can be drawn on the potential developmental toxicity of NVP from the available data.

10.7 Mutagenicity

The mutagenicity studies conducted with NVP are summarised in Table 10.

Mutagenicity studies conducted with NVP in a wide range of *in vitro* and *in vivo* test systems have produced negative results. It is therefore concluded that NVP is not a mutagenic compound under conditions of testing.

Table 10: Mutagenicity of NVP *in vitro* and *in vivo*

Test system	Species	Exposure	Results	Comments	Reference
In vitro					
Bacterial systems	*Salmonella typhimurium* strains TA 1535, TA 1537, TA98, TA100	3.1-10000 µg/plate with and without metabolic activation (S9*), positive and negative plates prepared.	Negative	No cytotoxicity at all doses.	(HRC*, 1978c)
	TA98	Up to 3000 µg/plate with S9 plus epoxide hydratase inhibitor and 1,1,1-trichloropropene 2,3-oxide, positive and negative plates prepared.	Negative	No cytotoxicity at all doses.	(BASF*, 1978b)
	Salmonella typhimurium strains TA 1535, TA 98, TA100 (Ames test)	NVP (purity >98%) at 0, 52, 104, 520, 1043 mg/dessicator for 7 h with and without S9 under closed system, positive and negative plates prepared.	Negative	No cytotoxicity at all doses.	(Simmon & Baden*, 1980)
	Salmonella typhimurium strains TA 98, TA100 (Ames test)	Closed system with up to toxic concentrations, with and without S9.	Negative	Few details of experiment.	(Knaap* et al., 1985)
	Klebsiella pneumoniae (fluctuation test)	Closed system with up to toxic concentrations.	Negative	Briefly reported study, no details on experiment method.	(Knaap* et al., 1985)
Mammalian cells	Human lymphocytes (chromosomal aberration)	NVP (purity 99.7%) in distilled water at 20, 40, 60 µg/mL without S9 for 2 h; 300, 600, 900 µg/mL with S9 for 24 h; positive, negative and solvent control cultures prepared.	Negative	Conducted according to contemporary regulatory protocols.	(BASF*, 1987c)

Table 10: Mutagenicity of NVP *in vitro* and *in vivo* (cont.)

Test system	Species	Exposure	Results	Comments	Reference
	Mouse lymphoma L5178Y(TK+/-) cells (gene mutation test)	NVP (purity unstated) at 0.39-10 µl/mL for 4 h with and without S9, positive and negative control cultures prepared.	Negative	Severe cytotoxicity observed at 7.5 µg/mL and moderate cytotoxicity at 5 µg/mL.	(Litton Bionetics*, 1980a)
	Mouse lymphoma L5178Y cells	Closed system with up to toxic concentrations, with and without S9.	Negative	Briefly reported study, no details on experimental method.	(Knaap* et al., 1985)
	Rat hepatocytes (Unscheduled DNA Synthesis test)	NVP (purity unstated) at 0.3-20 µl/mL for 1 h followed by a 3 h labeling period, 2 and 24 h viable cell counts done in additional cultures, positive and negative control cultures prepared.	Negative	Survival rates decreased with increasing concentrations. Completely lethal level was 18.2 µl/mL.	(Litton Bionetics*, 1980b)
	Whole blood and isolated human lymphocyte cultures [Sister Chromatid Exchange (SCE)]	No details of the test method.	Slight increases in SCEs in both cultures.	Poorly reported study.	(Norpa and Tursi*, 1984)
Drosophila melanogaster					
	Drosophila melanogaster (sex-linked recessive lethal test)	Up to toxic concentrations by injection.	Negative	No details on experiment method.	(Knaap* et al., 1985)
In vivo					
	NMRI Mice (micronucleus test, 5 male and 5 female/group)	NVP (purity 99.8%) at single doses of 0, 150, 300, 600 mg/kg in distilled water by gavage, positive and negative control groups prepared.	Negative	Conducted according to contemporary regulatory guideline. Irregular respiration, piloerection and squatting position observed in treated animals.	(BASF*, 1993)

*S9, Aroclor induced rat liver.

10.8 Carcinogenicity

The carcinogenic potential of NVP following inhalation exposure has been investigated in two rat studies (BASF*, 1992b; 1987a). No studies have been conducted to investigate the carcinogenicity of NVP in other animal species or by the oral or dermal routes.

2 year study (BASF*, 1992b)

Groups of 100 male and 100 female Sprague-Dawley rats were exposed whole body to NVP vapour at concentrations of 0, 5, 10, 20 ppm (purity 99.9%, stabilised with 3 ppm Kerobit) for 6 h/d, 5 d/week for 2 years. Twenty rats of each sex from each dose group and 10 male and 10 female controls were sacrificed after 3 months. After 12 months a further 10 males and 10 females from each dose group including controls were sacrificed. Another 10 rats of each sex from each dose group including controls were exposed for 18 months and allowed a 6 months recovery period before sacrifice. The remaining animals (60 animals in each dose group and 70 control animals of each sex) were sacrificed at the end of 2 years exposure.

Observations included clinical signs, body weight, blood biochemistry and hematology, urinalysis, opthalmoscopy, gross pathology, organ weights and histopathology of the liver, nasal cavities and pancreas. Not all investigations were performed at each sacrifice time. The effects observed in the study are described as non-neoplastic and neoplastic effects.

Non-neoplastic effects

No treatment-related mortality occurred. No significant changes were found in body weight. Urinalysis was conducted in rats after 3, 6, and 12 months exposure and no treatment-related changes were observed. No other outward signs of toxicity were observed and no treatment-related changes were identified by opthalmoscopy.

The biochemical changes noted were slight dysproteinaemia in both sexes at all doses after 3 months persisting in females after 12 months at top two doses, slightly increased serum cholesterol level in females at 20 ppm after 12 months, markedly decreased serum alanine aminotransferase (ALAT) levels at 3 and 12 months in females but the severity was not dose-related, increase in reduced glutathione levels at top 2 doses in males and the top dose in females after 3 months and at all doses in males and the top dose in females after 12 months, significantly increased γ-GT levels at 20 ppm in females at 3 months and in males at 12 months which persisted after the recovery period at the end of 18 months exposure.

Haematological changes included increase in platelet counts in both sexes and a slight decrease in mean corpuscular haemoglobin (MCH) in males at top two doses at 3 months, slight anaemia and signs of persistent inflammation in females at 20 ppm after 12 months, dose-related anaemia in females at 24 months. No haematological changes were seen in males at 12 and 24 months.

At necropsy, relative and absolute liver weights were increased at the top dose in both sexes and at 10 ppm in males after 3 months, in all animals at top two doses and in males at 5 ppm after 12 months, and at the top dose in both sexes after 24

months. Dark coloured foci were observed macroscopically in occasional animals at all time points.

Microscopic changes seen in the liver are detailed in Table 11. These changes occurred in treated rats at all dose levels after the recovery period at the end of 18 months but not in controls.

Table 11: Incidence of microscopic changes in the liver in the 2 year rat study (BASF*, 1992b)

Exposure Period and Effects		Dose (ppm)			
	Sex	**0**	**5**	**10**	**20**
3 months					
Areas of enlarged hepatocytes containing clear cell areas and early degenerative changes in some cell nuclei	M	6	3	10	20
	F	0	0	3	17
12 months					
Clear cell areas as in 3 months	M	9	10	10	10
	F	1	7	9	10
Degenerative changes with cyst-like complexes filled with granular material (spongiosis hepatis)	M	2	6	4	10
	F	0	0	1	2
24 months					
Areas of focal hepatocyte hyperplasia	M	3	8	14	21
	F	5	15	20	28
Eosinophilic foci	M	3	5	10	17
	F	1	6	13	22
Foci of spongiosis hepatis	M	37	36	45	55
	F	7	19	28	42

Treatment-related changes in nasal cavities at all time points included olfactory epithelium atrophy mainly in the area between the septum and nasoturbinates, focal hyperplasia of basal cells underlying the olfactory epithelium within the nasal cavity and respiratory epithelia within the anterior part of the nasal cavity, and mucopurulent inflammation. All findings were observed in some animals from each dose level. The incidence and severity of the above changes were dose and duration related. Control animals were not affected at 3 months. In addition, focal metaplasia of respiratory epithelium into squamous epithelium in the septum and lateral wall of the nasal cavity were seen in occasional rats after 12 months. Minimal to marked focal hyperplasia of submucosal gland also occurred after 12 months. Minimal to slight goblet cell hyperplasia in the nasal epithlium was observed in a few animals from each dose group with dose-related incidence after 24 months. The above changes persisted in rats from each dose group following recovery period of 6 months after exposure for 18 months.

Changes in the larynx occurred only in groups exposed for 24 months. Epithelial hyperplasia and focal mucopurulent inflammation were observed at top doses in both sexes with changes being dose related only in females. Epithelial hyperplasia in males was also found at 10 ppm.

Neoplastic changes:

The incidence of tumours observed in the liver and nasal cavity are shown in Table 12.

Table 12: Incidence of tumors in the 2 year rat study (BASF*, 1992b)

Exposure period		**Dose (ppm)**			
Liver tumours	**Sex**	**0**	**5**	**10**	**20**
3 months	M	0	0	0	0
	F	0	0	0	0
12 months					
Macroscopic masses	M	0	0	0	0
	F	0	0	0	0
Hepatocellular adenomas	M	0	0	0	1
	F	0	0	0	0
18 months + 6 month recovery period					
Surviving animals at study termination	M	7	5	4	6
	F	2	5	3	6
Macroscopic masses	M	0	2	0	1
	F	0	0	0	2
Hepatocellular adenomas	M	1	2	0	1
	F	0	0	0	2
24 months					
Surviving animals at study termination	M	39	38	30	34
	F	29	25	26	26
Macroscopic masses	M	1	3	4	15
	F	2	4	5	25
Hepatocellular carcinoma	M	1	6	5	17
	F	1	3	6	26

Table 12: Incidence of tumors in the 2 year rat study (BASF*, 1992b) (cont.)

Exposure period		Dose (ppm)			
Nasal cavity tumours	**Sex**	**0**	**5**	**10**	**20**
3 months	M	0	0	0	0
	F	0	0	0	0
12 months					
Macroscopic masses	M	0	0	0	0
	F	0	0	0	0
Adenomas (from the respiratory epithelium or from the submucosal glands in the anterior part of the nasal cavity)	M	0	1	0	1
	F	0	0	0	1
18 months + 6 month recovery period					
Surviving animals at study termination	M	7	5	4	6
	F	2	5	3	6
Macroscopic masses	M	0	0	0	0
	F	0	0	0	0
Adenomas	M	0	0	1	2
	F	0	0	0	2
24 months					
Surviving animals at study termination	M	39	38	30	34
	F	29	25	26	26
Macroscopic masses	M	0	0	1	2
	F	0	0	0	2
Adenomas (from the respiratory epithelium or from the submucosal glands in the anterior part of the nasal cavity)	M	0	8	9	10
	F	0	2	8	12
Adenocarcinomas (from the olfactory epithelium or from the submucosal glands)	M	0	0	4	6
	F	0	0	0	4

Squamous cell carcinomas of the larynx occurred in 4 males and 4 females rats at 20 ppm after 24 months exposure.

3 months study (BASF*, 1987a)

Groups of 40 female Sprague-Dawley rats were exposed whole body to 0 and 45 ppm unstabilised NVP vapour (purity 99.7 – 99.9%) for 6 h/d, 5 d/week for up to 3 months (BASF*, 1987a). Ten animals in each dose group were sacrificed after 7 weeks and 3 months exposure and after post exposure recovery periods of 9 and 21 months. The investigations were confined to the liver only.

The toxic effects in animals sacrificed after 7 weeks and 3 months were similar to those observed in the other BASF studies described in section 10.5. Treatment-related changes were also evident in animals in both recovery groups. Biochemical changes were an increase in γ-GT and reduced glutathione levels in liver homogenates.

Microscopically enlarged hepatocytes were found throughout the liver. Cellular proliferation foci with glycogen accumulation in the foci were observed. Foci of

cirrhosis-like metaplasia and neoplastic changes were found in the group with 21 months recovery period. Six out of 10 treated and 4/10 control rats survived at study termination. No rats died prematurely. Four of the 6 treated rats survived developed liver neoplasms, 2 with neoplastic nodes and 2 hepatocellular carcinomas. Cells taken from 3/4 rats with tumours contained elevated levels of glycogen. No neoplastic changes were observed in controls.

A NOAEL could not be identified from these two carcinogenicity studies as tumours occurred at 5 ppm which was the lowest dose used.

M*echanistic studies*

A study by van de Zande* et al (1986) investigated the ability of NVP to induce hepatic ornithine decarboxylase. This enzyme is thought to be an early marker of carcinogenic activity. Intraperitoneal injections of 0, 5, 23, or 65 mg/kg NVP in dimethylsulphoxide were administered to male rats. Enzyme activity decreased with increasing dose, however, results indicated that NVP was able to induce this enzyme.

In a cell transformation assay undertaken in BALB/3Ts mouse cells (Litton Bionetics*, 1980c), a concentration range of 0.1 nL/mL to 0.5 μL/mL was selected to give a survival range of 83 to 52.3%. The results showed that a small progressive increase in the number of transformed foci per flask, however, this increase was not statistically significant.

Mechanisms of tumour formation

NVP is not mutagenic and it is likely that non-mutagenic mechanisms are involved in the development of both the liver and nasal cavity tumours. In the liver, chronic cytotoxicity is a possible mechanism. There is also some uncertainty about the mechanisms underlying the formation of the nasal cavity and laryngeal tumours. Chronic inflammation in the nasal cavity and larynx was observed in most of the animal studies and this may partly lead to the formation of tumours. However, considering other chemicals such as methyl acrylate and ethyl acrylate which cause similar non-neoplastic effects in the nasal cavity as NVP but were not tumourigenic after long term exposure to high concentrations by inhalation, it is possible that other unknown factors may also be involved.

11. Human Health Effects

Very few studies investigating the health effects of NVP in humans have been reported. This section is based on the UK draft report (1998). No additional, published or unpublished data were provided by applicants for the assessment or were identified in the literature.

11.1 Acute toxicity

The effects to humans of single exposures to NVP have not been studied. A report by BASF (BASF*, 1941) stated that inhalation exposure to an unknown concentration of NVP vapour by workers led to "stupefaction and fatigue".

11.2 Irritation and corrosivity

A human skin irritation study has been reported briefly by BASF (BASF*, 1941). A cotton wool plug soaked in NVP (purity unstated) was bound to the skin of 6 volunteers. Localised slight erythema was observed in 3/6 individuals after 8 hours. No signs of irritation were seen in the other 3 subjects.

No human data relating to eye or respiratory tract irritation are available.

11.3 Sensitisation

No information on the skin or respiratory tract sensitising potential of NVP in humans was available.

11.4 Immunotoxicity

There is no information on the immunotoxicity of NVP in humans.

11.5 Chronic effects

A cross sectional morbidity study (Zober* et al., 1992) has been conducted to examine the health of NVP production workers at a German manufacturing plant. The majority of the workforce in the study underwent comprehensive medical examinations. The study stated that air fed respirators were provided to workers during handling of NVP. No signs of ill health related to NVP exposure were reported. However, the actual levels of NVP to which the workforce were exposed are not clear. This study was inadequate to assess the carcinogenic potential of NVP in humans.

No mortality studies of NVP workers have been reported.

11.6 Reproductive toxicity

No studies investigating the fertility effects or developmental toxicity of NVP in humans have been reported.

11.7 Mutagenicity

No human data is available.

12. Hazard Classification

This section integrates data on kinetics, animal toxicity and adverse health effects in humans to characterise potential human health hazards from exposure to NVP and to classify these hazards.

Workplace substances are classified as hazardous to health if they meet the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 1999a) and dangerous in terms of physicochemical properties if they satisfy the criteria of the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (ADG Code) by Federal Office of Road Safety (FORS, 1998)

12.1 Physico-chemical hazards

NVP is a non-flammable and non-explosive liquid with low volatility and a flash point of 93^0C.

Classification

NVP does not meet the ADG Code criteria for assignment to any classes pertaining to physico-chemical properties.

12.2 Kinetics and metabolism

Information on the toxicokinetics of NVP in humans is not available. The results of studies in rats and dogs show that NVP is readily absorbed by the oral and inhalation routes. Dermal application of NVP in dogs resulted in relatively low absorption. However, the physico-chemical properties of NVP suggest that it will also readily cross the skin. Absorbed NVP is distributed throughout the body and deposited mainly in liver, kidney and small intestine. Studies indicate that oral bioavailability of parent NVP can be reduced by hydrolysis and possibly by polymerisation of NVP in the stomach. Species differences have been noted in the half life of NVP in plasma, the half life being about 3 hours in rats and only 20 - 40 minutes in dogs. NVP is qualitatively metabolised into highly polar compounds, however, the two major metabolites of NVP have not been identified. The majority of metabolites (90%) are eliminated rapidly by the urinary route, other routes being small amounts in the faeces, via bile and CO_2 in exhaled air. Studies show that NVP and its metabolites do not bind to DNA, RNA and plasma proteins.

12.3 Health hazards

12.3.1 Acute effects

The effects to humans of single exposures to NVP have not been studied. Symptoms of "stupefaction and fatigue" have been reported following inhalation exposure to an unknown concentration of NVP vapour by workers.

In animals, the oral LD_{50} in rats ranged from 834 to 2500 mg/kg. The dermal LD_{50} ranged from 1043 - 4127 mg/kg in rats and 3000 - 5000 mg/kg in guinea pig. Inhalational LC_{50} (4h) to NVP aerosol was 666 ppm (3.07 mg/L) in rats, but no deaths were observed in a range of species following exposure to NVP vapour at concentrations up to 803 ppm (3.7 mg/L) for 6 or 8 hours in some earlier studies.

The acute effects of NVP in animals include irritation of respiratory tract, increased salivation and nasal secretion, respiratory distress, ataxia, narcosis and lack of appetite. High doses by the oral route caused lachrymation, ptosis, diuresis, and loss of righting reflex.

The predominant systemic effects by all three routes of exposure are on the liver such as centrilobular necrobiosis, isolated necrotic cells, and changes in cell nuclei (mitosis, polymorphism, pale karyoplasm). In addition, increases in alkaline phosphatase and reductions in total protein levels were noted. However, these non-lethal effects are reversible.

Classification

NVP meets the Approved Criteria (NOHSC, 1999a) for classification as a harmful substance on the basis of acute lethal effects by oral, dermal or inhalation exposure (R20/21/22 - harmful by inhalation, in contact with skin and if swallowed).

12.3.2 Irritant effects

Localised erythema was observed in an early human skin irritation study and several studies in rabbits at doses varying from 400 to 2500 mg/kg. Recent studies in animals have indicated that diluted and undiluted NVP does not cause skin irritation following occlusive dressing at doses up to 10430 mg/kg for 6 or 24 hours. Severe skin irritation was observed in earlier studies in rabbits and rats. It is unclear why this effect was produced in these earlier studies.

No human data relating to eye or respiratory tract irritation are available. Direct eye contact with liquid NVP in rabbits has been reported to cause irreversible corneal opacity, conjunctival chemosis, and iris lesions. No eye irritation was observed following repeated exposure to NVP vapour at a dose of 20 ppm in rats.

Increased nasal secretions were observed in a range of animal species following single exposure to NVP aerosol at concentrations ranging from 0.8 to 5.6 mg/L and to NVP vapour at around 120 ppm. Signs of respiratory tract irritation were observed in mice after repeated inhalation of 5 ppm NVP vapour for one week.

Classification

Liquid NVP meets the Approved Criteria for classification as an eye irritant (R41 – serious eye effects). NVP vapour and aerosol meet the Approved Criteria for classification as a respiratory tract irritant (R37 – irritating to respiratory system). NVP is not considered a skin irritant.

12.3.3 Sensitisation

No human data are available. A study in guinea pigs conducted according to contemporary regulatory protocols demonstrated that NVP did not induce skin sensitisation.

Classification

NVP does not meet the Approved Criteria for classification as a sensitiser.

12.3.4 Repeated dose toxicity (other than carcinogenicity)

Negative findings were reported in a cross sectional morbidity study conducted in NVP production workers. However, the actual levels of NVP to which the workforce were exposed are unknown.

In animal studies, effects after repeated or prolonged exposure to NVP by the inhalation and oral routes have been investigated in a range of species, using varying doses and exposure durations. Following repeated inhalation of NVP, mortality occurred at 45 ppm (0.207 mg/L) in mice and 120 ppm (0.553 mg/L) in rats. The liver and nasal cavities are the major target organs in rats and mice. Toxic effects reported in the liver in rats after exposure to 10 ppm (0.046 mg/L) NVP for 3 months include enlarged hepatocytes with clear cell areas and degenerative changes of the nucleus (BASF*, 1992b). Other liver effects such as centrilobular necrobiosis, fatty infiltration and glycogen accumulation within centrilobular hepatocytes were observed at higher doses. Consistent biochemical changes such as dysproteinaemia, increased levels of enzyme markers of liver toxicity and γ-GT and haematological changes indicative of anaemia were found after exposure to 15 ppm NVP for 7 weeks and 10 ppm after 3 months exposure. There were indications that these changes were irreversible. Cell hyperplasia and inflammatory changes in the olfactory and respiratory epithelia were observed in rats and mice at 5 ppm in a number of repeated exposure studies (BASF*, 1988d; 1986a; 1992b). The severity of the pathological changes was related to both dose and duration of exposure.

A NOAEL 1 ppm (1 mg/kg) was identified in a 3 month study using rats. However, it is not certain whether this NOAEL is applicable to longer or lifetime exposures as there are indications that at 5 ppm (5 mg/kg) hepatotoxicity takes longer than 3 months to develop.

Administration of NVP by the oral route also results in damage to the liver, however, the dose required to produce histopathological changes is much higher than that required by inhalation. This is probably due to some of the NVP undergoing hydrolysis in the acidic environment of the stomach prior to absorption. A NOAEL of 3.6 mg/kg has been identified in a drinking water study.

Toxic effects were observed in the nasal cavity at 5 ppm (0.023 mg/L) in 3 month studies in rats. However, these nasal cavity effects are not used as a basis for classification for repeated dose toxicity as they are considered to be local irritant effects of NVP.

Classification

NVP meets the Approved Criteria for classification as a harmful substance by inhalation (R48/20) based on the evidence of systemic toxicity in liver at 10 ppm (0.046 mg/L) in 3 month rat studies.

12.3.5 Reproductive toxicity

No studies investigating the effects on fertility or developmental toxicity of NVP in humans have been reported. No animal studies have been conducted to specifically investigate reproductive or developmental toxicity of NVP. No NVP induced adverse effects on the reproductive organs were observed in rats and mice in repeated dose toxicity studies following inhalation or oral administration of NVP.

Classification

NVP does not meet the Approved Criteria for teratogenicity for effects on fertility or developmental toxicity.

12.3.6 Mutagenicity

No human data is available. Negative results have been observed in mutagenicity tests conducted with NVP in a wide range of *in vitro* and *in vivo* test systems.

Classification

NVP does not meet the Approved Criteria for mutagenicity.

12.3.7 Carcinogenicity

No mortality studies of NVP workers have been reported. A 2-year carcinogenicity study (BASF*, 1992b) clearly shows that exposure to NVP by inhalation resulted in hepatocellular carcinomas, nasal adenomas and adenocarcinomas, and squamous cell carcinomas in the larynx in rats. Liver tumours were also observed in rats following inhalation of NVP for 3 months and allowing 21 months for recovery (BASF*, 1987a), indicating that irreversible liver lesions occur after a relatively short period of exposure and progress to form tumours even after exposure to NVP has stopped.

A NOAEL could not be identified from these studies as tumours occurred at 5 ppm which was the lowest dose tested. Given that NVP is not a mutagen, it is unknown what non-mutagenic mechanisms underlie the development of tumours induced by NVP vapour.

Carcinogenicity has not been tested in other experimental animals.

Classification

NVP produces liver and nasal cavity tumours in rats at 5 ppm and tumours in the larynx at 20 ppm. The available carcinogenicity studies have been conducted only in one species (rat) with no supporting evidence of the mutagenic potential of NVP and absence of human data. Based on this data NVP is classified as a Category 3 Carcinogen (R40).

13. Effects on Organisms in the Environment

No ecotoxicity tests were provided from applicants. The following toxicity results have been obtained from the IUCLID data sheet (EC, 1996a), or through the UK draft report (1998). Data from IUCLID are supplied by industry and not validated by the EU. Where IUCLID results do not appear in the UK draft report (1998), they are assumed by EA to be invalid tests. They are reported here nonetheless due to the lack of information available. EA has not viewed any of the test reports, and figures are stated as reported. No chronic testing on any trophic level appears to have been conducted.

Further results have been calculated using QSAR and obtained from the ASTER database (USEPA, 1998). QSAR generated results need to be treated with caution as they are calculated and based on data obtained for similar chemicals, and can only be used as a guide. One chronic value for fish has been calculated.

13.1 Toxicity to fish

The toxicity of NVP to fishes is summarised in Table 13.

Table 13: Toxic effects on fish

	Species	Test Duration	Result (mg/L)	Reference:
Fish	*Salmo gairdneri* (freshwater)	96 h	LC_{50} = 913 LC_{100} < 1000 NOEC = 464	(EC, 1996a)
	Rainbow trout *(Oncorhynchus mykiss)*	96 h	LC_5 = 557 LC_{50} = 913 LC_{95} = 1495	
	Rainbow trout *(Oncorhynchus mykiss)*	96 h	LC_{50} = 1325	(USEPA, 1998)
	Bluegill sunfish (*Lepomis macrochirus*)	96 h	LC_{50} = 1841	(USEPA, 1998)
	Fathead minnow (*Pimephales promelas*)	96 h	LC_{50} = 2585	(USEPA, 1998)
	Channel catfish (*Ictalurus punctatus*)	96 h	LC_{50} = 1109	(USEPA, 1998)
(Chronic)	Fathead minnow (*Pimephales promelas*)	32 d	LC_{50} = 302	(USEPA, 1998)

The results of both testing and modelling indicate that NVP can be considered practically non-toxic to fish under both acute and chronic exposure. There was generally good agreement between the modelled values and the tested values.

13.2 Toxicity to aquatic invertebrates

The toxic effects of NVP on aquatic invertebrates are showed in Table 14.

Table 14: Toxicity to aquatic invertebrates

	Species	Test Duration	Result (mg/L)	Reference:
Daphnia	*Daphnia* sp.	48 h	EC_0 = 3.6 EC_{50} = 45 EC_{100} = 450	(EC, 1996a)
	Daphnia magna	48 h	LC_{50} = 1093	(USEPA, 1998)

There was only one reported test on *Daphnia* from the IUCLID data sheet (EC, 1996a). This test indicated NVP can be considered slightly toxic to aquatic invertebrates, with a 48 h LC_{50} of 45 ppm. The modelled result showed a LC_{50} of 1093 ppm, which is 2 orders of magnitude higher than the tested result.

13.3 Toxicity to aquatic plants

Table 15 shows the toxicity of NVP to aquatic plants.

Table 15: Toxicity to aquatic plants

	Species	Test Duration	Result (mg/L)	Reference:
Algae	*Scenedesmus subspicatus*	96 h	$E_\beta C_{10}$ = 125 **$E_\beta C_{50}$ = 770** $E_\mu C_{10}$ = 640 **$E_\mu C_{50}$ > 1000**	(UK draft report, 1998)

$E_\beta C_{10}$ and $E_\beta C_{50}$ are based on inhibition of reproduction. $E_\mu C_{10}$ and $E_\mu C_{50}$ are based on inhibition of growth rate.

Based on the results of this solitary test NVP can be considered practically non-toxic to aquatic plants using either inhibition of reproduction or inhibition of growth rate as the end point.

13.4 Other studies

Table 16 shows the toxic effects of NVP on micro-organisms.

Table 16: Toxicity to micro-organisms

	Species	Test Duration	Result (mg/L)	Reference:
Micro-organisms	*Pseudomonas*	17 h	EC_{10} = 3400 EC_{50} = 4800 EC_{90} = 7200	(EC, 1996a)
	Active sludge	30 minutes	EC_{10} > 1995*	(EC, 1996a)

* no disturbance of degradative activity of active sludge expected when substance introduced to adapted STP

As reported from the draft UK report (1998), no effects of NVP on the inhibition of respiration of activated sludge was observed up to the highest tested concentration of 1995 mg/L.

13.5 Summary of environmental effects

Following the guidelines from Mensink *et al* (1995), NVP can be described as slightly to very slightly toxic to aquatic vertebrates, aquatic invertebrates and aquatic plants based on experimental acute exposure results. The only chronic value obtained was a calculated result which indicated very slight toxicity to fish.

The limited results available suggest invertebrates to be the most sensitive species in the aquatic system, with toxicity results for *Daphnia* (48h EC_{50} = 45 ppm) being at least an order of magnitude more sensitive than fish and algae.

13.6 Derivation of Predicted No Effect Concentration (PNEC) for aquatic organisms

Since only acute test results are available for three trophic levels, an assessment factor of 1000 is applied to the lowest acute toxicity result that is the EC_{50} of 45 mg/L for *Daphnia*. This gives a PNEC of 45 μg/L.

14. Risk Characterisation

14.1 Occupational risks

In this section, the results of the hazard and occupational exposure assessments have been combined to characterise the potential risks of adverse health effects in workers exposed to NVP.

Results from risk characterisation provide the basis for risk management strategies to reduce exposure and increase worker awareness of potential hazards and safe handling of NVP.

14.1.1 Methodology

The risk to human health from exposure to NVP has been characterised using methodology commonly adopted in international assessment (EC, 1994; OECD, 1993)

The following steps are used for risk characterisation of the critical effects caused by repeated or prolonged exposure:

1. Identification of the critical health effect(s).

2. Identification of the most appropriate/reliable NOAEL (if available) for the critical effect(s).

3. where appropriate, comparison of the NOAEL with the estimated human dose (EHD) to give a margin of exposure (MOE), that is:

$$MOE = \frac{NOAEL}{EHD}$$

   Where actual exposure monitoring data are unavailable or insufficient, the EHD may be determined using exposure assessment models, such as the EASE model.

4. Characterisation of risk by determining whether the margin of exposure indicates concern for the human population under consideration.

The MOE is a measure of the likelihood that the NOAEL exceeds estimated human exposure, i.e. as the MOE increases, the risk of potential adverse effects decreases. Expert scientific judgment is required when deciding whether the MOE is of significant magnitude. The process of characterising risk requires consideration of a number of parameters such as the completeness and quality of the database (including exposure data), nature and severity of the effects, inter/intra species variability and characteristics of the exposed human population.

14.1.2 Critical health effects

No useful human data are available for NVP and therefore risk characterisation is based on the results of animal studies.

Acute effects

Although the liver, lungs and kidneys are the major target organs following acute exposure to NVP by all three routes of exposure, the predominant effects are on the liver. Histopathological changes such as centrilobular necrobiosis, isolated necrotic cells, and changes in cell nuclei (mitosis, polymorphism, pale karyoplasm) were observed in animals after exposure for 2 days. In addition, increases in alkaline phosphatase and reductions in total protein levels were noted. However, these non-lethal effects are reversible.

Liquid NVP is a severe eye irritant. NVP vapour and aerosol are considered to be respiratory tract irritants.

Effects due to repeated exposure

The toxic effects identified from repeated inhalational exposure to NVP in animal studies were liver and nasal cavity effects. In a 3 month study in rats, no effects were seen at 1 ppm (NOAEL). However, it is not certain whether this NOAEL is applicable to longer or lifetime exposures as there are indications that at 5 ppm hepatotoxicity takes longer than 3 months to develop.

Carcinogenicity studies in animals by the inhalation route indicate that NVP is carcinogenic in rats. The principal tumour sites are the liver, the nasal cavity and larynx. A NOAEL could not be identified from these studies as tumours occurred at 5 ppm which was the lowest dose tested. NVP is not a mutagenic, however, the exact mechanisms underlying the development of tumours induced by NVP vapour is not known.

14.1.3 Uncertainties in risk characterisation

Uncertainties arise in any risk characterisation process due to factors such as inadequate information, assumptions made during the process and variability in experimental conditions. These uncertainties need to be considered when deciding if an estimated exposure is of concern. Examples of uncertainties inherent in the assessment of health risk for NVP are as follows:

Inadequate information

- lack of representative atmospheric monitoring;
- lack of data on the health effects of NVP in humans;
- appropriateness of the NOAEL identified from the 3 month rat study;
- lack of reliable data in bioavailability of NVP vapour across the lungs; and
- lack of data on the permeability of NVP through the skin or on dermal absorption of NVP.

Assumptions in the assessment process

- that dose-response relationships are likely to be similar in rats and humans;
- that occupational dermal absorption of vapours is minimal; and

- chronic liver and nasal cavity effects seen in animals may be relevant to humans.

14.1.4 Occupational health and safety risks

Risks from physicochemical hazards

NVP is a non-flammable and non-explosive liquid with low volatility and a flash point of 93^0C. Its flammability limits in air are 1.4% to 10% by volume. The risk of explosion is minimal.

NVP is relatively stable under controlled storage conditions and is marketed with a stabiliser/polymerisation inhibitor. However, it can react vigorously with oxidising materials. The risk of fire is low when NVP is exposed to heat or flame but it may decompose to produce toxic fumes of carbon monoxide (CO) and nitrogen oxides (NOx).

Risks during formulation

Acute effects

No atmospheric monitoring data were available during formulation of products containing NVP. Eye contact to liquid NVP is not expected under normal conditions during formulation of NVP products. However, there is the possibility of accidental exposure to liquid NVP, either from contaminated hands or as a result of splashing.

Vapour concentrations from single exposures are unlikely to be high enough to result in respiratory irritation under routine operating conditions where the operation is well-controlled, for example, with good ventilation. However, irritant effects may be experienced in work situations where aerosols are generated or where high vapour concentrations may occur, for example, during high speed mechanical mixing.

Adverse effects due to repeated exposure

According to the data provided for assessment, formulation is a batch process and exposure to NVP in this scenario will only occur on the days when NVP based products are formulated. Very little personal sampling has been carried out to determine the actual levels of NVP to which workers are exposed. The EASE model predicted exposures of up to 1.5 ppm with LEV and 6.25 ppm without LEV at workplaces (8-hour TWA) following inhalation exposure.

A low NOAEL (1 ppm) was identified for NVP from a 3 month rat study. Comparison of this low NOAEL with EHD would result in unacceptable MOEs even at very low exposures. In addition, this NOAEL of 1 ppm may not be the most appropriate as the NOAEL was obtained from a 3 month study, It is possible that adverse effects in the liver may develop in a longer term study at the same dose.

Liver and nasal cavity tumours were observed at 5 ppm (LOAEL) in rat studies. The workers exposure levels estimated by the EASE model range from 0.25 to 6.25 ppm during formulation. The lower level of the range is only about 20 times lower than the levels that produced liver and nasal cavity tumours whereas the higher level of the range is even higher than the NOAEL. In addition, dermal

contact to liquid NVP also occurs during formulation. Dermal exposure of 0.1 mg/cm^2/d was estimated by the EASE model. In addition to inhalation exposure, dermal exposure would result in higher levels of NVP in the body. As the relevance of these animal findings to humans is not known, the estimated exposures are considered to be of concern.

Risk during use of NVP in laboratory

No atmospheric monitoring data were available during use of NVP in laboratory in Australia or overseas. Exposure prediction for NVP using the EASE model was not conducted due to the nature of uses (one-off use in the laboratory) and immediate polymerisation of NVP in reactions.

The risk during use of NVP in laboratory is minimal as NVP is polymerised immediately in reactions and therefore the potential exposure of workers to NVP is likely to be low except during accidental spills.

Risk during use of NVP products

Occupational exposure of workers to NVP during paper coating is negligible as the process is enclosed and may only occur during cleaning of equipment. Therefore, the risk during use of paper coating products is minimal.

However, exposure to NVP during use of UV curing inks containing NVP is higher than during use of paper coating products although the inks are applied using an automated process in majority of workplaces. Modeled data for workplaces with LEV indicated a level of 0.1 - 0.6 ppm when using products containing 20% NVP. This higher end of this range is similar to the Australian measured data (0.7 ppm during printing, concentration of NVP in products not stated) and is only eight times lower than the LOAEL (5 ppm) which produced liver and nasal cavity tumours in rats. Similar as formulation of NVP products, dermal contact occurs during use of NVP products. Dermal exposure of 0.2 to 1 mg/cm^2/d was estimated by the EASE model for using products containing 20% NVP and this would result in higher levels of NVP in the body. As the relevance of these animal findings to humans is not known, exposure of workers to NVP in this scenario is of concern. The modeled data indicated that higher exposure levels may occur at workplaces without LEV (0.5 - 2.5 ppm using 5% NVP products). Therefore using NVP products containing as low as 5% NVP in workplaces with only general dilution ventilation is of concern for human health.

Risk during use of PVP and PVP products

The risk during use of PVP is substantially lower than during use of NVP products as the maximum residual NVP monomer level in PVP imported into Australia is 0.2% (2000 ppm) whereas the concentrations of NVP in NVP products range from 4 to 20%. Therefore risk characterisation for this scenario is not undertaken.

NICNAS did not identify the PVP content in products containing PVP. However, overseas data indicates that the concentrations of PVP in PVP products range from 0.05 to 10%. Occupational exposure of workers to residual NVP monomer is negligible and therefore the risk during use of PVP products is minimal.

14.1.5 Areas of concern

Risk characterisation has indicated that there are health concerns for workers exposed to NVP during formulation and use of NVP products.

There may be a risk of acute effects on the eyes during formulation of NVP products such as accidental contact with liquid NVP, either from contaminated hands or as a result of splashing.

As NVP is relatively non-volatile it is considered unlikely that, for uses identified in Australia, levels of vapour and/or aerosol would be high enough to result in respiratory irritation, although it may occur where inadequate ventilation exists during formulation.

Comparison of the estimated exposure and the LOAEL of 5 ppm for repeated exposure indicated that there was concern for workers repeatedly exposed to NVP during formulation of NVP products and use of UV curing inks containing NVP.

14.2 Environmental risks

The PEC/PNEC ratios show that NVP should not cause adverse effects on the aquatic compartment. No manufacture is conducted in this country, so the environmental risk is addressed in Table 17 for formulation and end use. A total risk is also determined, and assumes all release in a day comes from a single point source and goes through one STP.

Table 17: The environmental risk for formulation and end use

Process	$PEC_{effluent}$ (µg/L)	PEC/PNEC	PEC_{local} (µg/L)	PEC/PNEC
Formulation	1.48	0.03	0.15	<0.01
End Use				
Screen Printing	0.59	0.01	0.06	<0.01
Other[a]	0.23	<0.01	0.02	<0.01
TOTAL	**2.3**	**0.04**	**0.23**	**<0.01**

These values indicate that there will be no adverse effects on aquatic organisms, or on microbial activity in a STP arising from the formulation or end use of NVP in Australia.

14.3 Public health risks

The main potential source of public exposure to NVP is likely to be from consumer products, particularly cosmetic/toiletries. The main route of exposure is dermal contact. For calculation of consumer exposure, hair mousse, shampoo, conditioner and facial cream may be used as representatives of NVP containing cosmetic/toiletry products. Use levels of these products in the following calculations are adopted from the EC Technical Guidance Document (EC, 1994).

Assuming an NVP level of 200 µg/g (ppm) in hair mousses, 5 g product used on each application, one application per day and 10% of the product in contact with the scalp, the daily dermal exposure would be 100 µg (200 µg/g x 5 g x 10% x 1).

For facial creams, assuming an NVP level of 4 µg/g, 0.8 g on each application and one applications per day, the amount of NVP applied onto the skin would be around 3 µg/d (4 µg/g x 0.8 g x 1). The daily exposure to NVP from shampoos and conditioners would be 60 µg/d assuming a NVP level of 30 µg/g in the shampoo and 20 µg/g in the conditioner, 12 g of each product used on each application, 10% of the product remaining on the skin following rinsing and one application per day [(30 µg/g + 20 µg/g) x 12 g x 10% x 1]. Inhalation exposure may also occur from using cosmetic products, but the air level of NVP is expected to be very low in home situations.

There is no information on dermal absorption of NVP in humans. Poor dermal absorption was demonstrated in dogs; however, the physicochemical properties and oral and dermal LD_{50} values in rats suggest good dermal absorption. Taking an assumption of 100% dermal absorption, the systemic exposure from dermal contact with mousse, shampoo and facial cream would be 163 µg/d (100 + 3 + 60 µg) or 2.7 µg/kg/d for a 60 kg adult.

Toxicity studies in animals identified that the target organs of toxicity are the liver by oral or inhalation exposure and the respiratory tract by inhalation. NVP is carcinogenic in rats by inhalation exposure to NVP vapour at 5 ppm (the lowest dose) and above. The NOAEL for inhalation exposure is 1 ppm in a 3-month rat study. There are no long term oral or dermal studies. Assuming a respiratory volume of 0.161 m^3/d and body weight of 215 g for rats (Anderson & USEPA, 1983), and 100% absorption by inhalation, the systemic exposure to 1 ppm (equal to 4.61 mg/m^3) NVP vapour for 6 h/d would be 0.86 mg/kg/d (4.61 mg/m^3 x 0.161 m^3/d x 6 h/24 h /0.215 kg).

Based on the oral NOAEL of 3.6 mg/kg/d in a 3 month rat study, a systemic exposure of 2.7 µg/kg/d would represent a safety margin of about 1300. In comparison with the inhalation NOAEL of 1 ppm (equivalent to 0.86 mg/kg/d), the safety margin would be around 300. Since NVP is a non-mutagenic carcinogen and a NOAEL for long term exposure has not been established, a safety margin of at least 2000 is considered adequate for establishing acceptable public exposure levels.

In practice, NVP levels in cosmetic products may be lower, as one PVP importer showed the presence of only 1.6 ppm NVP in one batch PVP and another importer stated the presence of NVP at a maximum level of 10 ppm in PVP. However, consumer exposure to NVP may also occur from other cosmetic products and/or other consumer products. Without analytical data on the level of NVP in cosmetic products and reliable dermal absorption data, 100% dermal absorption and the maximum possible level (2000 ppm) of residual NVP monomer in PVP have to be used for the calculation of public exposure. Based on the above assumptions, the presence of high levels of NVP in PVP for cosmetic use does not give an adequate margin of safety for consumers.

In Europe, NVP residues in PVP are generally below 100 ppm (UK draft report, 1998). At the use level of up to 10% PVP in cosmetic products, a NVP level of 200 ppm in PVP would provide a safety margin of 3000 or higher based on the above calculations.

15 Risk Management

In this section, measures currently employed and/or recommended in the management of human health risks from occupational exposure to NVP and products containing NVP are discussed.

The key elements in the management of risks discussed in this section include:

- control measures;
- hazard communication;
- atmospheric monitoring;
- regulatory controls; and
- emergency procedures.

15.1 Control measures

According to the NOHSC *National Model Regulations for the Control of Workplace Substances* (NOHSC, 1994c), exposure to hazardous substances should be prevented or, where this is not practicable, adequately controlled, so as to minimise risks to health and safety. The NOHSC *National Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) provides further guidance in the form of a hierarchy of controls strategies, namely:

- elimination;
- substitution;
- isolation;
- engineering controls;
- safe work practices; and
- PPE.

15.1.1 Elimination and substitution

Elimination is the removal of a chemical from a process and should be the first option considered when minimising risks to health. Information provided during assessment indicates a decline in the use of NVP in UV printing inks. One manufacturer of UV inks reported that a NVP reduction program was being conducted to reduce or eliminate the use of NVP in ink products.

In situations where it is not feasible or practicable to eliminate the use of a chemical, substitution should be considered. Substitution includes replacing with a less hazardous substance, the same substance in a less hazardous form or the same substance in a less hazardous process.

A manufacturer of UV curing inks recently reported that a few suitable alternative products had been developed to replace NVP in printing inks. However, NVP continues to be used in some products.

NVP users need to evaluate the technical issues, cost, health and safety and environmental effects of each option when considering substitution of NVP. In

particular, if replacement of NVP with another substance is considered, the human health and environmental effects of the substitute need to be considered to ensure that NVP is not being replaced by a more hazardous substance. Substitutes for NVP should be of a lower toxicity.

15.1.2 Isolation

Isolation as a control measure aims to separate employees, as far as practicable, from the chemical hazard. This can be achieved by distance, use of barriers or enclosure.

At most of the printing ink formulation sites visited, isolation of the mixing process was achieved by either housing the mixing tank or containers in a separate workshop or operating at a distance from other activities.

There is limited scope for isolation of workers from potential exposure to NVP during laboratory applications as such applications usually require manual handling.

15.1.3 Engineering controls

Engineering controls are plant or processes which minimise the generation and release of hazardous substances. They include enclosure or partial enclosure, local exhaust ventilation and automation of processes.

Formulation

The types of engineering controls used during UV ink and paper coating formulation vary at different sites, such as, the extent of enclosure of the process and type of ventilation. The mixing process was open at two sites visited and partially open at another site. Local exhaust ventilation was the most common engineering control to ensure that the vapours are drawn away from the work area. Other types of ventilation such as industrial fans and general ventilation were also observed.

Best practice to be followed during formulation is total enclosure of the processes, such as transfer of NVP to the mixing vessel through enclosed pipes, emptying of the mixing vessel into smaller containers through closed pipelines, and use of a lid on the mixing vessel during mixing. Atmospheric monitoring at regular intervals ensures that the control measures are adequate to prevent exposure.

Use of NVP products

From the data available for assessment, control measures identified during use of NVP products vary from general ventilation to local exhaust ventilation.

Laboratory use of NVP

Laboratories using NVP were equipped with both mechanical exhaust ventilation and fume cupboards/hoods.

15.1.4 Safe work practices

Safe work practices are administrative practices which require people to work in safe ways. It is important in reducing exposure to solvent emissions. Information obtained during the assessment indicates that safe work practices followed at some of the work sites are:

- restricting the number of workers in the mixing process during formulation and during use of UV inks;
- excluding any access that is not essential to the mixing area during formulation and use of UV inks;
- using UV inks in a well ventilated area.

15.1.5 Personal protective equipment

PPE is used to minimise exposure to or contact with chemicals. As a general philosophy, PPE should be used where other control measures are not practicable or adequate to control exposure and in conjunction with engineering controls and not as a replacement.

PPE used in some of the worksites for handling NVP include the following:

- overalls;
- safety glasses;
- footwear; and
- protective gloves.

Information provided for assessment indicates that gloves are generally provided at most workplaces. Types of gloves specified by some formulators and end users of NVP were PVC, nitrile, and rubber gloves. It is important to select gloves that are resistant to the chemical exposed. Australian/New Zealand Standard AS 2161 (1998) *Industrial Safety Gloves and Mittens* provides guidance in selecting and use of protective gloves for handling hazardous substances.

Respiratory equipment is not normally used during routine use of NVP products. Disposable masks were used during screen printing at one workplace visited.

15.2 Hazard communication

15.2.1 Assessment of MSDS

Introduction

MSDS are the primary source of information for workers involved in the handling of chemical substances. Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers are obliged to provide an MSDS to their customers for all hazardous substances. Employers must ensure that MSDS for any hazardous substance used in the workplace is readily accessible to employees with potential for exposure to the substance.

NVP is a hazardous substance as defined under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 1999a).

Under the Approved Criteria, concentration cut-off points apply for the classification of hazardous substances according to their health effects. Mixtures are hazardous if any ingredient meets any of the health effects criteria and is present at a concentration above the minimum concentration cut-off level for that ingredient.

The concentration cut-off levels that apply to the health hazard classification of NVP and the relevant risk phrases are shown in Table 18.

Two MSDS for pure NVP, and 19 MSDS for mixtures containing NVP were provided to NICNAS in the course of this assessment. Seventeen MSDS for mixtures indicated that the product contained at least 1% NVP, making it a hazardous product according to the criteria shown in Table 18. The remaining two MSDS for mixtures stated that NVP was present in the range "<10%", and it could not be ascertained if NVP was present at levels above the hazardous concentration cut-off of 1%.

Table 18: Concentration cut-off levels for hazard classification of NVP

Health Hazard Criteria	Risk Phrases*	Concentration Cut-off
Category 3 carcinogen	R40	≥1%
Eye Irritant	R36	≥5%
Eye Irritant (serious eye damage)	R41	≥10%
Harmful by inhalation on the basis of effects after repeated or prolonged exposure	R48/20	≥10%
Irritating to respiratory system	R37	≥20%
Harmful on the basis of acute lethal effects	R20/21/22	≥25%

*R20/21/22	Harmful by inhalation, in contact with skin and if swallowed
R36	Irritating to eyes
R37	Irritating to respiratory system
R40	Possible risk of irreversible effects (Carcinogen Category 3)
R41	Risk of serious damage to eyes
R48/20	Danger of serious damage to health by prolonged exposure through inhalation

The two MSDS for pure NVP and 17 MSDS for mixtures containing hazardous levels of NVP were assessed against the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994b). The MSDS Code of Practice provides guidelines on the content and format of MSDSs. It identifies 'core' information that should be present in all MSDS. This assessment focussed on the adequacy of the information provided in relation to the following selected core elements of an MSDS: product identification; health hazard information; precautions for use; safe handling information; and company details.

Information considered most important in each of these sections was identified and listed in Table 19.

Table 19: The key information checked for inclusion in MSDS for pure NVP

MSDS Section	Items Checked
Introductory	Presence of statement of hazardous nature i.e. 'Hazardous according to the criteria of Worksafe Australia'.
Product Identification	• Product name; • UN Number[#];^ • Dangerous Goods Class[#];^ • HAZCHEM code[#];^ • Poisons Schedule[#];^ • Major recommended uses; • Disclosure of presence of NVP; • Disclosure of the exact proportion or a range.
Health hazards	• Acute and chronic health effects[1]; • Appropriate first aid statements[2].
Precautions for use	• Exposure standard[#]; • Advice on PPE.
Safe handling^	Advice on storage and transport, spills and disposal, fire/explosion hazard.
Company details and contact point	• Name, address and telephone number of company; • Emergency telephone number; • Title and telephone number of a contact point.

1. acute effects: respiratory distress, eye irritation, CNS effects, nasal irritation, and absorption through the skin. chronic effects: anaemia and carcinogenicity.

2. Inhalation: Remove from exposure. Keep warm and at rest until fully recovered; Swallowed: Do NOT induce vomiting. Give a glass of water;
Eyes: Immediately flush with plenty of water;
Skin: Remove contaminated clothing and wash skin thoroughly.

[#] NVP is not classified under these items, however in these circumstances, the MSDS Code requires a statement that no number/class/code/standard has been allocated.

^ items not checked in the case of MSDS for mixtures.

An MSDS for a product containing a mixture of ingredients must address the hazards posed by the end substance as a whole, taking into account the interactions of the chemicals in the mixture. Such full assessments of individual MSDS were outside the scope of this report. Therefore some of the elements listed in Table 19 were not addressed in the assessment of MSDS for mixtures, as the presence of other chemicals might alter the information from that required for pure NVP. However, with regard to health effects, mixtures were checked for inclusion of at least the health effects associated with NVP. In deciding which of the health effects should apply in each case, the concentrations of NVP in the product, and the cut-off levels associated with the different hazard criteria were taken into account.

A sample MSDS, prepared in accordance with the MSDS Code of Practice, is provided in this report at Appendix 5. The sample MSDS is for guidance purposes only. Under the NOHSC *National Model Regulations for the Control of*

Workplace Hazardous Substances (NOHSC, 1994c), manufacturers and importers have the responsibility to compile their own MSDS and ensure that information is up-to-date and accurate.

Results of assessment of MSDS for pure NVP

Statement of hazardous nature

Neither MSDS had a statement of hazardous nature.

Product identification

Both MSDS had the product name and disclosed the presence and proportion of NVP. Neither had information relating to UN Number, Dangerous Goods Class, HAZCHEM Code, Poisons Schedule Number, or major recommended uses.

Health hazard information

Overall, health effects were covered well, although neither mentioned anemia, and one MSDS did not mention the risk of CNS effects or nasal irritation. With regard to first aid statements, neither had an instruction not to induce vomiting. One MSDS had a contrary instruction to induce vomiting. Neither MSDS had an 'Advice to Doctor' section.

Precautions for use

Neither had a statement concerning exposure standards. Both had appropriate recommendations regarding PPE, and engineering controls.

Safe handling information

For both MSDS, little information was provided on storage of NVP. Some information was provided on spills and disposal. Fire/explosion hazard information was well addressed.

Company details

One MSDS had no Australian contact details at all. The other MSDS, while it contained the name of the company and a telephone number, did not contain an emergency telephone number or the title and telephone number of a person to contact.

Results of assessment of MSDS for mixtures containing NVP

Statement of hazardous nature

Fourteen products contained the required statement. The remaining three products indicated which ingredients in the mixture were hazardous according to the Approved Criteria. Under the MSDS Code of Practice, the statement of hazardous nature is intended to indicate the hazardous nature of the product as a whole, rather than individual ingredients. It is possible that the application of the statement as described in the MSDS Code of Practice may be being misunderstood in cases such as the three described above.

Product identification

All MSDS contained the following core information: name of the product, disclosure of the presence of NVP and an exact proportion or range of the ingredients in the mixture. Fourteen indicated the major recommended uses, however 3 MSDS contained no information on the recommended use of the product. Due to the presence of other ingredients, together with the fact that NVP is not classified under the ADG Code or the SUSDP, statements in regard to UN Number, Dangerous Goods Class, HAZCHEM Code, and Poison Schedule Number were not checked for accuracy. It was noted, however, that 3 MSDS did not contain any information in regard to Dangerous Goods Class, HAZCHEM Code and Poisons Schedule Number.

Health hazards

For the purposes of assessing health hazard information, products were divided according to concentration ranges of NVP associated with the concentration cut-off points for the various hazard criteria. The health effects considered important for each of the concentration ranges are shown in Table 20, with information on the number of products in each category that contained the relevant information.

Table 20: Important health effects for cut-off concentration ranges

Health Effects	Cut-off Concentration			
Acute effects	**1-<5%**	**5-<20%***	**20-<25%***	**>=25%**
Eye irritation	N/A	5/5	5/5	11/11
Respiratory distress	N/A	N/A	5/5	10/11
Nasal irritation (increased nasal secretion)	N/A	N/A	5/5	11/11
CNS effects (ataxia, narcosis)	N/A	N/A	N/A	9/11
Absorption through skin	N/A	N/A	N/A	7/11
Chronic effects				
Anaemia	0/1	0/5	0/5	0/11
Carcinogenicity (liver and nasal cavity tumours)	1/1	2/5	2/5	7/11

* health effects from these two concentration ranges were from the same MSDS as the products contain 10 to 30 % NVP.

No MSDS mentioned anaemia. Information on carcinogenicity (liver and nasal tumours) were absent from 7 of the 16 products which should have had this information, while the possibility of absorption through the skin was absent from 4 of the 11 MSDS. Three MSDS did not contain a section for Advice to Doctor.

Precautions for use

Four MSDS contained the correct information that there was no Australian exposure standard for NVP. The remainder (13/17) had an exposure standard that was suggested by the company, however this was made explicit in only four cases, through the mention of the company name in connection with the exposure limit (2/4), or the statement that the quoted exposure limits 'are suggested figures, not Worksafe Australia requirements' (2/4). Eight of the other 13 MSDS placed the word 'suggested' alongside the figure for the limit. One MSDS didn't have any qualifier at all.

All MSDS contained appropriate recommendations regarding the wearing of gloves, safety glasses, and respirators. All had appropriate recommendations regarding ventilation.

Company details and contact point

One MSDS did not contain the company details (name, address and telephone number). Three did not contain an emergency telephone number. Three others did not list a contact point (title and telephone number).

Summary

The two MSDS for pure NVP were deficient in much of the information considered important to be present on the MSDS. Missing in particular were a

statement of hazardous nature, some product identification information, including any indication of the product's use, information relating to regulatory status and exposure standards, and in the case of one MSDS, Australian company and contact details.

The MSDS for mixtures generally contained most of the information considered important to be present. It was noted that most of the MSDS contained industry recommended exposure limits, however it was not always made clear in the MSDS that this was an industry recommended standard and not a government regulated exposure standard.

15.2.2 Assessment of labels

Introduction

Under the NOHSC *National Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers of industrial chemicals are obliged to provide labels in accordance with the NOHSC *Code of Practice for the Labelling of Hazardous Substances* (Labelling Code) (NOHSC, 1994a).

Under the Labelling Code, hazardous substances require the presence of a signal word; the product name; the recognised chemical name of the hazardous ingredient and details of the amount present in the product (exact amounts or ranges); risk phrases and safety phrases as appropriate; first aid statements; instructions on the control of leaks, spills or fires; the name and address in Australia of the supplier and a telephone number where advice can be obtained; and a reference to the MSDS.

The signal word appropriate for NVP is HAZARDOUS.

NVP is not on the *List of Designated Hazardous Substances* (NOHSC 1999b). Appropriate risk phrases are determined by the hazard classification (see section 12). They are:

R20/21/22	Harmful by inhalation, in contact with skin and if swallowed
R37	Irritating to respiratory system
R40	Possible risk of irreversible effects
R41	Risk of serious damage to eyes
R48/20	Danger of serious damage to health by prolonged exposure through inhalation

Safety phrases provide information on safe storage, handling and personal protection, and address risks indicated by risk phrases. Safety phrases for NVP are determined according to the criteria for selection of safety phrases in the Labelling Code. They are:

S25	Avoid contact with eyes
S36/37/39	Wear suitable protective clothing, gloves and eye/face protection
S41	In case of fire and/or explosion, do not breathe fumes
S51	Use only in well ventilated area

For products containing NVP, the risk phrases and safety phrases required will vary according to the concentration of NVP in the mixture. The concentration

cut-off points determined for the various risk phrases and safety phrases are shown in Table 21:

Table 21: Risk and safety phrases labelling requirements for NVP products

	1 - <5%	5 - <10%	10 - <20%	20 - <25%	≥25%
Risk phrases	R40	R40, R36*	R40, R41, R48/20	R40, R41, R48/20, R37	R40, R41, R48/20, R37, R20/21/22
Safety phrases	S36/37, S41, S51	S25, S36/37/39, S41, S51	S25, S36/37/39, S41, S51	S25, S36/37/39, S41, S51	S25, S36/37/39, S41, S51

* R36, irritating to eyes for cut-off concentration of 5-10% NVP products.

Some suggested wording for first aid statements in MSDS for NVP is provided in the sample MSDS (Appendix 5).

Compliance with Labelling Code

Three labels for pure NVP and ten labels for products containing NVP were submitted and examined for compliance with the requirements listed above. Compliance with some other requirements of the Labelling Code such as directions for use were not examined in this assessment. The concentration of NVP in the products for which labels were supplied ranged from <5% to 53.12%, with four labels being ≥25%.

Labels for NVP

All three labels for pure NVP were overseas labels. Under the Labelling Code, workplace hazardous substances which are imported from overseas may be labelled in accordance with overseas requirements provided that the label contains equivalent information to that advised in the Labelling Code.

None had the signal word HAZARDOUS. All had product and chemical names. Two did not contain a statement of strength. Two contained four required risk phrases (or equivalent phrases) except R37 (irritating to respiratory system), while the other contained only one of the required risk phrases (equivalent to R40). One label contained none of the four required safety phrases, one contained three (equivalent to S51, S25, S36/37/39), the other contained two (equivalent to S51, S36/37). Two had no first aid instructions. Two labels did not have emergency instructions. None of the three labels contained company details or telephone numbers for the Australian supplier. One did not have a reference to the MSDS.

Labels for NVP products

One label contained a signal word WARNING. Eight contained a product name, however none contained any indication of the presence of NVP (there was no chemical name or statement of strength). None of the ten labels contained any risk phrases, and only one contained the required safety phrases. Only one label had first aid instructions. No labels contained emergency procedures. All had

supplier details, however two did not contain a telephone number. Eight of 10 labels contained a reference to the MSDS.

Summary

The assessment identified some serious deficiencies in compliance with the Labelling Code. They are:

- absence of risk and safety phrases on most labels (especially labels for mixtures);
- absence of Australian supplier details on labels for pure NVP;
- absence of a signal word on most labels;
- no disclosure of the presence and strength of NVP on most labels;
- absence of instructions for the control of leaks, spills or fires on most labels;
- absence of first aid instructions on most labels.

Overall, compliance was very poor, with most requirements not present. The three labels for pure NVP complied better than the labels for mixture. However none complied fully.

15.2.3 Education and training

Guidelines for the induction and training of workers exposed to hazardous substances are provided in the NOHSC *Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c). Under these regulations employers are obliged to provide training and education to workers handling hazardous substances.

No staff training material was provided by applicants/ notifiers for assessment. Most of the workplaces provide "on the job" training where the supervisor trains the new employee in the various activities involved. Only one of the four workplaces visited had a training manual and operating procedures and involved training at induction. One of the workplaces had a hazard card for NVP containing health effects and precautions for handling NVP.

15.3 Occupational monitoring and regulatory controls

15.3.1 Monitoring

Under the NOHSC *Model Regulations and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), employers are required to carry out an assessment of the workplace for all hazardous substances. The methodology is provided in the NOHSC *Guidance Note for the Assessment of Health Risks Arising from the Use of Hazardous Substances in the Workplace* (NOHSC, 1994d). Atmospheric monitoring should be conducted to measure NVP levels in the workplace if assessment indicates that the risk of exposure via inhalation is significant. Atmospheric monitoring indicates the effectiveness of control measures and if there is a need to improve measures to reduce worker exposure. Subsequent monitoring will be required to check effectiveness of the new control measures. Analytical methods for the measurement of NVP in air are detailed in Chapter 6.

Atmospheric monitoring for NVP was not conducted on a regular basis at workplaces in Australia. It was conducted at only two workplaces that responded to the NICNAS industry survey.

It should be noted that atmospheric monitoring might not provide an accurate estimate of total exposure in situations where significant dermal exposure occurs.

15.3.2 Exposure standards

No exposure standard has been assigned by NOHSC for NVP. The International Labour Organisation's (ILO) Occupational Exposure Limits for Airborne Toxic Substances (ILO, 1991) lists exposure limits for various substances from fifteen countries. Only one country, the USSR, is recorded as having a short-term exposure limit (STEL) of 1 mg/m^3 for NVP. The UK HSE Advisory Committee on Toxic Substances (ACTS) considered NVP as a candidate for setting a Maximum Exposure Limit (MEL) in March 1998 and concluded that a MEL is not currently justified. ACTS has recommended that the UK HSE review annually any new information on toxicity or significant increase on use (HSE, 1998).

In 1991, on the basis of the findings of the 2-year inhalation study in rats assessed in this report (BASF*, 1992b) that NVP causes nasal and liver tumors at dose levels greater than 5 ppm, ISP International Pty Ltd. lowered its recommended workplace NVP limit from 1 ppm to 0.1 ppm.

There is no information to indicate the level of 0.1 ppm is being achieved in UV ink formulation and screen printing industries.

15.3.3 Health surveillance

In accordance with NOHSC *Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), employers have a responsibility to provide health surveillance in those workplaces where the workplace assessment indicates that exposure to a hazardous substance may lead to an identifiable substance-related disease or adverse health effect. NVP is currently not listed in Schedule 3 (list of substances requiring health surveillance) of the Model Regulations and as such there are no mandated requirements for health surveillance programs for exposed workers.

15.4 Emergency procedures

Information on emergency procedures was not submitted for assessment. Information obtained from the sites visited indicates that very few places had written emergency procedures.

The availability of written procedures for workers to deal with unexpected releases during formulation and use of NVP, such as large spills, is good practice. All employees need to be trained in accident and emergency procedures. Procedures to be followed during clean up of spills and first aid procedures should be recorded on the MSDS. Local emergency services should be consulted on the appropriateness of emergency procedures developed.

16 Conclusions

In Australia, NVP is mainly used in manufacturing of UV curing inks which are used in printing on a variety of materials such as paper, plastic bottles, vinyl, rubber, particle-board, wood and metals. The final concentration of NVP in the ink ranges from 4 to 20%. NVP is also used in formulation of paper coating products which contain 2% NVP. Small amounts of NVP are also used in laboratories for research purposes. NVP and NVP products are not available to the general public. However, a NVP containing polymer, PVP, is imported into Australia and used widely in industries such as cosmetics, pharmaceuticals, and agriculture formulations. The residual NVP monomer content in the PVP ranges from 10 ppm to 2000 ppm.

Occupational and environmental exposure may occur from any of the above uses and also during transportation and disposal. Exposure to the general public may occur from use of PVP products.

Information on the toxicokinetics of NVP in humans is not available. Animal studies show that NVP is readily absorbed by the oral and inhalation routes. Dermal application of NVP in dogs resulted in relatively low absorption. However, the physicochemical properties of NVP suggest that it will readily cross the skin. Absorbed NVP is distributed throughout the body and deposited mainly in liver, plasma, kidney and small intestine. Studies indicate that oral bioavailability of NVP is reduced by hydrolysis in the stomach and possibly also by polymerisation. NVP is metabolised into highly polar compounds, however, the two major metabolites of NVP have not been identified. The majority of metabolites (90%) are eliminated rapidly by the urinary route, other routes being small amounts in the faeces, via bile and CO_2 in exhaled air. Studies show that NVP and its metabolites do not bind to DNA, RNA and plasma proteins.

Adverse health effects following short-term or prolonged exposure to NVP in humans have not been reported.

NVP exhibits acute toxicity by all three routes in animals. Oral LD_{50} in rats ranged from 834 to 2500 mg/kg. Dermal LD_{50} ranged from 1043 - 4127 mg/kg in rats, 560 mg/kg in rabbit and 3000 - 5000 mg/kg in guinea pigs. Inhalational LC_{50} (4h) to NVP aerosol was 3070 mg/m^3 (3.07 mg/L) in rats. Liquid NVP has been shown to cause severe eye irritation in animals. Signs of respiratory tract irritation were observed in a range of animal species following single exposure to NVP aerosol and repeated inhalation of NVP vapour. The predominant systemic effects after short-term exposure to NVP in animals are on the liver such as centrilobular necrobiosis, isolated necrotic cells, and changes in cell nuclei (mitosis, polymorphism, pale karyoplasm).

The target organs after repeated inhalational exposure to NVP in animal studies were the liver and nasal cavity. Liver effects included enlarged hepatocytes with clear cell areas, degenerative changes of the nucleus, centrilobular necrobiosis, fatty infiltration, cellular proliferation, cirrhosis-like metaplasia and glycogen accumulation within centrilobular hepatocytes in the liver. Cell hyperplasia and inflammatory changes in the olfactory and respiratory epithelia in the nasal cavity were observed. Administration of NVP by the oral route results in damage to the

liver only and the dose required to produce histopathological changes is much higher than that required by inhalation. The no observed adverse effect level (NOAEL) after repeated exposure in rats is 1 ppm (1 mg/kg) by inhalation route and 3.6 mg/kg following oral administration of NVP. However, it is not certain whether the NOAEL of 1 mg/kg for inhalation exposure is applicable to longer or lifetime exposures as the NOAEL was derived from a 3 month rat study. There are indications that at 5 ppm (5 mg/kg), the lowest observed adverse effect level (LOAEL), hepatotoxicity takes longer than 3 months to develop in rats.

Carcinogenicity studies in rats by the inhalation route indicate that NVP is clearly carcinogenic. The principal tumour sites are the liver, nasal cavity and larynx. A NOAEL could not be identified from these studies as tumours occurred at 5 ppm (5 mg/kg) which was the lowest dose tested. Irreversible changes can be produced in the liver of rats after only 3 months exposure to NVP, resulting in liver tumour development at the end of 2 years even in the absence of further NVP exposure. NVP is not a mutagenic and the exact mechanism of tumour formation in animals exposed to NVP is not known.

Currently NVP is not listed on the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b).

Based on the assessment of health effects and in accordance with the NOHSC *Approved Criteria for Classifying Workplace Hazardous Substances* (NOHSC, 1999a), it is recommended that NVP be classified as:

R20/21/22	Harmful by inhalation, in contact with skin and if swallowed
R37	Irritating to respiratory system
R40	Possible risk of irreversible effects, Carcinogen Category 3
R41	Risk of serious damage to eyes
R48/20	Harmful: danger of serious damage to health by prolonged exposure through inhalation

The occupational risk assessment concluded that a risk of acute eye effects is likely during formulation of NVP products due to accidental contact with liquid NVP during splashes. In the absence of appropriate monitoring data during formulation of NVP products and use of UV curing inks containing NVP, estimates for NVP exposure were obtained using the EASE model. Results from this modelling indicate that the atmospheric levels of NVP likely during these operations are only a few times lower than the LOAEL (5ppm) which produced liver and nasal cavity tumours in rats. As the relevance of these animal findings to humans is not known, exposure of workers to NVP in these scenarios are of concern.

Environmental risk assessment indicates that NVP does not cause adverse effects on the aquatic compartment. Adverse effects on aquatic organisms or on microbial activity during formulation or end use of NVP is not likely in Australia.

The public health risk assessment concluded that based on the available information, laboratory use of NVP in small quantities and industrial use in UV curing inks and paper coating do not present a significant risk to public health. However, NVP is present as a residual monomer in PVP, which is used in a number of consumer products including cosmetics/toiletries. Currently there is no analytical information on levels of NVP in cosmetic/toiletry products. Public

exposure estimates based on the upper limit (2000 ppm) of NVP levels in PVP and the PVP contents of 0.1% to 10% in cosmetic products do not give an adequate margin of safety for consumers in view of the nature of the potential hazards and incomplete toxicology database. The level of 200 ppm NVP in PVP for cosmetic use would provide an adequate safety margin for consumers based on available information.

This report identified a number of gaps in the available information/data for NVP. They are:

- the mechanism of action of carcinogenicity in liver and nasal cavity to enable the risk assessment to be refined;
- data to assist in the estimation of the skin absorption rate of NVP in humans (to provide a better estimate of skin absorption);
- studies on the developmental toxicity of NVP in animals; and
- appropriate exposure data for different use scenarios to assist to refine the risk assessment.

17 Recommendations

17.1 Hazard classification

Currently NVP is not listed in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b).

Based on an assessment of health hazards and in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 1999a), the recommended classification for NVP is:

R20/21/22 Harmful by inhalation, in contact with skin and if swallowed
R37 Irritating to respiratory system
R40 Possible risk of irreversible effects (Carcinogen Category 3)
R41 Risk of serious damage to eyes
R48/20 Harmful: danger of serious damage to health by prolonged exposure through inhalation

Consistent with this classification, classifications for products containing different concentrations of NVP are listed in Table 22.

Table 22: Classifications for NVP products

NVP Concentration	Classification	
1 - <5%	R40	Carcinogen Category 3
5 - <10%	R40, R36	Carcinogen Category 3 Irritating to eyes
10 - <20%	R40, R41, R48/20	Carcinogen Category 3 Risk of serious damage to eyes Harmful: danger of serious damage to health by prolonged exposure through inhalation
20 - <25%	R40, R41, R48/20, R37	Carcinogen Category 3 Risk of serious damage to eyes Harmful: danger of serious damage to health by prolonged exposure through inhalation Irritating to respiratory system
≥25%	R40, R41, R48/20, R37, R20/21/22	Carcinogen Category 3 Risk of serious damage to eyes Harmful: danger of serious damage to health by prolonged exposure through inhalation Irritating to respiratory system Harmful by inhalation, in contact with skin and if swallowed

17.2 Occupational control measures

Under the NOHSC *National Model Regulation and Code of Practice for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) control measures must be implemented to minimise health risks during handling and use of hazardous substances. With regard to NVP, control measures should be implemented to minimise worker exposure via skin and inhalation routes.

17.2.1 Elimination

Elimination is the removal of all chemicals from the process. To minimise health risks, elimination is the first option to be considered. During the assessment no non-chemical processes were identified.

17.2.2 Substitution

Any substitution of NVP should be with safer alternatives which have been tested and have demonstrated a lower toxicity and irritancy. No safe alternatives have been evaluated by NICNAS.

In order to minimise exposure, it is recommended that formulators reduce the concentrations of NVP in UV curing inks to the minimum efficacious levels.

17.2.3 Engineering controls

Formulation

It is appropriate that formulators consider the health and safety hazards of all ingredients in the formulation process and minimise exposure to NVP.

It is recommended that NVP liquid be charged into the mixing vessel in a safe manner, for example, by use of drum lifts and reducing the number of manual charging events. Mixing and transfer process should be enclosed with transfer of product through closed pipelines minimising emission of vapours. If this is not practicable, the mixing vessels should be covered and local extraction ventilation installed above them to remove any fugitive emissions. The mixing area should be bunded so that any spills can be confined.

At the point of filling NVP based inks into containers, the process should be enclosed as far as possible. It is recommended that local exhaust ventilation be installed if complete enclosure is not achievable.

Installation of local exhaust ventilation in the equipment cleaning area is also recommended.

Good dilution ventilation is essential in all production areas, with the ventilation rate capable of being substantially increased in case of emergencies such as spillage.

Use of NVP products

Paper coating with the products containing NVP occurs in an enclosed system.

During use of UV curing inks containing NVP, especially with silkscreen printing techniques, it is recommended that the application of the inks onto printing screens and the printing system be enclosed as far as possible. Local

exhaust ventilation should be installed above screens if complete enclosure is not practicable.

Installation of local exhaust ventilation for ink mixing and for initial cleaning of the screens is recommended to lower exposure to NVP in the mixing and cleaning area.

17.2.4 Safe work practices

Safe work practices are critical in keeping solvent emissions to a minimum. Safe practices that help to minimise emissions include:

- installation of the mixing tank in a well ventilated area so that any vapour resulting from high speed stirring will be quickly removed;
- minimal amounts of inks should be placed on screens to prevent excess handling of inks during colour changes;
- avoiding heat and vapour generation where possible;
- avoiding direct handling of NVP;
- dirty screens should not be left in the room during silkscreen cleaning;
- inks should be immediately washed off the screens to prevent unnecessary exposures;
- regular cleaning of equipment surfaces;
- keeping containers closed when not in use;
- avoiding splashes or spills during mixing and transfer operations;
- absorb spills or leaks with earth, sand or other inert material, and dispose of it according to regulations;
- prohibiting eating, drinking and smoking in contaminated areas; and
- wash hand thoroughly after handling.

17.2.5 Personal protective equipment

The following PPE is recommended where occupational exposure to NVP may occur:

- suitable solvent resistant gloves when handling NVP or NVP products;
- protective clothing which includes protection of the arms, legs and feet;
- eye protection when splash is likely, such as charging of NVP liquid into mixing vessel and during mixing.

It is not practicable to use respiratory protection during routine use of NVP products. However, a facemask with organic vapour cartridge should be worn when exposures are likely to be high, such as during mixing of NVP raw material with other substances and clean up of large spills.

17.3. Hazard communication

As NVP is a hazardous chemical, employers and suppliers are obliged to provide workers with MSDS containing information on the hazards of the chemical. Details of these obligations are provided in the NOHSC *National Model*

Regulations and Code of Practice for the Control of Workplace Hazardous Substances (NOHSC, 1994c).

17.3.1 MSDS

The NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994b) provides guidance for the preparation of MSDS.

It is recommended that suppliers rectify the deficiencies identified in this assessment and amend their MSDS where necessary with particular attention given to the following:

- inclusion of a statement of hazardous nature;
- appropriate product identification information relating to UN Number, Dangerous Goods Class, HAZCHEM Code, Poisons Schedule Number (the MSDS Code requires a statement that no number/class/code has been allocated);
- inclusion of information about exposure standards (the MSDS Code of Practice requires a statement that no standard has been allocated);
- inclusion of Australian company and contact details.

Some suggested wording in MSDS for NVP is provided at Appendix 5.

17.3.2 Labels

A large number of deficiencies were identified in the labels provided for assessment. It is therefore recommended that labels be updated by suppliers of NVP and NVP products, taking into account the deficiencies identified in this assessment. The labeling requirements are as follows:

- a signal word should be used in the labelling of hazardous substances. For NVP the signal words 'HAZARDOUS' is appropriate for workplace chemicals.
- NVP should be disclosed on the label together with the concentrations when NVP is above 1% in a mixture.
- The appropriate risk phrases as determined by the hazard classification (see section 12):

R20/21/22	Harmful by inhalation, in contact with skin and if swallowed
R37	Irritating to respiratory system
R40	Possible risk of irreversible effects
R41	Risk of serious damage to eyes
R48/20	Danger of serious damage to health by prolonged exposure through inhalation

For products containing NVP, the risk phrases and safety phrases required will vary according to the concentration of NVP in the mixture. The concentration cut-off points determined for the various risk phrases and safety phrases are shown in Table 23:

Table 23: Risk and safety phrases labelling requirements for NVP products

	1 - <5%	5 - <10%	10 - <20%	20 - <25%	≥25%
Risk phrases	R40	R40, R36*	R40, R41, R48/20	R40, R41, R48/20, R37	R40, R41, R48/20, R37, R20/21/22
Safety phrases	S36/37, S41, S51	S25, S36/37/39, S41, S51	S25, S36/37/39, S41, S51	S25, S36/37/39, S41, S51	S25, S36/37/39, S41, S51

* R36, irritating to eyes for cut-off concentration of 5-10% NVP products.

where

S25	Avoid contact with eyes
S36/37/39	Wear suitable protective clothing, gloves and eye/face protection
S41	In case of fire and/or explosion, do not breathe fumes
S51	Use only in well ventilated area

- In accordance with the SUSDP requirement, the following first aid instructions should on the label:
  - If swallowed, do not induce vomiting. Give a glass of water.
  - If skin contact occurs, remove contaminated clothing and wash skin thoroughly.
  - If inhaled NVP vapour, remove from contaminated area. Keep warm and at rest until recovered.
  - If in eyes, immediately flush eyes with plenty of water.

- Inclusion of Australian suppliers details on labels for pure NVP.
- Inclusion of instructions for the control of leaks, spills or fires.

17.3.3 Training and education

In accordance with the NOHSC *National Model Regulations to Control Workplace Hazardous Substances* (NOHSC, 1994c), it is recommended that workers potentially exposed to NVP be provided with training in the safe handling, storage, transportation and disposal of the chemical.

Accordingly, for NVP, matters which need to be addressed in training include:

- health effects of NVP;
- skin absorption potential;
- explanation of MSDS and labelling of NVP and NVP products;
- use and maintenance of PPE;
- safe procedures to be followed during use of NVP and NVP products; and
- procedures to be followed during clean up of spills.

Training should be given to the workers at induction and repeated at regular intervals to reinforce the information. Training and education needs for workers should be reviewed on a regular basis. Guidelines for the induction and training of workers are provided in the NOHSC *National Model Regulations and Code of Practice for the Control of Hazardous Substances* (NOHSC, 1994c).

17.4 Exposure standard and atmospheric monitoring

An exposure standard for NVP has not been assigned by NOHSC. A NOAEL of 1 ppm (1 mg/kg) was identified in a 3 month study in rats. However, it is not certain whether this NOAEL is applicable to longer or lifetime exposures as there are indications that at 5 ppm (5 mg/kg) hepatotoxicity takes longer than 3 months to develop. In the absence of an appropriate NOAEL it is recommended that an exposure standard for NVP not be developed by NOHSC.

As a safe level has not been identified and the assessment indicates a significant risk of exposure via inhalation during formulation of NVP products and during use of UV curing inks, atmospheric monitoring should be conducted, in conjunction with engineering controls, to ensure that the levels of NVP are low, particularly in those areas where inhalation exposure is likely to occur such as the mixing area.

17.5 Public health protection

Without analytical data on the level of NVP in cosmetic products and reliable dermal absorption data, it is recommended that the Department of Health and Age Care establish a maximum level of 200 ppm NVP present in PVP for cosmetic use. If this is unable to be addressed through voluntary industry mechanisms, NVP should be referred to the National Drugs and Poisons Scheduling Committee (NDPSC) for consideration of control via the scheduling process

It is recommended that the final Priority Existing Chemical report on NVP be forwarded to the Drug Safety Evaluation Branch of TGA, ANZFA and National Registration Authority (NRA) for Agricultural and Veterinary Chemicals for consideration of the public health impact of NVP in pharmaceuticals, food and agricultural formulations respectively.

17.6 Environmental protection

Based on available information, NVP is not expected to cause any significant adverse environmental impact. As such, no further regulatory controls for the use of this chemical in Australia are recommended.

18 Secondary Notification

Under Section 65 of the Act, the secondary notification of NVP may be required, where a person becomes aware of any circumstances which may warrant a reassessment of its hazards and risks. Specific circumstances for NVP include:

- the function or use of NVP has changed, or is likely to change, significantly;
- the amount of NVP introduced into Australia has increased, or is likely to increase, significantly;
- manufacture of NVP has begun in Australia; and
- significant new information about the adverse health and/or environmental effects of NVP has become available.

A number of gaps have been identified in this report from the available information/data for NVP. They are:

- the mechanism of action of carcinogenicity in liver and nasal cavity to enable the risk assessment to be refined;
- data to assist in the estimation of the skin absorption rate of NVP in humans (to provide a better estimate of skin absorption); and
- studies on the developmental toxicity of NVP in animals.

The Director must be notified within 28 days of the person becoming aware of any of the above circumstances.

Appendix 1

Appendix 2

N-VINYL-2-PYRROLIDONE (NVP) QUESTIONNAIRE (CAS No.* 88-12-0)

Who should complete this questionnaire?

This questionnaire is relevant to anyone who manufactures, imports, buys, repacks, re-sells, formulates, or uses NVP or products containing NVP.

For information on possible uses of NVP or products containing NVP, please see Page 5 **of this questionnaire.**

Please complete this questionnaire and return to:

NVP Survey
NICNAS - Existing Chemicals
GPO Box 58
Sydney NSW 2001
Fax: (02) 9577 9465

If you have any queries about the questionnaire or any of the questions, please contact:

Ms Jun Zhang Phone 02 9577 9577
Fax: 02 9577 9465
Email: zhangj@worksafe.gov.au

Company Information

Company name: _____

Address: _____

Contact person for this survey: _____

Position: _____

Telephone: _____ **Fax:** _____

Date: _____

*The Chemical Abstracts Service (CAS) Number.

General Information

Please tick applicable box(es) and fill in quantity.

Do you

	NVP	Quantity (kg/year)	**Products Containing NVP**	Quantity (kg/year)	**NVP Polymers (eg. PVP*)**	Quantity (kg/year)
Manufacture						
Import directly						
Purchase locally						

*PVP, polyvinyl pyrrolidone (CAS No. 9003-39-8)

If you purchase locally, please provide name of suppliers _____

_____

Guide to Complete This Questionnaire

If you purchase NVP or products containing NVP locally **and**

	Please ONLY Complete
Re-sell in same package (whether or not re-labelled)	Part A
Repackage only and re-sell	**Part A, D, E**
Use to formulate a product for re-sale (including simple dilution)	**Part B, D, E**
Use to formulate a product for own use (including simple dilution)	**Part B, C, D, E**
Use as supplied, for own use	**Part C, D, E**

Other (please specify)_____

Part A: Questions for re-sellers and repackers of NVP or products containing NVP.

If you simply re-sell or repack NVP or products containing NVP, please provide the following details.

A1. Please give details of the products that you re-sell:

Product Name	Typical End Use	% NVP	Annual sales of product (kg)	Avail at retail outlets?* Yes/No

Attach a separate list if needed.

*If yes, please give estimated volume (kg)_____

Please supply copies of MSDS and labels for these products.

A2. If you repack NVP or NVP products for re-sale, please describe the packaging process.

_____

_____

_____

A3. Please give details of the original and final package size and type, including type of closure eg. cap.

_____

_____

_____

A4. Please provide a complete list of contact details of your customers, including address, contact person, and numbers, to whom you sell NVP or products containing NVP. **This information will be kept confidential, and used only to send questionnaires if required**. Please attach the list to this questionnaire.

Part B: Questions for Formulators

If you formulate products containing NVP, either for your own use or for re-sale, please answer the following questions. Simple dilution is also counted as formulation.

B1. Please provide the following details for products you formulate:

Product Name	Typical end uses	% NVP	Product for sale Yes/No	Annual sales of product (kg)	Avail at retail outlets?* Yes/No

Attach a separate list if needed.

*If yes, please give estimated volume (kg)_____

Please supply copies of the MSDS and labels for these products.

B2. Please describe the manufacturing processes for your products.

_____

_____

_____

_____

B3. Please give details of package size and type of your products, including type of closure eg. cap.

_____

_____

B4. Please provide a complete list of contact details of your customers, including address, contact person, and numbers, to whom you sell the NVP products that you formulate. **This information will be kept confidential, and used only to send questionnaires if required.** Please attach the list to this questionnaire.

Part C: Questions for users of NVP or products containing NVP.

C1. Please indicate the uses of NVP or products containing NVP by your company.

UV screening printing — UV lacquers

Contact lenses manufacturing — Laboratory

Others (please specify)_____

If you use products containing NVP, please provide the following details.

Product Name	% NVP	Annual use of product (kg)

C2. Please describe how you use NVP or NVP products ie. Details of processes.

_____

_____

_____

_____

_____

Part D: Workplace Exposure

Questions for repackers, formulators, and users of NVP or products containing NVP.

D1. Are the processes you employ:

Open (eg. open tanks, NVP added to tanks manually)

Partially closed (eg. covered tanks, NVP added manually to tanks)

Closed (fully sealed process including automated addition of NVP to tanks)

Other (please specify) _____

_____

D2. Please describe numbers and activities of workers using NVP or NVP products.

Number	Description of Work	h/d	d/year

D3. How is the equipment used during packaging, formulating or use of NVP or NVP products cleaned? Please describe the cleaning procedure.

_____

_____

_____

_____

_____

D4. Please describe the engineering controls that are in place to reduce exposure of workers to NVP eg. exhaust ventilation, general dilute ventilation.

Process/Activity	Engineering Controls	Year installed

D5. Please give details of the personal protective equipment used by workers. eg type of gloves, goggles, respirators, protective clothing.

Process/Activity	Personal Protective Equipment	Type

D6. Are any other precautions taken to reduce exposure of workers to NVP?

Limited access to area of use,

Written procedures for safe use,

Special labeling or placarding.

Other_____

D7. Has atmospheric monitoring been conducted to determine levels of NVP in the workplace? Yes

No

If yes, please provide details of monitoring eg. testing equipment, methods, duration, and results.

_____

_____

_____

D8. Have there been any incidents involving spillage of NVP or NVP products at your workplace, whether or not they have led to human exposure? Yes

No

If yes, please give details:

_____

_____

_____

D9. Are you aware of any adverse health effects experienced at your workplace due to exposure and/or spillage of NVP or NVP products?

Yes

No

If yes, please give details:

_____

_____

_____

D10. What first aid measures do you have in place in case of worker exposure to NVP?

Trained first aid personnel

First aid box

Basin and soap

Emergency shower near operation site

First aid room or treatment corner

Other_____

Part E: Environmental Effects

Questions for repackers, formulators, and users of NVP or products containing NVP.

E1. If possible, please estimate (approximate) percentage of NVP lost to the atmosphere during repacking, formulation, or use.

Process or end use	% lost to atmosphere

E2. Are you aware of any discharges of NVP to land or water?

Yes No

If yes, please give details.

_____

_____

_____

_____

_____

E3. What forms of NVP waste do you generate?

raw material finished product

other_____

E4. What methods do you use to dispose NVP waste?

Blending with other products and re-use

Evaporation to atmosphere

Licensed discharges

Incineration eg. boiler fuel

Send to recycler

Waste collection

Other (please specify)_____

E5. Please describe how you dispose any cleaning residues.

_____

_____

_____

_____

E6. If possible, please estimate (approximate) the NVP waste disposed monthly (total of all above-mentioned methods)?

_____ kg/month

E7. Please indicate how you handle NVP or NVP products empty containers.

Rinse and/or re-use

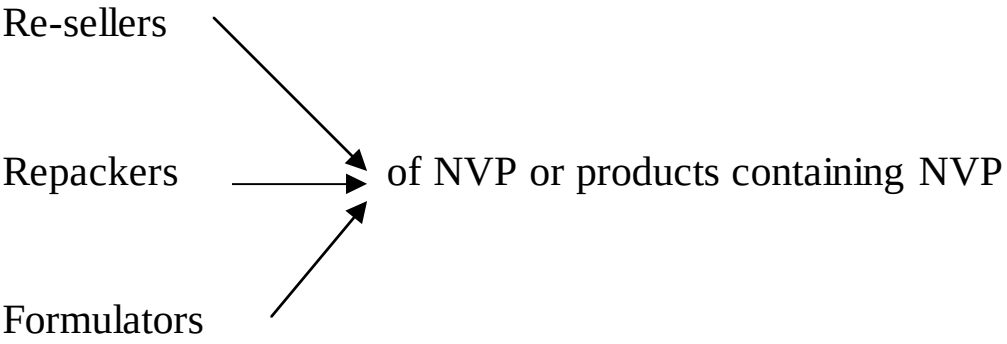
Return to supplier

Sell to drum recycler

Send to landfill

Other (please specify) _____

CHECK LIST



Have you attached

copies of MSDS and labels for your products?

a complete list of contact details of your customers?

any separate attachment?

Thank You for Responding to the Questionnaire!!

Appendix 3

EASE Model Printout

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log 1

The name of substance is NVP;

The temperature of the process is 20 °C;

The physical-state is liquid;

Aerosol-formed is false;

The exposure-type is gas/vapour/liquid aerosol;

The status of vapour pressure value is 'Measured at process temperature';

The vapour pressure value of the substance is 0.012;

The volatility of the substance is Low;

The use-pattern is Non-dispersive use;

The pattern-of-control is LEV;

The predicted gas/vapour/liquid aerosol exposure to NVP is 0.5 to 3 ppm.

Explanation:

Inhalation exposure to a gas, vapour or liquid aerosol which is not directly handled is determined by:

- the pattern of use (Non-dispersive use),
- the pattern of control (LEV), and
- the ability of the substance to become airborne (Low).

This results in an exposure range of 0.5 to 3 ppm.

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log 1-1

The name of substance is NVP;

The temperature of the process is 30 °C;

The physical-state is liquid;

Aerosol-formed is false;

The exposure-type is gas/vapour/liquid aerosol;

The status of vapour pressure value is 'Measured at process temperature';

The vapour pressure value of the substance is 0.029;

The volatility of the substance is Low;

The use-pattern is Non-dispersive use;

The pattern-of-control is LEV;

The predicted gas/vapour/liquid aerosol exposure to NVP is 0.5 to 3 ppm.

Explanation:

Inhalation exposure to a gas, vapour or liquid aerosol which is not directly handled is determined by:

- the pattern of use (Non-dispersive use),
- the pattern of control (LEV),
- and the ability of the substance to become airborne (Low).

This results in an exposure range of 0.5 to 3 ppm.

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log2

The name of substance is NVP;

The temperature of the process is 20 °C;

The physical-state is liquid;

Aerosol-formed is false;

The exposure-type is gas/vapour/liquid aerosol;

The status of vapour pressure value is 'Measured at process temperature';

The vapour pressure value of the substance is 0.012;

The volatility of the substance is Low;

The use-pattern is Non-dispersive use;

The pattern-of-control is direct handling;

The direct handling is dilution ventilation present;

The predicted gas/vapour/liquid aerosol exposure to NVP is 10 to 50 ppm.

Explanation:

Inhalation exposure to a gas, vapour or liquid aerosol which is directly handled is determined by:

- the pattern of use (Non-dispersive use),
- the ability of the substance to become airborne (Low), and
- the level of control applied to the handling (Dilution ventilation) present.

This results in an exposure range of 10 to 50 ppm.

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log2-1

The name of substance is NVP;

The temperature of the process is 30 °C;

The physical-state is liquid;

Aerosol-formed is false;

The exposure-type is gas/vapour/liquid aerosol;

The status of vapour pressure value is 'Measured at process temperature';

The vapour pressure value of the substance is 0.029;

The volatility of the substance is Low;

The use-pattern is Non-dispersive use;

The pattern-of-control is direct handling;

The direct handling is dilution ventilation present;

The predicted gas/vapour/liquid aerosol exposure to NVP is 10 to 50 ppm.

Explanation:

Inhalation exposure to a gas, vapour or liquid aerosol which is directly handled is determined by:

- the pattern of use (Non-dispersive use),
- the ability of the substance to become airborne (Low), and
- the level of control applied to the handling (Dilution ventilation) present.

This results in an exposure range of 10 to 50 ppm.

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log3

The name is NVP;

The temperature of the process is 20 °C;

The physical-state is liquid;

aerosol-formed is false;

The exposure-type is dermal;

The use-pattern is Non-dispersive use;

The pattern-of-control is Direct handling;

The contact-level is Intermittent;

The predicted dermal exposure to NVP is 0.1-1 mg/cm^2/d which is moderate.

Explanation:

Dermal exposure to NVP which is directly handled is determined by:

- the pattern of control (Direct handling),
- the use pattern (Non-dispersive use), and
- the contact level (Intermittent).

This results in an exposure range of 0.1-1 mg/ cm^2/d.

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log4

The name of substance is NVP;

The temperature of the process is 20 °C;

The physical-state is liquid;

Aerosol-formed is false;

The exposure-type is vapour;

The status of vapour pressure value is 'Measured at process temperature';

The vapour pressure value of the substance is 0.012;

The volatility of the substance is Low;

The use-pattern is Closed system;

Significant-breaching is false

The pattern-of-control is Full containment;

The predicted vapour exposure to NVP is 0-0.1 ppm.

Explanation:

Inhalation exposure to NVP vapour is very low (0-0.1 ppm) if the substance is being used within a closed system.

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log 5

The name of substance is NVP;

The temperature of the process is 20 °C;

The physical-state is liquid;

Aerosol-formed is false;

The exposure-type is vapour;

The status of vapour pressure value is 'Measured at process temperature';

The vapour pressure value of the substance is 0.012;

The volatility of the substance is Low;

The use-pattern is Non-dispersive use;

The pattern-of-control is LEV;

The predicted vapour exposure to NVP is 0.5 to 3 ppm.

Explanation:

Inhalation exposure to NVP vapour which is not directly handled is determined by:

- the pattern of use (Non-dispersive use),
- the ability of the substance to become airborne (Low), and
- the pattern of control (LEV).

This results in an exposure range of 0.5 to 3 ppm.

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log6

The name of substance is NVP;

The temperature of the process is 20 °C;

The physical-state is liquid;

Aerosol-formed is false;

The exposure-type is vapour;

The status of vapour pressure value is 'Measured at process temperature';

The vapour pressure value of the substance is 0.012;

The volatility of the substance is Low;

The use-pattern is Non-dispersive use;

The pattern-of-control is direct handling;

The direct handling is dilution ventilation present;

The predicted vapour exposure to NVP is 10 to 50 ppm.

Explanation:

Inhalation exposure to NVP vapour which is directly handled is determined by:

- the pattern of use (Non-dispersive use),
- the ability of the substance to become airborne (Low), and
- the level of control applied to the handling (Dilution ventilation) present.

This results in an exposure range of 10 to 50 ppm.

This log file was generated by the EASE system Version: 2.0

The log-file-name is log.log7

The name is NVP;

The temperature of the process is 20 °C;

The physical-state is liquid;

aerosol-formed is false;

The exposure-type is dermal;

The use-pattern is Non-dispersive use;

The pattern-of-control is Direct handling;

The contact-level is Intermittent;

The predicted dermal exposure to NVP is 0.1-1 mg/cm^2/d which is moderate.

Explanation:

Dermal exposure to NVP which is directly handled is determined by:

- the pattern of control (Direct handling),
- the use pattern (Non-dispersive use), and
- the contact level (Intermittent).

This results in an exposure range of 0.1-1 mg/ cm^2/d.

Appendix 4

List of NVP Products

Appendix 4 lists the uses of NVP products along with the concentration of NVP in the products. It also indicates if a MSDS and label was provided for assessment. This information was obtained from a NICNAS industry survey in October 1998. Formulation may have changed since the preparation of this list.

List of Products Containing NVP:

Product	MSDS	Label	%NVP	Formulator	Use
Solabond Thinner/Reducer 854877	Y	N	>60%	Sericol Australia Pty Ltd.	Viscosity reducer for Solabond Ink Series
Solabond Ink Series	Y	N	10-<30%	Sericol Australia Pty Ltd.	UV screen printing
Spektraflex Ink Series	Y	Y	10-<30%	Sericol Australia Pty Ltd.	UV screen printing
Solaflex Ink	Y	N	<10%	Sericol Australia Pty Ltd.	UV screen printing
UV Accelerator (Colours) UV 008	Y	Y	19.6%	Australian Specialty Inks Pty Ltd.	UV inks additives
UV Initiator SUV12	Y	N	40%	Australian Specialty Inks Pty Ltd.	UV inks additives
UV Initiator SUV13	Y	N	60%	Australian Specialty Inks Pty Ltd.	UV inks additives
UV Initiator SUV55	Y	N	50%	Australian Specialty Inks Pty Ltd.	UV inks additives
UV Initiator SUV80	Y	N	50%	Australian Specialty Inks Pty Ltd.	UV inks additives
UV Initiator SUV90	Y	N	40%	Australian Specialty Inks Pty Ltd.	UV inks additives
UV Inks	Y	Y	4-12%	Australian Specialty Inks Pty Ltd.	UV screen printing
UV Thinner	Y	Y	1.94%	Australian Specialty Inks Pty Ltd.	Screen printing ink reducer
UV White Accelerator UV 010	Y	Y	53.12%	Australian Specialty Inks Pty Ltd.	UV inks additives

List of Products Containing NVP (cont.):

Product	**MSDS**	**Label**	**%NVP**	**Formulator**	**Use**
Viospeed additive varnish	Y	Y	10-30%	Coates Brothers, Australia Pty Ltd.	UV screen printing
Viospeed Inks	Y	Y	10-30%	Coates Brothers, Australia Pty Ltd.	UV screen printing
UV Corflute Screen Ink	Y	N	1-10%	Tollchem Pty Ltd.	UV screen printing
UV Screen Bottle Ink	Y	N	1-10%	Tollchem Pty Ltd.	UV screen printing
UV Screen Vinyl Ink	Y	N	1-10%	Tollchem Pty Ltd.	UV screen printing

Appendix 5

SAMPLE MATERIAL SAFETY DATA SHEET FOR N-VINYL-2-PYRROLIDONE

Page x of Total y

Date of Issue

N-vinyl-2-pyrrolidone is considered hazardous according to the National Occupational Health and Safety Commission's *Approved Criteria for Classifying Hazardous Substances* [NOHSC: 1008(1999a)]

COMPANY DETAILS

Company Name:

Address:

Telephone Number:

Emergency Telephone Number:

Telex and Fax Numbers:

IDENTIFICATION

Chemical Name: N-vinyl-2-pyrrolidone

Other Names: 1-Vinyl-2-pyrrolidinone
2-Pyrrolidinone, 1-ethenyl- N-Vinyl-2-pyrrolidone
N-Vinylpyrrolidinone N-Vinylpyrrolidone Vinylbutyrolactam
1-Ethenyl-2-pyrrolidone

Manufacturer's Product Code:

UN Number:	None allocated
Dangerous Goods Class:	None allocated
Subsidiary Risk:	None allocated
Hazchem Code:	None allocated
Poisons Schedule Number:	None allocated
Packaging Group:	None allocated

Use: In producing UV screen printing inks and paper coating products.

PHYSICAL DESCRIPTION/PROPERTIES

Appearance: Colourless to light yellow liquid (darkens in the absence of stabiliser)

Odour:	not reported
Boiling Point:	148°C at 13.3kPa
Melting point	14°C
Vapour Pressure:	0.012 kPa at 20°C 0.029 kPa at 30°C
Density:	1.04 g/cm^3 at 25°C
Flashpoint:	98°C (open cup)
Flammability:	Combustible when exposed to heat or flame
Flammability Limits:	1.4 - 10% by volume
Solubility in Water:	Miscible with water at 20°C

OTHER PROPERTIES

Oxidising properties: Not an oxidising agent

Reactivity: Can polymerise exothermically in the absence of stabilisers particularly in acid conditions or if shelf life exceeded. Reacts vigorously with oxidising materials.

Auto-flammability: 240°C Auto-

ignition temperature: 364°C Vapour

density: 3.8

INGREDIENTS

Chemical Entity	**CAS Number**	**Proportion**
N-vinyl-2-pyrrolidone	88-12-0	
Stabiliser		

HEALTH HAZARD INFORMATION

HEALTH EFFECTS

Acute

Inhalation: No reliable human data. In animals, NVP may cause respiratory distress, CNS effects (ataxia, narcosis) and increased salivation and nasal secretion.

Swallowed: No data in humans. In animals, NVP causes increased secretions and discharge of tears and loss of righting reflex at high doses.

Eye: Irritant to the eyes. Liquid can produce corneal, conjunctival and iris damage.

Skin: Mild irritant. Liquid may be absorbed through the skin.

Chronic

No health effects reported in workers following long term exposure to NVP. Animal studies indicate that repeated exposure could result in anaemia and liver and nasal damage.

Repeated or prolonged exposure causes liver and nasal cavity tumours in rats.

FIRST AID

Inhalation: Remove from exposure. Keep warm and at rest until fully recovered.

Swallowed: Do NOT induce vomiting. Give a glass of water.

Eyes: Immediately flush eyes with plenty of water.

Skin: Remove contaminated clothing and wash skin thoroughly.

ADVICE TO DOCTOR

Treat symptomatically.

PRECAUTIONS FOR USE

Exposure Standards:

No exposure standard has been assigned to NVP by NOHSC.

Engineering Controls

Exhaust ventilation is necessary during use of NVP.

Personal Protection

If splashes are likely to occur during use, safety goggles conforming to Australian Standard AS/NZS 1337 (Standards Australia, 1992) should be worn.

Wear gloves, overalls and safety footwear in accordance with the manufacturer's recommendations if contact with liquid NVP is likely.

If inhalation exposure is likely, eg during cleanup of major spills, a respirator fitted with a gas filter such as type A (organic vapour) should be worn. An air-line respirator should be worn if working in a confined space or in poorly ventilated areas. Respiratory protective equipment should be in accordance with AS/NZS 1715 and AS/NZS 1716 (Standards Australia, 1994).

Flammability

NVP is not flammable under normal conditions of use. However, it is combustible when exposed to heat or flame.

SAFE HANDLING INFORMATION

Storage and Transport

When not in use, seal the container tightly and store in a dry and dark place. Keep away from light, heat or sources of ignition. Avoid long periods of storage. Always store away from incompatible compounds such as oxidizing agents, acids or acid forming substances.

Spillage and Disposal

Eliminate sources of ignition. Spills should be contained with absorbent material such as earth, sand or similar inert material, and disposed of to licensed landfill or incinerated.

Do not allow product to enter drains or waterways.

Fire/Explosion Hazard

Low fire hazard when exposed to heat or flame. During a fire, irritating/toxic nitrogen oxides (NO_x) may be generated. For fires, water spray, alcohol foam, dry chemical or carbon dioxide may be appropriate. Fire fighters should wear full protective equipment including self-contained breathing apparatus.

OTHER INFORMATION

Toxicological Information

Oral LD_{50} (rats): 834 - 2500 mg/kg
Oral LD_{50} (mice): 940 mg/kg
Dermal LD_{50} (rats): 1043 - 4127 mg/kg
Dermal LD_{50} (guinea pigs): 3000 - 5000 mg/kg
4h LC_{50} (rats): 3070 mg/m^3

Ecological Information

96 h LC_{50} (Bluegill sunfish): 1841 mg/L
96 h LC_{50} (Channel catfish): 1109 mg/L
96 h LC_{50} (Fathead minnow): 2585 mg/L
96 h LC_{50} (Rainbow trout): 913 – 1325 mg/L

CONTACT POINT

Contact Name:

Position Title:

Telephone Number:

Address:

References

Anderson EL & Carcinogenic Assessment Group of the USEPA (1983) Quantitative approaches in use to assess cancer risk. Risk Analysis **3**: 277-295.

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BASF (1963a) Study of acute toxicity and skin and eye irritation. Report No.: XIII 37. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

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BASF (1964) Report on the testing of the inhalation toxicity of vinylpyrrolidone. Report Nos.: XIII/38, XIII/139. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

BASF (1978a) Primary skin and eye irritation tests with N-vinylpyrrolidone in albino rabbits. TNO Report No.: B77/907-30. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

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BASF (1979) Report on the determination of the acute inhalation toxicity, LC_{50} of vinylpyrrolidone in a 4 hour exposure period on Sprague-Dawley rats. Report No.: 77/753. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

BASF (1986a) Study of the sub-chronic inhalation toxicity of N-Vinyl-2-pyrrolidone in Sprague Dawley rats (3-month study). Project No.: 42J0165/8005. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

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). Project No.: 42I0186/8233. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

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. Project No.: 12C0053/8404. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

BASF (1986d) Report on the study of the toxicity of N-vinyl-2-pyrrolidone in rats after 3-months administration in the drinking water. Project No.: 32C0250/8417. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG

BASF (1987a). 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). Project No.: 51I0186/8234. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

BASF (1987b). Preliminary study on the sub-chronic inhalation toxicity of N-vinylpyrrolidone-2 in Syrian hamsters (3-month study). Project No.: 52I0186/8235. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

BASF (1987c). In-vitro cytogenetic investigations of N-Vinylpyrolllidone-2 in Human lymphocytes. Project No.: 30M0161/8616. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

BASF (1988a). The inhalation toxicity of N-vinylpyrrolidone (extra pure) as vapour on Fischer 344 rats after 2 or 5 exposures or combination exposure. Project No.: 43I0459/8470S. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

BASF (1988b) The inhalation toxicity of N-vinylpyrrolidone (extra pure) as vapour on female C57 Black mice after 2 or 5 exposures or combination exposure. Project No.: 44I0459/8471S. unpublished data. Department of Toxicology, BASF Aktiengesellschaft, 6700 Ludwigshafen/Rhein, FRG.

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