European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

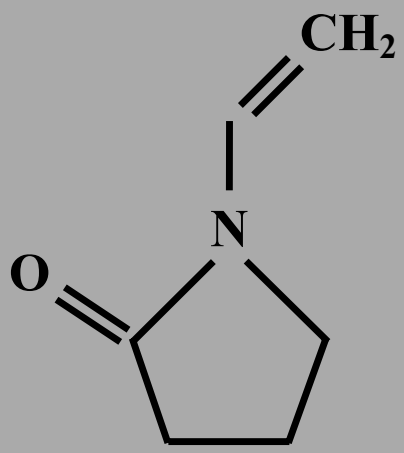
Existing Substances

European Union Risk Assessment Report

CAS No: 88-12-0

EINECS No: 201-800-4

1-vinyl-2-pyrrolidone



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European Union Risk Assessment Report

1-VINYL-2-PYRROLIDONE

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RISK ASSESSMENT

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RISK ASSESSMENT

Final Report, 2003

United Kingdom

This document has been prepared by the UK rapporteur on behalf of the European Union. The scientific work on the environmental part was prepared by the Building Research Establishment Ltd (BRE), under contract to the rapporteur.

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Date of Last Literature Search:	**1997**
Review of report by MS Technical Experts finalised:	**2001**
Final report:	**2003**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

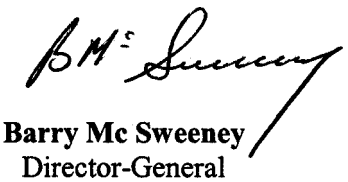
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



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1 O.J. No L 084, 05/04/199 p.0001 – 0075

2 O.J. No L 161, 29/06/1994 p. 0003 – 0011

3 Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS-No: 88-12-0
EINECS-No: 201-800-4
IUPAC name: 1-vinyl-2-pyrrolidone

Environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This applies to all environmental compartments for production, processing and use of 1-vinyl-2-pyrrolidone and release of 1-vinyl-2-pyrrolidone during use of polymers which contain residual 1-vinyl-2-pyrrolidone monomer.

Human health

Human health (toxicity)

Workers

Results

Conclusion (iii) There is a need for limiting the risks; risk reduction measure which are already being applied shall be taken into account

This conclusion is reached in the light of the uncertainty about the risks to humans arising from exposure to N-VP.

This conclusion applies to workers exposed to N-VP during its manufacture, during its use in the production of polymers, during manufacture of UV curing inks and lacquers and during use of UV curing inks, because of concerns for single exposure toxicity, respiratory tract irritation, repeated dose toxicity and carcinogenicity. In addition, it applies to the use of UV curing lacquers containing N-VP, and the use of N-VP in the manufacture of contact lenses because of concerns for repeated dose toxicity and carcinogenicity.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to workers exposed to residual N-VP monomer during use of its polymers. It also applies to all scenarios in relation to the eye irritation of the liquid substance, providing good occupational hygiene practices are in operation. However, if there is contact with the eye, which could occur accidentally, then local damage is possible.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Combined exposure

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The combined exposure is dominated by worker exposure and therefore the conclusions of the risk characterisation for workers also apply for combined exposure.

Human health (risks from physicochemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

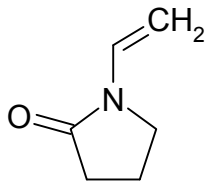
CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS-No:	88-12-0
EINECS-No:	201-800-4
IUPAC name:	1-vinyl-2-pyrrolidone
v	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
Molecular weight:	111.14
Molecular formula:	$C_6H_9N_1O_1$
Structural formula:	



1-Vinyl-2-pyrrolidone is an organic liquid. The abbreviation N-VP will be used in some sections of this report.

1.2 PURITY/IMPURITIES, ADDITIVES

No impurities/additives are listed in IUCLID 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 (Richardson and Gangolli, 1994).

1.2.1 Purity

The purity indicated by the suppliers was > 95% w/w.

The impurities present included:

Water	<	0.05%
2-Pyrrolidone	≤	0.2% w/w
1-Vinyl-3-methyl-pyrrolidone	≤	0.1% w/w.

1.2.2 Additives

The stated additive was N, N'-di-sec-butyl-p-phenylenediamine at 10 ppm.

1.3 PHYSICO-CHEMICAL PROPERTIES

1.3.1 Physical state (at ntp)

N-Vinyl pyrrolidone (N-VP) is a colourless to light yellow liquid at room temperature. In the absence of stabilisers it tends to darken on standing.

1.3.2 Melting point

The melting point of this substance is variously quoted as 13.5°C (e.g. Richardson and Gangolli, 1994) and this is verified by the original literature reference (Drechsel, 1957), the IUCLID data giving 13-14°C (BASF, 1995a) when measured to BS 523/1964.

A value of 13-14°C will be used in this assessment, for commercially available material.

1.3.3 Boiling point

The boiling point is quoted as 46°C at 0.1333 kPa, 88°C at 1.33 kPa, 147°C at 13.3 kPa and 219°C at 101.3 kPa (Kirk-Othmer, 1991 - original reference not specified). Further values from secondary sources (CRC Handbook of Chemistry and Physics, 1995; Richardson and Gangolli, 1994) include 193°C at 400 mmHg (53.3 kPa), 148°C at 100 mmHg and 93°C at 11 mmHg (1.47 kPa). The Beilstein Handbook of Organic Chemistry (Beilstein, 1984) quotes 148°C at 100 mmHg (13.3 kPa; Drechsel, 1957), 94-96°C at 13-14 mmHg (1.8 kPa; Reppe et al., 1956), 86.5°C at 8 mmHg (1.0 kPa; Frank, 1954) and 75-6°C at 2.5 mmHg (0.33 kPa) and 64-66°C at 2 mmHg (0.27 kPa; Puetzer et al., 1952). The IUCLID data (BASF, 1995a) quotes 90-92°C at 13 hPa (1.3 kPa), measured to DIN 53 406.

The boiling point at atmospheric pressure is reported to be circa 218°C (Kirk-Othmer, 1991) although this has not been validated. Given the structure of this substance it is likely that decomposition may occur at elevated temperatures.

The boiling point will be accepted as 90-92°C at 1.3 kPa. The values quoted in Beilstein can be accepted as they are referenced to original literature values.

1.3.4 Relative density

The density has been quoted in the primary literature at 1.045 $g \cdot cm^{-3}$ at 20°C (Frank, 1954) although the method of determination is not mentioned. This value has been confirmed at an approved testing laboratory (IUCLID data set quoting BASF, 1985).

A value of 1.045 $g \cdot cm^{-3}$ at 20°C will be accepted and the relative density 1.045/0.99997 is therefore 1.045.

1.3.5 Vapour pressure

Aldrich (1995) quotes a value of 0.1 mmHg (0.013 Pa) at 24°C. Values of 0.012 kPa at 20°C, 0.123 kPa at 50°C (BASF, 1982) and 0.197 kPa at 56.9°C (BASF, 1976, cited in IUCLID) have been measured at an approved testing laboratory using > 99% pure vinyl pyrrolidone. Copies of the original papers have been supplied.

It can be seen that this substance has a relatively low vapour pressure at ambient temperatures. The vapour pressure at 20°C will be accepted as 0.012 kPa (12 Pa).

1.3.6 Solubility

N-VP is fully miscible with water and is soluble in many organic solvents (BASF, 1995a).

1.3.7 Partition coefficient (log $K_{o/w}$)

Values of -0.37 (calculated, BASF, 1989) and 0.4 (shake flask method to OECD test guideline 107, BASF, 1988a) have been quoted in the IUCLID data set. The methods used to arrive at these values have been described. No other sources of data on the partition coefficient of this substance have been located. A log Kow value of 0.4 will be used in this assessment.

1.3.8 Flash point

Values quoted include 98.4°C (Kirk-Othmer, 1991), 201 F (93.9°C) (Aldrich, 1995) and 93°C (Richardson and Gangolli, 1994); the National Fire Protection Association (1994) states 98°C. The references or test methods applicable to these values are not stated.

The IUCLID data set quotes a value of 95°C (closed cup) when measured to DIN 51 758 (BASF, 1995a). The flash point will be accepted as 95°C.

1.3.9 Autoflammability

Values quoted include 364.2°C (Sax and Lewis, 1989), 240°C (BASF, 1995a), when carried out to DIN 51 794 and 685 F (362.7°C) in Aldrich (1995).

The reason for the large variation is not clear, although the most acceptable value is 240°C when tested to the DIN standard. This is also the lowest figure and hence will be used in this assessment.

1.3.10 Explosivity

The explosive limits in air have been quoted in IUCLID as 1.4-10.0% by volume (BASF, 1975). No other sources of this data have been established.

1.3.11 Oxidising properties

No measured test results are available on oxidising properties of the substance. As the substance has no functional groups that lead to an oxidising potential, no additional test is necessary for risk assessment.

1.3.12 Additional remarks

In acid conditions or if the shelf life or storage temperature are greatly exceeded, polymerisation with significant evolution of heat can occur (BASF, 1995a).

1.3.13 Summary of physico-chemical properties

The basic physico-chemical properties of N-VP are described in the literature although most of the data on parameters such as vapour pressure, partition coefficient and flammability have come from verified company (BASF) data. (The test reports and methods have been submitted).

Further physico-chemical data on >99% pure material includes the surface tension, measured at 0.0405 $N.m^{-1}$ at 20°C using the ring method, tensiometer TE 1C (BASF, 1985), and the viscosity as 2.4 $mPa.s^{-1}$ at 20°C (BASF, 1995a).

The data set is complete and the values can be considered as the best available.

A summary of the physicochemical properties is given in **Table 1.1**. Values in bold are used in the risk assessment.

Table 1.1 Physico-chemical properties of 1-vinyl-2-pyrrolidone

Property	Value	Comments
Molecular weight	**111.14** a) c), 111.15 d)	
Physical state at ntp	Colourless to light yellow liquid	darkens in absence of stabilisers
Melting point	**13-14°C** a), 13.5°C c) d)	
Boiling point	**90-92°C** at 13 hPa a), 148°C c), 90-93°C d)	
Density	1.045 g/cm^3 at 20°C g)	
Vapour pressure	**0.12 hPa** at 20°C b, 0.1 mmHg at 24°C d) (= 0.13 Pa)	
Vapour density	3.8 d)	
Partition coefficient (log K_{ow})	-0.37 (calc.) e), **0.4 at 25°C** (measured) f)	
Solubility	miscible with water at 20°C a) c)	soluble in acetone, diethyl ether, ethanol, toluene and benzene b)

Table 1.1 continued overleaf

Table 1.1 continued Physico-chemical properties of 1-vinyl-2-pyrrolidone

Property	Value	Comments
Flash point	**95°C** [a], 93°C [c]	BASF data to DIN 51 758
Auto-flammability	240°C [a]	BASF data to DIN 51 794
Explosive properties	explosive limits in air: 1.4-10% by volume [h]	
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	

a) BASF (1995a)
b) BASF (1982)
c) Richardson and Gangolli (1994)
d) Ashford (1994)
e) BASF (1989)
f) BASF (1988a)
g) BASF (1985)
h) BASF (1975)

1.4 CLASSIFICATION AND LABELLING

1.4.1 Current classification

The classification and labelling of 1-vinyl-2-pyrrolidone as listed in Annex 1 to Directive 67/548/EEC (28th ATP, January 2001) is as follows:

Xn; R40 Carcinogen Category 3; R20/21/22-37-41-48/20 S26-36/37/39

Xn indicates:	"harmful"; substances and preparations which may cause death or acute or chronic damage to health when inhaled, swallowed or absorbed via the skin.
R40 states:	Limited evidence of a carcinogenic effect.
Carcinogen Cat. 3 is for:	Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies but this is insufficient to place the substance in Category 2.
R20/21/22 states:	Harmful by inhalation, in contact with the skin and if swallowed.
R37 states:	Irritating to respiratory system.
R41 states:	Risk of serious damage to eyes.
R48/20 states:	Harmful: danger of serious damage to health by prolonged exposure through inhalation.
S26 states:	"In case of contact with eyes, rinse immediately with plenty of water and seek medical advice".
S36/37/39 states:	"Wear suitable protective clothing, gloves and eye/face protection.

Note D applies.

There is no classification for effects on the environment.

2 GENERAL INFORMATION ON EXPOSURE

It should be noted that the number of producers and users for this substance is small. Therefore only limited information on quantities produced or used in the EU has been included in this assessment report on the grounds of confidentiality. Information relating to production and use is discussed more fully in the Confidential Annex, Production and supply.

N-Vinyl pyrrolidone (N-VP) is produced by the vinylisation of pyrrolidone in a continuous process using acetylene. The raw product is purified by distillation. There are understood to be only two producers of N-VP worldwide, one in Germany and one in the USA. The annual production volume in 1999 was 10,000-50,000 tonnes.

2.1 USES

The majority of the N-VP that is sold within the EU is used in the production of polyvinyl pyrrolidone (e.g. for pharmaceuticals, cosmetics and food additives) or copolymers (used as viscosity improvers in oils and in water-borne paints and adhesives). N-VP is also used as a reactive thinner in UV cured inks and lacquers and in the manufacture of contact lenses.

A breakdown of the use pattern of N-VP is given in the Confidential Annex.

3 ENVIRONMENT

3.1 EXPOSURE ASSESSMENT

3.1.1 Environmental releases

There is no information in IUCLID about the potential release of 1-vinyl-2-pyrrolidone to the environment. However, some site-specific data are available for production and processing of 1-vinyl-2-pyrrolidone. These are given in a Confidential Annex together with more information about the use of 1-vinyl-2-pyrrolidone and polyvinyl pyrrolidone.

3.1.1.1 Releases during production and processing

Site-specific information for production

Site-specific information is available for European production sites that manufacture and process 1-vinyl-2-pyrrolidone. This information is included in the Confidential Annex and has been used in the assessment. PECs based on releases during production and use are given in Section 3.1.8.

Site-specific information for polymer manufacture

The majority of 1-vinyl-2-pyrrolidone that is sold within the EU is used as a monomer in the production of polyvinyl pyrrolidone (PVP) or copolymers. It is also used to form copolymers in UV-cured inks and coatings.

The polymerisation of 1-vinyl-2-pyrrolidone in the EU is largely carried out by the producers of 1-vinyl-2-pyrrolidone, accounting for more than 90% of its use. Site-specific information for the releases arising from these sites is summarised in the Confidential Annex. PECs calculated for these releases are given in Sections 3.1.4 to 3.1.6.

There are also a number of small producers of polymers containing 1-vinyl-2-pyrrolidone in the EU (in this context, smaller producers/sites refers to the amount of 1-vinyl-2-pyrrolidone used at the site rather than the overall activity at the site). Less than 10% of the total 1-vinyl-2-pyrrolidone, some of which is imported from outside the EU, are thought to be used by these producers. Of this, at least 75 tonnes are believed to be used in inks and varnishes as discussed below. Further information covering the total annual tonnages for use in polymerisation to form polyvinyl pyrrolidone or copolymers is included in the Confidential Annex.

Data giving the size and distribution of plants for approximately 50% of the total tonnage used at these smaller plants are considered in the Confidential Annex. Information on the use pattern of around a further 25-35% of the total tonnage at these smaller plants is also known. It is thought that a similar size distribution and use pattern is applicable to all the remaining tonnage used at these small sites.

Site-specific information regarding releases to the environment from several of the larger plants is included in the Confidential Annex and has been used to derive PECs in this report.

Generic information for polymer manufacture

For the remaining sites, generic worst-case scenarios have been derived using the information in the Confidential Annex. The information provided allows the remaining sites to be split into a relatively large number of sites which use very small amounts (e.g. <5 tonnes/year) and a smaller number of other sites which use larger amounts. The releases to air, wastewater and soil estimated for these sites are shown in **Table 3.1**. These releases are based on generic worst-case scenarios, assuming that polymerisation is carried out at the very small sites (<5 tonnes/year (E-H in **Table 3.1**)), and taking into account the actual likely use at the other sites (Uses A-D; mainly polymerisation, but also formulation into inks and coatings). It should be noted that the available site-specific information indicates that actual releases may be much lower than indicated by the generic calculations. These generic scenarios, along with those given in later for inks and coatings, are thought to cover all the likely uses at these smaller sites.

The regional and continental releases in **Table 3.1** have been estimated based on the release from the polymerisation process, as this is the main use of 1-vinyl-2-pyrrolidone. Table A3.10 of the Technical Guidance Document (TGD, EC, 1996) gives emission factors to air, water and soil of 0.001, 0.01 and 0, respectively. This assumes that 1-vinyl-2-pyrrolidone is in Type I monomers. As a worst case the processes have been assumed to be 'wet' polymerisations (although the limited available data shows that, in at least in some cases, the processes are dry). The vapour pressure is 12 Pa and the water solubility is in excess of 1,000 mg/l.

Table 3.1 Emissions to air and water and soil during processing (for smaller sites)

Process	Amount used (t/a)	Release to air (kg/a)	Release to water (kg/a)	Temission (days)	$Elocal_{air}$ (kg/day)	$Elocal_{water}$ (kg/day)
Local releases from smaller sites						
Use A	-	-	-	-	0.15-0.49	1.5-4.89
Use B	-	-	-	-	0.37	1.46
Use C	-	-	-	-	0.58	2.33
Use D	-	-	-	-	0.7	7
Polymerisation–E	5	5	50	10	0.5	5
Polymerisation–F	5	5	50	10-25	0.2-0.5	2-5
Polymerisation–G	5	5	50	7-17	0.29-0.7	2.9-7.0
Polymerisation–H	5	5	50	14-34	0.147-0.357	1.47-3.57
Regional release [a]	-	73.5	735 [c]			
Continental release [b]	-	662	6,615 [c]			

a) estimated based on 10% of the total tonnage used by small users being processed in the region
b) estimated from total tonnage used by small users-regional tonnage used by small users
c) in the EUSES model a 70% connection rate to wastewater treatment plants is assumed.

A key input into the local release estimates is the amount of 1-vinyl-2-pyrrolidone typically used on a site/day. Information provided by industry indicates that this is around 0.3-0.5 tonnes/day for small users. The amounts used on a site/day calculated in the generic scenarios given in **Table 3.1** (ca. 0.1-0.7 tonnes/day) are consistent with this figure.

Continental and regional releases from production and polymer processing

Regional and continental environmental releases for production and processing have been averaged over 365 days. The available information indicates that the smaller plants are widely distributed. It has therefore been assumed that the use is consistent throughout the EU. The maximum releases for this scenario, derived from the worst-case emissions at the local scale, combined with the site-specific releases from production and large processing sites are given in **Table 3.2**. In the estimates, it is assumed that one large production and processing site, and 10% of the smaller processing activity occurs in the region as a worst-case.

Table 3.2 Regional and continental release of 1-vinyl-2-pyrrolidone to the environment from production and polymer processing

	Release to air (kg/day)	Release to water (kg/day) [a)]
Regional	2.42	21.19
Continental	1.812	18.12

a) in the EUSES model a 70% connection rate to wastewater treatment plants is assumed.

Releases from the production and use of radiation-cured coatings and inks

About 75 tonnes per annum of 1-vinyl-2-pyrrolidone are thought to be used to make radiation-cured inks. The use of these materials includes printing on advertising hoardings, point of sale advertising, car fascia panels, compact discs and plastic bottles. These inks contain up to about 14% 1-vinyl-2-pyrrolidone. There are about 40 companies throughout the EU producing or supplying these inks although 1-vinyl-2-pyrrolidone is only used in selected products.

Radiation-cured coatings and varnishes are used for coating printed circuit boards, finish on wood veneers, on polycarbonate car headlights and children's toys. Available information on use of coatings for printed circuit boards in the USA suggests that 1-vinyl-2-pyrrolidone is present at levels of between 2% and 7.5%. Laquers used for the other applications listed above are reported to contain about 9% 1-vinyl-2-pyrrolidone. Prepolymers such as urethanes and acrylates, pigments, flow additives and a photo-initiator are also present. The available information suggests that water is not included in the product. However, water-based products may also exist.

The release of 1-vinyl-2-pyrrolidone from use in inks and coatings has been estimated using the default values for Industry Category 14 (Paints, lacquers and varnishes industry) in the TGD. The releases from inks and coatings have been considered together and the average 1-vinyl-2-pyrrolidone content assumed to be 10%. The release from formulation has been taken from Table 2.10 of the TGD and emission factors are 0.005, 0.02 and 0.0001 for air, water and soil, respectively (assuming main category 3, water solubility ≥ 1,000 mg/l and vapour pressure 12 Pa). Table B2.3 has been used to calculate the number of emission days and the fraction of the main source. The release from use of the material (equivalent to processing) has been taken from Table A3.15 (assuming a solvent-based product, use category 55/0 (other), water solubility ≥ 1,000 mg/l, vapour pressure 12 Pa) and emission factors are 0.001, 0.01 and 0.005 for air, water and soil, respectively. Table B3.13 has been used to calculate the number of emission days and the fraction of the main source. This results in around 7.5 tonnes/year of 1-vinyl-2-pyrrolidone being used on a site. This is consistent with the confidential information provided by industry (see Confidential Annex). PECs based on releases during the manufacture and use of inks and coatings are summarised in Section 3.1.8. The releases are given in **Table 3.3**. Regional and continental releases, averaged over 365 days are given in **Table 3.4**.

Table 3.3 Local releases of 1-vinyl-2-pyrrolidone to the environment from ink/coating production and use

	Compartment	Emission factor	Regional release [a] (t/a)	Continental release [b] (t/a)	Fmain source	Temission (days)	Elocal (kg/day)
Formulation (Tables A2.1 and B2.3)	Air Water Industrial soil	0.005 0.02 0.0001	0.0375 0.15 [c] 0.00075	0.338 1.35 [c] 0.0068	1	300	0.125 0.5 0.0025
Processing (Tables A3.15 and B3.13)	Air Water Industrial soil	0.001 0.01 0.005	0.0075 0.075 [c] 0.0375	0.0675 0.675 [c] 0.338	0.3	75	0.030 0.30 0.150

a) estimated based on 10% of the total tonnage of 75 tonnes/year being processed in the region.
b) estimated from total tonnage used inks-regional tonnage used in inks.
c) in the EUSES model a 70% connection rate to wastewater treatment plants is assumed.

Table 3.4 Regional and continental releases of 1-vinyl-2-pyrrolidone to the environment from ink/coating production and use

	Release to air (kg/day)	Release to water (kg/day) [a]	Release to industrial soil (kg/day)
Regional	0.123	0.616	0.10
Continental	1.11	5.55	0.93

a) in the EUSES model a 70% connection rate to wastewater treatment plants is assumed.

3.1.1.2 Release during use of polymer

No information has been provided in IUCLID regarding release of 1-vinyl-2-pyrrolidone during use of polyvinyl pyrrolidone (PVP). PVP is used in various applications and the amount of residual monomer varies with different uses. The maximum amount of residual monomer in polyvinyl pyrrolidone has been reported to be as high as 1% (IARC, 1979). However, recent information from the manufacturers puts the amount of residual monomer at less than 1,000 ppm in all polymers.

For this assessment, it has been assumed that the total amount of PVP used in the EU is 20,000 tonnes/annum. As a worst-case, it has been assumed that the amount of residual monomer is 1,000 ppm in all polymers. These assumptions are also considered to cover possible releases of residual 1-vinyl-2-pyrrolidone from inks and coatings in use. If use is evenly spread throughout the EU and throughout the year, and assuming that all residual monomer from one year's production is released over the year, the total release of monomer is then 54.79 kg/day. Therefore, the regional release is 5.48 kg/day. These releases have been assumed to occur to wastewater and/or the atmosphere. Three scenarios have been considered to address the range of potential releases. These are:

a) all of the residual monomer is released to the atmosphere,
b) all of the residual monomer is released to water,
c) half of the residual monomer is released to water and half to the atmosphere.

The releases for each scenario are summarised in **Table 3.5**.

Table 3.5 Releases to air and water for residual monomer in PVP (3 scenarios)

Scenario	Release to water	Release to air
100 % to water	regional 5.48 kg/day continental 49.32 kg/d	regional 0 continental 0
50% to water 50% to air	regional 2.74 kg/day continental 24.66 kg/d	regional 2.74 kg/day continental 24.66 kg/d
100% to air	regional 0 continental 0	regional 5.48 kg/day continental 49.32 kg/d

At the local scale, the releases of the residual monomer from sites formulating or processing the polymers are likely to be very small due to the potentially large number of sites involved and also the low residual monomer content (<0.1% by weight) of the polymer. Thus if during the formulating/processing on the site, 1% of the polymer is lost to wastewater, the loss to wastewater of 1-vinyl-2-pyrrolidone would be 0.1% of this. As an extreme example, if all 20,000 tonnes of the polymer were used on one site, the total release of 1-vinyl-2-pyrrolidone at the site would be only 200 kg/year, or 0.66 kg/day, which is less than many of the local scenarios considered in Section 3.1.1.1. This indicates that the actual local releases of residual 1-vinyl-2-pyrrolidone from sites using polymers or copolymers will be very small, with resulting very low PECs. For this reason, the releases from residual monomer are considered on the regional and continental scale only in the assessment, as outlined in **Table 3.5**.

3.1.1.3 Total regional and continental releases

The total regional and continental emissions to air and wastewater are summarised in **Table 3.6**.

Table 3.6 Total regional and continental releases

		Residual monomer released to atmosphere	Residual monomer released to water	Residual monomer released 50% to water and 50% to atmosphere
Regional	air	8.02 kg/day	2.54 kg/day	5.28 kg/day
	water [a)]	21.81 kg/day	27.29 kg/day	24.55 kg/day
	industrial soil	0.10 kg/day	0.10 kg/day	0.10 kg/day
Continental	air	52.2 kg/day	2.92 kg/day	24.66 kg/day
	water [a)]	23.67 kg/day	72.99 kg/day	48.33 kg/day
	industrial soil	0.93 kg/day	0.93 kg/day	0.93 kg/day

a) in the EUSES model a 70% connection to wastewater treatment plants is assumed.

3.1.2 Environmental fate

3.1.2.1 Degradation

3.1.2.1.1 Abiotic degradation

The rate constant for the reaction of 1-vinyl-2-pyrrolidone with hydroxyl radicals in aqueous solution has been measured and is $7.3 \cdot 10^9$ l/mol·sec (Buxton et al., 1988). No other experimental information on abiotic degradation is available.

The SRC program AOP gives a calculated value for the rate constant for reaction with atmospheric hydroxyl radicals (k_{OH}) of $3.72 \cdot 10^{-11}$ cm^3/molecule·s. Assuming an atmospheric hyroxyl radical concentration of $5 \cdot 10^5$ molecules/cm^3, this equates to an atmospheric half-life of 10.4 hours. This value will be used in the EUSES modelling.

3.1.2.1.2 Biodegradation

The biodegradation of 1-vinyl-2-pyrrolidone by bacteria in active sludge was measured (BASF, 1979a) using the Zahn-Wellens test. The experiment was a permanent experiment using TOC and the concentration of 1-vinyl-2-pyrrolidone used was 400 mg/l. 1-Vinyl-2-pyrrolidone was 100% degraded after 14 days. It was remarked that the substance is easily eliminated from water and biologically degradable.

The biodegradability of 1-vinyl-2-pyrrolidone in active sludge from laboratory sewage plants has been measured using the reduction in DOC in accordance with EC Guideline 92/69/EEC and OECD Guideline 301 A (BASF, 1995b) for ready biodegradability. Activated sludge from laboratory sewage treatment plants was used. The test concentration was 29.4 mg/l. The test substance was found to be readily biodegradable (with >70% degraded within 10 days). The sample was 100% decomposed after 28 days.

Rate constants for degradation used in the assessment are summarised in **Table 3.7**.

Table 3.7 Summary of degradation rates for 1-vinyl-2-pyrrolidone

Description	Rate constant	Source
Rate constant for hydrolysis in surface water	0	default value
Rate constant for photolysis in surface water	0	default value
Rate constant for biodegradation in surface water	0.0462 d^{-1}	from the TGD assuming ready biodegradability
Rate constant for biodegradation in bulk soil	0.0231 d^{-1}	from the TGD assuming ready biodegradability and Koc of 16.9
Rate constant for biodegradation in aerated sediment	0.0231 d^{-1}	from the TGD assuming ready biodegradability and Koc = 16.9
Rate constant for biodegradation in bulk sediment	0.00231 d^{-1}	from the TGD assuming ready biodegradability, Koc = 16.9 and fraction of sediment that is aerobic = 0.1
Rate constant for atmospheric degradation by hydroxyl radicals	1.6 d^{-1}	from $k_{OH} = 3.72 \cdot 10^{-11}$ $cm^3 \cdot molecule^{-1} \cdot s^{-1}$ and $[OH] = 5 \cdot 10^5$ molecule/cm^3

3.1.2.2 Distribution

Based on the Henry's law constant of 0.0056 $Pa \cdot m^3 \cdot mol^{-1}$ (calculated from the SRC HENRY model using the bond contribution method) 1-vinyl-2-pyrrolidone is expected to volatilise slowly. This value of the Henry's law constant is used in the EUSES modelling.

Based on the low value of log Kow, 1-vinyl-2-pyrrolidone is not expected to adsorb to soil, sediment or suspended matter to a significant extent. The organic carbon-water partition coefficient (Koc) has been estimated to be 16.9 using the model given for non-hydrophobics in Chapter 4 of the TGD. This value for Koc is used in the EUSES modelling.

3.1.2.3 Accumulation

No information is available on accumulation of 1-vinyl-2-pyrrolidone. However, the log Kow value is 0.4 which suggests that bioaccumulation of 1-vinyl-2-pyrrolidone is not likely to occur to a significant extent. A fish bioconcentration factor of 1.41 l/kg is estimated in EUSES (see Appendix A) from the log Kow value using the methods outlined in the TGD.

3.1.3 Regional and continental PECs

The EUSES model has been used to estimate the regional and continental Predicted Environmental Concentrations (PECs) for the six scenarios discussed above, using the methods outlined in the TGD (see Appendix A). It has been assumed that 1-vinyl-2-pyrrolidone is readily biodegradable. The model uses the default values for a typical European regional environment as given in the TGD. The scenario in which releases from large production and processing sites occur within one region and releases of residual monomer in PVP occur 50% to air and 50% to water has been used as a worst-case although some values may be higher in other scenarios as discussed in Appendix B. Regional and continental PECs for this scenario are given in **Table 3.8** and these have been used in later stages of the assessment. Regional and continental PECs for other release scenarios are summarised in Appendix B.

Table 3.8 PECs at the regional and continental levels

Compartment	Regional PEC	Continental PEC
Air	$3.52 \cdot 10^{-8}$ mg/m^3	$2.93 \cdot 10^{-9}$ mg/m^3
Surface water (dissolved)	$3.88 \cdot 10^{-5}$mg/l	$1.28 \cdot 10^{-6}$mg/l
Agricultural soil	$3.09 \cdot 10^{-6}$ mg/kg wet wt.	$2.42 \cdot 10^{-7}$ mg/kg wet wt.
Porewater of agricultural soil	$7.34 \cdot 10^{-6}$ mg/l	$5.83 \cdot 10^{-7}$ mg/l
Natural soil	$6.67 \cdot 10^{-6}$ mg/kg	$5.56 \cdot 10^{-7}$ mg/kg
Industrial soil	$1.26 \cdot 10^{-5}$ mg/kg	$1.16 \cdot 10^{-6}$ mg/kg
Sediment	$3.48 \cdot 10^{-5}$ mg/kg wet wt.	$1.14 \cdot 10^{-6}$ mg/kg wet wt.

3.1.4 Aquatic compartment (incl. sediment)

3.1.4.1 Calculation of Predicted Environmental Concentration (PEC) for water

PEClocal

The local PECs have been calculated for the releases discussed in Section 3.1.1 using the equations in the TGD. For production/processing, site-specific information on the release to water and flow in the receiving water has been used and it has been assumed that release occurs over 300 days per year.

Other releases have been assumed to occur to a standard WWTP with an average wastewater flow of 200 l per capita per day for a population of 10,000 inhabitants and the dilution factor in the receiving water is 10 as specified in the TGD (for processing at small sites – Use D, the receiving water is a large river, and so the river flow of 60 m^3/s as recommended in the Emission Scenario document for chemicals used in synthesis is appropriate, giving a dilution of 2592). Using the Simple Treat model in EUSES (see Appendix A) the fraction of emission directed to water by STP is 12.6% with 0.0024% directed to air and 0.159% directed to sludge, with the remaining 87.2% being degraded. This is based on a readily biodegradable substance with log H of -2.3 and log Kow of 0.4. The results are in **Table 3.9**. In all cases the regional surface water concentration of 0.0388 µg/l has been added to the local concentration in order to derive the PEC_{local}. Values for the concentration of 1-vinyl-2-pyrrolidone in the sewage treatment plant, PEC_{stp}, have also been calculated in accordance with the TGD. These values are given in **Table 3.9**.

As discussed in Section 3.1.1.2, the local PECs resulting from release of residual monomer from sites using polyvinyl pyrrolidone or copolymers are likely to be very low.

Table 3.9 PEC values for water for production and processing

Scenario	PEClocal (µg/l)	$PEClocal_{ann}$ (µg/l)	$PEClocal_{sed}$ (µg/kg wet wt.)	PEC_{stp} (µg/l)
Production and processing (site-specific information for main producer)	0.085	0.077	0.098	1,480
Processing at small sites (site-specific)	0.040	0.0388	0.046	$8.8 \cdot 10^{-3}$
Processing at small sites – Use A	9.5-31	4.0	10.9-35.7	95-310
Processing at small sites – Use B	9.27	7.62	10.7	92.3
Processing at small sites – Use C	14.8	12.1	17	147
Processing at small sites – Use D	0.21	0.045	0.241	442
Processing at small sites – polymerisation – E	31.6	0.90	36.4	316
Processing at small sites – polymerisation – F	12.7-31.6	0.90	14.6-36.4	127-316
Processing at small sites – polymerisation – G	18.4-44.3	0.88-0.89	21.1-50.9	183-442
Processing at small sites – polymerisation - H	9.3-22.6	0.90	10.7-26.0	93-226
UV inks formulation	3.20	2.64	3.68	31.6
UV inks processing	1.93	0.43	2.22	19.0

3.1.4.2 Calculation of Predicted Environmental Concentration (PEC) for sediment

The PEClocal for sediment has been calculated from the PEClocal for surface water using the equilibrium partitioning method. The results are shown in **Table 3.9**.

3.1.5 Atmosphere

For the atmospheric compartment the local concentration in air during an emission episode was calculated using site-specific data for production and processing which occurs over 300 days per year. The annual average concentration in air at 100 m from the point source was then calculated and added to the PECregional to give the annual average PEClocal. For processing at various sites, and formulation, processing and use of inks/varnishes, releases have been calculated using the TGD default values. For use of the polymer, it has been assumed that all residual monomer is released to the atmosphere with release being evenly spread throughout the year and throughout the EU. The results are in **Table 3.10**.

Table 3.10 Local PECs for the atmosphere

Scenario	Clocal (μg/m³)	$Clocal_{ann}$ (μg/m³)	$PEClocal_{ann}$ (μg/m³)
Production and processing (site-specific information for main producer)	0.753	0.619	0.619
Processing at small sites (site-specific)	$7.5 \cdot 10^{-5}$	$7.4 \cdot 10^{-6}$	$4.3 \cdot 10^{-5}$
Processing at small sites – Use A	0.042-0.136	0.018	0.018
Processing at small sites – Use B	0.103	0.085	0.085
Processing at small sites – Use C	0.161	0.133	0.133
Processing at small sites – Use D	0.195	$6.9 \cdot 10^{-3}$	$6.9 \cdot 10^{-3}$
Processing at small sites – polymerisation – E	0.14	$3.8 \cdot 10^{-3}$	$3.8 \cdot 10^{-3}$
Processing at small sites – polymerisation – F	0.056-0.14	$3.8 \cdot 10^{-3}$	$3.8 \cdot 10^{-3}$
Processing at small sites – polymerisation – G	0.081-0.20	$3.8 \cdot 10^{-3}$	$3.8 \cdot 10^{-3}$
Processing at small sites – polymerisation – H	0.041-0.099	$3.8 \cdot 10^{-3}$	$3.8 \cdot 10^{-3}$
Ink formulation	0.0348	0.0286	0.0286
Ink processing	$8.34 \cdot 10^{-3}$	$1.7 \cdot 10^{-3}$	$1.7 \cdot 10^{-3}$

3.1.6 Terrestrial compartment

The PEClocal has been calculated using the method in the TGD. The release to soil is by deposition, and also by adsorption to sludge in the WWTP (a very small percentage of the substance (0.159%) is predicted to be directed to sludge in the wastewater treatment plant model; see Section 3.1.4). For production/processing, site-specific information is available which shows there is no direct release to soil. For processing at various sites and formulation and use of inks/varnishes, default data from the TGD has been used. The results are in **Table 3.11**.

Table 3.11 Local PECs for soil

Scenario	PEClocal (µg/kg)		
	Agricultural soil (averaged over 30 days)	Grass	$PEClocal_{porewater}$ (µg/l)
Production and processing (site-specific information for main producer)	0.13	0.22	0.31
Processing at small sites (site-specific)	$7.0 \cdot 10^{-3}$	$6.7 \cdot 10^{-3}$	0.016
Processing at small sites – Use A	3.1-10.0	0.34-1.1	2.2-7.2
Processing at small sites – Use B	3.0	0.35	2.2
Processing at small sites – Use C	4.8	0.55	3.5
Processing at small sites – Use D	14.3	1.5	10.3
Processing at small sites – polymerisation – E	10.2	1.1	7.4
Processing at small sites – polymerisation – F	4.1-10.2	0.44-1.1	3.0-7.4
Processing at small sites – polymerisation – G	5.9-14.3	0.63-1.5	4.3-10.3
Processing at small sites – polymerisation – H	3.0-7.3	0.32-0.78	2.2-5.3
Ink formulation	1.03	0.12	0.76
Ink processing	0.62	0.072	0.46

3.1.7 Secondary poisoning

The log Kow for 1-vinyl-2-pyrrolidone is 0.4 and there are no other indications of bioaccumulation potential. Therefore, no assessment of secondary poisoning has been carried out.

3.1.7.1 Predicted environmental levels in biota

The predicted levels of 1-vinyl-2-pyrrolidone in biota and foodstuffs calculated using EUSES for the regional and local scales are included in **Table 3.12**. The predicted daily human intake is summarised in **Table 3.13**. The EUSES printout is included in Appendix A.

Table 3.12 Concentrations in human intake media

	Regional	Production and processing	Processing at small sites	Processing at small sites				Processing at small sites - polymerisation				Ink/varnish formulation	Ink/varnish processing
		(site specific)	(site specific)	Use A	Use B	Use C	Use D	E	F	G	H		
Concentration in wet fish (mg/kg)	$5.47 \cdot 10^{-5}$	$1.1 \cdot 10^{-4}$	$5.5 \cdot 10^{-5}$	$5.7 \cdot 10^{-3}$	0.011	0.017	$6.3 \cdot 10^{-5}$	$1.3 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$	$3.7 \cdot 10^{-3}$	$6.1 \cdot 10^{-4}$
Concentration in root tissue of plant (mg/kg)	$7.15 \cdot 10^{-6}$	$3.0 \cdot 10^{-4}$	$1.6 \cdot 10^{-5}$	$2.1 \cdot 10^{-3}$ - $6.9 \cdot 10^{-3}$	$2.1 \cdot 10^{-3}$	$3.4 \cdot 10^{-3}$	$9.9 \cdot 10^{-3}$	$7.1 \cdot 10^{-3}$	$2.8 \cdot 10^{-3}$- $7.1 \cdot 10^{-3}$	$4.1 \cdot 10^{-3}$- $9.9 \cdot 10^{-3}$	$2.1 \cdot 10^{-3}$- $5.1 \cdot 10^{-3}$	$7.4 \cdot 10^{-4}$	$4.4 \cdot 10^{-4}$
Concentration in leaves of plant (mg/kg)	$1.61 \cdot 10^{-5}$	0.24	$2.2 \cdot 10^{-5}$	$7.5 \cdot 10^{-3}$- $9.2 \cdot 10^{-3}$	0.034	0.053	$6.0 \cdot 10^{-3}$	$3.9 \cdot 10^{-3}$	$2.5 \cdot 10^{-3}$- $3.9 \cdot 10^{-3}$	$2.9 \cdot 10^{-3}$- $4.8 \cdot 10^{-3}$	$2.2 \cdot 10^{-3}$- $3.2 \cdot 10^{-3}$	0.011	$8.3 \cdot 10^{-4}$
Concentration in drinking water (mg/l)	$3.88 \cdot 10^{-5}$	$3.1 \cdot 10^{-4}$	$3.9 \cdot 10^{-5}$	$4.0 \cdot 10^{-3}$- $7.2 \cdot 10^{-3}$	$7.6 \cdot 10^{-3}$	0.012	0.0103	$7.4 \cdot 10^{-3}$	$3.0 \cdot 10^{-3}$- $7.4 \cdot 10^{-3}$	0.0043- 0.010	$2.2 \cdot 10^{-3}$- $5.3 \cdot 10^{-3}$	$2.6 \cdot 10^{-3}$	$4.6 \cdot 10^{-4}$
Concentration in air (mg/m^3)	$3.52 \cdot 10^{-8}$	$6.2 \cdot 10^{-4}$	$4.3 \cdot 10^{-8}$	$1.8 \cdot 10^{-5}$	$8.5 \cdot 10^{-5}$	$1.3 \cdot 10^{-4}$	$6.9 \cdot 10^{-6}$	$3.8 \cdot 10^{-6}$	$3.8 \cdot 10^{-6}$	$3.8 \cdot 10^{-6}$	$3.8 \cdot 10^{-6}$	$2.9 \cdot 10^{-5}$	$1.7 \cdot 10^{-6}$
Concentration in meat (mg/kg)	$2.56 \cdot 10^{-9}$	$1.3 \cdot 10^{-5}$	$2.9 \cdot 10^{-9}$	$5.6 \cdot 10^{-7}$- $7.3 \cdot 10^{-7}$	$2.1 \cdot 10^{-6}$	$3.3 \cdot 10^{-6}$	$6.6 \cdot 10^{-7}$	$4.5 \cdot 10^{-7}$	$2.3 \cdot 10^{-7}$- $4.5 \cdot 10^{-7}$	$2.9 \cdot 10^{-7}$- $5.9 \cdot 10^{-7}$	$1.9 \cdot 10^{-7}$- $3.4 \cdot 10^{-7}$	$7.2 \cdot 10^{-7}$	$6.0 \cdot 10^{-8}$
Concentration in milk (mg/kg)	$2.56 \cdot 10^{-8}$	$1.3 \cdot 10^{-4}$	$2.9 \cdot 10^{-8}$	$5.6 \cdot 10^{-6}$- $7.3 \cdot 10^{-6}$	$2.1 \cdot 10^{-5}$	$3.3 \cdot 10^{-4}$	$6.6 \cdot 10^{-6}$	$4.5 \cdot 10^{-6}$	$2.3 \cdot 10^{-6}$- $4.5 \cdot 10^{-6}$	$2.9 \cdot 10^{-6}$- $5.9 \cdot 10^{-6}$	$1.9 \cdot 10^{-7}$- $3.4 \cdot 10^{-7}$	$7.2 \cdot 10^{-6}$	$6.0 \cdot 10^{-7}$

Table 3.13 Daily human doses (mg/kg/day)

Daily dose (mg/kg/d)	Regional	Production and processing (site specific)	Processing at small sites (site specific)	Processing at small sites				Processing at small sites - polymerisation				Ink/varnish formulation	Ink/varnish processing
				Use A	Use B	Use C	Use D	E	F	G	H		
Intake of drinking water	$1.1 \cdot 10^{-6}$	$8.9 \cdot 10^{-6}$	$1.1 \cdot 10^{-6}$	$1.2 \cdot 10^{-4}$-$2.1 \cdot 10^{-4}$	$2.2 \cdot 10^{-4}$	$3.5 \cdot 10^{-4}$	$2.9 \cdot 10^{-4}$	$2.1 \cdot 10^{-4}$	$8.4 \cdot 10^{-5}$-$2.1 \cdot 10^{-4}$	$1.2 \cdot 10^{-4}$-$2.9 \cdot 10^{-4}$	$6.2 \cdot 10^{-5}$-$1.5 \cdot 10^{-4}$	$7.5 \cdot 10^{-5}$	$1.3 \cdot 10^{-5}$
Intake of fish	$9.0 \cdot 10^{-8}$	$1.8 \cdot 10^{-7}$	$9.0 \cdot 10^{-8}$	$9.3 \cdot 10^{-6}$	$1.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-5}$	$1.0 \cdot 10^{-7}$	$2.1 \cdot 10^{-6}$	$2.1 \cdot 10^{-6}$	$2.1 \cdot 10^{-6}$	$2.1 \cdot 10^{-6}$	$6.1 \cdot 10^{-6}$	$9.9 \cdot 10^{-7}$
Intake of leaf crops	$2.8 \cdot 10^{-7}$	$4.1 \cdot 10^{-3}$	$3.7 \cdot 10^{-7}$	$1.3 \cdot 10^{-4}$-$1.6 \cdot 10^{-4}$	$5.8 \cdot 10^{-4}$	$9.0 \cdot 10^{-4}$	$1.0 \cdot 10^{-4}$	$6.7 \cdot 10^{-5}$	$4.2 \cdot 10^{-5}$-$6.7 \cdot 10^{-5}$	$4.9 \cdot 10^{-5}$-$8.2 \cdot 10^{-5}$	$3.8 \cdot 10^{-5}$-$5.5 \cdot 10^{-5}$	$2.0 \cdot 10^{-4}$	$1.4 \cdot 10^{-5}$
Intake of root crops	$3.9 \cdot 10^{-8}$	$1.6 \cdot 10^{-6}$	$8.6 \cdot 10^{-8}$	$1.2 \cdot 10^{-5}$-$3.8 \cdot 10^{-5}$	$1.2 \cdot 10^{-5}$	$1.9 \cdot 10^{-5}$	$5.4 \cdot 10^{-5}$	$3.9 \cdot 10^{-5}$	$1.6 \cdot 10^{-5}$-$3.9 \cdot 10^{-5}$	$2.3 \cdot 10^{-5}$-$5.4 \cdot 10^{-5}$	$1.2 \cdot 10^{-5}$-$2.8 \cdot 10^{-5}$	$4.0 \cdot 10^{-6}$	$2.4 \cdot 10^{-6}$
Intake of meat	$1.1 \cdot 10^{-11}$	$5.6 \cdot 10^{-8}$	$1.2 \cdot 10^{-11}$	$2.4 \cdot 10^{-9}$-$3.1 \cdot 10^{-9}$	$9.1 \cdot 10^{-9}$	$1.4 \cdot 10^{-8}$	$2.8 \cdot 10^{-9}$	$1.9 \cdot 10^{-9}$	$9.8 \cdot 10^{-10}$-$1.9 \cdot 10^{-9}$	$1.3 \cdot 10^{-9}$-$2.6 \cdot 10^{-9}$	$8.1 \cdot 10^{-10}$-$1.5 \cdot 10^{-9}$	$3.1 \cdot 10^{-9}$	$2.6 \cdot 10^{-10}$
Intake of milk	$2.1 \cdot 10^{-10}$	$1.0 \cdot 10^{-6}$	$2.3 \cdot 10^{-10}$	$4.5 \cdot 10^{-8}$-$5.8 \cdot 10^{-8}$	$1.7 \cdot 10^{-7}$	$2.7 \cdot 10^{-7}$	$5.3 \cdot 10^{-8}$	$3.6 \cdot 10^{-8}$	$1.8 \cdot 10^{-8}$-$3.6 \cdot 10^{-8}$	$2.4 \cdot 10^{-8}$-$4.8 \cdot 10^{-8}$	$1.5 \cdot 10^{-8}$-$2.8 \cdot 10^{-8}$	$5.8 \cdot 10^{-8}$	$4.8 \cdot 0^{-9}$
Intake of air	$7.5 \cdot 10^{-9}$	$1.3 \cdot 10^{-4}$	$9.1 \cdot 10^{-9}$	$3.8 \cdot 10^{-6}$	$1.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-5}$	$1.5 \cdot 10^{-6}$	$8.2 \cdot 10^{-7}$	$8.2 \cdot 10^{-7}$	$8.1 \cdot 10^{-7}$	$8.2 \cdot 10^{-7}$	$6.1 \cdot 10^{-6}$	$3.8 \cdot 10^{-7}$
Total	$1.5 \cdot 10^{-6}$	$4.28 \cdot 10^{-3}$	$1.7 \cdot 10^{-6}$	$2.7 \cdot 10^{-4}$-$4.2 \cdot 10^{-4}$	$8.4 \cdot 10^{-4}$	$1.3 \cdot 10^{-3}$	$4.5 \cdot 10^{-4}$	$3.2 \cdot 10^{-4}$	$1.5 \cdot 10^{-4}$-$3.2 \cdot 10^{-4}$	$2.0 \cdot 10^{-4}$-$4.3 \cdot 10^{-4}$	$1.1 \cdot 10^{-4}$-$2.4 \cdot 10^{-4}$	$2.9 \cdot 10^{-4}$	$3.1 \cdot 10^{-5}$

3.1.8 Summary of local PECs

A summary of the calculated PECs for the local compartment is given in **Table 3.14**.

Table 3.14 Summary of Local PECs

Scenario	Air [a)] (μg/m³)	Surface water [a)] (μg/l)	Sediment [a)] (μg/kg wet wt.)	Soil (agri; ave. over 30 days) (μg/kg wet wt.)	Soil porewater (μg/l)
Production and processing (site-specific information for main producer)	0.753	0.085	0.098	0.13	0.31
Processing at small sites (site-specific)	$7.5 \cdot 10^{-5}$	0.040	0.046	$7 \cdot 10^{-3}$	0.016
Processing at small sites – Use A	0.042-0.136	9.5-31	10.9-35.7	3.1-10.0	2.2-7.2
Processing at small sites – Use B	0.103	9.27	10.7	3.0	2.2
Processing at small sites – Use C	0.161	14.8	17	4.8	3.5
Processing at small sites – Use D	0.195	0.21	0.241	14.3	10.3
Processing at small sites – polymerisation – E	0.14	31.6	36.4	10.2	7.4
Processing at small sites – polymerisation – F	0.056-0.14	12.7-31.6	14.6-36.4	4.1-10.2	3.0-7.4
Processing at small sites – polymerisation – G	0.081-0.20	18.4-44.2	21.1-50.9	5.9-14.3	4.3-10.3
Processing at small sites – polymerisation – H	0.041-0.099	9.3-22.6	10.7-26.0	3.0-7.3	2.2-5.3
Ink/varnish formulation	0.0348	3.20	3.68	1.03	0.76
Ink/varnish processing	$8.34 \cdot 10^{-3}$	1.93	2.22	0.62	0.46

Note: a) concentration during release episode

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) – RESPONSE (EFFECT) ASSESSMENT

3.2.1 Aquatic compartment (including sediment)

3.2.1.1 Effects on aquatic organisms

Acute ecotoxicity tests are available for fish, Daphnia and algae. However, no other tests have been found. The results are given in **Table 3.15**. Two tests are also available on toxicity of 1-vinyl-2-pyrrolidone to microorganisms and these results are also given in **Table 3.15**.

3.2.1.1.1 Toxicity to fish

A 96-hour LC_{50} of 913 mg/l has been derived for Rainbow Trout (*Salmo gairdneri* in the report, but now renamed *Oncorhyncus mykiss*) (BASF, 1987a) for a static test. A NOEC of 464 mg/l and an LC_{100} of greater than 1,000 mg/l (the highest concentration tested) were also reported. OECD guideline 203 was followed.

3.2.1.1.2 Toxicity to aquatic invertebrates

The only reported test (Fraunhofer Institut fur Umweltchemie und Ökotoxikologie, 1989a; BASF, 1988b) on aquatic invertebrates, using the water flea (*Daphnia magna*) is summarised in **Table 3.15**. Four groups of five animals were used at each dose level of 0.7, 1.6, 3.8, 8.0, 17.9, 40.0, 89.4, 200.0, 447.0 and 1,000 mg/l. Only one control group was used. An EC_{50} of 45.04 mg/l and a NOEC of 3.6 mg/l after 48 hours were derived from the results. An EC_{100} of 447 mg/l after 48 hours was also reported. OECD guidelines were followed although the report does not indicate whether concentrations were measured at the end of experiments to confirm concentrations. A static system has been assumed although there are no details given in the report.

3.2.1.1.3 Toxicity to aquatic plants

The effect of 1-vinyl-2-pyrrolidone on the growth rate and reproduction of planktonic algae (*Scenedesmus subspicatus*) has been investigated (Fraunhofer Institut fur Umweltchemie und Ökotoxikologie, 1989b; BASF, 1988b). Five dose levels in a geometric series (31.25, 62.5, 125.0, 250, 500 and 1,000 mg/l) replicated four times, plus two controls were used. The 96-hour $E\beta C_{50}$ (inhibition of reproduction) and $E\mu C_{50}$ (inhibition of growth rate) were 770 mg/l and >1,000 mg/l, respectively. OECD guidelines were followed although the variation in pH exceeded 1 unit by the end of the test (96 hours) and the results therefore need to be treated with care.

3.2.1.1.4 Other studies

The effects of 1-vinyl-2-pyrrolidone on the inhibition of respiration of activated sludge has been investigated (BASF, 1979a). No effect was observed up to the highest tested concentration of 1995 mg/l.

Table 3.15 Results of ecotoxicity tests for 1-vinyl-2-pyrrolidone

	Species	Test method	Exposure period	Test result	Reference
Fish	*Oncorhyncus mykiss* (freshwater)	OECD Guideline 203 no analytical monitoring or GLP	96 hours	LC_{50} = 913 mg/l LC_{100} >1,000 mg/l NOEC = 464 mg/l	BASF (1987a)
	Oncorhyncus mykiss	OECD Guidelines	72 hours	LC_5 = 548 mg/l LC_{50} = 976 mg/l LC_{95} = 1,741 mg/l	BASF (1987b)
Daphnia	*Daphnia* sp.	OECD Guideline 202, part 1 (immobilisation)	24 hours	EC_0 = 18 mg/l EC_{50} = 130 mg/l EC_{100} = 1,000 mg/l	BASF (1988b)
	Daphnia sp.		48 hours	EC_0 = 3.6 mg/l EC_{50} = 45 mg/l EC_{100} = 450 mg/l	BASF (1988b)
Algae	*Scenedesmus subspicatus*	Cell multiplication inhibition test, DIN 38412, part 9	72 hours	$E\beta C_{10}$ = 115 mg/l $E\beta C_{50}$ = 780 mg/l $E\mu C_{10}$ = 530 mg/l $E\mu C_{50}$ > 1,000 mg/l	BASF (1988b)
	Scenedesmus subspicatus		96 hours	$E\beta C_{10}$ = 125 mg/l $E\beta C_{50}$ = 770 mg/l $E\mu C_{10}$ = 640 mg/l $E\mu C_{50}$ > 1,000 mg/l	BASF (1988b)
Microorganisms	*Pseudomonas*	Cell multiplication inhibition test, DIN 38412, part 8	17 hours	EC_{10} = 3,400 mg/l EC_{50} = 4,800 mg/l EC_{90} = 7,200 mg/l	BASF (1988b)
	Active sludge	Respiratory demand, highest conc. Tested = 1995 mg/l	30 minutes	EC_{10} > 1,995 mg/l *	BASF (1979a)

Note: $E\beta C_{10}$ 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.
* no disturbance of degradative activity of active sludge expected when substance introduced to adapted STP

3.2.1.2 Derivation of PNEC for aquatic organisms

Since only acute test results are available for three trophic levels, an assessment factor of 1,000 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.

The data on toxic effects of vinyl pyrrolidone to microorganisms given in **Table 3.15** are very limited and should be used with caution. Use of the NOEC of 1995 mg/l with an assessment factor of 100 (chosen to reflect the lack of data and the caution with which the extant data should be applied) gives a PNEC of 19.95 mg/l.

The PNEC for sediment has been provisionally calculated using equilibrium partitioning which gives a PNEC of 51.8 μg/kg based on the method used in the TGD (the form of the equation using the properties of suspended sediment has been used).

3.2.2 Atmosphere

It is not possible to derive a PNEC for the atmospheric compartment. There is no information about the degradation pathway of 1-vinyl-2-pyrrolidone in the atmosphere except that it polymerises in the presence of oxygen (IARC, 1979).

3.2.3 Terrestrial compartment

No relevant studies have been found for the terrestrial compartment. The PNEC for the terrestrial compartment has been calculated using the equilibrium partitioning method in the TGD. This gives a PNEC of 18.7 μg/kg.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

The calculated PEC values have been compared with the PNEC value. The results are given in **Table 3.16**.

There are no specific data available for the sediment compartment. The sediment concentrations are estimated from those in the water compartment, and the PNEC for sediment is estimated from that for water using the equilibrium partitioning method. Hence the assessment for sediment is the same as that for surface water.

Table 3.16 Comparison of PEC and PNEC values for the aquatic compartment

Scenario	PEC	PEC/PNEC
Water – PNEC = 45 μg/l		
Production and processing (site-specific information for main producer)	0.085 μg/l	$1.9 \cdot 10^{-3}$
Processing at small sites (site-specific)	0.040 μg/l	$8.9 \cdot 10^{-4}$
Processing at small sites – Use A	9.5-31 μg/l	0.21-0.68
Processing at small sites – Use B	9.27 μg/l	0.21
Processing at small sites – Use C	14.8 μg/l	0.33
Processing at small sites – Use D	0.21 μg/l	$4.7 \cdot 10^{-3}$
Processing at small sites – polymerisation - E	31.6 μg/l	0.70
Processing at small sites – polymerisation - F	12.7-31.6 μg/l	0.28-0.70
Processing at small sites – polymerisation - G	18.4-44.3 μg/l	0.41-0.98
Processing at small sites – polymerisation - H	9.3-22.6 μg/l	0.21-0.50
Ink/varnish formulation	3.20 μg/l	0.071
Ink/varnish processing	1.93 μg/l	0.043
Regional	0.0388 μg/l	$8.6 \cdot 10^{-4}$
Continental	$1.28 \cdot 10^{-3}$ μg/l	$2.8 \cdot 10^{-5}$
Microorganisms in an STP - PNEC = 19.95mg/l		
Production and processing (site-specific information for main producer)	1.48 mg/l	0.074
Processing at small sites (site-specific)	$8.8 \cdot 10^{-3}$μg/l	$4.4 \cdot 10^{-7}$
Processing at small sites – Use A	95-310 μg/l	0.0048-0.016
Processing at small sites – Use B	92.3 μg/l	$4.6 \cdot 10^{-3}$
Processing at small sites – Use C	147 μg/l	$7.4 \cdot 10^{-3}$
Processing at small sites – Use D	442 μg/l	0.022
Processing at small sites – polymerisation - E	316 μg/l	0.016
Processing at small sites – polymerisation - F	127-316 μg/l	0.0064-0.016

Table 3.16 continued overleaf

Table 3.16 continued Comparison of PEC and PNEC values for the aquatic compartment

Scenario	PEC	PEC/PNEC
Water (continued)		
Processing at small sites – polymerisation - G	183-442 µg/l	0.0092-0.022
Processing at small sites – polymerisation - H	93-226 µg/l	0.0047-0.011
Ink/varnish formulation	31.6 µg/l	$1.6 \cdot 10^{-3}$
Ink/varnish processing	19.0 µg/l	$9.5 \cdot 10^{-4}$
Sediment – PNEC = 51.8 µg/kg		
Production and processing (site-specific information for main producer)	0.098 µg/kg wet wt.	$1.9 \cdot 10^{-3}$
Processing at small sites (site-specific)	0.046 µg/kg wet wt.	$8.9 \cdot 10^{-4}$
Processing at small sites – Use A	10.9-35.7 µg/kg wet wt.	0.21-0.69
Processing at small sites – Use B	10.7 µg/kg wet wt.	0.21
Processing at small sites – Use C	17 µg/kg wet wt.	0.33
Processing at small sites – Use D	0.241 µg/kg wet wt.	$4.6 \cdot 10^{-3}$
Processing at small sites – polymerisation - E	36.4 µg/kg wet wt.	0.70
Processing at small sites – polymerisation – F	14.6-36.4 µg/kg wet wt.	0.28-0.70
Processing at small sites – polymerisation – G	21.1-50.9 µg/kg wet wt.	0.41-0.98
Processing at small sites – polymerisation – H	10.7-26.0 µg/kg wet wt.	0.21-0.50
Ink/varnish formulation	3.68 µg/kg wet wt.	0.071
Ink/varnish processing	2.22 µg/kg wet wt.	0.043
Regional	0.035 µg/kg wet wt.	$6.8 \cdot 10^{-4}$
Continental	1.1 · 10-3 µg/kg wet wt.	$2.1 \cdot 10^{-5}$

The values for PEC_{stp} given in **Table 3.16** indicate that there will be no adverse effects on microbial activity in an STP arising from these processes.

Based on the site-specific information and generic scenarios, the production and use of 1-vinyl-2-pyrrolidone, and release of 1-vinyl-2-pyrrolidone during use of polymers that contain residual 1-vinyl-2-pyrrolidone monomer, are unlikely to cause adverse effects on the aquatic environment or wastewater treatment processes. The available site-specific information indicates that the actual releases to surface water from sites carrying out polymerisations of 1-vinyl-2-pyrrolidone may be much lower than indicated by the generic calculations.

Conclusion (ii).

3.3.2 Atmosphere

It was not possible to calculate a PNEC for the atmosphere. However, the amount of 1-vinyl-2-pyrrolidone released to the atmosphere is very small and is not expected to cause any adverse effects. The calculated half-life indicates that it will degrade rapidly in the atmosphere.

Conclusion (ii).

3.3.3 Terrestrial compartment

The calculated PEC and PNEC values have been compared and are given in **Table 3.17**.

Table 3.17 Comparison of PEC and PNEC values for agricultural soil

Scenario	PEC (µg/kg)	PEC/PNEC
Soil – PNEC = 18.7 µg/kg		
Production/processing - site-specific information	0.13	$7.0 \cdot 10^{-3}$
Processing at small sites (site specific)	$7 \cdot 10^{-3}$	$3.7 \cdot 10^{-4}$
Processing at small sites – Use A	3.1-10.0	0.17-0.53
Processing at small sites – Use B	3.0	0.16
Processing at small sites – Use C	4.8	0.26
Processing at small sites – Use D	14.3	0.76
Processing at small sites – polymerisation – E	10.2	0.55
Processing at small sites – polymerisation – F	4.1-10.2	0.22-0.55
Processing at small sites – polymerisation - G	5.9-14.3	0.32-0.76
Processing at small sites – polymerisation – H	3.0-7.3	0.16-0.39
Ink/varnish formulation	1.03	0.055
Ink/varnish processing	0.62	0.033
Regional soil	$3.1 \cdot 10^{-3}$	$1.7 \cdot 10^{-4}$
Continental soil	$2.4 \cdot 10^{-4}$	$1.3 \cdot 10^{-5}$

The PEC/PNEC ratios for both site-specific and default calculations show that 1-vinyl-2-pyrrolidone should not cause adverse effects on the terrestrial compartment.

Conclusion (ii).

3.3.4 Secondary poisoning

The log Kow for 1-vinyl-2-pyrrolidone is 0.4 and there are no other indications of bioaccumulation potential. Therefore no assessment of secondary poisoning has been carried out.

Conclusion (ii).

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure Assessment

4.1.1.1 Occupational exposure

4.1.1.1.1 General discussion

Definitions and limitations

In this document, unless otherwise stated, the term exposure is used to denote personal exposure as measured or otherwise assessed without taking into account the attenuating effect of any respiratory protective equipment (RPE) which might have been worn. The effect of RPE is dealt with separately. This definition permits the effects of controls, other than RPE, to be assessed and avoids the considerable uncertainty associated with attempting to precisely quantify the attenuation of exposure brought about by the proper use of RPE.

The section entitled general discussion summarises the more important issues arising from the exposure assessments and bring together measured exposure data with that predicted from the EASE (Estimation and Assessment of Substance Exposure) model. EASE is a general purpose predictive model for workplace exposure assessments. It is an electronic, knowledge based, expert system which is used where measured exposure data is limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances.

All models are based upon assumptions. Their outputs are at best approximate and may be wrong. EASE is only intended to give generalised exposure data and works best in an exposure assessment when the relevance of the modelled data can be compared with and evaluated against measured data.

EASE predicts exposures as ranges in the form of conventional 8-hour time weighted averages (TWAs). It does not directly predict short-term exposures. However, because these exposures are process specific, they can be thought of as those experienced for that process either over the whole eight hours or over any shorter period. These shorter periods can be further time weighted to construct other 8-hour time weighted averages. Although this device allows short-term exposures to be dealt with by EASE, such constructs should be regarded with caution. Dermal exposure is assessed by EASE as potential exposure rate predominantly to the hands and forearms (approximately 2,000 cm^2).

Air sampling data is presented in the following sections from a number of sources and, where reported to HSE, information on the sampling methods is also presented. HSE, in general, does not have information on the validity of the techniques used and the sampling strategies adopted. There was, however, no reason to doubt the quality of the air sampling data used in this occupational hygiene exposure assessment. Occupational exposure data derived from the EASE model may sometimes provide values that are approaching the saturated vapour concentration

(SVC) for N-VP (131 ppm - calculated). It is unlikely that such airborne concentrations of vapour would be achieved in practice.

Overview of exposure

Occupational exposure to N-VP can be discussed in three categories:

(a) the manufacture of N-VP monomer and polymers,
(b) the manufacture and use of UV curing inks and lacquers, and contact lenses,
(c) the use of N-VP polymers.

There are about 450 to 750 workers exposed to N-VP during the manufacture of the monomer and its polymers. It was estimated that a few hundred are exposed during the manufacture of UV inks and lacquers. HSE has very limited occupational exposure data for N-VP on its National Exposure Database (NEDB). Three results (all 3 ppm) were reported from a survey at a site manufacturing contact lenses (see Section 4.1.1.1.6). A large amount of occupational exposure data was received for the manufacture of the monomer and its polymers. This showed most exposures (80 to 90%) to be less than 0.1 ppm 8-hour TWA, with the highest result being 7.4 ppm 8-hour TWA.

The highest exposures were for the manufacture and use of UV curing inks (obtained using the EASE model). Although generally below 1 ppm and in some cases below 0.5 ppm, they may be up to 5 ppm 8-hour TWA for the manufacture of inks where local exhaust ventilation (LEV) is not present and up to 7 ppm 8-hour TWA for manual screen printing without LEV.

Dermal exposures of up to 1.0 mg/cm^2/day were modelled using EASE. This was for operators changing filters in an N-VP production plant.

Occupational exposure limits

The only country with an occupational exposure limit for N-VP is Russia, which is 1 ppm (International Labour Office, 1991). Suppliers of N-VP recommend that companies using N-VP control exposure to below 0.1 ppm.

These limits are provided for information and not as an indication of the level of control of exposure achieved in practice in workplaces in EU member states.

4.1.1.1.2 Occupational exposure during the production of N-VP and its use in the production of polymers

The manufacture of N-VP and its polymers is carried out in closed systems. There are an estimated 450 to 750 workers exposed during the manufacture of the monomer and polymers throughout the EU (excluding end users of monomers). Some of these, who work in the technical and research laboratories, may only have limited exposure. The number of workers exposed increases when contract workers are included, and significantly decreases to several hundred during periodic shutdowns. There is one production plant and a number of polymerisation plants in the EU, with the vast majority of polymerisation carried out on the same site as N-VP production. Occupational exposure for workers on these closed plants is intermittent and as a result of performing tasks for which the system is breached. Consequently 8-hour TWA exposure arises from a series of short-term exposures. The nature of these tasks and the approach of companies to controlling emissions are likely to be similar for the producers and users. Occupational exposure during production and polymerisation can therefore be considered

together. Occupational exposure may also occur from fugitive emissions, for example, leaks from pump seals. The tasks that give rise to occupational exposure may include the following.

- Material sampling. During polymerisation the potential exposure to N-VP will progressively decrease. Therefore the actual exposure during sampling on the polymer plants is likely to be significantly less than during production of the monomer. This exposure is likely to be very short (less than 1 minute) and dependent on how the emission is controlled.
- Filling road and rail tankers, and drums. Although this work may take about 60 minutes, the actual exposure time will again be very short and primarily when the delivery line is uncoupled. Exposure, however, may be for the duration of the filling if contaminated air displaced from the road or rail tanker, or storage vessel is not controlled. Exposure during coupling is likely to be negligible, assuming lines are clean. The significance of the release during uncoupling will depend on how this is carried out and controlled. Exposure during drum filling will be dependent on how this is carried out and what control measures, such as LEV, are used.
- Planned routine breaches, for example, changing process filters. With this task the potential for exposure exists for the duration of the time taken to remove the old filter and replace with a new one.
- Periodic and unplanned maintenance. The potential for exposure will depend on the steps taken to ensure the system is uncontaminated prior to breaching. Periodic maintenance to inspect and renew plant takes place every 3 or 4 years and takes about three weeks.
- Fugitive emissions. In addition to the above tasks, exposure may also arise from process leaks, which will depend on the integrity of the equipment and again the industry's approach to monitoring and controlling such leaks.

The nature of the above tasks and the potential for exposure are similar for all chemical manufacturing processes. The significance of the resulting exposure will depend on the industries and the individual companies' approach to controlling or preventing emissions.

The monomer and polymer producing plants in Germany were visited in order to study the control regimes employed. The philosophy adopted by the company was to employ and develop measures to reduce exposure to as low a level as reasonably practicable. There may be some variation in the control regimes used by the German monomer and polymer manufacturer and polymer manufacturers in other member states. At the site visited steps had been taken to reduce occupational exposure during tasks where the system was breached. These steps included:

- Sampling points. Most sampling points employed were enclosed with vapour return, referred to as the “Dopak” system. This “Dopak” system involves pushing a sample bottle with a rubber seal direct onto an injection needle with vapour return for the displaced air. This allows N-VP to be released into the closed bottle with minimal emission. Release with this system is only likely to result from residual N-VP on the needle once the bottle is removed. It is understood that this system cannot be used where there is the potential for blockage of the needle by contaminants in the raw product. Where this system cannot be used other measures were employed to minimise emissions such as enclosing the sampling point as far as possible.

  Where polymerisation is on the same site as production of the monomer there is unlikely to be any sampling on the plant using N-VP, except post reaction where the concentration of N-VP is significantly reduced. Therefore for the production of N-VP polymers in the EU there is little exposure from taking process samples.

- Filling and emptying of road and rail tankers, and drums. Most N-VP (90%) is used on-site and therefore transported by pipeline. The transporting of N-VP to customers is carried out by road and rail tankers, and by drums.

  Vapour returns are fitted to the road and rail tanker filling points and the drum filling station is equipped with general and local exhaust ventilation. This LEV is fitted around the filling head and is lowered and sealed to the drum during delivery. The system is therefore closed during filling, with the extraction designed to minimise any fugitive emissions from the seal, and to control releases during capping of the drum.

- System breaching - unplanned and planned maintenance. The company reported that breaks in to the system to carry out maintenance are rare, and usually restricted to periodic shut downs. One task which requires the operator to routinely breach the system is filter changing. This filter changing requires the operator to remove the N-VP wet filter and place it in a sealed drum. This filter is designed to remove any solid polymer from the system and is replaced once a shift. The operator wears air fed respiratory protective equipment and nitrile rubber gloves during the work. A continuous reading instrument is positioned about 2 metres away from the filter housing and has recorded N-VP concentrations of 20 to 80 ppm. Personal air sampling has also been carried with the sampling head placed inside the operator's air fed hood to provide a measure of the actual exposure. See subsequent sections for discussion of the data.

Plant shut-downs take place every 3 or 4 years and it takes 2 to 3 weeks to complete the maintenance. The procedure for opening the system is as follows:

- empty system,
- flush with water for 2 to 3 days (N-VP is extremely soluble in water), and
- check rinse water until no N-VP is detected (this is primarily for waste control, although the system is not opened until the water is free of N-VP).

This system would also be used for unplanned maintenance on the system. During system breaching gloves, eye protection and where appropriate, chemical suits are worn.

- Fugitive emissions. The company visited reported the use of magnetic delivery pumps (canned pumps) on their plant. These have the advantage of being completely sealed and therefore minimise the opportunity for fugitive emissions. It is, however, understood that they are not used where there is the chance of particulate clogging the pump.

Measured exposure data for monomer and polymer production

Occupational exposure data were received from three sources: industry, the German Competent Authority (CA) and Zober et al. (1991). Since there is only one EU producer, these measurements are all likely to be from the same site (monomer and polymer units), and may in some cases be the same measurements. They all generally showed about 80 to 90% of results to be less than 0.1 ppm 8-hour TWA. It was difficult to establish how many actual results were above 0.1 ppm 8-hour TWA, although it appears to be about 15, with 3 results above 1 ppm 8-hour TWA. These estimations are primarily based on the data received directly from industry. However, the measurements provided by the German CA and Zober et al. (1991) tend to agree with these. Zober et al. (1991) reported that only 5 of the 59 results were above 0.15 ppm 8-hour TWA. The highest result reported both by industry and by Zober et al. (1991) was 7.4 ppm 8-hour TWA, which probably confirms that many of the results are from the same measurements. This exposure resulted from an incident involving contaminated clothing. It is reasonable to assume that exposures in excess of 0.1 ppm 8-hour TWA represent the

upper end of routine exposure, and are probably from unplanned, although identifiable releases. The original submissions provided insufficient clarification of the results between 0.1 and 1 ppm 8-hour TWA to allow understanding of the significance of these higher results. However, more recent communications have clarified the small number of higher results, showing them to be infrequent and to be less representative of current working practices. In view of these clarifications and that even with these included 80 to 90% of results are less than 0.1 ppm 8-hour TWA, the figure taken forward to the risk characterisation will be 0.1 ppm. These results are presented in detail in the following three subsections.

Industry exposure data

Occupational exposure data were received from the EU producer of N-VP and are detailed in **Table 4.1**. Although not stated, it is assumed that these results are from personal air sampling measurements. The method involves the collection of N-VP on sampling tubes containing activated charcoal and desorption with dichloromethane and methanol, and subsequent analysis by gas chromatography.

The exposure data in **Table 4.1** have been collated from personal air sampling carried out since 1979 on workers on the monomer and polymer production plants. Approximately 90% of all the results were less than 0.1 ppm 8-hour TWA. Production (N-VP and PVP) was the only activity with results above 0.1 ppm 8-hour TWA. The author reported that for the polymer production plants results were generally less than 0.03 ppm 8-hour TWA and for other tasks generally less than 0.05 ppm 8-hour TWA. Although not specifically stated by the author it therefore appears that the only results approaching or above 0.1 pm 8-hour TWA were for production workers on the monomer plant. As stated earlier in this section, work on the monomer plant involves sampling, drum and tanker filling, and filter changing, whereas on the polymer plant the N-VP is received by pipeline and sampling is not carried out prior to reaction. The opportunities for exposure on the polymer production plants are thus greatly reduced.

Table 4.1 Occupational exposure to N-VP during its production and use as a polymer - 8-hour TWAs

Activity	No. of samples	Range (ppm)	Arithmetic mean (ppm) +	Percentage of results in range		
				< 0.1	0.1 to 1	> 1 to 10
Production *	108	0 to 7.4	0.19	86	11.2	2.8
Decanting / storage	5	0 to 0.02	not reported	100	0	0
Technical	9	0 to 0.05	not reported	100	0	0
Laboratory	38	0 to 0.1	0.04	100	0	0
Workshop	4	0.05 to 0.63	not reported	100	0	0
Total	164	0 to 7.4	0.14	90.3	7.9	1.8

* "production" includes polymerisation.
\+ assumed to be arithmetic mean.

The task described in the previous section, involving the replacement of filters, which recorded levels of 20 to 80 ppm, was not specifically highlighted in the results received from industry. The most likely activity to which this specific task would be categorised is production workers. If this filter changing is included in the shift averages in **Table 4.1** then it does not appear to be a significant contributor to shift exposure, probably due to the mitigation offered by the air fed respirator. The exposure was measured with the sampling head positioned inside the hood.

Elsewhere in the document the results (measured and modelled) represent exposure unmitigated by the use of RPE.

German competent authority exposure data

Exposure data were also received from the German CA. These exposure data are presented in **Table 4.2**.

Table 4.2 Occupational exposure to N-VP during its manufacture and polymerisation *

Work area	No. of samples	8-hour TWA (ppm)	Arithmetic mean (ppm)
Production	41 **	< 0.15 (95% of all results)	0.06
Maintenance	6 **	0.05 to 0.63	0.18
Drum filling	15	up to 0.25; short term = 1	not reported
Use	18	0.01 to 0.1	0.05
Laboratory / pilot	not reported	0.01 0.13	not reported

* results received from Bundesanstalt für Arbeitsschutz. Reference for data :"Begründungen zu den TRK-Werten" - Annex to TRGS 102, Bundesarbeitsblatt 10/1995, page 54-55. These are as reported to HSE.

* reported as personal sampling results. The origin of the other results was not reported.

It is likely that some of these measurements were taken from plants also represented in **Table 4.1**.

Published exposure data

Zober et al. (1991) carried out a morbidity study of N-VP production workers at the German manufacturing plant. The study group consisted of 94 production and production support personnel. Of the 94 personnel, 57 were production workers, 4 were distribution personnel, 7 were laboratory technicians, 11 were mechanics, 1 was a bricklayer, 8 were measurement and control technicians and 6 were supervisors.

One third of the production unit was dedicated to N-VP. The authors reported that the potential for exposure was greatest during sampling, filling operations, maintenance work and laboratory work with N-VP. Where there was the potential for higher exposures additional precautions were taken, which included the use of respiratory protective equipment when changing filters.

The authors reported the results of 59 air sampling measurements taken between 1980 and 1990, which were from personal and fixed location samplers. Only one result was above 1 ppm, with over 80% less than 0.1 ppm. Five results were above 0.15 ppm, three in 1983 and two in 1985. The result above 1 ppm (7.4 ppm) was reported to be due to an incident involving contaminated clothing. The sampling period and its relation to the 8-hour TWA were not reported for these results. However, it was assumed that the authors presented the results to demonstrate TWA exposure over a full shift, and they therefore represent 8-hour TWAs.

Modelled inhalation exposure data

Although the measured 8-hour TWAs are relatively low, they result from exposure over short-term tasks, for example, sampling. The only measured short-term exposure data, of up to 1 ppm, was for drum filling. It is therefore appropriate to model short-term exposure. This exposure modelling was carried out for sampling, tanker and drum filling, and maintenance.

During these tasks there will be brief periods of exposure followed by longer periods of no exposure. For these predictions it is assumed that exposure during these periods of "no exposure" is negligible.

During the period of filling / emptying of road and rail tankers releases are unlikely to be significant as vapour returns are understood to be in use. Releases will therefore only occur during uncoupling. During coupling the line is likely to be free of N-VP. The exposure during uncoupling is likely to last about 1 minute. The EASE scenario that best describes this is non-dispersive use with dilution ventilation (i.e. natural ventilation). This results in an EASE prediction of 10 to 50 ppm for the period of the task. This can be converted to provide a short-term (15 minute reference period) exposure prediction. In this 15 minute reference period there will be 14 minutes of no exposure and 1 minute at 10 to 50 ppm, which results in a calculated 15 minute TWA range of 0.67 to 3.3 ppm.

During sampling the operator will only be exposed for the short time needed to take the sample, which is likely to be about 30 seconds. The EASE scenario that best describes this short-term exposure is non-dispersive use without ventilation (assuming some of these samples may be taken inside a plant building with no ventilation). This results in an EASE prediction of between 50 and 100 ppm for the period of the task. This can be converted to provide a short-term (15 minute reference period) exposure prediction. In this 15 minute reference period there will be 14½ minutes of no exposure and 30 seconds at 50 to 100 ppm, which results in a calculated short-term exposure range of 1.67 to 3.3 ppm.

During drum filling short-term exposure may occur each time a full drum is capped and a new drum is moved to the filling point. During the actual filling operation the LEV is sealed to the drum and releases are therefore likely to be minimal. The EASE scenario that best describes this is non-dispersive use with LEV. This results in an EASE exposure prediction of 0.5 to 3 ppm for the period of the task. This can be converted to take account of the period of no exposure (13 minutes) and 2 minutes for drum change, with a resulting 15 minute TWA exposure range of 0.03 to 0.2 ppm.

During planned and unplanned releases exposure is likely to be for the full duration of the task. For example, filter changing where the filter is wet with N-VP. The EASE scenario that best describes this is non-dispersive use with uncontrolled direct handling, which results in a prediction of 50 to 100 ppm. This compares reasonable well with the direct reading results of 20 to 80 ppm in the vicinity of the activity, reported by the producer. Exposure during such operations is mitigated by the use of air fed respiratory protective equipment. The saturated vapour concentration (SVC) of N-VP is 131 ppm and thus exposure as high as the modelled values seem unlikely. The measured value of 80 ppm also seems high when compared to the SVC.

These exposure predictions do not take any account of the use of control measures such as enclosed sampling points.

Modelled dermal exposure data

Dermal exposure can occur during the production and use of N-VP, where operators come into contact with surfaces contaminated from splashing or condensed vapour, or as a result of direct contact with the skin. As processing is in closed systems, dermal exposure is only likely during activities such as sampling and the uncoupling of pipes.

The best EASE scenario for this exposure is direct handling with incidental contact, where incidental refers to one significant contact in a shift, for example spilling N-VP whilst taking samples or touching a wet surface. This results in a prediction of 0 to 0.1 mg/cm^2/day, although

on most days no such accidental contacts will occur. Operators are understood to wear gloves where the potential for skin contact exists and thus in reality exposure will be towards the bottom of this range.

One activity where higher dermal exposure may occur is during filter changing. This is only likely to happen once in a shift, therefore the operator may have increased exposure for the period of time taken to change the filter. An exposure of 0.1 to 1 mg/cm2/day was predicted using EASE for shifts where a filter change takes place. Since operators are understood to wear gloves where the potential for skin contact exists, exposure will be towards the bottom of this range.

4.1.1.1.3 Occupational exposure to N-VP during the manufacture of UV curing inks and UV curing lacquers

The manufacture of both UV curing inks and lacquers generally involves the same steps, which are charging, mixing, and filling product containers. These two industries are therefore discussed together. The number of workers potentially exposed in the EU and UK was estimated to be 400 to 800 and 50 to 100, respectively. Since the use of N-VP in these industries has fallen significantly it is likely that most of these workers receive only intermittent exposure and in some cases none at all. For example, the operator may be exposed for a full shift and then not use N-VP for a month.

The manufacture of UV curing inks involves the charging of materials to a vessel and subsequent mixing. The resulting product, which contains no pigment, is referred to as a "varnish". This contains about 20% N-VP. This "varnish" is transferred to drums and stored. This drummed material is subsequently charged to smaller mixing vessels containing different pigment concentrates to meet customer orders.

At a UK manufacturer of UV curing inks, N-VP is charged to vessels by lifting the 200 litre drums above the vessel and pouring in. The vessel is equipped with LEV. The ingredients are then blended at about 60^{o}C for 3 to 4 hours with the vessel covered. A mechanical mixer is used which blends at a relatively high speed. The mixing vessel is then raised above 200 litre drums and the "varnish" is tapped in ready for later use. The cool "varnish" is then poured into smaller mixing vessels, which already contain the pigment concentrate. These final batch sizes may be as low as 5 kg and may be blended with a small mixer similar to a domestic food processor. The final product is poured into tins for the customer. The smaller vessels in this pigment mixing area are not fitted with LEV. However, general ventilation is in place in this mixing area. The final product contains about 14% N-VP. The plant set-up was found to be similar at a second company visited.

The manufacture of UV lacquers is similar. One UK Company that was contacted reported that they blended in open vessels with LEV. The resulting blend is charged to a hopper for filling into containers. This filling point also uses LEV.

During the manufacture of inks and lacquers operators are therefore likely to be exposed during the charging of mixing vessels and during the filling of product containers. Occupational exposure data, both modelled and measured, are presented below.

Industry exposure data

A UK manufacturer of UV curing inks supplied occupational exposure data from personal samples collected using charcoal tubes. These data covered the activities of one operator

during the manufacture of a batch containing N-VP. The results are detailed in **Table 4.3**.

Table 4.3 Occupational exposure to N-VP during the manufacture of a UV curing ink

Activity	Sampling time (min)	Result (ppm)
Initial stages of production - contents of pan relatively cool	85	0.06
Additions to pan being made - left overnight	80	0.17
Varnish cooled overnight, at lower temperature than previous sample	90	0.05
Mixing carried out	90	0.09
Completion of manufacture	60	0.13

The above manufacturer of UV curing inks also carried out air sampling (using charcoal tubes) during the manufacture of two varnishes, with results of 0.037 ppm (23 minute sample) and 0.150 ppm (40 minute sample). The company also reported these two results as 8-hour TWAs of 0.001 ppm and 0.012 ppm, respectively assuming that the operator was not exposed to N-VP for the rest of the shift.

Another UK manufacturer of UV curing inks containing N-VP also provided air sampling data from their plant. The company carried out static sampling using charcoal tubes, solvent desorption and GC. Sampling equipment was located in the position most likely to be occupied by the operator with the sampling head at the level of the operator's breathing zone. Sampling equipment was positioned in a number of locations, for example, near mixers and storage. The company collected 69 air samples between 1990 and 1993 from nine separate surveys, with exposures ranging from less than 0.037 ppm to 0.56 ppm. LEV was reported to be in use during all the surveys. The company, however, did not report to which locations the higher results related.

Modelled inhalation exposure data

Although occupational exposure data were received from companies manufacturing UV curing inks this was primarily from static sampling equipment and may therefore not represent actual exposure. Predictions are provided for plants where LEV is in place above mixing vessels and filling points and for those plants where such extraction is not provided. It is, however, likely that most manufacturers of UV curing inks use LEV. As a minimum it is likely that LEV is fitted to the blending vessel, although it may not be fitted to the product filling point.

Plants operating with LEV fitted to all plant handling N-VP

The EASE scenario that best describes this is non-dispersive use with LEV, which results in a prediction of 0.5 to 3 ppm 8-hour TWA. This assumes that the operator spends the full-shift working on a batch containing N-VP. As stated above the operator is exposed during the charging of vessels and the filling of product containers. For the remainder of the shift the operator will only be exposed to very low background levels from fugitive emissions, which are assumed to be nil for the purposes of this exposure modelling. One manufacturer reported that this mixing time takes 3 to 4 hours. It is therefore reasonable to assume that the operator only spends half the shift (i.e. 4 hours) exposed to N-VP. The EASE prediction can therefore be time weighted to take account of this period of no exposure, with a resulting 8-hour TWA of 0.25 to 1.5 ppm. The EASE prediction also assumes that the operator is exposed to N-VP alone, and not a formulation containing only a proportion of N-VP. This will only be the case during the addition of the N-VP to the batch. During subsequent work the N-VP may be as low as 14% in the batch. Although a figure cannot be established for an average shift concentration for the

formulation and thus be used to further model the exposure, it is reasonable to assume that exposure will be at the bottom of the range 0.25 to 1.5 ppm.

Plants operating with only general dilution ventilation

Although the companies contacted had LEV fitted to mixing vessels and filling points it is reasonable to assume that some plants operate without LEV. A minimum standard of control is likely to be general ventilation to the plant. The EASE scenario that best describes this is non-dispersive use with direct handling and dilution ventilation, which results in a prediction of 10 to 50 ppm 8-hour TWA. This assumes that the operator spends the full-shift working on a batch containing N-VP. However, it is again assumed that the operator in reality only spends half the shift (i.e. 4 hours) exposed to N-VP. The EASE prediction can be time weighted to take account of this period of no exposure, with a resulting 8-hour TWA of 5 to 25 ppm. The EASE prediction also assumes that the operator is exposed to N-VP alone, and not a formulation containing only a proportion of N-VP. This will only be the case during the addition of the N-VP to the batch. During subsequent work the N-VP may be as low as 14% in the batch. Although a value cannot be established for an average shift concentration for the formulation and thus use this to further model the exposure, it is reasonable to assume that exposure will be at the bottom of this range.

Short-term exposure is likely to be highest during activities such as cleaning and maintenance. In these situations exposure will not always be mitigated by extraction ventilation, depending on the nature of the work and proximity of the operator to the plant. EASE predicts exposure to N-VP in non-dispersive uncontrolled situations to be 50 to 100 ppm over any 15-minute period. In situations where exposure cannot be controlled by procedural or engineering means, operators may need to wear RPE. The saturated vapour concentration (SVC) of N-VP is 131 ppm and thus exposure as high as the modelled values seems unlikely.

Modelled dermal exposure data

Dermal exposures during the manufacture of inks and lacquers may occur when charging vessels and filling containers. Due to the low volatility of N-VP, surfaces may remain contaminated with ink or lacquer, for example, hand rails and the outsides of vessels. The EASE scenario that best describes this is non-dispersive use with intermittent contact (two to ten contacts in a shift), which results in an EASE prediction of 0.1 to 1 mg/cm^2/day. With the exception of handling the N-VP, the operators will come into contact with blends with relatively low concentrations of N-VP and the exposure is therefore likely to be at the bottom of the above range.

4.1.1.1.4 Occupational exposure to N-VP during the use of UV curing inks

The number of workers exposed during the use of UV curing inks containing N-VP was not established. There are, however, many thousands of screen printers in the EU. Several thousand of these companies are likely to be using UV curing inks, although only a small percentage of this market will be using UV curing inks containing N-VP. The number of workers exposed could therefore be several thousand, although realistically it is more likely to be a few hundred.

Screen printers range from small workshops with one printing line through medium sized workshops with 2 or 3 lines, to large companies operating 10 screen printing lines.

Larger screen printers will tend to be carrying out large-scale production of, for example, roll labels for bottles or printing on to compact discs. The printing heads on these machines are small and partially enclosed. They also tend to be automated as a result of the need for large-scale production and may use rotary screen printing machines which facilitate high speed printing.

Rotary printing heads have the squeegee (applies ink) inside the tubular printing head and push the ink through onto the medium being printed.

At the other end of the scale, printing may be applied to large advertising banners. The printing heads on these machines will be large and the ink applied manually. One manufacturer reported that N-VP is generally not used in inks for large banners in the UK, although it may still have some use in other member states. Slot exhaust ventilation can be fitted to the sides of the screen printing area for automated or manual machines, although this is understood to be rare.

Occupational exposure may occur during the addition of the ink to the printing head, which is often manual. The ink is pumped to the printing head in the roll label market. Exposure may then occur from emissions during application, particularly if ink is applied manually. Once the ink has been applied and UV cured there should not be any appreciable exposure to N-VP. Measured and modelled occupational exposure data are presented below.

Industry exposure data

An EU supplier of N-VP provided air sampling results for a company using N-VP for screen printing in Germany, which are reproduced in **Table 4.4**.

Table 4.4 Airborne concentrations of N-VP during screen printing (Germany) *

Sample details	Result (ppm)
Personal air sample - refining rollers, no ventilation	0.53
Personal air sample - screen printer	0.90
Environmental air sample by the screen printer	0.66
Environmental air sample by the screen printer	1.94

* These results are assumed to be 8-hour TWAs

Air sampling data from measurements in 1992 was also received from a UK screen printer using N-VP inks for printing on to bottles. Six fixed location samples were collected (using a charcoal tube and analysis by gas chromatography) from the front of the screen printers in the area of the operator's breathing zone. These results ranged from none detected to 0.05 ppm and were taken over periods of 60 minutes to 240 minutes. No details about the process or methods of control were provided.

A UK manufacturer of UV curing inks containing N-VP also provided air sampling data carried out at their screen print training workshops. The company carried out static sampling using charcoal tubes and solvent desorption and GC. Sampling equipment was located in the position most likely to be occupied by the operator with the sampling head at the level of the operator's breathing zone. This was generally around the printer. The company collected 12 air samples in 1990 from three separate surveys, with exposures ranging from less than 0.05 ppm to 3.07 ppm. The results for one survey ranged from 0.87 ppm to 3.07 ppm, with the results for the other two surveys less than 0.5 ppm (one result 0.51 ppm). The company attributed the higher results to the use of a “squeegee” during this particular survey. LEV was not in place at any of the three printers, although in one case there appeared to be general ventilation. This survey reported the lowest results of less than 0.05 ppm.

Modelled inhalation exposure data

Although air sampling data was received from companies manufacturing UV curing inks this was primarily from static sampling equipment and may therefore not represent actual exposure. For the purposes of modelling occupational exposure to N-VP two scenarios were used, which were deemed to cover the range of processes used by this industry. These were:

- automated UV screen printing lines without LEV,
- manual UV screen printing lines without LEV.

Automated UV screen printing lines without LEV

The EASE scenario that best describes this is non-dispersive use with segregation, which results a prediction of 3 to 10 ppm 8-hour TWA. "Segregation" was selected, as the operator will spend a significant part of the time not at the printing head. For the purposes of this modelling it was assumed that the operator spends the full-shift working on the printing line, although as stated not at the printing head. This prediction takes no account of the low concentration of N-VP in the ink (i.e. about 14%). The EASE prediction can therefore be further refined to give a predicted 8-hour TWA exposure range of 0.42 ppm to 1.4 ppm.

Manual UV screen printing lines without LEV

The EASE scenario that best describes this is non-dispersive use with uncontrolled direct handling, which results in a prediction of 50 to 100 ppm 8-hour TWA. This assumes that the operator spends the full-shift working on the printing line. Although this is unlikely to be the case for most of the time it is reasonable to assume that this may sometimes happen. This EASE prediction also assumes that the operator is exposed to N-VP alone, and not a formulation containing only a small proportion of N-VP. The formulation contains 14% N-VP, which results in a calculated exposure of 7 to 14 ppm 8-hour TWA.

Short-term exposure is likely to be highest during activities such as cleaning and maintenance, where ink containing N-VP is present. In these situations exposure will not always be mitigated by extraction ventilation, but will depend on the nature of the work and proximity of the operator to the plant. EASE predicts exposure to N-VP in non-dispersive uncontrolled situations to be 50 to 100 ppm over any 15-minute period. The operator will be exposed to an ink with 14% N-VP, therefore the EASE prediction can be refined to give an 8-hour TWA exposure range of 7 to 14 ppm.

Modelled dermal exposure data

Dermal exposures during the use of inks may occur when charging printer heads. This will be greater when pouring is manual. Dermal exposure may also occur when manually applying inks to the medium being printed. The operator, however, will be holding the fixed squeegee applicator (i.e. hand away from the ink). Due to the low volatility of N-VP surfaces may also remain contaminated with ink, for example, hand rails and the outsides of vessels. The worse-case scenario would therefore be manual printing. The EASE scenario that best describes this is non-dispersive use with extensive contact (more than ten contacts in a shift), which results in an EASE prediction of 1 to 5 mg/cm^2/day. The operator will, however, be using an ink with only about 14% N-VP, therefore the EASE prediction can be further refined to give an exposure range of 0.14 to 0.7 mg/cm^2/day.

4.1.1.1.5 Occupational exposure to N-VP during the use of UV lacquers containing N-VP

UV lacquers are applied in three different ways, namely:

- by spray coating,
- by vacuum coating, and
- by roller coating.

The most widely used method for applying UV curing lacquers was reported by contacts in the industry to be vacuum coating. However, one UK supplier reported that they only had one customer using an N-VP lacquer, who used spray coating. Spray coating of UV lacquers is automated in an enclosed, ventilated tunnel. Parts are loaded at one end, sprayed and then taken off at the other end of the production line. A UK company spraying UV lacquers was visited. The spraying process at this plant was automated, with the spray area under extraction. The automated spray area was then further segregated from the plant operators.

Vacuum coating, by necessity is carried out in an enclosed chamber into which the lacquer is sprayed to give an even coating around the object. This involves a semi-automated process, as would roller coating.

Modelled inhalation exposure data

The EASE scenario that best describes this is non-dispersive use with LEV, which results in a prediction of 0.5 to 3 ppm 8-hour TWA. This EASE prediction also assumes that the operator is exposed to N-VP alone, and not a formulation containing only a small proportion of N-VP. These lacquers are understood to contain about 9% N-VP. The above EASE predictions can therefore be further refined to give 8-hour TWAs of 0.045 to 0.27 ppm. This is likely to be an overestimate of exposure as it does not take account of the process being automated.

Modelled dermal exposure data

Dermal exposures during the use of lacquers may occur when charging the lacquer reservoir. Due to the low volatility of N-VP, surfaces may remain contaminated with lacquer, for example, hand rails and the outsides of vessels. The EASE scenario that best describes this is non-dispersive use with intermittent contact (two to ten contacts in a shift), which results in an EASE prediction of 0.1 to 1 mg/cm^2/day. The operator will, however, be using an ink with about 9% N-VP, therefore the EASE prediction can be further refined to give an exposure range of 0.009 to 0.09 mg/cm^2/day.

4.1.1.1.6 Occupational exposure to N-VP during the manufacture of contact lenses

During the manufacture of contact lenses there is the potential for occupational exposure during the preparation of the pre-polymer mix and when it is put into the moulds. Premixed monomers of N-VP and hexamethyl methacrylate (50/50) are purchased and an initiator is added by the chemist in the laboratory. This mixing by the chemist is carried out infrequently and takes about 20 minutes. This mixture is then refrigerated to inhibit polymerisation.

The monomer mixture is automatically injected into contact lens moulds. This process removes the mould lid and replaces it after injecting. The trays of moulds are then removed by two operators, ready for placing in a vented curing oven. The automatic injection area is enclosed in an extracted cabinet.

HSE exposure data

In 1994 HSE carried out a survey of exposure to N-VP at a plant manufacturing contact lenses using N-VP. Three air samples were collected, one personal and two static samples. The results were all 3 ppm for the period of sampling, which was about one hour. As a result the company improved the plant control regimes, including LEV to the injecting area and venting to the oven.

Modelled inhalation exposure data

The EASE scenario that best describes the manufacture of contact lenses is non-dispersive use with LEV, which results in a prediction of 0.5 to 3 ppm 8-hour TWA. From the information obtained it appears that application is always automated with ventilation. This EASE prediction also assumes that the operator is exposed to N-VP alone, and not a formulation containing only a small proportion of N-VP. As the monomer polymerises the potential for exposure will reduce. At the start of production the mixture contains 50% N-VP; therefore the above predicted values can be reduced to 0.25 to 1.5 ppm 8-hour TWA. The potential for exposure, however, is low as the automated machine removes the top of the mould, injects the monomer mixture and the replaces the top of the mould. It is therefore reasonable to assume that exposure will be at the bottom of this range.

Modelled dermal exposure data

The potential for dermal exposure during the manufacture of contact lenses will generally occur during the addition of the initiator. During further work, steps are taken to avoid contact with the lenses. The EASE scenario that best describes this is non-dispersive use with incidental contact (one contact in a shift), which results in an EASE prediction of 0 to 0.1 mg/cm^2/day. The operator, however, will be handling a mixture containing only 50% N-VP, therefore the EASE prediction can be reduced to 0 to 0.05 mg/cm^2/day

4.1.1.1.7 Occupational exposure to residual N-VP during the use of its polymers

The concentration of residual monomer in the polymers ranges from 1 to 100 ppm, see **Table 4.5** (personal communication). Occupational exposure data or any detailed information on the workplace use of these polymers was not established. It is, however, possible to model a reasonable worst-case scenario to demonstrate the relatively low exposure to residual N-VP.

Table 4.5 Concentration of polymer in uses of PVP and the residual N-VP content (personal communication)

Polymer use	Average concentration of polymer in product (%)	Maximum concentration of residual N-VP in the polymer (ppm)
Pharmaceuticals	2	1
Food additives	0.05	100
General polymers	100	100
Adhesives	10	100
Cosmetics	1	100
Washing additives	0.5	50
Paint dispersions	0.5	not reported

For this reasonable worst-case scenario it is assumed that a plant is handling a polymer containing 100 ppm N-VP. For example, a company using N-VP polymer to formulate adhesive using open vessels fitted with LEV. The EASE scenario that best describes this is non-dispersive use with LEV, which results in a prediction of 0.5 to 3 ppm 8-hour TWA. This assumes that the operator is exposed to monomer alone, and not the residual monomer content in a polymer. Taking account of the low concentration of N-VP in the polymer (100 ppm), this exposure can be further refined to give exposure ranges of 0.00005 to 0.0003 ppm 8-hour TWA. Clearly, if LEV is not present exposure may be higher. For example, if it is assumed that exposure is uncontrolled (i.e. non-dispersive and uncontrolled direct handling) then EASE predicts 50 to 100 ppm 8-hour TWA. This is refined to an exposure range of 0.005 to 0.01 ppm 8-hour TWA for the residual monomer, although this scenario is unlikely.

End users of products containing polymers with residual monomer are likely to receive lower exposures than the above due to the relatively low concentrations of polymer in the product (see **Table 4.5**).

4.1.1.1.8 Inhalation exposure (general discussion)

Occupational exposure to N-VP can be discussed in three categories:

- the manufacture of N-VP monomer and polymers,
- the manufacture and use of UV curing inks and lacquers, and contact lenses, and
- the use of N-VP polymers.

Tables 4.6 and **4.7** summarise the data used in this exposure assessment for 8-hour TWA and short-term exposure, respectively.

Manufacture of N-VP monomer and its polymers

Occupational exposure occurs during the manufacture of N-VP and its polymers, with about 450 to 750 workers exposed. The production of N-VP and that of its polymers are discussed together as they are both carried out in closed plant. In addition, they are generally both carried out on the same site, as there is only one EU producer, which also manufactures more than 90% of the N-VP polymers produced in the EU. This site was visited in 1996 to gain an understanding of the measures adopted by this industry to control exposure.

This industry's approach to the control of N-VP is to employ and develop measures that reduce exposure to as low a level as is reasonably practical. This includes the use of:

- enclosed sampling systems,
- vapour returns for filling road and rail tankers,
- LEV to drum filling points,
- magnetic delivery pumps,
- systems for purging and testing process lines and vessels prior to breaching,
- the use of RPE where the potential for exposure exists.

Results were received direct from industry, the German CA and Zober et al. (1991), although many of the results are likely to represent the same measurements. They all generally showed about 80 to 90% of results to be less than 0.1 ppm 8-hour TWA. There were a few results above 0.1 ppm 8-hour TWA. Zober et al. (1991) reported that only 5 of the 59 results were above 0.15 ppm 8-hour TWA. The highest result reported by industry and by Zober et al. (1991) was in both cases 7.4 ppm 8-hour TWA, which probably confirms that many of the results are from the

same measurements. This exposure resulted from an incident involving contaminated clothing. It is reasonable to assume that exposures in excess of 0.1 ppm 8-hour TWA represent the upper end of routine exposure, and are probably from accidental releases. The original submissions provided insufficient clarification of the results between 0.1 and 1 ppm 8-hour TWA to allow understanding of the significance of these higher results. However, more recent communications have clarified the small number of higher results, showing them to be infrequent and to be less representative of current working practices. In view of these clarifications and that even with these included, 80 to 90% of results are less than 0.1 ppm 8-hour TWA, the figure taken forward to the risk characterisation will be 0.1 ppm.

These 8-hour TWA exposures result from short-term tasks, such as sampling, tanker and drum filling, and filter changing. Very little short-term exposure data (up to 1 ppm for drumming) was received, therefore exposure during the above tasks was modelled. Using the EASE model and further calculating for duration of exposure, 15 minute TWA exposures of 0.067 to 3.3 ppm were modelled and refined for exposure duration for these tasks (except filter changing). For filter changing, where the operator directly handles the filter, exposures of 50 to 100 ppm were predicted, which correlated reasonably well with the 20 to 80 ppm found by the company from a fixed position continuous monitor. The operator, however, wears air fed RPE which should significantly reduce this exposure.

Table 4.6 Summary of the occupational exposure data used in this exposure assessment - 8-hour TWAs

Industry / process	No. of samples	Range (ppm)	Arithmetic mean (ppm)	Comments	Source
Monomer / polymer production	164	0 to 7.4	0.14	90% < 0.1 ppm	German industry
	nk	nk	0.05 to 0.18	range of means for tasks	German CA
	59	up to 7.4	nk	80% < 0.1 ppm, five above 0.15 ppm, 1 above 1 ppm	Zober et al. (1991)
Manufacture of UV inks and lacquers	5	0.05 to 0.17	na	exposures during production of one batch	UK industry
	2	0.001 & 0.012		exposure for 23 and 40 min, respectively	UK industry
	69	0.037 to 0.56	nk	static sampling	UK industry
	na	0.25 to 1.5	na	with and without LEV. exposure at lower end of the range	EASE
	na	5 to 25	na		
Use of UV curing inks	4	0.53 to 1.94	na	two personal and two static sampling results	German industry
	6	nd to 0.05		static sampling results	UK industry
	12	< 0.05 to 3.07		static sampling results	UK industry
	na	0.42 to 1.4	na	automated screen printing, with no LEV	EASE
	na	7 to 14	na	manual screen printing with no LEV	
Use of UV curing lacquers	na	0.045 to 0.27	na	automated lines, with LEV	EASE
Manufacture of contact lenses	3	all 3 ppm	na	prior to improvements by company	HSE
	na	0.25 to 1.5	na	exposure at lower end of range	EASE
Exposure to residual monomer in polymers	na	0.0005 to 0.01	na	reasonable worst-case scenarios	EASE

nk = not known; na = not applicable; nd = not detected

Manufacture and use of UV curing inks and lacquers, and the manufacture of contact lenses

N-VP is also used in UV curing inks and lacquers. In both cases it appears that the use has significantly reduced and is continuing to fall. The number of workers exposed is potentially large due to the large number of UV screen printers and users of lacquers, although realistically due to its falling use the numbers exposed are only likely to be in the hundreds. The manufacture of both inks and lacquers generally involves the same steps; charging, blending and product filling. Static sampling results of 0.037 to 0.56 ppm were reported by a UK manufacturer. Exposures of 0.25 to 1.5 ppm and 5 to 25 ppm were modelled using EASE and refined for exposure duration, for plants with and without LEV, respectively. Exposure was considered to be at the bottom of these ranges as the figures take no account of the low percentage of N-VP in the formulation. The highest exposure from either measured or modelled data was therefore 5 ppm 8-hour TWA. This is likely to be an overestimate as most companies are likely to use LEV or at least general ventilation.

During the use of inks the highest exposure is likely to result from manual UV screen printing on a large frame, for example, banners. LEV is generally not used by screen printers. Measured exposure data was not available for such a scenario, therefore exposures of 7 to 14 ppm 8-hour TWA were obtained using EASE and refined for the amount of N-VP concentration in the ink. Most UV screen printers operate with automated machines, for which exposures of 0.42 to 1.4 ppm were modelled using EASE and again refined for N-VP concentration. These latter results are generally similar to the measured data, although these are from static sampling equipment and therefore cannot be used, for this purpose, with any degree of confidence. The value of 14 ppm will therefore be used for the purposes of risk characterisation.

Table 4.7 Summary of short-term exposure data used in this exposure assessment

Industry / process	No. of samples	Range (ppm)	Mean (ppm)	Comments	Source
Monomer / polymer production	nk	up to 1	nk	no details other than drumming	German CA
	nk	20 to 80	nk	during filter changing	Industry
	na	0.67 to 3.3	na	tanker filling	EASE
	na	1.67 to 3.3	na	sampling	
	na	0.067 to 0.4	na	drum filling	
Manufacture of UV inks and lacquers	na	50 to 100*	na	maintenance / cleaning	EASE
Use of UV curing inks	na	7 to 14	na	maintenance / cleaning	EASE

* exposure unlikely as calculated saturated vapour concentration is only 131 ppm.
nk = not known; na = not applicable

UV curing lacquers are sprayed in closed chambers or semi-enclosed and ventilated tunnels by automatic guns. Measured exposure data was not obtained for this. Results of 0.045 to 0.27 ppm 8-hour TWA were modelled using EASE and refined for N-VP concentration in the lacquer, although these only take limited account of the control regime and are therefore likely to be overestimates. Exposure during the manufacture of contact lenses was modelled and refined to give ranges of 0.25 to 1.5 ppm 8-hour TWA, although these again only take limited account of the control regime and are likely to be overestimates.

Use of N-VP polymers

Occupational exposure from residual monomer during the use of polymers is relatively low. Where no controls are in place exposures of up to 0.01 ppm 8-hour TWA were obtained using EASE and refined for residual N-VP content. However, a more realistic exposure where a polymer is used in an open vessel with LEV is 0.00005 to 0.0003 ppm 8-hour TWA.

Summary

In summary, occupational exposure during the manufacture and use of N-VP was found to be as follows:

- Most exposures were less than 0.1 ppm 8-hour TWA for production of the monomer and its polymers, with exposures low at polymer plants. A figure of 0.1 ppm 8-hour TWA will be taken forward to the risk characterisation.
- Occupational exposures of up to 5 ppm 8-hour TWA were obtained using the EASE model for the manufacture of UV curing inks and lacquers where LEV was not present. However, many plants will have LEV and have exposures of about 0.5 ppm 8-hour TWA. A value of 5 ppm 8-hour TWA will be used for the risk characterisation.
- Occupational exposures of 7-14 ppm 8-hour TWA were obtained using the EASE model for UV screen printers operating without LEV and manually printing. The value of 14 ppm will be taken forward to the risk characterisation.
- Occupational exposures of 0.045 to 0.27 ppm 8-hour TWA and 0.25 to 1.5 ppm 8-hour TWA were obtained using the EASE model for users of UV lacquers and manufacturers of contact lenses, respectively. However, these exposures are likely to be overestimates as they do not take sufficient account of the control regimes adopted. For risk characterisation purposes, the lower end of these ranges will be used i.e. 0.045 ppm 8-hour TWA for use of UV lacquers and 0.25 ppm for manufacture of contact lenses.
- During the use of polymers exposure to residual monomer was found to be negligible, by means of the EASE model.

Short-term exposure during the manufacture and use of UV curing inks and lacquers may occur during tasks such as cleaning and maintenance. In these cases, where operators are likely to need to wear RPE, exposures of 50 to 100 ppm were obtained using the EASE model, where no LEV is present at ink and lacquer manufacturing plants. Taking account of the concentration of N-VP in the ink the values were refined to 7 to 14 ppm 8-hour TWA. However, as N-VP has a calculated saturated vapour concentration of only 131 ppm, it is unlikely that exposures of 100 ppm would be achieved in practice.

4.1.1.1.9 Dermal exposure (general discussion)

Dermal exposure can occur during the production and use of N-VP, where operators come into contact with surfaces contaminated from splashing or condensed vapour, or as a result of direct contact onto the skin. As processing is in closed systems, dermal exposure is only likely during activities such as sampling and the uncoupling of pipes. This was predicted using EASE to be 0 to 0.1 mg/cm^2/day, should it occur, although on most days no such accidental contacts will occur. One activity where higher dermal exposure may occur is during filter changing. This is only likely to happen once in a shift, therefore the operator may have increased exposure for the period of

time taken to change the filter. An exposure of 0.1 to 1 mg/cm2/day was predicted using EASE for shifts where a filter change takes place. Operators are understood to wear gloves where the potential for skin contact exists and thus in reality exposure will be towards the bottom of these ranges.

Dermal exposures during the manufacture of inks and lacquers may occur when charging vessels and filling containers. Due to the low volatility of N-VP, surfaces may remain contaminated with ink or lacquer, for example, hand rails and the outsides of vessels. Dermal exposure was predicted using EASE to be 0.1 to 1 mg/cm^2/day. With the exception of handling the N-VP the operators will come into contact with blends with relatively low concentrations of N-VP and the exposure is therefore likely to be at the bottom of the above range.

During the use of the inks dermal exposure may occur when charging printer heads or manually applying the ink to the media being printed. Due to the low volatility of N-VP surfaces may also become contaminated with ink or lacquer, for example, hand rails and the outsides of vessels. The worst-case scenario would therefore be manual printing, for which EASE predicted dermal exposure to be 1 to 5 mg/cm^2/day. The operator will, however, be using an ink with only about 14% N-VP, therefore the EASE prediction was further refined to 0.14 to 0.7 mg/cm^2/day.

Dermal exposures during the use of lacquers may occur when charging the lacquer reservoir. Due to the low volatility of N-VP, surfaces may also become contaminated with ink, for example, hand rails and the outsides of vessels. Dermal exposure was predicted using EASE to be 0.1 to 1 mg/cm^2/day. The operator will, however, be using a lacquer with only about 9% N-VP, therefore the EASE prediction was further refined to 0.009 to 0.09 mg/cm^2/day.

The potential for dermal exposure during the manufacture of contact lenses will generally occur during the addition of the initiator. During further work steps are taken to avoid contact with the lenses. Dermal exposure was predicted using EASE to be 0 to 0.1 mg/cm^2/day. The operator, however, will only be using a 50% N-VP mixture therefore this exposure was further refined to 0 to 0.05 mg/cm^2/day

Operators may wear gloves where the potential for skin contact exists and thus further reduce the above predicted exposures.

4.1.1.2 Consumer exposure

4.1.1.2.1 Introduction

N-VP has no direct consumer use as a monomer but the homopolymer, polyvinyl pyrrolidone (PVP) has a wide variety of consumer uses owing to its biological compatibility, low toxicity, film-forming and adhesive characteristics, unusual complexing ability and resistance to thermal degradation in solution. There are two forms of the polymer available: soluble PVP is a long chain polymer and insoluble PVP is a cross-linked polymer.

For all of the applications of the polymer there will be a residual monomer level present which will determine the significance of the consumer exposure. Levels of residual monomer in the polymer have been progressively reduced from 1,000 ppm to below 100 ppm and in many cases to below 10 ppm. For applications such as pharmaceutical use the residual levels of monomer are below 5 ppm. Because these levels vary from product to product an initial assessment was made of each use before some applications were considered in greater detail. Because of the multiplicity of polymer uses, only those uses likely to result in measurable levels of monomer

exposure or that were of major significance have been considered. In any event no single consumer could possibly be exposed as a result of all of the uses on a daily basis, so for a reasonable worst-case scenario only the major exposures, which could occur together have been summed.

4.1.1.2.2 Pharmaceuticals

PVP, when wetted, becomes sticky and is used to bind tablets. It is also used as a coating aid. PVP is used as a tablet constituent of vitamins, minerals and sweeteners as well as being a crystallisation inhibitor in liquid medicines.

Both soluble and insoluble forms of PVP are widely used in the pharmaceutical industry and a co-polymer with vinyl acetate is also available. PVP is used in wet granulation, in tablet production, oral solutions, injectables, topical solutions and in film coatings on tablets. PVP complexed with iodine (povidone iodine) is widely used as a germicide in antimicrobial soaps, surgical hand scrubs, patient pre-operative skin cleansers, antiseptics and skin wound cleaners. It may also be used as a mouthwash or as eye drops. The insoluble form of PVP may also be used at a concentration of up to 10% in suppositories where it functions as a disintegrant.

Information obtained from the Association of the British Pharmaceutical Industry (ABPI) indicates that the maximum level of PVP in a tablet is 50 mg, that in povidone iodine the PVP is present as 90% (iodine 8%) of a 10% solution and in liquid medicines the PVP level is a maximum of 0.5%. For modelling purposes, a reasonable worst-case intake of pharmaceuticals is assumed. No individual is likely to take all the forms of medication and therefore only some will be considered together.

A reasonable worst-case scenario for consumer use of pharmaceuticals would involve the daily ingestion of 30 tablets, with the maximum of 50 mg of PVP per tablet. This gives an intake of residual monomer of $30 \cdot 50 \cdot 5 \cdot 10^{-6} = 7.5 \cdot 10^{-3}$ mg (7.5 μg), assuming a maximum monomer level of 5 ppm.

Another scenario envisages the intake of 10 ml of liquid medicine containing 0.5% PVP. This is equivalent to about 50 mg of PVP, which is the same as that which may be contained in one tablet. Therefore only the tablet intake needs to be considered.

Povidone iodine contains about 8% iodine and about 90% PVP. The formulation used as lotion, mouthwash or eye drops contains a maximum level of 10% povidone iodine. Therefore the maximum possible exposure to N-VP from povidone iodine can be calculated. This equals $0.9 \cdot 0.1 \cdot 5 \cdot 10^{-6} \cdot$(amount of product used). Assuming that 20 ml (assumed to be equivalent to 20 g) of lotion or mouthwash is used this means that no more than 9 μg of free monomer is present. This use of povidone iodine is not considered as additional to the tablet intake as this is not considered to be reasonable. There is also the strong possibility that, in fact, no residual monomer exists at all because iodine reacts so readily with the acetylenic groups.

Overall, exposure to N-VP monomer in pharmaceutical products can be taken as a maximum of 10 μg daily, on the assumption that either tablets or the lotion or mouthwash are used daily.

4.1.1.2.3 Other tablets

PVP can be used for tablets for non-pharmaceutical purposes, such as some brands of campden tablets and tannin tablets used in wine making. Here, PVP is used as binder at a concentration of less than 1%. PVP is also present in tablets of paint for paint boxes. Some brands of water

purification tablets contain PVP as a coating. It is assumed that consumer exposure to N-VP monomer is insignificant in all these applications.

4.1.1.2.4 Foods and beverages

The WHO Joint Expert Committee on Food Additives (JECFA) has granted an acceptable daily intake (ADI) of up to 50 mg/kg/day for PVP. However, the uses of soluble and insoluble PVP in foods are extremely limited. Soluble PVP (E 1201) and insoluble PVP (E 1202) may be used in food supplements and as a solvent/carrier in table top sweeteners. The prohibitive cost of the PVP when compared to the alternatives means that this usage remains very small.

The insoluble form of PVP is used in the brewing industry to clarify the product. Although it is relatively infrequently used for draught beers, it is more common in bottled or canned beer production. It is added to beer at rates of between 10 and 50 $g \cdot hl^{-1}$ (0.1 to 0.5 $g \cdot l^{-1}$) as a process aid. It removes polyphenols that would otherwise contribute to colloidal haze and the development of harsh astringent flavours. The PVP is added before filtration and it forms hydrogen bonds with the polyphenols; the insoluble PVP and bound polyphenols should then be removed during the filtration process.

In the wine industry, insoluble PVP is used non-routinely, at a level of between 0.1 and 0.3 $g \cdot l^{-1}$, for over pressed grapes, where there is a risk of high polyphenol levels. It is left in the wine for 45 minutes before being filtered out.

Overall it is considered that exposure to N-VP in foods and beverages are insignificant.

4.1.1.2.5 Cosmetics and toiletries

Both soluble and insoluble PVP and its co-polymers are used as a thickener, dispersing agent and binder in cosmetics. It acts as a stiffener in hair setting lotions and improves the consistency of shampoos.

For cosmetic use, all PVP contains less than 1,000 ppm of monomer and this figure is being progressively reduced to 100 ppm. Some data on actual levels of residual monomer in cosmetics is available and although limited and somewhat historical, indicates that the levels are generally below 40 ppm. However, there are a few exceptions to this, and so the value of 100 ppm will be taken as the maximum likely concentration of residual N-VP monomer in PVP used in cosmetics and toiletries. The potential exposure of the consumer to the residual monomer during the use of cosmetics is calculated below.

When used in shampoos, PVP is present at a level of 1%. Assuming that 12 g of shampoo is used daily, with a partition coefficient of 10% (TGD default values), then the amount of N-VP available for absorption is $1.2 \cdot 10^{-2}$ (PVP concentration in shampoo) $\cdot 10^{-4}$ (residual monomer level) g = 1.2 μg.

In styling gels, the PVP is present at a concentration of 3%. Assuming that two applications of 5 g are used daily, with a partition coefficient of 10%, then 30 mg of PVP or $30 \cdot 10^{-4}$ (residual monomer level) mg = 3 μg of N-VP is available for absorption.

In hairsprays, PVP is present at a concentration of 2%. Assuming that 10 g is used twice daily, with a 10% partition coefficient, a similar calculation to the above shows that 4 μg of N-VP is available for absorption. In terms of the potential airborne concentration of N-VP to which a

consumer may be exposed, this is estimated to be 7 $\mu g \cdot m^{-3}$ per event, assuming that the inhalable fraction of the aerosol is 70% and that exposure occurs in a volume of 2 m^3, in the immediate vicinity of the user (i.e. 0.2 g (amount of PVP in 10 g hairspray) $\cdot 10^{-4}$ (residual monomer level) $\cdot 0.7$ (inhalable fraction) $\cdot 2^{-1}$ m^3 (volume in immediate vicinity of user)). Each event will last for a relatively short period, in the region of 0.1 hours.

In pre-shave gels, the PVP level is 2%. Assuming that 2 g is used daily, with a 10% partition coefficient, a similar calculation to those above gives a value of 0.4 μg of N-VP exposure daily.

These four applications give total exposure of less than 9 μg of N-VP daily. There are other possible exposures to PVP in cosmetic use but it is extremely unlikely that all possible exposures would occur on the same day. The four scenarios above, for which potential exposure has been calculated, are likely to represent a reasonable worst-case scenario.

4.1.1.2.6 Adhesives

Rewettable bonding

Glue-sticks (solid glues) are used in the office and childrens sector (both educational and private). The European market is dominated by two manufacturers and the total market is around 50 million sticks (of varying sizes) annually. The UK market is around 14 million sticks. This is equivalent to about 300 tonnes of glue and about 30 tonnes of PVP. As can be inferred from these figures, the PVP content of the glue sticks in the UK is now, in general, less than 10%, as the PVP has been partially replaced by a starch polymer. The European market however, still uses many glue sticks with PVP levels of around 20%. The PVP supplied for these glue sticks has a residual monomer level of less than 100 ppm but the manufacturers aim to produce PVP with less than 10 ppm of residual monomer. The usual sizes sold are 10 g, 20 g, and 40 g, with the 20 g size being the best seller; a 90 g 'jumbo' size is available for special jobs.

It is possible that dermal exposure could arise during the use of such glue sticks. If a child were to be exposed to the total N-VP content of a 'jumbo' glue stick this would amount to 90 (weight of glue stick) $\cdot 0.2$ (maximum PVP content) $\cdot 100 \cdot 10^{-6}$ (assuming a maximum monomer content of 100 ppm) = 1.8 mg. However, it is unlikely that a child would be exposed to the total N-VP content of one of these sticks and therefore only a small proportion of this is likely to be available for absorption. If it assumed that a maximum of 10% of this total is likely to be available for dermal absorption, these results in a potential exposure of 180 μg per event. However, it is recognised that this represents a worst-case exposure estimate, and such exposure is not anticipated to occur on a daily basis, but will be a relatively infrequent event. For these reasons, this scenario will not be taken forward to the risk characterisation.

The use of PVP in tile adhesives, flooring adhesives and cement-based adhesives is now only of historical interest. Manufacturers have moved on to cheaper alternatives in the UK and it is expected that European use has similarly changed.

Remoistenable adhesives for paper

PVP may also used in wettable gums for postage stamps and envelopes, as the form used is readily soluble in water. It is usually used as a co-polymer with vinyl acetate. Consumer exposure to the low levels of residual monomer in the small quantities of PVP which may be used is considered to be insignificant.

4.1.1.2.7 Contact lenses

All lenses need to be gas-permeable to enable the eyes to gain the oxygen they need to breathe. Hard lenses are used now only for astigmatism, owing to their low oxygen permeability. Soft lenses are made of materials that absorb water, readily allowing oxygen to permeate, and provide a high level of comfort. The higher the water content the greater the oxygen permeability but the more fragile are the lenses. PVP is ideal as a constituent of soft lenses because of its hygroscopicity and inertness. It is used in a purified form for lenses that are very soft and can be disposed of daily. Daily disposal ensures that lenses remain sterile and do not build up protein deposits. A further advantage of the softness is that if they are retained *in situ* overnight by mistake the eye still has sufficient oxygen.

There are three ways of manufacturing lenses: lathing, spin casting or cast moulding. In cast moulding two plastic precision moulds are produced. N-VP is added with the HEMA and the initiator to produce sterile disposable lenses. The N-VP is polymerised in the moulds, leaving only residual monomer.

Levels of residual monomer in the lens fluid are around 250 ppm. Each lens weighs about 35 mg and consists of 73% fluid and 27% plastic. Therefore the overall residual N-VP content of a pair of contact lenses is $35 \cdot 2 \cdot 0.73 \cdot 250 \cdot 10^{-6}$ = 0.013 mg (13 μg) N-VP. This monomer is available daily for absorption through the eye.

4.1.1.2.8 Suspensions, dispersions and emulsions

PVP stabilises aqueous suspensions, dispersions and emulsions. They are adsorbed in a thin layer on the surface of colloidal particles.

One example is the use of PVP in certain types of washing powders where it is used to stabilise enzymes used in the detergent. There will be a maximum of 0.5% PVP in the washing powder and the PVP contains less than 55 ppm of residual monomer. For hand washing purposes, it is assumed that 30 g of powder is used in 7 litres of water. Overall therefore, a maximum of $30 \cdot 0.005 \cdot 55 \cdot 10^{-6} = 8.25 \cdot 10^{-6}$ g (8 μg) N-VP in the 7 litres of washing water will be available for absorption. Since it is not possible to determine how much of the total N-VP content of the washing water will deposit on the skin, it will be assumed that the total N-VP content of the washing water (i.e. 8 μg) is available for absorption. It is recognised that this will overestimate exposure to N-VP for this scenario.

PVP may also be used in some concrete mixtures where it helps the spreading action. However levels of the polymer are low and the exposure of consumers to the residual monomer is likely to be insignificant.

4.1.1.2.9 Miscellaneous uses

PVP is used in denture fixative. This is applied to the gums to anchor false teeth. Levels of PVP in fixative are around 10% and residual monomer levels are less than 10 ppm. To model the potential exposure it is assumed that 3 g of fixative is used twice daily. This means that $3 \cdot 2$ (daily usage of fixative) $\cdot 0.1$ (concentration of PVP in fixative) $\cdot 10 \cdot 10^{-6}$ (residual monomer level) g = 6 μg N-VP is available for absorption daily.

A major but declining use of N-VP is in the UV curing of inks and coatings. Radiation curing is a free radical polymerisation initiated by a high-energy source. The formulation consists of oligomers, reactive diluent, photo-initiator and additives. Coatings and inks are cured *in situ* and used to coat metal, wood, plastic, textiles and rubber. N-VP monomer is used as a reactive diluent for many of these applications, often with urethane polyesters, polyethers or epoxies as the oligomers. The N-VP has the advantage of fast cure speeds and extremely low levels of residual monomer. The measurements available have indicated that the residual levels are below the detectable limits. For this reason it is considered that consumer exposure is likely to be negligible.

PVP acts as a protective colloid and silver halide-suspending agent in photography and it is used as a processing aid. Consumer exposure from this use is considered to be insignificant.

N-VP was formerly used to produce a viscosity improver for oils. It was reacted with polymethacrylates to produce a co-polymer with some residual monomer, which was used in car crankcase oils. This application is now very limited and will not be considered in the risk characterisation.

4.1.1.2.10 Overall exposures

Because of the multiplicity of exposures and the very low levels of residual monomer present, it is difficult to calculate an exposure that is both "reasonable" and "worst case". However, it has been assumed that a consumer may be exposed daily to N-VP monomer from contact lenses, pharmaceuticals, denture fixatives, cosmetics and washing powder. It is assumed that the other potential exposures are negligible and/or infrequent and will not add significantly to the overall exposure.

A daily worst-case exposure to N-VP monomer is estimated to be 13 μg (contact lenses)+10 μg (pharmaceuticals)+6 μg (denture fixatives)+9 μg (cosmetics)+8 μg (washing powder), making a total of 46 μg. This value will be taken forward to the risk characterisation section.

4.1.1.3 Humans exposed via the environment

Data from the environment section have been repeated here (**Tables 4.8** and **4.9**) and give the predicted environmental exposures to N-VP and the daily human doses arising from releases from production and processing of N-VP and N-VP related products, and for releases at the regional level.

It can be seen that the highest daily human intake via the environment based upon typical human consumption and inhalation rates arises from N-VP production and processing and is estimated to be $4.28 \cdot 10^{-3}$ mg/kg/day. Regional exposures result in an intake of $1.5 \cdot 10^{-6}$ mg/kg/day. These values will be taken forward to the risk characterisation. In addition, in view of the concerns for the development of nasal cavity and laryngeal tumours, exposures due to inhalation of N-VP will also be taken forward to the risk characterisation. The greatest daily dose of inhaled N-VP, 0.13 μg/kg/day, comes from N-VP production. For regional exposures, the daily dose of inhaled N-VP is $7.5 \cdot 10^{-9}$ mg/kg/day. These values have also been taken forward to the risk characterisation.

Table 4.8 Concentrations in human intake media

	Regional	Production and processing (site specific)	Processing at small sites (site specific)	Processing at small sites				Processing at small sites - polymerisation				Ink/ varnish formulation	Ink/varnish processing
				Use A	Use B	Use C	Use D	E	F	G	H		
Concentration in wet fish (mg/kg)	$5.47 \cdot 10^{-5}$	$1.1 \cdot 10^{-4}$	$5.5 \cdot 10^{-5}$	$5.7 \cdot 10^{-3}$	0.011	0.017	$6.3 \cdot 10^{-5}$	$1.3 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$	$1.3 \cdot 10^{-3}$	$3.7 \cdot 10^{-3}$	$6.1 \cdot 10^{-4}$
Concentration in root tissue of plant (mg/kg)	$7.15 \cdot 10^{-6}$	$3.0 \cdot 10^{-4}$	$1.6 \cdot 10^{-5}$	$2.1 \cdot 10^{-3}$ - $6.9 \cdot 10^{-3}$	$2.1 \cdot 10^{-3}$	$3.4 \cdot 10^{-3}$	$9.9 \cdot 10^{-3}$	$7.1 \cdot 10^{-3}$	$2.8 \cdot 10^{-3}$ - $7.1 \cdot 10^{-3}$	$4.1 \cdot 10^{-3}$ - $9.9 \cdot 10^{-3}$	$2.1 \cdot 10^{-3}$ - $5.1 \cdot 10^{-3}$	$7.4 \cdot 10^{-4}$	$4.4 \cdot 10^{-4}$
Concentration in leaves of plant (mg/kg)	$1.61 \cdot 10^{-5}$	0.24	$2.2 \cdot 10^{-5}$	$7.5 \cdot 10^{-3}$ - $9.2 \cdot 10^{-3}$	0.034	0.053	$6.0 \cdot 10^{-3}$	$3.9 \cdot 10^{-3}$	$2.5 \cdot 10^{-3}$ - $3.9 \cdot 10^{-3}$	$2.9 \cdot 10^{-3}$ - $4.8 \cdot 10^{-3}$	$2.2 \cdot 10^{-3}$ - $3.2 \cdot 10^{-3}$	0.011	$8.3 \cdot 10^{-4}$
Concentration in drinking water (mg/l)	$3.88 \cdot 10^{-5}$	$3.1 \cdot 10^{-4}$	$3.9 \cdot 10^{-5}$	$4.0 \cdot 10^{-3}$ - $7.2 \cdot 10^{-3}$	$7.6 \cdot 10^{-3}$	0.012	0.0103	$7.4 \cdot 10^{-3}$	$3.0 \cdot 10^{-3}$ - $7.4 \cdot 10^{-3}$	0.0043-0.010	$2.2 \cdot 10^{-3}$ - $5.3 \cdot 10^{-3}$	$2.6 \cdot 10^{-3}$	$4.6 \cdot 10^{-4}$
Concentration in air (mg/m^3)	$3.52 \cdot 10^{-8}$	$6.2 \cdot 10^{-4}$	$4.3 \cdot 10^{-8}$	$1.8 \cdot 10^{-5}$	$8.5 \cdot 10^{-5}$	$1.3 \cdot 10^{-4}$	$6.9 \cdot 10^{-6}$	$3.8 \cdot 10^{-6}$	$3.8 \cdot 10^{-6}$	$3.8 \cdot 10^{-6}$	$3.8 \cdot 10^{-6}$	$2.9 \cdot 10^{-5}$	$1.7 \cdot 10^{-6}$
Concentration in meat (mg/kg)	$2.56 \cdot 10^{-9}$	$1.3 \cdot 10^{-5}$	$2.9 \cdot 10^{-9}$	$5.6 \cdot 10^{-7}$ - $7.3 \cdot 10^{-7}$	$2.1 \cdot 10^{-6}$	$3.3 \cdot 10^{-6}$	$6.6 \cdot 10^{-7}$	$4.5 \cdot 10^{-7}$	$2.3 \cdot 10^{-7}$ - $4.5 \cdot 10^{-7}$	$2.9 \cdot 10^{-7}$ - $5.9 \cdot 10^{-7}$	$1.9 \cdot 10^{-7}$ - $3.4 \cdot 10^{-7}$	$7.2 \cdot 10^{-7}$	$6.0 \cdot 10^{-8}$
Concentration in milk (mg/kg)	$2.56 \cdot 10^{-8}$	$1.3 \cdot 10^{-4}$	$2.9 \cdot 10^{-8}$	$5.6 \cdot 10^{-6}$ - $7.3 \cdot 10^{-6}$	$2.1 \cdot 10^{-5}$	$3.3 \cdot 10^{-4}$	$6.6 \cdot 10^{-6}$	$4.5 \cdot 10^{-6}$	$2.3 \cdot 10^{-6}$ - $4.5 \cdot 10^{-6}$	$2.9 \cdot 10^{-6}$ - $5.9 \cdot 10^{-6}$	$1.9 \cdot 10^{-7}$ - $3.4 \cdot 10^{-7}$	$7.2 \cdot 10^{-6}$	$6.0 \cdot 10^{-7}$

Table 4.9 Daily human doses (mg/kg/day)

Daily dose (mg/kg/d)	Regional	Production and processing (site specific)	Processing at small sites (site specific)	Processing at small sites				Processing at small sites - polymerisation				Ink/varnish formulation	Ink/varnish processing
				Use A	Use B	Use C	Use D	E	F	G	H		
Intake of drinking water	$1.1 \cdot 10^{-6}$	$8.9 \cdot 10^{-6}$	$1.1 \cdot 10^{-6}$	$1.2 \cdot 10^{-4}$-$2.1 \cdot 10^{-4}$	$2.2 \cdot 10^{-4}$	$3.5 \cdot 10^{-4}$	$2.9 \cdot 10^{-4}$	$2.1 \cdot 10^{-4}$	$8.4 \cdot 10^{-5}$-$2.1 \cdot 10^{-4}$	$1.2 \cdot 10^{-4}$-$2.9 \cdot 10^{-4}$	$6.2 \cdot 10^{-5}$-$1.5 \cdot 10^{-4}$	$7.5 \cdot 10^{-5}$	$1.3 \cdot 10^{-5}$
Intake of fish	$9.0 \cdot 10^{-8}$	$1.8 \cdot 10^{-7}$	$9.0 \cdot 10^{-8}$	$9.3 \cdot 10^{-6}$	$1.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-5}$	$1.0 \cdot 10^{-7}$	$2.1 \cdot 10^{-6}$	$2.1 \cdot 10^{-6}$	$2.1 \cdot 10^{-6}$	$2.1 \cdot 10^{-6}$	$6.1 \cdot 10^{-6}$	$9.9 \cdot 10^{-7}$
Intake of leaf crops	$2.8 \cdot 10^{-7}$	$4.1 \cdot 10^{-3}$	$3.7 \cdot 10^{-7}$	$1.3 \cdot 10^{-4}$-$1.6 \cdot 10^{-4}$	$5.8 \cdot 10^{-4}$	$9.0 \cdot 10^{-4}$	$1.0 \cdot 10^{-4}$	$6.7 \cdot 10^{-5}$	$4.2 \cdot 10^{-5}$-$6.7 \cdot 10^{-5}$	$4.9 \cdot 10^{-5}$-$8.2 \cdot 10^{-5}$	$3.8 \cdot 10^{-5}$-$5.5 \cdot 10^{-5}$	$2.0 \cdot 10^{-4}$	$1.4 \cdot 10^{-5}$
Intake of root crops	$3.9 \cdot 10^{-8}$	$1.6 \cdot 10^{-6}$	$8.6 \cdot 10^{-8}$	$1.2 \cdot 10^{-5}$-$3.8 \cdot 10^{-5}$	$1.2 \cdot 10^{-5}$	$1.9 \cdot 10^{-5}$	$5.4 \cdot 10^{-5}$	$3.9 \cdot 10^{-5}$	$1.6 \cdot 10^{-5}$-$3.9 \cdot 10^{-5}$	$2.3 \cdot 10^{-5}$-$5.4 \cdot 10^{-5}$	$1.2 \cdot 10^{-5}$-$2.8 \cdot 10^{-5}$	$4.0 \cdot 10^{-6}$	$2.4 \cdot 10^{-6}$
Intake of meat	$1.1 \cdot 10^{-11}$	$5.6 \cdot 10^{-8}$	$1.2 \cdot 10^{-11}$	$2.4 \cdot 10^{-9}$-$3.1 \cdot 10^{-9}$	$9.1 \cdot 10^{-9}$	$1.4 \cdot 10^{-8}$	$2.8 \cdot 10^{-9}$	$1.9 \cdot 10^{-9}$	$9.8 \cdot 10^{-10}$-$1.9 \cdot 10^{-9}$	$1.3 \cdot 10^{-9}$-$2.6 \cdot 10^{-9}$	$8.1 \cdot 10^{-10}$-$1.5 \cdot 10^{-9}$	$3.1 \cdot 10^{-9}$	$2.6 \cdot 10^{-10}$
Intake of milk	$2.1 \cdot 10^{-10}$	$1.0 \cdot 10^{-6}$	$2.3 \cdot 10^{-10}$	$4.5 \cdot 10^{-8}$-$5.8 \cdot 10^{-8}$	$1.7 \cdot 10^{-7}$	$2.7 \cdot 10^{-7}$	$5.3 \cdot 10^{-8}$	$3.6 \cdot 10^{-8}$	$1.8 \cdot 10^{-8}$-$3.6 \cdot 10^{-8}$	$2.4 \cdot 10^{-8}$-$4.8 \cdot 10^{-8}$	$1.5 \cdot 10^{-8}$-$2.8 \cdot 10^{-8}$	$5.8 \cdot 10^{-8}$	$4.8 \cdot 10^{-9}$
Intake of air	$7.5 \cdot 10^{-9}$	$1.3 \cdot 10^{-4}$	$9.1 \cdot 10^{-9}$	$3.8 \cdot 10^{-6}$	$1.8 \cdot 10^{-5}$	$2.8 \cdot 10^{-5}$	$1.5 \cdot 10^{-6}$	$8.2 \cdot 10^{-7}$	$8.2 \cdot 10^{-7}$	$8.1 \cdot 10^{-7}$	$8.2 \cdot 10^{-7}$	$6.1 \cdot 10^{-6}$	$3.8 \cdot 10^{-7}$
Total	$1.5 \cdot 10^{-6}$	$4.28 \cdot 10^{-3}$	$1.7 \cdot 10^{-6}$	$2.7 \cdot 10^{-4}$-$4.2 \cdot 10^{-4}$	$8.4 \cdot 10^{-4}$	$1.3 \cdot 10^{-3}$	$4.5 \cdot 10^{-4}$	$3.2 \cdot 10^{-4}$	$1.5 \cdot 10^{-4}$-$3.2 \cdot 10^{-4}$	$2.0 \cdot 10^{-4}$-$4.3 \cdot 10^{-4}$	$1.1 \cdot 10^{-4}$-$2.4 \cdot 10^{-4}$	$2.9 \cdot 10^{-4}$	$3.1 \cdot 10^{-5}$

4.1.2 Effects assessment: hazard identification and dose (concentration) - response (effect) assessment

The toxicity of N-VP has been extensively characterised in animal models. In a number of inhalation studies, N-VP containing a stabiliser, Kerobit (N,N'-di-2-butyl-p-phenylenediamine, CAS 101-96-2), was used. Since the concentration of Kerobit in N-VP is low (at most 10 ppm), and the results of comparable toxicity tests using N-VP containing Kerobit and Kerobit-free N-VP were similar. In general the presence of Kerobit is not thought to affect the interpretation of any study results.

4.1.2.1 Toxicokinetics, metabolism and distribution

The kinetics of N-VP have been studied in varying detail depending on the route of exposure. In addition, metabolism has been examined in rats given N-VP by intravenous injection and studies have been undertaken to investigate the ability of N-VP to alkylate DNA *in vitro* and plasma proteins *in vitro* and *in vivo*.

One notable feature of N-VP is that it is readily hydrolysed in acidic conditions such as those in the stomach. Hawi et al. (1987) studied the hydrolysis of N-VP at 37^{o}C and pHs ranging from 1.2-7.2. They found that the rate of hydrolysis was inversely related to pH such that at a pH of 1.2 the half-life of N-VP in aqueous solution was only around 1.5 minutes; at pHs ranging from 2.2-2.5, half-lives of 20-40 minutes were observed; at a pH of 3.5, the half-life had risen to over 6 hours and at a pH of 7.2, N-VP was stable in aqueous solution for at least 24 hours. As part of a study in which N-VP was administered in drinking water, N-VP was shown to be stable in drinking water for at least 4 days (BASF, 1986d). Hawi et al. (1987) also attempted to identify the hydrolysis products of ^{14}C-vinyl labelled N-VP. The major hydrolysis products, accounting for around 95% of hydrolysed N-VP, were identified as 2-pyrrolidone and acetaldehyde (in hydrated form) with acetaldehyde-hemihydrate accounting for the remaining 5%.

N-VP is also known to undergo spontaneous polymerisation but no information on this phenomenon under physiological conditions is available.

4.1.2.1.1 Studies in animals

Inhalation

The concentration of N-VP in plasma following inhalation has been briefly investigated in two dogs, sequentially whole-body exposed for 6 hours to N-VP vapour at concentrations of 0.69, 5.5, 24 and 62 $mg \cdot m^{-3}$ (BASF, 1992a). Starting with the lowest dose, animals received exposures every seventh day. No measures were apparently taken to ensure that the dogs did not lick their coats during exposure. There were substantial differences in plasma N-VP concentrations between the two dogs, but plasma concentrations rose with ascending exposure concentration. The results demonstrated that N-VP can be absorbed from the respiratory tract. However, it is not possible to draw any quantitative conclusions given the small group size, large inter individual variations and the possible contribution to plasma N-VP levels from uptake via the oral route.

Oral

More extensive studies to determine the bioavailability and tissue distribution of aqueous solutions of N-VP (purity not stated) and its metabolites have been carried out by the oral route in male rats and female dogs (Digenis, 1990). HPLC/UV was used to quantify N-VP in serum (the limit of detection was 0.05 $mg \cdot l^{-1}$ and the limit of quantification 0.2 $mg \cdot l^{-1}$).

In the rat, both single and repeated dose studies have been carried out. Initially, groups of 5 or 7 fasted rats were given a single 0.5 or 5 mg/kg dose respectively in aqueous solution by gavage. A further 5 non-fasted rats were given a single gavage dose of 5 mg/kg. Finally, another group of 5 non-fasted rats was given two 0.5 mg/kg doses per day at 12-hour intervals for 6 days. In each case, blood samples were taken immediately before dosing and then at 0.5, 1, 2, 3, 4, 5 and 7 hours after dosing. In the multiple dose experiment, blood samples were withdrawn 12 hours after the final dose and then at the times stated above.

In fasted rats, the maximum concentrations of N-VP in plasma were reached between 0.5 to 3 hours after dosing, irrespective of dose, and were directly proportional to the dose. Similarly, the areas under the time concentration curves were directly proportional to the dose. Elimination from plasma roughly followed a linear pattern with a half-life of 3-4 hours for both doses. It was still possible to detect N-VP in plasma 7 hours after dosing for both dose levels. Under the conditions of this study, the absolute bioavailability was determined to be around 80% for each dose. N-VP is therefore rapidly and extensively absorbed from the gastrointestinal tract.

However, when kinetic parameters were examined in non-fasted rats it was found that while the maximum plasma concentrations were rapidly reached, at around 0.5 hours for non-fasted rats, they were approximately half of the maximum concentrations measured in fasted rats. Furthermore, the area under the time concentration curve was smaller and the absolute bioavailability had dropped to 26% of the dose. The reason why the absolute bioavailability should drop so much is unclear but a possible explanation is that the increased gastric emptying time caused by food in the stomach allowed a greater proportion of the dose to be hydrolysed or to polymerise prior to absorption (the pH of the rat stomach is thought to range from around 3-5). The kinetic parameters in non-fasted rats given multiple doses were very similar to those from non-fasted rats given a single dose, indicating that N-VP does not bioaccumulate and that there is no enzyme induction which might speed elimination of parent N-VP from plasma.

Also in this series of experiments, fasted rats were given around 1 mg/kg of ^{14}C-N-VP to investigate tissue distribution. After 2, 5 or 7 hours groups of 3 rats were sacrificed and the levels of radioactivity determined in a wide range of organs. Urine, faeces and expired air were not analysed. After 2, 5 and 7 hours, 52, 22 and 30%, respectively of the administered radioactivity was accounted for. Radioactivity was detected in all tissues. In general, at each time point, most tissues contained less than 1% of the administered radioactivity and the percentage contained within each tissue remained fairly constant. A notable exception was the liver, which showed a time dependent increase from 3.4% of the administered radioactivity after 2 hours to 10.4% after 7 hours. High levels were also found in whole blood, plasma, kidneys, small intestine and pancreas. Small amounts were also located in the testes. These results indicate that radioactivity derived from ^{14}C-N-VP distributes widely throughout the body. However, it is not clear if these percentages represent parent N-VP, metabolites or ^{14}C which has entered the endogenous carbon pool.

N-VP in aqueous solution was also administered by naso-gastric tube to 3 fasted dogs at successive dose levels of 5, 10 and 20 mg/kg and non-fasted dogs (fasted overnight then allowed a meal 30 minutes before dosing) at 20 mg/kg. These dogs had also been used to investigate the kinetics following intravenous injection (see below), but it is not clear which study was conducted first

and what length of time elapsed between doses. Blood samples were withdrawn 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3 and 4 hours post dosing. In addition, each dog received 50 μCi Tc99m-DTPA (Technetium-99m-diethylenetriaminepentaacetic acid) orally at the same time that N-VP was administered and the dog placed beneath the head of a gamma scintillation camera for at least 1 hour to follow the time course of gastric emptying. The percentage of N-VP bound to plasma proteins was also determined for dogs given 5 or 20 mg/kg, although it is not clear at what time the blood samples for this measurement were taken.

In contrast to the situation in the rat, administration of a meal prior to dosing with N-VP did not seem to affect the uptake or plasma elimination kinetics. The maximum concentrations of N-VP in plasma were recorded at 0.25-0.75 hours. Peak plasma concentrations generally increased with increasing dose, although wide variations between dogs were recorded. When gastric emptying profiles were compared, it was found plasma N-VP concentration correlated well with gastric emptying time. Around 13% and 10%, respectively for the low and high dose was apparently bound to plasma proteins. Areas under the time concentration curves were directly proportional to the dose but a graph of area under the curve versus dose did not pass through the origin, implying that parent N-VP would not reach the circulation below a certain oral dose level. This is consistent with a fraction of the dose undergoing hydrolysis and/or polymerisation prior to absorption (the pH of the dog stomach is thought to be similar to that of the human stomach). Elimination from plasma followed an exponential pattern, with half-lives ranging between 0.3 and 0.6 hours, and was independent of dose. At the low dose and in fed dogs, N-VP was no longer detectable 5 hours after dosing. At the two higher dose levels, N-VP could still be detected in 1/3 fasted dogs, 5 hours after dosing. Absolute bioavailability in fasted dogs was determined to be around 29, 69 and 89% for each dose. One explanation for the decrease in bioavailability with decreasing dose is that a greater proportion of the dose at lower dose levels undergoes hydrolysis and/or polymerisation before it can be absorbed. Absolute bioavailability for fed dogs given 20 mg/kg N-VP was around 92%. Although gastric emptying was slightly reduced as a result of feeding, the expected reduction in bioavailability was not observed. It is not clear why this is the case, although the presence of food may have raised the pH of the stomach contents and thereby inhibited the hydrolysis and/or polymerisation of N-VP. These results confirm that N-VP is well absorbed from the gastrointestinal tract.

In a much less extensive study, blood plasma concentrations were determined in two fasted beagle dogs given a 5 mg/kg gavage dose of N-VP in water (BASF, 1992a). Levels of N-VP in the blood were similar to those obtained in the previous study for dogs given 5 mg/kg.

Dermal

The kinetics of dermal uptake have been briefly characterised in a limited study in the dog (BASF, 1992a). Using the same dogs that had been used to study the inhalation and oral kinetics, 5 mg/kg undiluted N-VP was applied to a 25 cm^2 area of shaved skin and covered with a semi-occlusive dressing. Blood samples were taken immediately before application and then 0.5, 1, 2, 4 and 6 hours after application.

N-VP was detectable at all time points but at levels below the limit of quantification (0.1 $mg \cdot l^{-1}$). No attempts were made to measure total recovery. This shows that N-VP in liquid form will cross the skin, although in comparison with peak plasma concentrations of around 1 $mg \cdot l^{-1}$ obtained for dogs given 5 mg/kg orally (Digenis, 1990), this suggests that dermal uptake was relatively low in this experimental situation. Given the small dose levels that were used and lack of information relating to total recovery, it was not possible to estimate percentage bioavailability by the dermal route. However, the physicochemical characteristics of N-VP (ready solubility in water and most organic solvents and a log Pow of around 0.4) and

comparison with the structurally similar compound N-methyl-2-pyrrolidone, suggest that good dermal absorption could be predicted for this substance. This is supported by the findings of the acute dermal toxicity studies. An LD_{50} value of 560 mg/kg has been observed in rabbits and one out of 4 rats given a dermal dose of 1,043 mg/kg, died. The oral LD_{50} value lies around 1,000 mg/kg (see Section 4.1.2.2.1 for details).

Other

An extensive series of experiments has been carried out in male rats to characterise the distribution and metabolism of N-VP following intravenous dosing (Digenis and McClanahan, 1982; McClanahan et al., 1983; 1984). In each experiment, anaesthetised rats were given ^{14}C(vinyl)-N-VP in aqueous solution via the jugular vein.

Initially, groups of 3 rats were given a single dose of 1.1 mg/kg and blood samples were taken at frequent intervals up to 6 hours post-dosing. Rats were then sacrificed, urine samples were taken by means of bladder puncture and major organs were collected. Levels of both total radioactivity and parent N-VP were measured in blood and urine. Total radioactivity only was measured in major organs. The distribution of radiolabel was investigated in more detail using satellite groups of one or 3 rats given 1.1 mg/kg, which were sacrificed after 15, 30 or 90 minutes and the levels of total radioactivity measured in an extensive range of tissues.

Plasma levels of intact ^{14}C(vinyl)-N-VP dropped rapidly from around 6% of the dose, 10 minutes after injection to 0.5% of the dose 6 hours after injection. Elimination from the blood followed a biphasic pattern and half-lives for the slow phase of around 1.5 to 1.9 hours were calculated. These half-life values are somewhat higher than those calculated in the previous oral and other intravenous studies. Around 40-65% of the administered radioactivity was found in urine samples collected at sacrifice, of which less than 0.2% was in the form of N-VP suggesting that N-VP is extensively metabolised and the metabolites rapidly eliminated. As in the previous oral study, radioactivity distributed to all major organs.

More detailed investigations into the nature of the urinary metabolites were carried out in a separate experiment. Groups of 2 or 4 rats were given doses of around 0.3, 0.5, 0.8 or 1.3 mg/kg. Animals were then housed individually in metabolism cages for up to 6 days to enable urine, faeces and expired air to be collected. Urine samples were analysed to determine the levels of total radioactivity and certain samples were further analysed to determine the levels of parent N-VP or to identify the chemical nature of the urinary metabolites. Faeces were analysed for total radioactivity only and levels of $^{14}CO_2$ were measured in expired air collected from certain groups. In addition, fat from the greater omentum was collected from some animals at 42 and 145 hours after dosing, to check whether ^{14}C-labelled two-carbon fragments were being used for lipid synthesis.

Most radioactivity (70-90% of the administered dose) was eliminated in urine within the first 18 hours, of which approximately 60% was eliminated in the first 6 hours. In the first 12 hours post dosing, no more than 0.6% of the dose was eliminated in urine as intact N-VP, confirming the extensive metabolism of N-VP and rapid elimination of metabolites of N-VP. Chemical analysis revealed the urinary metabolites of N-VP to be highly polar. Acidic species accounted for around 89% of the urinary metabolites (of which 12% was accounted for by acetic acid). The remaining metabolites were mostly neutral species but a small fraction, around 1.7%, were identified as basic species.

Faecal elimination over the first day accounted for between 1 and 8% of the dose, and between 1 and 3% of the dose was exhaled as $^{14}CO_2$. Generally less than 1% of the dose was recovered

from any subsequent sample of urine, faeces or exhaled air. Very little radioactivity was recovered from the two samples of adipose tissue (0.02 and 0.09% of the dose) suggesting that any two-carbon fragments that are formed from N-VP are not generally incorporated into endogenous fatty acids.

Finally, 2 or 4 rats were given around 1.1 mg/kg and samples of bile collected at intervals up to 6 hours post dosing. Analysis of bile revealed that 19% of the administered radioactivity (of which about 0.5% represented intact N-VP) was excreted by this route. Given that only 0.4% of the administered radioactivity had been recovered from faeces 12 hours after administration of this dose, this shows that biliary metabolites of N-VP undergo extensive enterohepatic recirculation.

N-[^{14}C-vinyl]-2-pyrrolidone (side chain labelled) and [4-^{3}H]-N-vinyl-2-pyrrolidone (ring labelled) were co-administered as a single intravenous dose to male rats (McClanahan et al., 1987). Three separate studies were carried out. In the first, 4 rats were given the radiolabelled N-VPs (a total dose of around 6 mg/kg) and housed in metabolism cages for 6 days for collection of urine and faeces. All samples were analysed for total ^{14}C and ^{3}H activity. In addition, the levels of intact ^{14}C- or ^{3}H-labelled N-VP were measured in the 6 and 12 hour urine samples. Urine samples were further analysed by radiomonitored HPLC in an attempt to identify metabolites of N-VP.

The urinary and faecal elimination profiles for both ^{14}C and ^{3}H were very similar. Around 68% of each label was recovered from the urine within the first 12 hours, of which less than 0.3% was represented by intact N-VP for each label. Over the same period, around 0.2% of the dose was eliminated in the faeces. By day 2, a total of around 90% of either label had been recovered from the urine, very little N-VP was eliminated by this route thereafter, and by day 6 around 5-8% of either label had been eliminated in the faeces. These results are in good agreement with those obtained previously for ^{14}C-N-VP alone. More detailed analysis of urine samples revealed the presence of two major metabolites containing both ^{14}C and ^{3}H and accounting for around 50 and 33% of the dose. It was not possible to identify the structures of either major metabolite. Three minor metabolites were tentatively identified as N-vinylsuccinimide, accounting for around 5% of the dose, 2-pyrrolidone, around 6% and N-acetyl-γ-aminobutyric acid (N-acetyl-GABA), around 5.6%, but a further two minor metabolites accounting for around 5% of the ^{14}C labelled metabolites and 2.2% of the ^{3}H labelled metabolites respectively, could not be identified.

In the second study, the radiolabelled N-VPs (a total dose of around 5.2 mg/kg) were given to a group of 5 bile duct cannulated rats. Bile was collected at intervals up to 6 hours and as before samples analysed for total ^{14}C and ^{3}H activity and intact ^{14}C and ^{3}H-N-VP. Around 24% of the dose of both labels was eliminated in bile over the 6-hour period, of which only 0.9% was in the form of intact N-VP.

Finally the distribution of ^{14}C and ^{3}H was investigated in 3 rats given a total dose of around 4.4 mg/kg N-VP and sacrificed 6 hours later. No significant differences were apparent in the distribution of each radiolabel among the organs examined.

IRI (1985) investigated the potential for N-VP and its metabolites to bind to DNA and proteins using groups of 3 male CD rats given single or repeated intraperitoneal injections of 150 or 300 mg/kg N-vinyl[α,β-^{14}C]-2-pyrrolidone (label on vinyl group) or N-vinyl-2-pyrrolidone[5-^{14}C] (ring labelled) in aqueous solution. The results indicated that radiolabel was not associated with liver DNA, RNA or protein under any of the treatment regimens.

Studies *in vitro*

The ability of N-VP to bind to plasma proteins (Yamakita et al., 1992) or microsomal proteins (McClanahan et al., 1983) *in vitro* has been briefly investigated. At most, 12% of N-VP or its metabolites were bound to proteins, lending further weight to the conclusion that N-VP is not metabolised to an alkylating species.

4.1.2.1.2 Studies in humans

No useful information is available on the toxicokinetics of N-VP in humans.

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

No useful information is available on the toxicokinetics of N-VP in humans. In animals, the toxicokinetics of N-VP have been extensively characterised in the rat. Information is also available from the dog. N-VP is rapidly and extensively absorbed by the oral and inhalation routes and the physicochemical characteristics suggest that it will also readily cross the skin. There is evidence that oral bioavailability of parent N-VP may be reduced by hydrolysis and/or polymerisation of N-VP in the stomach. In rats the half-life of N-VP in plasma is around 3 hours, but in the dog it is only 20-40 minutes. The reason for this species difference is unclear. Metabolism studies have been performed only in the rat. In this species, N-VP is extensively metabolised to form highly polar compounds, which are rapidly eliminated, predominantly by the urinary route. However, the two major urinary metabolites of N-VP have not been characterised. Other routes of elimination include the faeces (via the bile), and CO_2 in exhaled air, accounting for around 5-8% and 3% of the dose, respectively. N-VP and its metabolites do not bind to plasma proteins or DNA to any great extent.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Inhalation

Single exposure inhalation studies have been carried out using aerosols of N-VP and using N-VP vapour. A 4-hour LC_{50} value of 3,070 $mg \cdot m^{-3}$ (3.07 $mg \cdot l^{-1}$) has been obtained from a study in which groups of 10 male and 10 female Sprague-Dawley rats were exposed head only to aerosols of around 800, 2,000, 2,800, 5,200 or 5,600 $mg \cdot m^{-3}$ N-VP (purity > 99%, stabilised with 10 ppm Kerobit, particle size not stated) (BASF, 1979b). Following exposure, rats were observed for 14 days and underwent gross necropsy at the end of the study. Deaths occurred in all but the lowest dose group within 2-4 days of exposure, and clinical signs of toxicity including increased respiration rates, ataxia, narcosis, bloodshot eyes and nasal secretions were observed in all dose groups. Necropsy revealed changes in decedents only. In the lungs, isolated areas of oedema were recorded; in the heart, acute hyperaemic obstruction and acute dilation of the fore chambers occurred; the liver had a sandy grey appearance; multiple bloody ulcerations were apparent in the stomach and blood was apparent in intestinal contents suggesting irritation of the gastrointestinal tract. There was also some discolouration of the kidneys. No details on the

severity of these changes were provided.

No deaths occurred in earlier studies in which cats, rabbits, guinea pigs, rats and mice or rats alone were exposed to for 6 or 8 hours to air saturated with N-VP vapour (BASF, 1941; 1963b; c; 1964a). Signs of toxicity during exposure were limited to salivation and nasal secretion, and at necropsy, slight irritation of the mucous membranes was occasionally observed. Based on the reported vapour pressure of 0.12 hPa, the saturated vapour concentration would be 0.6 $mg \cdot l^{-1}$ (600 $mg \cdot m^{-3}$).

A study has also been performed in which groups of 2 rats or 2 mice were exposed whole body to 0, 23, 69 or 207 $mg \cdot m^{-3}$ N-VP vapour for 6 hours on 2 consecutive days and sacrificed immediately post exposure on the second day (BASF, 1988d). No mortality occurred. Top dose animals of both species appeared to be in a poor general state with altered breathing behaviour after each exposure. Blood samples revealed clear reductions in levels of total protein (to 84% of control levels) and increases in alkaline phosphatase (to 114% of control levels) in top dose rats. Levels of glutathione were increased in liver homogenates from this group to 145% of control levels. Histopathological examinations were confined to the liver. Changes were most severe in rats. Top dose animals showed moderate generally centrilobular fatty change, centrilobular necrobiosis (degenerative change falling short of actual necrosis) and isolated necrotic cells. Changes were also evident in the nuclei of some cells consisting of isolated areas of mitosis, nuclear wall hyperchromatism, polymorphism and pale karyoplasm. Minimal centrilobular fatty change and an increased incidence of mitosis in nuclei were also observed in rats receiving 69 $mg \cdot m^{-3}$. The livers of mice exposed to 207 $mg \cdot m^{-3}$ showed a slight yellowish grey discolouration attributed to centrilobular fatty change. No signs of toxicity were visible in mice exposed to 69 $mg \cdot m^{-3}$ or either species exposed to 23 $mg \cdot m^{-3}$.

These results show that N-VP vapour can cause changes in the liver at fairly low dose levels after just two days exposure and the lack of any changes in animals surviving single high doses suggests that these changes are recoverable.

Oral

Several, mainly briefly reported studies have been carried out to characterise the effects of single oral doses of N-VP. In the rat, an LD_{50} value of between 834-1,314 mg/kg was identified in a study in which groups of 2 male and two female CFY rats were given 0, 834, 1,314 or 2,085 mg/kg N-VP (purity not stated) in aqueous solution by gavage (HRC, 1978a). Deaths occurred amongst the mid and top dose groups within 2 days of dosing and three rats in the top dose group were in a comatose condition within one hour of dosing. Signs of toxicity in all treated animals included piloerection, lethargy, decreased respiration, hunched posture, increased salivation, waddling gait and pallor shortly after dosing. At higher dose levels lachrymation, ptosis, diuresis, ataxia and loss of the righting reflex were observed. Autopsy of decedents revealed congestion and haemorrhage of the lungs and pallor of the liver, kidney and spleen. Survivors recovered within 6 days of dosing and with the exception of one low dose rat, bodyweight gains over the 14-day observation period were normal. No abnormalities were apparent in survivors at necropsy.

Other LD_{50} values obtained for the rat are 1,043, 1,022, 1,700, 2,500 mg/kg (BASF, 1953; 1955; 1963b; c). Where stated, the dosing vehicle was distilled water. Group sizes, dose levels and times of death were not stated. Signs of toxicity in decedents included staggering gait, prostration and respiratory distress. At necropsy, irritation to the mucous membranes of the stomach was seen, occasional animals had haemorrhagic enteritis and unspecified slight liver and kidney damage was also observed.

An LD_{50} of 940 mg/kg has been determined for the mouse in a study in which groups of 10 male and 10 female Swiss mice were given 420, 630, 940 or 1,400 mg/kg N-VP by gavage and followed up for 10 days (Schwach; Hofer 1978). Mortality occurred at all dose levels, all deaths occurred within three days of dosing. Signs of toxicity showing a dose-related increase in severity at all dose levels included convulsive twitching with arching of the back and ataxia immediately post dosing, evolving into continual trembling a few hours later. The extremities were pale and eyes dull with partly or completely closed lids, and the fur was dull, unkempt and ruffled around the nose. At the highest two dose levels, these signs persisted for over a week but had resolved by day three at the lower dose levels. No signs of toxicity were seen on the final day. No histopathological examinations were performed.

The effects of single oral gavage doses of N-VP (purity not stated) in aqueous solution have also been studied in guinea pigs, cats and rabbits (BASF, 1964b). One out of a group of 4 guinea pigs given 520 mg/kg, died. All animals showed a lack of appetite, apathy, slight atony and one developed enteritis after 3 days. Groups of 3 rabbits received 417 or 1,043 mg/kg. No deaths occurred. At both dose levels, slight weight loss and lack of appetite were recorded. Groups of two cats received 100, 210 or 520 mg/kg N-VP. One top dose cat died 3 days after dosing. Salivation and emesis were apparent at all dose levels, accompanied by a lack of appetite, slight weight loss and loss of balance at the top dose level, which persisted until the surviving cat was sacrificed 28 days post exposure.

Dermal

The effects of single dermal exposures to N-VP have been studied in rats, rabbits and guinea pigs. Results from a study in the rat indicated that the dermal LD_{50} value for this species lay between 1,043 and 4,127 mg/kg (HRC, 1978b). Groups of two male and two female CFY rats were given 0, 668, 1,043, 4,127 or 10,430 mg/kg N-VP over an area approximately 10% of body surface under an occlusive dressing for 24 hours. There was no evidence of irritation at the site of application. Deaths occurred in all but the low dose group within three days of dosing and non-specific signs of toxicity were seen in all rats given 1,043 mg/kg or more. Signs of toxicity in the lowest dose group were limited to slight diarrhoea in the two males. Autopsy of decedents revealed congestion of the lungs, pallor of the liver, kidneys and spleen and injection of the blood vessels into the subcutaneous tissue at the site of application. Bodyweight gains of treated rats were reduced during the first week of observation but were normal during the second week. No abnormalities were seen in survivors at necropsy.

In an early study, all three rats died after having been exposed to around 2,000 mg/animal N-VP held in contact with the skin for 4 hours by means of a special chamber (BASF, 1953). Deaths occurred within 4 hours post-exposure. Signs of toxicity included apathy, respiratory distress, prostration and "severe" skin irritation. No histopathological examinations were performed.

In a preliminary test conducted to determine an appropriate dose level for a skin sensitisation study, a volume of 0.5 ml N-VP (purity 99.7%) undiluted and as 75, 50 and 25% solutions in distilled water was held in contact with the flanks of 4 female guinea pigs under an occlusive dressing for 6 hours (BASF, 1996). The total dose these animals received is estimated to be around 3,000-5,000 mg/kg. This dose level resulted in signs of severe systemic toxicity and there were two deaths. No skin irritation was observed.

A dermal LD50 value of 560 mg/kg has been estimated from a study in which groups of 5 rabbits were given 200, 375, 800, 1,000 or 2,000 mg/kg on intact skin (FDRL, 1975). The conditions of exposure were not stated. Deaths occurred in all but the lowest dose group within 5 days of dosing and all animals in the top two groups died. No information on local skin

effects or systemic toxicity was provided.

No mortality was observed in one study in which 5 male and 5 female Viennese white rabbits were given a single 400 mg/kg dose of undiluted N-VP stabilised with 10 ppm Kerobit on the dorsal skin (BASF, 1979c). An occlusive dressing was used and remained in place for 24 hours. Animals were observed for 8 days post-exposure. The only sign of toxicity was slight apathy. No local irritation was observed and no abnormalities were apparent at necropsy.

In earlier studies cotton wool plugs soaked in N-VP were bound to the ears of rabbits. Deaths occurred in rabbits given between 1,200-3,000 mg/kg for 20 hours (BASF, 1953; 1963b; c). No systemic toxicity was apparently observed but severe skin irritation was reported in one study. Localised blistering was also apparent in a rabbit exposed to N-VP in this manner for 16 hours (BASF, 1941).

4.1.2.2.2 Studies in humans

The effects on humans of single exposures to N-VP have not been studied. A brief comment is made in an early report that inhalation by workers of an unknown concentration of N-VP vapour led to "stupefaction and fatigue" (BASF, 1941).

4.1.2.2.3 Summary of acute toxicity

There is no information available regarding direct observation of the acute toxicity of N-VP in humans following single exposure. In experimental animals a 4-hour LC_{50} value of 3,070 $mg \cdot m^{-3}$ for aerosols of N-VP has been identified in the rat. Exposure of a range of species to 0.6 $mg \cdot l^{-1}$ N-VP vapours produced some local irritation but no deaths. LD_{50} values following oral doses are around 1,000 mg/kg for the rat and mouse. A dermal LD_{50} value of 560 mg/kg has been reported for rabbits. Deaths among rats given around 1,000 mg/kg indicate that the LD_{50} value in this species may also lie below 2,000 mg/kg. Pathological changes were evident in decedents only. The liver and kidneys have been identified as target organs by all three routes of exposure and irritation of the mucous membranes lining the gastrointestinal or respiratory tracts commonly occurs following oral or inhalation exposure.

4.1.2.3 Irritation

4.1.2.3.1 Studies in animals

Skin

In a Draize test, 520 mg N-VP (purity and presence of stabilisers not stated) was applied under an occlusive dressing to the intact or abraded skin of groups of 6 New Zealand White rabbits and remained in contact with the skin for 24 hours (BASF, 1978a). Sites were graded for skin reactions 24 and 72 hours after the initial application. For intact skin, grade one erythema was observed in all rabbits at 24 hours and 5/6 rabbits at 72 hours. There was no evidence of oedema. The severity of the reaction on intact skin was below the threshold for classification as a skin irritant under the EU classification and labelling system. In abraded skin, grade 4 erythema was

observed in all cases and grade 1 oedema seen in most of the rabbits at both time points. In another similar study, N-VP again produced little irritation on intact skin (CPT, 1978)

In two other briefly reported skin irritation studies, slight or very slight erythema with or without slight oedema occurred in groups of 4 or 8 rabbits to whose backs, 1,250 or 2,500 mg/kg undiluted N-VP was applied for 1, 5 or 15 minutes or 20 hours (BASF, 1963b; c). The nature of any dressing used was not stated. It was reported that the erythema and oedema had subsided by the 24-hour observation point, but slight scaling was apparent in rabbits exposed for the full 20 hours.

No evidence of skin irritation was seen in a dermal toxicity study in which 400 mg/kg N-VP was held in contact with the dorsal skin of 10 Viennese white rabbits under an occlusive dressing for 24 hours (BASF, 1979c). Nor was there any evidence of skin irritation in a dermal toxicity study in the rat in which up to 1,043 mg/kg N-VP (purity not stated) was applied over an area approximately 10% of body surface and held in contact for 24 hours under an occlusive dressing (HRC, 1978b).

In contrast, severe skin irritation was apparent in an early dermal toxicity study in which cotton wool plugs soaked in N-VP (stated to be chemically pure and containing up to 2% acetaldehyde) were bound to the ear of 3 rabbits (BASF, 1941). Transient swellings, which bled profusely, were reported for the rabbit exposed for 4 hours. Exposures of 8 or 16 hours led to swelling and blistering. The animal exposed for 16 hours subsequently died. Skin lesions in the animal exposed for 8 hours formed crusts with egg white-like secretions, which healed after 6 weeks leaving scarring. Severe skin reactions (localised erythema developing into a brown necrosis within 1 hour of removal of N-VP from the skin) were also reported in a dermal toxicity study in the rat in which 2 ml undiluted N-VP was held in contact with the ventral skin by means of a "special chamber" for up to 4 hours (BASF, 1953). Similar reactions were observed in 2/3 rabbits to whose ears cotton wool plugs soaked in 2 ml N-VP had been attached for 20 hours (BASF, 1953). As before, localised erythema and oedema appeared which developed into a brown perforating necrosis eventually forming crusts. No skin irritation was observed in the third rabbit.

The reason why these early studies produced such effects is not clear. However, given that little or no irritation was seen in the more recently conducted conventional skin irritation and dermal toxicity studies, the results of the earlier studies are called into question. It is therefore concluded that liquid N-VP should not be regarded as a significant skin irritant.

Eye

The irritancy to the eye of liquid N-VP has been investigated in a number of studies. Most recently, a Draize test was carried out in which 0.1 ml N-VP (purity and use of stabilisers not stated) was applied to the eye of 6 New Zealand white rabbits and the eyes examined after 1, 24, 48, 72 hours and 7 days (BASF, 1978a). One hour after application, grade 1 redness and grade 1 or 2 chemosis of the conjunctiva and grade 1 iris lesions were recorded for all animals. In addition, one animal showed grade 1 corneal opacity. Using the EU classification and labelling system for scoring eye irritation, the mean scores indicated conjunctival chemosis grade 2.2, conjunctival redness grade 1.9 and grade 1 iris lesions across the 24-72 hour time points. In addition, corneal opacities of grade 1.8 were observed, which extended over an area of three-quarters to the entire cornea. The lesions of the iris and conjunctiva did not show any signs of diminishing up to day 7 and corneal opacities became worse. By day 7, grade 2 (1 rabbit) or grade 3 (5 rabbits) opacities were observed covering an area of half to the entire cornea. Discharge, grade 1 or 2, was also apparent from the eyes of all rabbits at all observation points. There was no

evidence of reversibility and in fact some indications that lesions were becoming more severe with time. It is therefore concluded that N-VP should be regarded as a severe eye irritant.

In two very briefly reported studies, "slight" to "strong" chemosis, oedema and corneal clouding leading to scarring was stated to have occurred in the eyes of rabbits for the entire 8-day observation period after application of undiluted N-VP (purity not stated) (BASF, 1963b;c). Group size and dose were not reported.

The irritancy of N-VP vapour to the eye has not been studied, although no evidence was found in repeated inhalation studies that N-VP vapour causes eye irritation. The highest dose level at which effects on the eye were specifically investigated in repeated inhalation studies was 20 ppm in rats exposed for 12 months and sacrificed immediately or after 18 months, with a 6 month recovery period (see Section 4.1.2.6.1 for details).

Respiratory tract

No studies have been undertaken specifically to investigate the sensory irritancy of N-VP to the respiratory tract. N-VP could be predicted to cause respiratory tract irritancy on the basis of increased respiration rates and nasal secretions observed in inhalation toxicity studies and the knowledge that the substance is severely irritating to the eye. Clear signs of altered breathing behaviour were apparent in rats and mice exposed to 45 ppm (207 $mg \cdot m^{-3}$) or more (see Sections 4.1.2.2.1 and 4.1.2.6.1 for details). In addition, salivation was observed in occasional dams exposed to 20 ppm in the developmental toxicity study suggesting that this concentration may be very slightly irritating (see Section 4.1.2.9.1 for details). There was no evidence of altered breathing behaviour or salivation in any study at concentrations of 15 ppm (69 $mg \cdot m^{-3}$) or less, therefore this concentration will be taken to represent a NOAEL for sensory irritation.

4.1.2.3.2 Studies in humans

An early report included brief details of a study in which a cotton wool plug soaked in N-VP was bound to the skin of 6 volunteers (BASF, 1941). After 8 hours, localised slight erythema was observed in 3/6 individuals. No signs of irritation were seen in the other 3 subjects. This was the same series of investigations in which severe skin irritation was reported for liquid N-VP in rabbits. It is noted that such effects have not been reproduced in the more modern investigations reported above. There are no human data relating to eye or respiratory tract irritancy.

4.1.2.3.3 Summary of irritation

There is no useful, reliable information available from studies in humans. In experimental animals, recent studies conducted to investigate skin irritation have shown that N-VP does not possess significant skin irritant potential. However, liquid N-VP is severely irritating to the eye. No evidence was found in repeated inhalation studies that N-VP vapour causes eye irritation, although the highest dose level at which effects on the eye were specifically investigated in repeated inhalation studies was only 20 ppm. The ability of N-VP to cause sensory irritation in the respiratory tract has not been studied. It is predicted that N-VP has the potential to cause respiratory tract irritation based on observations of increased respiration rates and nasal secretions in inhalation toxicity studies and the knowledge that N-VP is severely irritating to the eye. Based on observations from inhalation toxicity studies, the NOAEL for sensory irritation may lie around 15 ppm.

4.1.2.4 Corrosivity

No useful reliable information is available from studies in humans. In experimental animals, although severe skin reactions were observed in early dermal toxicity studies, no such reactions were seen in more recently conducted studies. It is therefore concluded that N-VP is not corrosive.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

The ability of N-VP to induce skin sensitisation has been investigated in a Buehler test conducted according to contemporary regulatory protocols (BASF, 1996). During the induction phase, 0.25 ml N-VP (purity 99.7%) was applied under an occlusive dressing to the flanks of 20 guinea pigs, and held in place for 6 hours. The treatment occurred once per week on three successive weeks. Since N-VP was applied without use of a vehicle, the control group of 10 guinea pigs remained untreated. No signs of irritation and no systemic toxicity were observed during the induction phase. Fourteen days after the final induction application, 0.25 ml N-VP was applied under an occlusive dressing to the opposite flanks of all treated and control animals for 6 hours and application sites scored 24 and 48 hours after removal of the patches. Again no skin reactions were observed, indicating that N-VP had not induced skin sensitisation. Although a concurrent positive control assay was not performed, the laboratory had obtained a positive result in a Buehler test using α-hexylcinnamaldehyde within 6 months of this test, thus validating the sensitivity of the assay protocol.

Respiratory tract

The ability of N-VP to cause respiratory tract sensitisation has not been studied in animals. However, since the substance does not cause skin sensitisation and does not bind to proteins to any great extent (see Section 4.1.2.1.1), it would not be predicted to cause respiratory tract sensitisation, at least not by an immunological mechanism.

4.1.2.5.2 Studies in humans

No investigations have been carried out to investigate whether N-VP causes skin or respiratory tract sensitisation in humans.

4.1.2.5.3 Summary of sensitisation

There is no information available from studies in humans. N-VP did not demonstrate skin sensitisation potential in guinea pigs. The ability of this substance to cause respiratory sensitisation has not been investigated. However, since the substance does not cause skin sensitisation and does not bind to proteins to any great extent it would not be predicted to cause respiratory tract sensitisation, at least not by an immunological mechanism.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Inhalation

The toxicity of N-VP by the inhalation route has been investigated in a series of detailed, well-reported studies of varying durations up to 2 years and covering a range of concentrations, between 1-120 ppm, many conducted according to GLP and following contemporary regulatory protocols. The most comprehensive studies are 7-week studies in the rat (BASF, 1988e; Klimisch et al., 1997b) and the mouse (BASF, 1988f; Klimisch et al., 1997b) and a 2-year study in the rat (BASF, 1992b; Klimisch et al., 1997a). These studies allow the essential features of N-VP toxicity to be characterised. As satellite groups were included in all of these studies to enable interim kills to be performed, a fairly detailed picture of the toxicity of N-VP in rodents on repeated inhalation exposure can be obtained from these studies alone. To avoid repetition, only notable findings from other studies have been discussed in detail. Inhalation studies were carried out with N-VP vapour and animals were exposed whole body for 6 hours per day on 5 days per week unless otherwise stated. In the following text, where findings have been reported at a number of dose levels, the incidence has been given in order of ascending concentration starting with the incidence among controls.

The toxicity of N-VP following short-term repeated exposures has been evaluated in 7-week inhalation studies in which groups of 20 male and female F344 rats (BASF, 1988e; Klimisch et al., 1997b) or C57 Black mice (BASF, 1988f; Klimisch et al., 1997b) were exposed to N-VP (purity 99.94%) stabilised with 3 ppm Kerobit at concentrations of 0, 5, 15 or 45 ppm (23, 69 or 207 $mg \cdot m^{-3}$) for up to 7 weeks. For each species, five animals of each sex per group were sacrificed after 1 week and a further 5 animals of each sex per group sacrificed after 3 weeks. Bodyweight gains were assessed after 3 and 7 weeks exposure only. Blood samples were taken from all animals immediately prior to necropsy for extensive biochemical and haematological analyses and liver homogenates were prepared for both species to determine the levels of gamma-glutamyltransferase (γ-GT) and reduced glutathione. A full necropsy was conducted on all animals. In rats, microscopic examinations were carried out on all tissues viewed as being abnormal at necropsy plus the liver and nasal cavity from all animals and the lungs, trachea, heart, spleen, kidneys, adrenals and testes from control and top dose rats. In mice, microscopic examinations encompassed tissues viewed as being abnormal at necropsy plus the nasal cavity, trachea, lungs and liver from all animals and the heart, spleen, kidneys, adrenals and testes from control and top dose mice.

In rats, no mortality occurred. Outward signs of toxicity were apparent in rats exposed to 45 ppm only. During the first week, poor general state, apathy, altered breathing behaviour and slight anaemia were seen in all animals. However, as the study progressed, many signs lessened and were no longer apparent after 2 weeks. At 45 ppm, bodyweight gains were still reduced after three weeks exposure ($p<0.01$) but had recovered by the end of the study.

Blood samples taken after 1 and 3 weeks revealed dysproteinaemia in rats exposed to 15 or 45 ppm; reductions in total proteins to around 80-90% of control levels were mainly due to reductions in globulins but albumin levels were also reduced in males. The dysproteinaemia lessened in severity with increasing duration of exposure, although slight reductions in globulin in top dose males and albumin in top dose females were still present at study termination. There were also initial increases in serum enzyme markers of liver toxicity, specifically alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and alkaline phosphatase (AP),

and serum cholesterol levels rose throughout the study. At study termination, statistically significant increases in serum cholesterol levels were observed in rats of the 15 ppm group (115% of control) and the 45 ppm group (120% of control).

Some haematological changes in rats were noted, which also became more marked with increasing duration of exposure. Statistically significant changes were seen in a number of red blood cell parameters (e.g. haemoglobin, erythrocytes and haematocrit) in both males and females from the 15 and 45 ppm groups and although most were within 20% of control levels, the pattern of change suggested that rats were developing an anaemia. Increases in platelet counts were also seen in mid dose males (109% of control) and top dose animals of both sexes (129% of control for males and 109% of control for females). Analysis of liver homogenates showed statistically significant increases in levels of γ-GT (between 160 and 1,440% of control) and glutathione (between 110 and 170% of control) occurring in both sexes of the 15 and 45 ppm groups at all time points.

In the rats at necropsy, absolute liver weights of top dose females were significantly increased (110-130% of control) at all time points and occasionally this parameter was also increased in mid dose group females. Testicular weights were not affected by treatment. Macroscopic changes were visible in the liver only (livers appeared pale, particularly in centrilobular areas, with visible lobule markings). These changes were seen in some or all rats exposed to 45 ppm at each time point. No gross abnormalities were observed in rats exposed to 15 or 5 ppm and no treatment-related gross abnormalities were identified in reproductive organs including the testes, epididymides, uterus and ovaries from rats at any dose level. Microscopic changes occurred in both the liver and the nasal cavities. In all top dose rats after one and three weeks exposure, hepatic centrilobular necrobiosis and moderate fatty infiltration was seen, accompanied in some cells by changes in the nucleus (hyperchromatism or polymorphism and isolated mitoses). Centrilobular necrobioses were also seen in occasional animals from the 15 ppm group. After 7 weeks, centrilobular hepatocytes from all top dose animals were becoming enlarged, occasional necrotic cells could be seen and foci of cells accumulating glycogen were visible within lobules. No changes were seen in livers from animals exposed to 15 ppm for 7 weeks, but centrilobular necrobiosis was present in the liver of one 5 ppm group male. In the nasal cavity, large areas of the olfactory epithelium in the nasal mucosa from all top dose animals appeared atrophied at all time points. Focal, incipient or slight atrophy of the olfactory epithelium was also present in all mid dose females after 1 week and all mid dose animals after 3 and 7 weeks. Focal atrophy of the olfactory epithelium was also present in one male from the 5 ppm group after 7 weeks (the same rat showing centrilobular necrobiosis in the liver). No treatment-related microscopic abnormalities were observed in the testes of top dose rats.

In mice, treatment-related mortality was observed in the top dose group. One male died on day 4, one female died on day 9 and two females were sacrificed in a moribund condition on day 53. Cause of death was not established. All top dose mice including decedents were seen to be in a poor general state with altered breathing behaviour during exposure. Mice of this top dose group initially lost bodyweight, but as was the case in rats, signs of toxicity lessened in severity with increasing duration of exposure. Bodyweight gains were reduced throughout the study in top dose mice such that terminal bodyweights were around 15% lower in top dose animals than controls. Bodyweight gains were occasionally reduced in males of the 15 ppm group. No outward signs of toxicity were seen in the 5 ppm group.

Biochemical and haematological changes in mice were less marked than those in rats. In mice of the 15 and 45 ppm groups, signs of dysproteinaemia were first evident after three weeks exposure but as with rats, the severity was less at study termination. The only other treatment-related changes in biochemical parameters were increases in levels of reduced glutathione in

liver homogenates from the 15 and 45 ppm groups (between 130 and 280% of control), which lessened in severity as the study progressed. Fewer red blood cell parameters were affected in mice and although changes were statistically significant, no parameter was altered by more than 10% of the control level. Platelet counts were again increased (levels were between 110 and 160% of control) in both sexes from the 15 and 45 ppm groups after 3 and 7 weeks. An increase in lymphocyte counts in top dose group mice was probably due to persistent inflammation in the nasal cavity.

At necropsy, absolute kidney weights were decreased at all time points, initially only in top dose group animals but at later time points, males from the mid dose group were also affected. However, the kidney weight changes were not accompanied by any pathological change, and hence the toxicological significance is uncertain. Absolute lung weights were increased in top dose mice (to between 140 and 200% of control) at all time points and absolute liver weights were increased by about 10% in top dose females from three weeks and males from this group at study termination. Mid dose females also showed increased liver weights at the three-week sacrifice only. Testicular weights were not determined for mice. Macroscopic examination of mice sacrificed after one week revealed the centres of liver lobules from all top dose mice to be pale and the adrenals of some mice of the 15 ppm group and all but one female of the 45 ppm group to be a reddish brown colour. These changes were not visible at later time points. No treatment-related gross abnormalities were observed in the reproductive organs including the testes, epididymides, uterus and ovaries from mice at any dose level. Microscopically, changes observed in the liver from top dose animals were very similar to those found in rats. Histopathological changes were found at all time points and there was evidence that the glycogen content in the liver of top dose animals was increasing from 3 weeks onwards. No histopathological changes were seen in livers taken from animals of the 15 and 5 ppm groups after one and three weeks but diffuse hypertrophy was apparent in the liver of one male from the 15 ppm group at study termination.

Microscopic changes were also observed in the respiratory tract of mice. In contrast to rats, at all time points, slight diffuse epithelial proliferation with isolated necrotic cells could be seen in the trachea of most top dose group animals. Minimal to very slight perivascular and peribronchial granulocytic infiltrates were found in the lungs of all top dose group females, although only at the one-week sacrifice, and the bronchial epithelium of all top dose group animals and one female of the 15 ppm dose group appeared disarranged (epithelial cells appeared to be irregularly arranged and slightly proliferated, some cells appeared flattened and the nuclei were slightly polymorphic). This disarrangement increased in severity with increasing dose and duration of exposure in all N-VP exposed females and all top dose and most mid dose males with minimal to moderate severity at study termination. In the nasal cavities, catarrhal-purulent rhinitis was observed at all dose levels and all time points. After one week, one low dose female, many mid dose animals and all top dose animals were affected. At study termination, many low dose, most mid dose and all top dose animals were affected. In addition, the nasal olfactory epithelium of mice from all dose groups appeared atrophied. After one week, focal atrophy was observed in most low dose and all mid dose mice, with extensive atrophy apparent in all top dose mice. At study termination, focal atrophy was present in one low dose female, all other animals showing extensive atrophy. Hyperplasia of the submucous glandular cells affected many low and all mid and top dose mice by the end of the study and areas of slight hyperplasia of the nasal respiratory epithelium were also present in occasional animals at all dose levels at all time points. No treatment-related microscopic findings were observed in the testes from top dose mice.

This study shows that the effects of N-VP in rats and mice are generally similar. In both species, outward signs of toxicity decreased as the study progressed, and many early biochemical

changes, particularly the dysproteinaemia, were showing signs of recovery after 7 weeks. Target tissues were clearly identified as the liver and respiratory tract epithelia; the latter appeared to be the most sensitive tissue. In the liver, signs of fatty degeneration and necrobiosis were apparent at all sacrifice times and there were suggestions that glycogen was building up in hepatocytes towards the end of the study. In mice, liver toxicity was seen only at 45 ppm and not at 15 or 5 ppm, but occasional rats exposed to 15 or 5 ppm also had signs of liver toxicity. In relation to the respiratory tract, the olfactory epithelia of both species appeared atrophied, the severity of this effect increasing with increasing dose and there was other evidence of nasal epithelial damage in mice. Inflammatory changes in the bronchial epithelium were also seen in mice, again at all three dose levels. Overall, no clear NOAEL can be identified in either species from this study.

The effects of inhaling N-VP for longer periods have been investigated in a carcinogenicity study in which groups of 100 male and 100 female Sprague-Dawley rats were exposed to concentrations of 0, 5, 10 or 20 ppm (equivalent to 23, 46 or 92 $mg \cdot m^{-3}$) (purity 99.9%, stabilised with 3 ppm Kerobit) for 2 years (BASF, 1992b; Klimisch et al., 1997a). Of these rats, a group of 20 male and 20 female rats from each dose group and 10 male and 10 female controls were sacrificed after 3 months, a further 10 male and 10 female rats from each dose group including controls were sacrificed after 12 months and a third group of 10 animals of each sex from each dose group including controls were exposed for 18 months and allowed a 6 month recovery period. The remaining 60 animals in each dose group and 70 control animals of each sex were sacrificed after 24 months exposure. Examinations of animals encompassed clinical observations, body weight determination, blood biochemistry and haematology, urinalysis, ophthalmoscopy, gross pathology, organ weights (liver, kidneys, adrenals, lungs, brain and testes) and histopathology of the liver, nasal cavities, larynx, trachea, lungs and pancreas from all animals and a range of other organs including the testes, prostate glands, seminal vesicles and epididymides or uterus and ovaries from controls and top dose animals. Not all investigations were performed at each sacrifice time.

No treatment-related mortality occurred and generally at least half of the animals from each dose group survived until their scheduled sacrifice. Slight dose-related reductions in bodyweight gain were apparent in treated animals during the first few weeks of exposure, although by 3 months, bodyweights of treated animals were generally within 10% of those of controls. The difference in bodyweights between treated animals and controls was related to dose. No other outward signs of toxicity were observed and no treatment-related lesions were identified by ophthalmoscopy.

Biochemical analyses revealed the presence of slight dysproteinaemia in both sexes at all dose levels after 3 months exposure; changes were more pronounced in females, although no parameter was more than 15% below control levels. A slight dysproteinaemia was still evident in females of the 10 and 20 ppm groups after 12 months. The only other biochemical changes were seen in females and consisted of a slight increase in serum cholesterol levels in top dose females after 12 months. Statistically significant reductions in serum ALAT in females at the 3 and 12-month time points were also reported, although the severity was not related to dose. Usually serum ALAT levels increase in response to liver toxicity, therefore the biological significance of this change is unclear. Blood biochemistry tests were not performed on animals from the remaining dose groups. Analysis of liver homogenates revealed increased levels of reduced glutathione (to around 150% of control) in both sexes at 20 ppm and males of the 10 ppm group after 3 months and 12 months and males at 5 ppm after 12 months. Levels of γ-GT were also markedly increased (to around 300% of control levels), initially in females at 20 ppm only but the finding was also present in males of the 20 ppm group after 12 months. Liver homogenates were not prepared from rats at 24 months. Interestingly, levels of γ-GT were still markedly increased in mid and top dose males (to 330-530% of control levels) 6 months after the end of an 18-month

exposure period. Slight but non-statistically significant increases were also seen in females.

Haematological changes after 3 months were limited to increased platelet counts in both sexes of the 10 and 20 ppm groups and a slight reduction in MCH in males of the 10 and 20 ppm groups, although several red blood cell parameters were affected in top dose females after 12 months, including an increase in anisocytosis and microcytosis, suggesting the presence of slight anaemia. Dose-related increases in anisocytosis, microcytosis and macrocytosis were also evident in females from all dose levels after exposure to N-VP for 24 months. An increase in white blood cell count in females exposed to 20 ppm N-VP for 12 months was accounted for by slight increases in numbers of leucocytes, lymphocytes, monocytes and neutrophilic polymorphonuclear granulocytes and was probably indicative of a persistent inflammatory process. No haematological changes were seen in males. Urinalysis was performed on rats after 3, 6 and 12 months exposure; no changes were observed.

At necropsy, absolute and relative liver weights were increased in both sexes of the 20 ppm group and males of the 10 ppm group after 3 months, with females of the mid dose group and males of the low dose group also affected after 12 months. However, by study termination liver weights in all but the top dose group were similar to control weights. No treatment-related changes were observed in testicular weights at any time point. Macroscopic examinations revealed the presence of dark coloured foci in the liver in occasional animals at all time points and although some foci were present in the livers of control animals these occurred more frequently in the livers of treated animals. No treatment-related macroscopic changes were observed in reproductive organs.

Microscopic changes were found only in the liver, nasal cavities and larynx. No treatment-related microscopic abnormalities were observed in reproductive organs. Neoplastic changes in these organs are discussed in more detail in Section 4.1.2.8.1.

Examinations of the liver at 3 and 12 months revealed the presence of areas of enlarged hepatocytes containing clear cell areas (cytoplasm clear of stainable material) whose size ranged between 3-4 cells to entire lobules and which were located randomly throughout the liver. The nuclei of some cells within these areas showed early degenerative changes. No mitotic figures were observed. The finding occurred in both treated and control animals. After 3 months, 6, 3, 10 and 20 males and 0, 0, 3 and 17 females were affected and the frequency of these findings was clearly related to dose. After 12 months, clear cell areas occurred in 9, 10, 10 and 10 males and 1, 7, 9 and 10 females and again the frequency in individual rats was related to dose. In addition, after 12 months, focal hyperplasia was present in the livers of occasional animals including one control male; some cells within these areas of hyperplasia contained mitotic figures and normal liver cells around these areas appeared compressed. A degenerative change termed "spongiosis hepatis" (described as the presence of cyst-like complexes filled with granular material) was also observed in 2, 6, 4 and 10 males and 0, 0, 1 and 2 females. After 24 months, microscopic examinations revealed the discoloured foci to consist mainly of areas of focal hepatocyte hyperplasia (affecting 3, 8, 14 and 21 males and 5, 15, 20 and 28 females), eosinophilic foci (affecting 3, 5, 10 and 17 males and 1, 6, 13 and 22 females) and foci of spongiosis hepatis (affecting 37, 36, 45 and 55 males and 7, 19, 28 and 42 females).

There were suggestions that some treatment-related changes in the liver persisted after exposure had stopped. In rats exposed to N-VP for 18 months and allowed a 6-month recovery period, focal hyperplasia occurred more often in top dose females and foci of eosinophilic cellular alteration occurred at all dose levels in treated animals, but not in controls, without any clear dose-relationship.

In the nasal cavity, changes related to treatment at all time points included focal atrophy of the olfactory epithelium, located mainly in the region between the septum and nasoturbinates; focal hyperplasia of the basal cells underlying the olfactory epithelium within the nasal cavity; focal hyperplasia of basal cells underlying the respiratory epithelium within the anterior part of the nasal cavity and mucopurulent inflammation. Changes were of minimal to moderate severity and the incidence and severity was clearly related to both dose and duration of exposure. All findings were observed in some animals from each dose level. Focal hyperplasia of the olfactory epithelium affected all top dose animals after 3 and 12 months and focal atrophy of the olfactory epithelium affected all top dose animals after 12 months. No control animals were affected by changes of any kind in the nasal cavity at 3 months, although very occasionally some of the above findings also occurred in control rats at later time points. In addition, after exposure for 12 months or longer, focal metaplasia of respiratory epithelium into squamous epithelium could be seen in the septum and lateral wall of the nasal cavity from occasional animals, and minimal to marked focal hyperplasia of the submucosal glands occurred. In animals exposed to N-VP for 24 months, minimal to slight hyperplasia of goblet cells in the nasal epithelium was found in a few animals from each dose group, including the controls, but with dose-related incidence.

All of these findings were still present in some rats from each dose group 6 months after the end of an 18-month exposure and areas of focal metaplasia could also be found in the lateral wall of the nasal cavity in a few treated females. Although the incidence and severity of most lesions in animals of the 5 ppm recovery group was only slightly greater than that seen in controls, these results indicate that changes in the nasal cavity induced by exposure to N-VP at concentrations of 5 ppm and above persisted for 6 months post exposure.

In the larynx, changes were evident only in animals exposed for 24 months. Minimal to moderate focal epithelial hyperplasia was found in 3 males of the 10 ppm group and 6 males and 4 females of the 20 ppm group and focal mucopurulent inflammation was also apparent in occasional animals although the incidence was clearly related to dose in females only. No treatment-related changes were seen in any other tissues at any time point.

Overall, therefore, the results of this study confirm that the key non-neoplastic effects of exposure to N-VP vapour are hepatotoxicity and upper respiratory tract irritancy. Changes occurred at dose levels down to 5 ppm, the lowest exposure level tested, and there was evidence that some of the changes in the liver and nasal cavities persisted for at least 6 months after cessation of exposure.

A series of three brief investigations have been carried out in male F344 rats (BASF, 1988c; Klimisch et al., 1997b) and female C57 Black mice (BASF, 1988d; Klimisch et al., 1997b) using N-VP (99.94% purity), stabilised with 3 ppm Kerobit. Groups of 2 or 5 rats or mice were exposed to 0, 5, 15 or 45 ppm (0, 23, 69 or 207 $mg \cdot m^{-3}$) for 2 or 5 consecutive days. A sub-group received an additional 5-day exposure to 45 ppm. Signs of toxicity at 15 or 45 ppm were similar to those described previously and were apparent after just 2 days. No signs of toxicity were observed in either species exposed to 5 ppm but histopathological examinations were confined to the liver.

A wider range of concentrations was investigated in a standard 3-month study in the rat (BASF, 1986a; Klimisch et al., 1997b). Groups of 10 male and female Sprague-Dawley rats were exposed to 0, 5, 15, 45 and 120 ppm (0, 23, 69, 207 or 553 $mg \cdot m^{-3}$) unstabilised N-VP vapour (purity >99%). At the highest exposure level, most animals died during the first few days of the study. Clinical signs of toxicity prior to death included apathy, atonia, ptosis, dyspnoea and haematuria. Histopathological findings at this exposure level included stomach mucosal ulceration, centrilobular hepatocyte hypertrophy and inflammation and necrosis of the respiratory tract epithelium. Treatment-related findings at 5, 15 and 45 ppm were consistent

with those of the studies described above. Reproductive organs (testes, ovaries, uterus) were examined microscopically from all animals inhaling 0, 45 or 120 ppm N-VP. No treatment-related findings were observed. Use of electrophoreses to separate the plasma protein fractions indicated that the dysproteinaemia was due to a specific effect on α1-globulin. There was evidence that glycogen was accumulating within the foci of cellular alteration occurring in the liver.

In order to determine a NOAEL, a follow up study was conducted in which groups of 10 male and 10 female Sprague-Dawley rats were exposed to 0 or 1 ppm (0 or 4.61 $mg \cdot m^{-3}$) N-VP (purity 99.7-99.9%) for 3 months (BASF, 1986b; Klimisch et al., 1997b). Histopathological examinations were limited to the liver and nasal cavities since these had been shown to be the target tissues. No treatment-related changes were seen, therefore 1 ppm could be regarded as a NOAEL for this species. However, it is not clear if this NOAEL is applicable to longer durations of exposure. Although exposure to 5 ppm for 3 months caused clear adverse changes in the nasal cavity, no histopathological changes were found in the livers of rats exposed to 5 ppm N-VP for 3 months. Apart from the nasal cavity damage the only other finding in rats exposed to 5 ppm for 3 months was slight dysproteinaemia. In contrast, adverse changes in both the liver and nasal cavity were clearly present in rats exposed to 5 ppm N-VP for 12 months or longer. Given that hepatotoxicity takes longer than 3 months to clearly manifest itself at 5 ppm, it is not clear whether or not hepatotoxicity could eventually occur in rats exposed to 1 ppm. On this basis, it is considered that the NOAEL of 1 ppm observed in a 3-month study may not apply to exposures of longer duration. Hence the NOAEL of 1 ppm will not be carried forward to the risk characterisation and instead a LOAEL of 5 ppm will be used.

A further 3-month study was conducted to investigate the progression of N-VP induced liver lesions in more detail (BASF, 1987c; Klimisch et al., 1997a). Groups of 40 female Sprague-Dawley rats were exposed to 0 or 45 ppm (0 or 207 $mg \cdot m^{-3}$) unstabilised N-VP (purity 99.7-99.9%) for up to three months. Animals were sacrificed after 7 weeks or 3 months exposure and after post-exposure recovery periods of 9 or 21 months. Results in animals sacrificed after 7 weeks or 3 months were comparable to those previously observed. Treatment-related changes were also evident in animals from both recovery groups. Biochemical tests revealed that levels of γ-GT and reduced glutathione in liver homogenates remained above control levels. Hepatocytes of treated animals appeared to be enlarged and areas of enlarged hepatocytes were spread fairly uniformly throughout the liver. Foci of cellular proliferation were apparent and glycogen was clearly accumulating within these foci. Some cells contained large nuclei. In addition, foci of cirrhosis-like metaplasia were observed in rats allowed a 21-month recovery period and neoplastic changes were present (see Section 4.1.2.8.1 for details). These results suggest that N-VP can induce adverse changes in the liver, which persist for long periods of time after cessation of exposure.

Limited 6-month studies have been conducted in rats and mice exposed to 0 or 10 ppm N-VP (0 or 46 $mg \cdot m^{-3}$) (purity > 99.9%) stabilised with 3 ppm Kerobit (BASF, 1988g, h; Klimisch et al., 1997b). However, the findings do not add to those described above.

A 3-month study was also set up to investigate the effects of N-VP in the liver of Syrian golden hamsters exposed to 0 or 45 ppm (0 or 207 $mg \cdot m^{-3}$) unstabilised N-VP (purity 99.7-99.9%) (BASF, 1987d; Klimisch et al., 1997b). Pathological examinations were confined to the liver. Although hamsters exposed to N-VP initially lost weight and bodyweight gains were reduced throughout the exposure period ($p < 0.01$), signs of toxicity consisting of salivation, watery nasal discharge, unsteady and high-legged gait, apathy, wet noses and ruffled fur were observed during exposure on the first day only. By the second day, only slight eye irritation was apparent (eyes-half closed). Thereafter no signs of toxicity were observed and no degenerative changes or

cellular alteration of the type previously observed in rats and mice were apparent. The results of this study show that hamsters are clearly different to rats and mice in the way in which they respond to N-VP but the reason for this species difference is unclear.

Two early inhalation studies are also available (BASF, 1964a; 1941). In each case, cats, rabbits, guinea pigs, rats and in one study mice were simultaneously exposed to N-VP vapour at concentrations apparently ranging from 500 to 2,200 $mg \cdot m^{-3}$. Given that a large volume of data obtained from well conducted inhalation studies is available, the results of these studies are not considered to add anything useful for the purposes of risk assessment.

One study has been conducted to investigate the toxicity of aerosols (generated by atomisation, particle size not stated) of N-VP (purity not stated) (FDRL, 1976). Groups of 15 male and female FDRL Wistar rats were whole body exposed to 0 or 75 $mg \cdot m^{-3}$ N-VP in water or 300 $mg \cdot m^{-3}$ undiluted N-VP for 4 hours per day, 5 days per week for 4 weeks. Rats were checked daily for any outward signs of toxicity. Immediately before and at the end of the study, ophthalmoscopic examinations were performed and blood and urine samples were collected for haematology and urinalysis. Extensive examinations were performed at necropsy including reproductive organs.

No treatment related mortality occurred. No outward signs of toxicity were observed and no changes were detected from the haematological examinations, ophthalmoscopy and urinalysis. No gross abnormalities were seen at necropsy. However, microscopic changes were seen in the lungs and mucosal tissues of the nasal cavity and trachea. In the lungs, peribronchial lymphoid hyperplasia was seen more frequently in treated males of both dose levels than controls although the severity of the finding in individual animals was not dose-related. "Sub-acute or chronic" interstitial inflammation occurred more frequently in top dose females and the severity of the finding was greater among females of both dose groups than in controls. In addition, a leukocytic exudate was observed on the mucosal surfaces around the turbinates within the nasal cavity and increased numbers of leukocytes were seen within the mucosa with dose-related severity, indicating an inflammatory process. The lack of any change in the liver is noteworthy since exposure to vapours at concentrations around 200 $mg \cdot m^{-3}$ for an equivalent time period resulted in significant liver damage. This may be related to an intrinsic difference in the way vapours and aerosols are handled in the respiratory tract. No adverse treatment-related findings were observed in the reproductive organs including the testes, epididymides, ovaries and uterus.

In conclusion, the effects of repeated inhalation of N-VP vapour have been extensively studied. A level of 120 ppm was lethal to rats within 1 week. Deaths of mice exposed to 45 ppm N-VP also appeared to be treatment-related. In rats and mice, inhalation of N-VP resulted in cytotoxic damage to the liver and upper respiratory tract irritation at exposure levels down to 5 ppm and there was evidence that some of the changes in these tissues persisted for long periods after cessation of exposure. A NOAEL of 1 ppm for changes in the liver and nasal cavity was identified in a 3-month study in the rat, but it is not clear if this concentration would also be a NOAEL in a longer-term study. In contrast to the findings in rats and mice, very few signs of toxicity were seen in hamsters exposed to 45 ppm N-VP for 3 months. The reason for this species difference is unclear. One study has been conducted to investigate the effects of exposure to N-VP aerosols. Signs of irritation were observed in the nasal cavity and trachea, but on a mass concentration basis, N-VP aerosols appeared to be less toxic to the liver. This may be due to an intrinsic difference in the way that vapours and aerosols are handled in the lungs.

Oral

The repeated dose toxicity of N-VP by the oral route has been assessed in studies in which N-VP was administered by gavage or in drinking water. Again, many studies were conducted according to contemporary regulatory protocols, though not all studies were conducted to GLP standards.

N-VP (purity > 96.5%) in water was administered by gavage to groups of 5 male and 5 female Wistar rats at dose levels of 0, 40, 60 or 100 mg/kg on 5 days per week for 3 months (BASF, 1986c; Klimisch et al., 1997b). Blood samples were taken immediately prior to necropsy. Comprehensive biochemical and haematological investigations were carried out and protein fractions were separated by electrophoresis to determine levels of albumin, $\alpha 1$, $\alpha 2$, β and γ globulins. At necropsy, in addition to gross examinations, the livers were examined microscopically. Specific staining for glycogen and γ-GT were carried out.

Food consumption was slightly reduced in male rats given 100 mg/kg. In contrast, water consumption was increased in dose-dependent fashion in all treated animals, with females in the 100 mg/kg group consuming up to 60% more water than controls over the study period. No significant changes in body weight gain were recorded. No clinical signs of toxicity were seen. The only biochemical change considered to be treatment-related was an increase in γ-GT activity in liver homogenates prepared from females at all dose levels. This enzyme was also raised in liver homogenates taken from males but the changes were not statistically significant. Platelet counts were statistically significantly increased in both sexes given 60 mg/kg or more. No other haematological changes were detected and at necropsy, no gross changes were seen. Liver weights were slightly increased in females from all dose groups and males given 60 or 100 mg/kg (weights were between 110 and 120% of control weights). No microscopic changes were found. In the 100 mg/kg dose group, foci of cellular alterations morphologically similar to those described in animals inhaling N-VP were found in liver parenchyma of 4/5 females and 1/5 males. However, the foci were small in number and size, and none stained positive for glycogen or γ-GT.

These results indicate that the effects of N-VP are much less severe following gavage dosing than via inhalation. Even in rats receiving 100 mg/kg/day, no evidence of dysproteinaemia was found and only minor microscopic changes were observed in the liver. Based on an average body weight of 300 g for rats in this study, and a respiratory volume of 6 $l \cdot hr^{-1}$ for the rat (Gold et al., 1984), assuming 100% absorption, an oral dose of 100 mg/kg would be equivalent to an inhaled dose of around 800 $mg \cdot m^{-3}$. Inhalation of around 550 $mg \cdot m^{-3}$ N-VP vapour was very rapidly lethal (BASF, 1986a). Hydrolysis and/or polymerisation in the acidic environment of the stomach of a substantial portion of an oral dose prior to uptake is one probable reason for this difference.

A study has also been conducted in which groups of 10 male and 10 female Wistar rats received N-VP (purity > 99.48%) in drinking water for 3 months at concentrations of 0, 5, 12, 30 or 75 ppm, corresponding to initial dose levels of 0.5, 1.3, 3.6 and 8.3 mg/kg/day (BASF, 1986d; Klimisch et al., 1997b). By the end of the study the actual dose to males in mg/kg/day was approximately half that at the beginning of the study and the dose to females was approximately 2/3 of the dose received at the start of the study. The stability of N-VP in the drinking water had been established over a period of 4 days, therefore drinking water solutions were prepared twice weekly. Blood samples were taken after approximately 6 and 12 weeks and a comprehensive range of biochemical and haematological investigations carried out. The eyes were examined ophthalmoscopically before treatment began and at the end of the study. At study termination, gross examinations and extensive microscopic examinations of a variety of tissues were carried out, which included the reproductive organs of the control and top dose animals.

Results indicated that at the top dose only, slight reductions in water consumption occurred (around 90-95% of that in controls). No other clinical signs of toxicity were observed and no abnormalities were detected in ophthalmoscopic investigations. Biochemical changes were consistent with those observed in inhalation studies and were limited to signs of dysproteinaemia in top dose animals only. At 6 weeks, total proteins were reduced in females and globulins were reduced in both sexes. At the end of the study, total proteins and globulins were reduced in both sexes, and albumin in females. No other biochemical or haematological parameters were altered and no changes in the level of γ-GT in liver homogenates were found. It is noteworthy that there was no evidence of dysproteinaemia in rats given up to 100 mg/kg/day by gavage. The reasons for this difference are unclear but it may point to a difference between gavage dosing and the more gradual ingestion that occurs with drinking water administration. The only finding related to treatment at necropsy was a slight increase in kidney weights in males from the 30 and 75 ppm groups (weights in the top dose group were 12% greater than control) with no accompanying pathological changes. No signs of toxicity were seen at 5 or 12 ppm. No adverse treatment-related effects were observed in the testes, prostate glands, epididymides and seminal vesicles or ovaries and uterus from top dose animals. Given that the only treatment-related finding in the 30 ppm (3.6 mg/kg/day) group was a slight increase in kidney weights in males, this dose level is considered to be the NOAEL for this study.

Pilot studies were conducted in which N-VP (purity > 96.5%) was administered in the drinking water to groups of 5 male and 5 female Wistar rats at concentrations of 0, 50, 100 or 200, 400, 700, 1,600 or 6,400 ppm for 21 or 28 days (BASF, 1986c; Klimisch et al., 1997b). However, the actual doses animals ingested were around 5, 10, 20, 25, 30, 25 and 40 mg/kg/day owing to the unpalatability of N-VP at higher concentrations. Concentrations of 700 ppm or more resulted in severely restricted food and water consumption and deaths occurred. At lower concentrations, food and water consumption were not significantly affected and signs of toxicity were limited to slight reductions in bodyweight gain in females given 50 ppm or more and evidence of dysproteinaemia in females given 100 ppm or more and males given 200 ppm or more. At necropsy, three top dose males were found to have gastritis, which was of erosive-ulcerative nature in two males. Two females from the 700 ppm group had slight yellow brown discolouration of the liver parenchyma, assumed to be fatty infiltration, although these lesions were not examined microscopically. Treatment-related abnormalities were not observed at lower dose levels. Microscopic investigations were performed.

One other early gavage study was also available in which groups of three rabbits, two cats and four guinea pigs were used (BASF, 1964b). Control groups were not used. The results of this study are not considered to add anything useful.

Overall therefore, the key effect of exposure to N-VP in the drinking water of rats seems to be an inhibition of food and water consumption, possibly due to unpalatability. Although signs of dysproteinaemia are present in rats at relatively low dose levels, around 8 mg/kg/day, no other biochemical or haematological parameters were altered, and degenerative changes were not observed in the liver.

In conclusion, administration of N-VP by the oral route results in damage to the liver, although the dose required to produce histopathological change is much greater than that required by inhalation. A NOAEL of 3.6 mg/kg has been identified in a drinking water study, but oral gavage doses of 60 mg/kg/day or below produced no significant liver changes and only slight changes in a few biochemical and haematological parameters.

Dermal

No studies of repeated dose toxicity have been carried out by the dermal route.

4.1.2.6.2 Studies in humans

Only one study has been conducted to examine the health of N-VP production workers, a cross-sectional morbidity study (Zober et al., 1992). The study included comprehensive medical examinations of the majority of the workforce and no signs of ill health related to N-VP exposure were identified. However, the actual levels of N-VP to which the workforce was exposed are unclear. It is stated that workers were provided with air fed respirators during operations likely to involve exposure to N-VP. Furthermore it is not clear which of the hygiene data provided in this report were obtained from static and which from personal monitoring techniques (see Section 4.1.1.1.2). Given the uncertainty about the actual levels of N-VP that these workers might have inhaled, the results of this study are considered to add nothing useful for the purposes of risk assessment.

4.1.2.6.3 Summary of repeated dose toxicity

There is little useful information available on the effects of repeated exposure to N-VP in humans. However, extensive studies have been conducted in rodents. Repeated inhalation of N-VP by rats and mice resulted in dysproteinaemia, haematological changes suggestive of anaemia and pathological changes in the liver, nasal cavity and larynx. In the liver, centrilobular necrobiosis and fatty infiltration accompanied by degenerative changes in the nucleus occurred and there was evidence of an accumulation of glycogen within centrilobular hepatocytes. In the nasal cavity, N-VP caused inflammatory changes in the olfactory and respiratory epithelia. Inflammatory changes were also observed in the larynx after prolonged exposure. A NOAEL of 1 ppm (4.61 $mg \cdot m^{-3}$) has been identified in a 3-month study in the rat. Signs of toxicity in rats inhaling 5 ppm (23 $mg \cdot m^{-3}$) N-VP vapour for 3 months included clear evidence of nasal cavity irritation and slight dysproteinaemia. Although no histopathological changes were found in the livers of rats exposed to 5 ppm N-VP for 3 months, liver toxicity became more marked when rats inhaled 5 ppm for longer durations. This suggests that NOAELs derived from 3-month studies might not apply to studies of longer duration and the lifetime exposure NOAEL might be below 1 ppm for rats and mice. Hence this NOAEL of 1 ppm will not be carried forward to the risk characterisation and instead a LOAEL of 5 ppm will be used. Inhalation of concentrations of 15 ppm (69 $mg \cdot m^{-3}$) N-VP vapour or more resulted in liver toxicity and nasal cavity irritation within 1 week and mortality occurred at concentrations of 45 ppm (207 $mg \cdot m^{-3}$) in mice and 120 ppm (553 $mg \cdot m^{-3}$) in rats.

In contrast, when N-VP is given by gavage to rats, the dose levels required to induce histopathological changes in the liver are considerably greater than those required by inhalation; the respiratory tract is not a target tissue with oral dosing. One explanation for the much lower toxicity of N-VP by the oral route is that the substance undergoes hydrolysis in the acidic environment of the stomach prior to absorption. A NOAEL of 3.6 mg/kg/day has been identified in a drinking water study. However, gavage doses of up to 60 mg/kg/day produced no clear pathological changes in the liver and only slight changes in a few biochemical and haematological parameters. There are no data relating to the effects of repeated dermal exposure to N-VP.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies *in vitro*

Bacterial systems

N-VP has been extensively tested in bacterial systems. Tests using the overlay method have been conducted in which *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 were exposed to N-VP (purity not stated) in dimethylsulfoxide at concentrations of 3.1-10,000 µg/plate in the presence and absence of Aroclor induced rat liver S9 (HRC, 1978c; BASF, 1978b). In addition, further cultures of TA 98 were exposed to N-VP in the presence of S9 to which the epoxide hydrolase inhibitor and glutathione depletor 1,1,1-trichloropropene-2,3-oxide had been added. Negative results were obtained in both cases. Both positive and negative control plates were prepared for each treatment and responded as expected. Cytotoxicity was not observed across the dose range.

An Ames test using N-VP (> 98% pure) has also been conducted in the presence and absence of exogenous metabolic activation using *Salmonella typhimurium* strains TA 1535, TA 98 and TA 100 under closed system conditions (Simmon and Baden 1980). In this instance the metabolic activation system was a liver S9 fraction prepared from rats induced with mixture of PCBs including Aroclor 1,254. Plates were exposed to concentrations of 0, 52, 104, 520 or 1,043 mg/dessicator for 7 hours and were then incubated for a further 40-50 hours prior to counting colonies. Positive and negative control plates responded as expected. Negative results were obtained for N-VP. Cytotoxicity was not observed.

N-VP was also reportedly non-mutagenic in an Ames test using *Salmonella typhimurium* strains TA 98 and TA 100 (Knaap et al., 1985). Very few experimental details were given, although it was stated that tests were carried out in a closed system both in the presence and absence of S9 and that N-VP had been tested up to toxic concentrations.

In another briefly reported study, negative results were obtained in a fluctuation test in *Klebsiella pneumoniae* (Knaap et al., 1985). Testing was carried out in a closed system up to toxic concentrations. No further details were reported.

Mammalian cells

Extensive testing has also been carried out in mammalian cell systems. The genotoxic potential of N-VP (purity 99.7%) in distilled water has been evaluated in an *in vitro* cytogenetics study conducted according to contemporary regulatory protocols (BASF, 1987e). In this test, duplicate cultures of human lymphocytes (number of donors not stated) were incubated with dose levels of 20, 40 or 60 µg N-VP/ml in the absence of exogenous metabolic activation and 300, 600 or 900 µg N-VP/ml in the presence of Aroclor induced rat liver S9. The dose levels were selected on the basis of cytotoxicity seen in a preliminary study. Positive, negative and solvent control cultures were also prepared. In the presence of S9, cultures were exposed for 2 hours and fixed 24 hours after the start of exposure. In the absence of S9 cells were exposed for 24 hours and then fixed. No change in the mitotic index was seen in any culture. Exposure to N-VP did not result in an increase in chromosome aberrations. Positive and negative controls gave appropriate responses.

Negative results were also obtained in a gene mutation test in mouse lymphoma L5178Y (TK+/-) cells (Litton Bionetics, 1980a). In this test, cells were exposed to N-VP (purity not stated) for

4 hours at concentrations of 0.39 to 10 µl/ml in the presence or absence of Aroclor 1,254 induced rat liver S9. Cells were then allowed a two to three day expression period and a further 10-day period for colony formation. Severe cytotoxicity was apparent at concentrations of 7.5 µl/ml and greater and moderate cytotoxicity at a concentration of 5 µl/ml for both treatments. Positive and negative control cultures were prepared and gave expected responses.

In a very briefly reported study, the mutagenicity of N-VP in L5178Y mouse lymphoma cells was examined at both the HPRT and TK loci, both in the presence and absence of S9 (Knaap et al., 1985). Testing was carried out in a closed system up to toxic concentrations. Negative results were obtained. No further details were given.

An *in vitro* UDS test in rat hepatocytes was also negative (Litton Bionetics 1980b). In this test, triplicate cultures were exposed for 1 hour to concentrations of N-VP (purity not stated) ranging from 0.3-20 µl/ml followed by a three-hour labelling period. Additional cultures were established to determine 2- and 24-hour viable cell counts. No increase in UDS activity occurred in cells treated with N-VP. Cell counts indicated that a concentration of 18.2 µl/ml was completely lethal. In the two hour cell counts, survival rates across the concentration range 0.3-9.09 µl/ml decreased from 100 to 25%, although further slight reductions in survival rates to 84.5 and 6.2% were noted across this concentration range in the 24 hour viable cell counts. Positive and negative controls gave expected responses.

The ability of N-VP to induce SCEs has also been assessed using both whole blood and isolated human lymphocyte cultures as part of an investigation into the ability of erythrocytes to metabolically activate substances to genotoxicants (Norppa; Tursi 1984). It was stated that slight increases in SCEs were observed in both systems. However, no details of the test method and no actual data were reported. Given the overwhelmingly negative genotoxicity picture for N-VP, no significance should be accorded to the apparent slight increase in SCEs claimed in this poorly reported study.

4.1.2.7.2 Studies in *Drosophila melanogaster*

Negative results were apparently obtained from a sex-linked recessive lethal test in *Drosophila melanogaster* (Knaap et al., 1985). It was stated that N-VP was administered by injection up to toxic concentrations. No further details were reported.

4.1.2.7.3 *In vivo* tests in mammalian systems

Only one standard genotoxicity test, a micronucleus test carried out according to contemporary regulatory guidelines, has been performed to investigate the potential genotoxicity in N-VP *in vivo* (BASF, 1993). Groups of 5 male and 5 female NMRI mice received single gavage doses of 0, 150, 300 or 600 mg/kg N-VP (purity 99.8%) in distilled water. Mice receiving 600 mg/kg were sacrificed after 16, 24 or 48 hours. Lower dose groups and positive and negative control groups were sacrificed after 24 hours only.

There were clear signs of toxicity in all N-VP treated animals, including irregular respiration, piloerection and a squatting posture. In addition, the animals of the top dose group were in a generally poor state of health. The P:N ratio remained unchanged. No increase in micronuclei was seen in any N-VP treated animal. Positive and negative controls gave expected responses.

An *in vivo* DNA binding study has also been conducted in the rat (see Section 4.1.2.1.1). IRI (1985) found no evidence that N-VP or its metabolites bound to rat liver proteins, DNA or RNA in a study in which groups of 3 male rats received radiolabelled N-VP intraperitoneally. The liver is a target tissue for N-VP induced carcinogenicity.

4.1.2.7.4 Studies in humans

No studies have been conducted to assess the genotoxicity of N-VP in humans directly.

4.1.2.7.5 Summary of mutagenicity

N-VP has yielded consistently negative results in genotoxicity tests in a wide variety of *in vitro* systems, and one well conducted *in vivo* test. On this basis, it can be concluded that N-VP is not a genotoxicant.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

The carcinogenic potential of N-VP has been investigated in the Sprague-Dawley rat in a 2-year bioassay conducted according to contemporary regulatory protocols (BASF, 1992b; Klimisch et al., 1997a). Groups of 100 male and 100 female Sprague-Dawley rats were exposed whole body to concentrations of 0, 5, 10 and 20 ppm (23, 46 or 92 $mg \cdot m^{-3}$) N-VP vapour (purity 99.9%, stabilised with 3 ppm Kerobit) for 2 years. Of these rats, a group of 20 male and 20 female rats from each dose group and 10 male and 10 female controls were sacrificed after 3 months, a further 10 male and 10 female rats from each dose group including controls were sacrificed after 12 months and a third group of 10 animals of each sex from each dose group including controls were exposed for 18 months and allowed a 6 month recovery period. The remaining 60 animals in each dose group and 70 control animals of each sex were sacrificed after 24 months exposure. The methods and non-neoplastic findings from this study have been reported in detail in Section 4.1.2.6.1.

No treatment-related mortality occurred. Neoplastic changes first became evident after 12 months. No animals in this group died prematurely. Although no macroscopic changes could be detected at this time, microscopic examinations revealed the presence of a hepatocellular adenoma in one top dose male and adenomas of the nasal cavity in one low dose male and one male and female from the top dose group. These adenomas arose from the respiratory epithelium or from the submucosal glands in the anterior part of the nasal cavity. Metaplasia of respiratory epithelium into squamous epithelium was also seen at this time in rats from the top dose group (see Section 4.1.2.6.1).

In rats exposed for 18 months and allowed a 6 month recovery period, 7, 5, 4 and 6 males and 2, 5, 3 and 6 females survived until their scheduled sacrifice time. Masses could be discerned macroscopically in the liver of 2 low dose males and one male and two females from the high dose group. Microscopically, hepatocellular carcinomas were found in 1, 2, 0 and 1 male and 0, 0, 0 and 2 females and in the nasal cavity, adenomas were seen in one mid dose group male and 2 males and 2 females from the high dose group. Findings occurred both in animals surviving until

study termination and in those dying prematurely.

A total of 39, 38, 30 and 34 males and 29, 25, 26 and 26 females survived until the end of the study. In rats exposed to N-VP for 24 months, the incidence of macroscopically detectable masses in the liver was clearly dose-related. In males, masses could be seen in 1, 3, 4 and 15 animals and in females, masses were visible in 2, 4, 5 and 25 animals. Masses were also evident in the nasal cavities of 1 male in the 10 ppm group and 2 males and 2 females in the 20 ppm group. Most macroscopically visible masses in the liver were identified microscopically as hepatocellular carcinomas. In males the incidence of microscopically detectable hepatocellular carcinoma was 1, 6, 5 and 17 and in females 1, 3, 6 and 26.

Nasal cavity adenomas and adenocarcinomas were found in N-VP treated animals only and the incidence was clearly dose-related. Most adenomas were located in the anterior part of the nose and appeared to have arisen from the respiratory epithelium or from the submucosal glands in areas lined by respiratory epithelium. The incidence of adenomas in males was 0, 8, 9 and 10 and in females was 0, 2, 8 and 12. In contrast, most adenocarcinomas arose in areas lined with olfactory epithelium and appeared to have arisen from olfactory epithelium or from submucosal glands. Many were poorly differentiated. Adenocarcinomas arose in 0, 0, 4 and 6 males and 0, 0, 0 and 4 females. The difference in morphology of the adenomas and adenocarcinomas indicated that they were separate tumour types.

Microscopically detectable tumours were also found in the larynx. These were identified as squamous cell carcinomas, and were found in 4 top dose males and 4 top dose females.

This study clearly shows that N-VP containing 3 ppm Kerobit is carcinogenic in rats, causing hepatocellular carcinomas, nasal adenomas and adenocarcinomas and squamous cell carcinomas in the larynx. It was not possible to identify a NOAEL from this study, increased tumour incidences being produced at 5 ppm, the lowest dose used.

Neoplastic changes were also seen in a group of 10 female Sprague-Dawley rats exposed to 45 ppm unstabilised N-VP (purity 99.7-99.9%) for 6 hours per day, 5 days per week for 3 months and allowed a 21 month recovery period (BASF, 1987c; Klimisch et al., 1997a). In this study, investigations were confined to the liver. A total of 6 treated and 4 control rats survived until study termination. Non-neoplastic findings are discussed in Section 4.1.2.6.1. Neoplastic changes were seen in 4 treated rats surviving until the end of the study. No rats dying prematurely and no control rats had neoplastic changes. Of the 4 rats with tumours, two had lesions described as neoplastic nodes, and cells from these neoplasms were found to contain elevated levels of glycogen. The remaining two rats had lesions described as hepatocellular carcinomas and in one rat, the cells of the carcinoma had elevated levels of glycogen. The development of liver tumours in rats inhaling N-VP free of Kerobit after only 3 months exposure to the substance shows that the liver lesions which occur after relatively short periods of exposure are able to progress to form tumours in the absence of continued exposure to N-VP, suggesting that irreversible changes have taken place within the initial three month period. This supports the conclusion that the liver tumours observed in the 2-year study were due to N-VP and not the small quantities of Kerobit present. Although these changes may have arisen because of cytotoxicity in the liver, the precise nature of these irreversible changes is unclear. The possibility exists that the liver tumours may be arising through some species specific mechanism. Although N-VP is clearly hepatotoxic in rats and mice, hamsters showed very little evidence of hepatotoxicity at dose levels that caused severe hepatotoxicity in rats and mice. Again the mechanism underlying this apparent species difference is unclear.

No studies have been conducted to investigate the carcinogenicity of N-VP by the oral or dermal routes.

Other

The ability of N-VP to induce hepatic ornithine decarboxylase (thought to be an early marker of carcinogenic activity) has been briefly studied in male rats given intraperitoneal injections of 0, 5, 23 or 65 mg/kg N-VP in dimethylsulfoxide (van de Zande et al., 1986). Results showed that N-VP could induce this enzyme, although enzyme activity appeared to decrease with increasing dose. The significance of these results in terms of the carcinogenic activity shown by N-VP *in vivo* is unclear.

Negative results were also obtained from a cell transformation assay conducted in BALB/3T3 mouse cells (Litton Bionetics 1980c). For this test, a concentration range of 0.1 nl/ml to 0.5 μl/ml was selected, giving a survival range of 83 to 52.3%. Although a small progressive increase in the number of transformed foci per flask was seen, only 9 foci per 15 flasks were seen at the top dose level compared with 4 per 15 flasks for the negative control cultures and this increase was not statistically significant. In contrast, around 4 foci per flask were found in positive control cultures.

Relevance to humans of the carcinogenicity findings in animals

The results of the above studies show that N-VP (either with or without Kerobit) is carcinogenic in rats, causing hepatocellular carcinomas. N-VP with Kerobit also caused nasal cavity adenomas and adenocarcinomas and squamous cell carcinomas in the larynx. No evidence of genotoxic activity was found in a comprehensive battery of genotoxicity tests, including an *in vitro* USD assay in rat hepatocytes. There is also evidence that N-VP and its metabolites do not bind to liver proteins, DNA or RNA *in vivo*. It is therefore considered that these tumours must be arising through non-genotoxic mechanisms. However, there is uncertainty surrounding the mechanisms that are involved in the development of both the liver and nasal cavity tumours.

Considering first the liver, if the hepatocellular tumours were arising solely as a result of chronic cytotoxicity it is unlikely that tumours would have arisen in rats exposed to 45 ppm N-VP for just 3 months. The fact that tumours did arise suggests that irreversible changes, the nature of which is not clear, are occurring after exposure for a relatively short period of time. There is also some uncertainty about the mechanisms underlying the development of the nasal cavity and laryngeal tumours. While chronic tissue inflammation may be partly responsible, it is possible that other factors may also be involved. Chemicals such as methyl acrylate produce similar non-neoplastic pathology to N-VP in the nasal cavity but when tested in long term, 2-year inhalation studies produced no tumours at irritating dose levels (Reininghaus et al., 1985). Ethyl acrylate is also a nasal cavity irritant but was not tumorigenic in a long-term, 27 month, inhalation study (Miller et al., 1985).

Overall therefore, the toxicological processes underlying the formation of N-VP vapour-induced tumours are unclear. It is also unclear where a no-effect level lies for the potential carcinogenicity of inhaled N-VP in rats. Given the uncertainty about the mechanism underlying the development of N-VP vapour-induced tumours, in the absence of evidence to the contrary, it must be assumed that these tumours are of relevance for human health.

4.1.2.8.2 Studies in humans

No mortality studies of N-VP workers have been carried out, and no useful data on the potential carcinogenicity of N-VP to humans can be obtained from the one cross-sectional morbidity study that has been conducted.

4.1.2.8.3 Summary of carcinogenicity

There is no information available on the carcinogenic potential of N-VP in humans. N-VP vapour (both with and without Kerobit) is clearly carcinogenic in rats, causing tumours in the liver, nasal cavity and larynx. Carcinogenicity has not been tested in other experimental animals. Interestingly, irreversible changes can be produced in the liver of rats after only 3 months exposure to N-VP, resulting in liver tumour development at the end of two years even in the absence of further N-VP exposure. N-VP has not displayed genotoxic activity. However, the observation of liver tumours produced with only a 3-month exposure period suggests that the liver tumours, and possibly also the nasal and laryngeal tumours, arise by a process involving more than simply chronic tissue damage/inflammation. Overall, it is unclear what toxicological processes underlies the formation of N-VP vapour-induced tumours. It is also unclear where a no-effect level lies for the potential carcinogenicity of inhaled N-VP in rats. Given the uncertainty about the mechanism underlying the development of N-VP vapour-induced tumours, in the absence of evidence to the contrary, it must be assumed that these tumours are of relevance for human health. The carcinogenicity of N-VP by the oral and dermal routes has not been studied.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

Fertility and general reproductive performance

No studies specifically investigating fertility and reproductive performance have been conducted. However, there were no indications from repeated dose studies (see Section 4.1.2.6.1 for details) that N-VP had an adverse effect on the reproductive organs of experimental animals. Comprehensive microscopic examinations of the testes, prostate glands, seminal vesicles and epididymides or uterus and ovaries were performed for control and top dose (20 ppm) rats in the two year inhalation study (BASF, 1992b). These tissues were also examined microscopically for control and top dose (8.3 mg/kg/day) rats in the three-month drinking water study (BASF, 1986d). Examinations were also performed of the testes, epididymides, ovaries and uterus from rats inhaling N-VP aerosols of up to 300 $mg \cdot m^{-3}$ for 4 weeks (FDRL, 1976); the testes, ovaries and uterus from rats inhaling 45 or 120 ppm N-VP for up to 3 months (BASF, 1986a) and the testes from rats and mice inhaling 45 ppm N-VP for 7 weeks (BASF, 1988e,f). In no study was there any evidence that treatment-related adverse effects were occurring in these tissues. Impairments to motor function could also have an effect on fertility by affecting the animals' physical ability to mate. There is no evidence to suggest that N-VP has adverse motor effects. Overall therefore, it is considered that there is no evidence to suggest that N-VP is likely to have an adverse effect on fertility.

Developmental toxicity

The potential for N-VP to induce developmental toxicity has been examined in an guideline inhalation study in which groups of 25 mated female Wistar rats were exposed (whole-body) to 0, 1, 5 and 20 ppm (4.6, 23 and 92 $mg \cdot m^{-3}$) N-VP (purity 99.8%) for 6 hours per day on gestational days 6-19 (BASF, 2001; unpublished data). Clinical signs were assessed at least daily throughout the study and bodyweights measured every 2 or 3 days. Histopathological examinations of dams were limited to gross pathology and specific examinations of the uterus and ovaries. External foetal examinations encompassed foetal weight and viability. In addition, placental weights and general placental condition were assessed and the umbilical cords, foetal membranes and fluids examined. Half the foetuses were examined for skeletal abnormalities and half for soft tissue abnormalities.

No mortality occurred. Outward signs of toxicity in dams were apparent only at 20 ppm and comprised salivation in 3 animals on the first two exposure days and urine-smeared genital regions in up to 4 animals on study days 19 and 20. At the top two dose levels there were marked treatment-related reductions in net maternal bodyweight gain (terminal body weight on day 20, minus the weight of the unopened uterus minus body weight on day 6), with that at 20 ppm being 68% lower than control and that at 5 ppm being 31% lower than control. Body weight indices at 1 ppm were unaffected. There were no gross histopathological findings in any group and there were no differences between the groups in gravid uterine weights, mean number of corpora lutea and implantation sites or in the values calculated for the pre- and post-implantation losses, the number of resorptions and viable fetuses. The view that significant maternal toxicity was likely to have occurred in this study at 20 ppm is supported by evidence of biochemical and haematological changes and occasional histopathological changes in the liver of rats in repeated dosing studies of 1-3 weeks duration at a concentration of 15 ppm (see Section 4.1.2.6.1 for details). It is also noted that the magnitude of the reductions in bodyweight gain seen at 5 and 20 ppm exceed reductions in bodyweight gain reported at comparable exposure concentrations in repeated inhalation exposure studies in non-pregnant rats (see Section 4.1.2.6.1). This finding suggests that pregnant animals may be more susceptible to the toxicity of inhaled N-VP than non-pregnant animals.

The only treatment-related effects in foetuses were slight reductions in foetal weights (9% below control) at 20 ppm. This was accompanied by a greater incidence of incomplete ossification of supraoccipital or hyoid bones (indicating maturational delay) and wavy ribs (indicative of maternal toxicity). Mean percentage of foetuses affected per litter were as follows for the control, low, intermediate and high dose groups: incomplete ossification of supraoccipital bones 6.3, 11.5, 11.8, 22.4 (historical control range (HC) 4.0-9.7); incomplete ossification of hyoid bones 0.7, 1.4, 0.6, 5.8 (HC 0-0.8); wavy ribs 0.8, 4.2, 4.2, 15.4 (HC 1.4-5.5). These findings are consistent with delays in development. No signs of foetal toxicity were apparent at 1 and 5 ppm and there was no evidence that N-VP induced specific malformations of any kind in any dose group.

Overall, there was no evidence in this study that N-VP induced specific malformations or was foetotoxic at concentrations that were not also maternally toxic. A NOAEL of 1 ppm was indicated for maternal toxicity, with a NOAEL of 5 ppm for effects on the foetus. In addition, there was some evidence that pregnant rats may be more susceptible to the toxicity of N-VP than non-pregnant rats.

4.1.2.9.2 Studies of human reproductive performance

No studies have been conducted to investigate human reproductive performance.

4.1.2.9.3 Summary of toxicity for reproduction

There is no information on the effects of N-VP on reproductive performance in humans. The potential for N-VP to adversely affect fertility has not been specifically investigated in experimental animals. However, there were no indications from repeated dosing studies that N-VP had an adverse effect on the reproductive organs. Reproductive organs were examined from rats and mice inhaling up to 45 ppm N-VP for 3 months and rats inhaling up to 20 ppm N-VP for 2 years. Reproductive organs were also examined from rats given up to 8.3 mg/kg N-VP in drinking water for 3 months. On this basis it is considered that there is no evidence to suggest that N-VP is likely to have an adverse effect on fertility.

A developmental toxicity study has been conducted in the rat by the inhalation route. There was no evidence that N-VP induced specific malformations or was foetotoxic at concentrations that were not also maternally toxic. A NOAEL of 1 ppm was indicated for maternal toxicity, with a NOAEL of 5 ppm for effects on the foetus. In addition, there was some evidence that pregnant rats may be more susceptible to the toxicity of N-VP than non-pregnant rats.

4.1.3 Risk characterisation

4.1.3.1 General aspects

No useful data are available relating to the effects of N-VP in humans and therefore the risk characterisation is based on the results of animal studies.

N-VP is rapidly and extensively absorbed by the inhalation and oral routes and its physicochemical properties suggest that it will readily cross the skin. However, there is evidence that the bioavailability of small oral doses can be dramatically reduced by hydrolysis of N-VP in the stomach. In rats, the half-life of N-VP in plasma is around 3 hours but in the dog it is only 20-40 minutes. The reason for this species difference is unclear. N-VP is readily metabolised to form highly polar compounds, which are rapidly eliminated, within the first 24 hours after dosing, predominantly in the urine. There is no evidence that N-VP is retained in any tissue and it has been shown that N-VP and its metabolites do not bind to plasma proteins or DNA to any great extent.

A 4-hour LC_{50} value of 3,070 $mg \cdot m^{-3}$ for aerosols of N-VP has been identified in the rat. In other studies, 6-8 hour exposures to air saturated with N-VP vapour (estimated exposure concentration 600 $mg \cdot m^{-3}$) in a range of species produced some local irritation but no deaths. No clinical or histopathological changes were observed in rats or mice inhaling 23 $mg \cdot m^{-3}$ N-VP vapours for 6 hours on 2 consecutive days, though slight liver toxicity was evident in rats immediately after 2 six-hour exposures to 69 $mg \cdot m^{-3}$ N-VP vapour. LD_{50} values following oral doses are around 1,000 mg/kg for the rat and mouse. A dermal LD_{50} value of 560 mg/kg has been reported for rabbits. A dermal LD_{50} value in rodents has not been identified, although deaths among rats given around 1,000 mg/kg indicate that the LD_{50} value may lie below 2,000 mg/kg. The liver and kidneys have been identified as target organs by all three routes of exposure and following oral or inhalation exposure, irritation of the mucous membranes lining the gastrointestinal or respiratory tracts commonly occurs.

N-VP is not a skin irritant. However, liquid N-VP is severely irritating to the eye. No evidence was found in repeated inhalation studies that N-VP vapour causes eye irritation, although the highest dose level at which effects on the eyes were specifically investigated in repeated inhalation studies was only 20 ppm. The ability of N-VP vapour to cause sensory irritation in the respiratory tract has not been studied. It is predicted that N-VP has the potential to cause respiratory tract irritation based on observations of increased respiration rates and nasal secretions in inhalation toxicity studies and the knowledge that N-VP is severely irritating to the eye. Based on observations from inhalation toxicity studies the NOAEL for sensory irritation may lie around 15 ppm.

N-VP did not demonstrate skin sensitisation potential in guinea pigs. The ability of this substance to cause respiratory sensitisation has not been investigated. However, since the substance does not cause skin sensitisation and does not bind to proteins to any great extent it would not be predicted to cause respiratory sensitisation, at least not by an immunological mechanism.

Repeated inhalation of N-VP by rats and mice resulted in dysproteinaemia, haematological changes suggestive of anaemia and pathological changes in the liver, nasal cavity and larynx. In the liver, centrilobular hepatocyte damage occurred. In the nasal cavity, N-VP caused inflammatory changes in the olfactory and respiratory epithelia. Inflammatory changes were also observed in the larynx after prolonged exposure. A NOAEL of 1 ppm (4.61 $mg \cdot m^{-3}$) has been identified in a

3-month study in the rat. Signs of toxicity in rats inhaling 5 ppm (23 $mg \cdot m^{-3}$) N-VP vapour for 3 months included clear evidence of nasal cavity irritation and slight dysproteinaemia. Although no histopathological changes were found in the livers of rats exposed to 5 ppm N-VP for 3 months, liver toxicity became more marked when rats inhaled 5 ppm for longer durations. This suggests that NOAELs derived from 3-month studies might not apply to studies of longer duration and the lifetime exposure NOAEL might be below 1 ppm for rats and mice. Hence this NOAEL of 1 ppm will not be carried forward to the risk characterisation and instead a LOAEL of 5 ppm will be used. Inhalation of concentrations of 15 ppm (69 $mg \cdot m^{-3}$) N-VP vapour or more resulted in liver toxicity and nasal cavity irritation within 1 week and mortality occurred at concentrations of 45 ppm (207 $mg \cdot m^{-3}$) in mice and 120 ppm (553 $mg \cdot m^{-3}$) in rats.

In contrast, when N-VP is given by gavage to rats, the dose levels required to induce histopathological changes in the liver are considerably greater than those required by inhalation; the respiratory tract is not a target tissue with oral dosing. One explanation for the much lower toxicity of N-VP towards the liver by the oral route is that the substance undergoes hydrolysis in the acidic environment of the stomach prior to absorption. A NOAEL of 3.6 mg/kg/day has been identified in a drinking water study. However, gavage doses of up to 60 mg/kg/day produced no clear pathological changes in the liver and only slight changes in a few biochemical and haematological parameters. There are no data relating to the effects of repeated dermal exposure to N-VP.

N-VP has yielded consistently negative results in genotoxicity tests in a wide variety of *in vitro* systems, and one well conducted *in vivo* test. On this basis, it can be concluded that N-VP is not a genotoxicant.

N-VP vapour is clearly carcinogenic in rats, causing tumours in the liver, nasal cavity and larynx. Carcinogenicity has not been tested in other experimental animals. Interestingly, irreversible changes can be produced in the liver of rats after only 3 months exposure to N-VP, resulting in liver tumour development at the end of two years even in the absence of further N-VP exposure. N-VP has not displayed genotoxic activity. However, the observation of liver tumours produced with only a 3-month exposure period suggests that the liver tumours, and possibly also the nasal and laryngeal tumours, arise by a process involving more than simply chronic tissue damage/inflammation. Overall, it is unclear what toxicological processes underlies the formation of N-VP vapour-induced tumours. It is also unclear where a no-effect level lies for the potential carcinogenicity of inhaled N-VP in rats. Given the uncertainty about the mechanism underlying the development of N-VP vapour-induced tumours, in the absence of evidence to the contrary, it must be assumed that these tumours are of relevance for human health. The carcinogenicity of N-VP by the oral and dermal routes has not been studied.

There is no information on the effects of N-VP on reproductive performance in humans. The potential for N-VP to adversely affect fertility has not been specifically investigated in experimental animals. However, there were no indications from repeated dosing studies that N-VP had an adverse effect on the reproductive organs. Reproductive organs were examined from rats and mice inhaling up to 45 ppm N-VP for 3 months and rats inhaling up to 20 ppm N-VP for 2 years. Reproductive organs were also examined from rats given up to 8.3 mg/kg N-VP in drinking water for 3 months. On this basis it is considered that there is no evidence to suggest that N-VP is likely to have an adverse effect on fertility.

A developmental toxicity study has been conducted in the rat by the inhalation route. There was no evidence that N-VP induced specific malformations or was foetotoxic at concentrations that were not also maternally toxic. A NOAEL of 1 ppm was indicated for maternal toxicity, with a

NOAEL of 5 ppm for effects on the foetus. In addition, there was some evidence that pregnant rats may be more susceptible to the toxicity of N-VP than non-pregnant rats.

Overall therefore, with the exception of reproductive toxicity (effects on fertility), the hazardous properties of N-VP have been evaluated in animals to the extent that the minimum data requirements according to Article 9(2) of Regulation 793/93 have been met. The results of the repeated dose studies do not suggest that N-VP is likely to have the potential to produce effects on fertility. The lead health effects of concern are acute toxicity, eye and respiratory tract irritation, effects on the liver following repeated exposure and carcinogenicity. In relation to developmental toxicity, there is no evidence that N-VP induced direct effects on the foetus; however some foetotoxicity, consistent with delayed development, was seen at exposure levels producing significant maternal toxicity (20 ppm) in a study in rats. No foetal effects were seen at 5 ppm. In this case, given the relatively low exposure level at which maternal toxicity occurs, it is appropriate to consider the potential for maternal toxicity and subsequent foetal effects in the risk characterisation. In addition, the results of this study suggest that pregnant animals may be more susceptible to the toxicity of N-VP than non-pregnant animals; a marked reduction in bodyweight gain was seen in pregnant animals in this study at 5 ppm, whereas no such effect on bodyweight gain was seen at comparable exposure concentrations in repeated inhalation studies in non-pregnant rats. This potential for greater susceptibility during pregnancy should therefore also be taken into account in the risk characterisation. For N-VP, the NOAEL for developmental effects and the LOAEL for reduced bodyweight gain in the pregnant dams are identical to the LOAEL for repeat dose toxicity (5 ppm). Therefore, the conclusions of the risk characterisation for repeat dose toxicity will be applicable to a risk characterisation for developmental effects and for maternal toxicity. Given this, no separate risk characterisation for developmental or maternal effects will be performed.

There are no concerns for skin irritancy, skin sensitisation, asthmagenicity, mutagenicity and effects on fertility. Overall conclusion (ii) is reached for these endpoints.

In order to carry out the risk characterisation the following assumptions have been made. The body weight of the average worker is 70 kg and the worker inhales 10 m^3 air per working day. The body weight of the average adult consumer is assumed to be 60 kg and that of a child is 10 kg. The surface area of both hands of an adult is assumed to be 840 cm^2 and that of the hands and forearms is assumed to be 2,000 cm^2. In the absence of quantitative data on the bioavailability of N-VP by the inhalation and dermal routes, it has been assumed that there will be 100% absorption by both routes. Similarly, 100% absorption by the oral used is assumed.

In the assessment of the risk of liver tumour development in workers resulting from combined inhalation/dermal exposures, the estimated body burdens have been compared to data from repeated inhalation studies in rats. This is because the bioavailability of orally administered N-VP is reduced by hydrolysis in the stomach, and so comparisons to oral doses would not be appropriate for estimating effects on the liver resulting from inhalation/dermal exposure.

In the assessment of the risk of liver tumour development in consumers, the estimated body burdens have been compared to data from repeated inhalation studies. This is because the results of repeated oral dosing studies of up to 3 months duration suggest the liver would be a target tissue for N-VP induced carcinogenicity by this route. However, no long-term studies have been conducted by the oral route to investigate the dose response for N-VP induced carcinogenicity by this route. It is recognised that the dose levels required to produce effects in rodents following oral dosing are greater than those required by the inhalation route. This consumer risk assessment therefore represents a very conservative view.

The body burden which represents the inhalation LOAEL in rats has been calculated on the basis of exposure to 5 ppm for 6 hours/day, assuming a rat inhales 6 l/hour, 100% absorption and a rat bodyweight of 0.5 kg. Based on these assumptions, the estimated body burden is ~1,700 μg/kg/day.

4.1.3.2 Workers

4.1.3.2.1 Introduction

N-VP is mainly used to make PVP polymers and copolymers. Polymerisation generally occurs on site at the German manufacturers although other companies also manufacture polymers of N-VP. The manufacture and polymerisation of N-VP is carried out in closed systems, therefore exposure will mainly occur during deliberate breaches of the system for operations such as sampling, tanker filling and emptying and plant maintenance. Dermal exposure from incidental contact with contaminated surfaces is also possible. It is estimated that 450-750 workers may be exposed to N-VP during the manufacture of N-VP monomer and its polymers.

N-VP monomer is also used in the manufacture of UV curing inks and lacquers and contact lenses. It is estimated that 400-800 workers in the EU are exposed to N-VP during the manufacture of UV curing inks and lacquers. Due to a decline in the use of such products, exposure is likely to be intermittent. The main sources of exposure are thought to arise during the charging of mixing vessels and during the filling of product containers and from incidental dermal contact with contaminated surfaces. The number of workers exposed to N-VP while using UV curing inks and lacquers is unknown, although it is thought that only a small percentage of the thousands of screen printers in the EU use N-VP based inks. The main source of exposure to N-VP during the manufacture of contact lenses is during the preparation of the pre-polymer mix and when this mix is put into the moulds.

Exposure to N-VP may also occur during the manufacture of products containing PVP polymers and copolymers due to the presence of unreacted N-VP residues.

The key adverse effects of concern are the nasal cavity, laryngeal and liver tumours and the non-neoplastic lesions that occur in these tissues after repeated exposures to N-VP. As the nasal/laryngeal pathology is observed only in inhalation studies, these are considered to be local site of contact phenomena, and thus the risks for effects at these sites are dependent only on the levels of inhalation exposure. However, the pathological effects produced by N-VP in the liver are dependent on the total body burden, and hence the combined body burden resulting from inhalation and dermal exposure needs to be considered in the occupational risk assessment.

In addition, liquid N-VP has been identified as a severe eye irritant. For the exposure scenarios discussed below, under normal conditions eye contact is not expected. However, there is the possibility of accidental contamination, either as a result of splashing or via contaminated hands. It is therefore recommended that steps should be taken to prevent accidental eye contact in any situation where this could occur.

4.1.3.2.2 Acute toxicity

Concerns for acute inhalation toxicity may arise where there is a potential for exposure to peak levels of N-VP. Potential exposure to short-term peaks occurs during the production of N-VP

and its use in the production of polymers, during the manufacture of UV curing inks and UV curing lacquers and during the use of UV curing inks containing N-VP. The highest peak exposure to N-VP determined from the EASE model occurs during maintenance and cleaning tasks in the manufacture of UV inks and lacquers. Short-term peak exposures of up to 100 ppm are estimated, although it is thought operators would generally wear RPE where exposure levels cannot be controlled by other means. As N-VP has a calculated saturated vapour concentration of 131 ppm it is unlikely that an exposure of 100 ppm would be achieved in practice. The exposure level of 100 ppm (460 $mg \cdot m^{-3}$) is close to the level at which a single 6-8 hour exposure produced some local irritation but no deaths in a range of species. Minimal histopathological changes have been seen in the livers of rats exposed for 6 hours to 15 ppm on two successive days and the results of the acute toxicity tests show that altered breathing behaviour is exhibited by animals during after a 6-hour exposure to 45 ppm, with more severe signs of toxicity at higher concentrations. On this basis it is possible that regular short-term exposures to high levels of N-VP could lead to adverse effects and therefore regular peak exposures give cause for concern. Therefore **conclusion (iii)** is reached for this endpoint.

4.1.3.2.3 Respiratory tract irritation

Potential exposure to short-term peaks occurs during the production of N-VP and its use in the production of polymers, the manufacture of UV curing inks and UV curing lacquers and the use of UV curing inks containing N-VP. For the production of N-VP and its use in the production of polymers, on the basis of modelled data, sampling and tanker filling/ emptying operations may result in 15 minute TWA exposures of up to 3.3 ppm but it is thought likely that substantially higher peaks will be encountered within these 15 minute periods. For the manufacture of UV curing inks and UV curing lacquers, peak exposures could be encountered for maintenance and cleaning operations, although it is thought operators would generally wear RPE where exposure levels cannot be controlled by other means. During the use of UV inks, modelled data indicated levels of 0.42-1.4 ppm (8-hour TWA) with peaks of 7-14 ppm occurring during maintenance and cleaning operations.

A NOAEL for respiratory tract irritation of 15 ppm has been identified. Given that peak exposures of up to 14 ppm, or possibly higher, may occur, there are concerns for immediate respiratory tract irritancy. Also the long-term consequences of regular peak exposures are unclear. Minimal histopathological changes have been seen in the nasal cavities of rats and mice exposed to 15 ppm for 6 hours per day for 1 week. On this basis it is possible that regular short-term exposures to high levels of N-VP could lead to adverse effects and therefore regular peak exposures give cause for concern. Therefore **conclusion (iii)** is reached for this endpoint.

4.1.3.2.4 Eye irritation

For all scenarios the eye irritation of the liquid substance is unlikely to be expressed during normal handling and use because exposure is low, providing good occupational hygiene practices are in operation. However, if there is contact with the eye, which could occur accidentally, then local damage is possible. Overall, however, **conclusion (ii)** is reached.

4.1.3.2.5 Repeated dose toxicity and carcinogenicity

Production of N-VP and its use in the production of polymers

Exposure to N-VP during its production and its use in the production of polymers may occur by both the inhalation and dermal routes. For inhalation, personal measurements taken during production of N-VP indicate 8-hour TWAs are generally below 0.1 ppm, although higher levels have been recorded. It is considered that 0.1 ppm 8-hour TWA represents a reasonable worst-case scenario. These 8-hour TWAs are thought to arise from exposures received during short-term tasks.

In relation to the risks of nasal and laryngeal tumour development, the worst-case exposure estimate of 0.1 ppm (8-hour TWA), is only 50 fold lower than the concentration producing nasal tumours in rats and 200 fold lower than the concentration producing laryngeal tumours. In the absence of any evidence to the contrary it must be assumed that these tumours are of relevance to humans. This level of occupational exposure gives cause for concern for the development of nasal tumours. Therefore **conclusion (iii)** is reached.

The body burden of N-VP corresponding to the worst-case predicted occupational inhalation exposure (0.1 ppm 8-hour TWA) is 0.07 mg/kg/day. In addition, modelled data indicate that dermal exposures of between 0.1-1 mg/cm^2/day could occur. Assuming both hands are exposed (840 cm^2), this would give a potential additional body burden of 12 mg/kg/day. Worst-case body burdens of N-VP are therefore dominated by the dermal exposure of 12 mg/kg/day. Liver tumours developed in rats inhaling 5 ppm for 6 hours per day, a concentration which would correspond to a body burden of 1.7 mg/kg/day in this species, assuming a bodyweight of 0.5 kg and that the rat inhales 6 litres of air per hour (Gold et al., 1984). This is less than the predicted body burdens in workers engaged in the production of N-VP and its polymers. In the absence of any evidence to the contrary it must be assumed that these tumours are of relevance to humans. This worst-case estimate of the potential uptake of N-VP from combined inhalation/dermal exposure therefore gives cause for concern for human health and **conclusion (iii)** is reached.

Manufacture of UV curing inks and UV curing lacquers

Exposure to N-VP during the manufacture of UV curing inks and UV curing lacquers may also occur by both the inhalation and dermal routes. However, exposure to N-VP in this scenario will only occur on the days when N-VP based inks and lacquers are being made and owing to the declining use of such products this is considered to be a relatively infrequent event. Very little personal sampling has been carried out to determine the actual levels of N-VP to which workers are exposed. The worst-case scenario using modelled data indicated exposures of up to 5 ppm as an 8-hour TWA could arise.

Exposure at the worst-case 8-hour TWA level of 5 ppm gives cause for concern in relation to the risk of development of tumours at the site of contact in the respiratory tract, as this is a level of exposure which produced nasal cavity tumours in rats and is only four times lower than a level of exposure which produced laryngeal tumours in rats. Therefore **conclusion (iii)** is reached.

In relation to the risk of liver tumour development, the worst-case predicted level of occupational inhalation exposure corresponds to a body burden of 3.3 mg/kg/day. Dermal exposures of 0.1 to 1 mg/cm^2/day are predicted to arise, but since most dermal contact will be to blends containing relatively low concentrations of N-VP it is thought that exposures would tend to be at the lower end of the range. Assuming that the hands and forearms of a worker may become contaminated during vessel charging and container filling, and taking the lower end of the predicted dermal exposure range, this gives a worst-case additional body burden of 2.9 mg/kg/day. Therefore for

the days when N-VP based lacquers and inks are being made, a worst-case body burden of 6.2 mg/kg/day could occur. This is over 3.5 times greater than the body burden arising in rats from inhalation exposure to 5 ppm (1.7 mg/kg/day), a level at which liver tumours developed. These predicted levels of exposure are of concern for human health. Therefore **conclusion (iii)** is reached.

Use of UV curing inks containing N-VP

Exposure to N-VP during the use of UV curing inks containing N-VP is higher than that experienced during the manufacture of such inks. In the majority of workplaces, the inks will be applied using an automated process.

The predicted worst-case 8-hour TWA level of 1.4 ppm is less than 4 fold below the level of exposure which causes nasal cavity tumours in rats and only 14 times lower than the level of exposure which caused laryngeal tumours in rats. This gives cause for concern in relation to the risk of development of tumours at the site of contact in the respiratory tract in workers and **conclusion (iii)** is reached.

There is also concern in relation to the risk of liver tumour development. The worst-case occupational inhalation exposure of 1.4 ppm (8-hour TWA) gives rise to a body burden of 0.9 mg/kg/day. Dermal exposures during the use of inks of up to 0.7 mg/cm^2/day are predicted. Assuming the hands and forearms (2,000 cm^2) may become contaminated, this gives a worst-case additional body burden of 20 mg/kg/day. The total daily body burden would therefore be 20.9 mg/kg/day. This is over 12 times higher than the body burden arising from inhalation exposure of rats to 5 ppm. Therefore **conclusion (iii)** is reached.

Manual screen printing with N-VP based inks may also be occurring. Modelled data for this scenario indicate occupational inhalation exposure levels of 7 to 14 ppm (8-hour TWA), nearly three times greater than a level causing nasal cavity tumours in rats and close to a level causing laryngeal tumours in rats. This gives grounds for concern in relation to the risk of development of tumours at the site of contact in the respiratory tract. Therefore **conclusion (iii)** is reached.

In relation to the risk of development of liver tumours, the predicted worst-case occupational inhalation exposure of 14 ppm (8-hour TWA) would give a daily body burden of 9.2 mg/kg/day. Dermal exposures of up to 0.7 mg/cm^2/day would provide an additional 20 mg/kg/day assuming the hands and forearms were contaminated. This would lead to a daily body burden of 29.2 mg/kg/day, nearly 17 times higher than the body burden in rats exposed to 5 ppm. This gives cause for concern for human health and **conclusion (iii)** is reached.

Use of UV lacquers containing N-VP

The use of N-VP based UV curing lacquers will also lead to exposure by both the inhalation and dermal routes. Modelled data predicted that worst-case levels of 0.045-0.27 ppm (8-hour TWA) could occur during the use of UV lacquers. However, the modelling process was not thought to have taken adequate account of the control regimes that would be in place in such situations, therefore realistically, worst-case exposures are likely to be at the bottom end of this range. Occupational exposure to 0.045 ppm (8-hour TWA) is over 100 times lower than a level causing nasal cavity tumours in rats and over 400 times lower than a level causing laryngeal tumours in rats. In the absence of any evidence to the contrary it must be assumed that these tumours are of relevance to humans. However, given that N-VP is not thought to act by a genotoxic mechanism, the size of this margin of difference does not indicate any obvious grounds for concern. **Conclusion (ii)** is reached.

In relation to the development of liver tumours, exposure to 0.045 ppm (8-hour TWA) would give a body burden of 0.03 mg/kg/day. Dermal exposures are thought to arise when charging the lacquer reservoir and through contamination of nearby surfaces. Levels of up to 0.09 mg/cm^2/day are predicted. Assuming the hands and forearms may become contaminated, this gives a worst-case additional body burden of 2.57 mg/kg/day, leading to a total daily body burden of 2.6 mg/kg/day. This estimated body burden is one and a half times greater than the body burden that would arise in rats from inhalation exposure to 5 ppm. This gives cause for concern for human health and **conclusion (iii)** is reached.

Manufacture of contact lenses

During the manufacture of contact lenses, exposure may arise during the preparation of the pre-polymer mix and its application to moulds. Modelled data indicate a worst-case exposure of 0.25 ppm (8-hour TWA), 20 times lower than a level causing nasal cavity tumours in rats and 80 times lower than a level causing laryngeal tumours in rats. In the absence of any evidence to the contrary it must be assumed that these tumours are of relevance to humans. This level of occupational exposure therefore gives cause for concern for human health and **conclusion (iii)** is reached.

In relation to the development of liver tumours, exposure to the predicted worst-case occupational exposure level would give a daily body burden of 0.16 mg/kg/day. Dermal exposures will mainly arise during addition of the initiator. The worst-case dermal exposure is predicted to be 0.05 mg/cm^2/day. Assuming the hands and forearms may become contaminated, this gives a worst-case additional body burden of 1.4 mg/kg/day, leading to a total daily body burden of 1.56 mg/kg/day. This is close to the body burden that would arise after inhalation of 5 ppm N-VP, and for the reasons outlined in Section 4.1.3.1.2, is of concern for the development of liver tumours in workers. Therefore **Conclusion (iii)** is reached.

Exposure to residual N-VP monomer during use of its polymers

Exposure of up to 0.01 ppm (8-hour TWA) was modelled for situations where polymers of N-VP are used without any controls. This is two orders of magnitude below a potentially carcinogenic dose. Given that the tumours are arising through a non genotoxic mechanism, this is considered to represent an adequate margin of safety and therefore does not give cause for concern. Where LEV is in place, a worst-case level of 0.0003 ppm (8-hour TWA) is predicted, which is four orders of magnitude below a carcinogenic dose. In view of the very low percentage of N-VP in N-VP based polymers, dermal contact has not been modelled.

Table 4.10 Summary of MOSs for nasal cavity/ laryngeal pathology

Scenario	LOAEL for nasal cavity pathology (ppm)	Realistic worst-case workplace exposure level (ppm)	MOS	Conclusion
Production of N-VP and its use in the production of polymers	5	0.1*	50	**iii**
Manufacture of UV curing inks and lacquers	5	5 †	1	**iii**
Use of UV curing inks containing N-VP in an automated process	5	1.4 †	< 4	**iii**
Use of UV curing inks containing N-VP in a manual process	5	14 †	Exposure nearly 3 times the LOAEL	**iii**
Use of UV lacquers containing N-VP	5	0.045 †	> 100	ii
Manufacture of contact lenses	5	0.25 †	20	**iii**
Exposure to residual N-VP monomer during use of its polymers	5	0.01 †	500	ii

N.B Neoplastic and non-neoplastic changes were also observed in the larynx at 20 ppm

* based on actual exposure data

† based on modelled exposure data

Table 4.11 Summary of total systemic doses arising from inhalation and dermal exposures for workplace exposure scenarios

Scenario	Inhalation exposure	Body burden (mg/kg/day)	Dermal exposure ($mg/cm^2/day$) #	Body burden (mg/kg/day)	Total body burden (mg/kg/day)
Production of N-VP and its use in the production of polymers	0.1 ppm *	0.07	0.1-1 †	12	12
Manufacture of UV curing inks and lacquers	5 ppm †	3.3	0.1 †	2.9	6.2
Use of UV curing inks containing N-VP in an automated process	1.4 ppm †	0.9	0.7 †	20	21
Use of UV curing inks containing N-VP in a manual process	14 ppm †	9.2	0.7 †	20	29
Use of UV lacquers containing N-VP	0.045 ppm †	0.03	0.09 †	2.57	2.6
Manufacture of contact lenses	0.25 ppm †	0.16	0.05 †	1.4	1.6

* based on actual exposure data

† based on modelled exposure data

\# these values do not take into account use of gloves, which would reduce predicted exposures

Table 4.12 Summary of MOSs for liver pathology in rats

Scenario	Systemic dose in rats at the LOAEL of 5 ppm (mg/kg/day) ‡	Total systemic dose from workplace exposure (mg/kg/day)	MOS	Conclusion
Production of N-VP and its use in the production of polymers	1.7	12	<1	iii
Manufacture of UV curing inks and lacquers	1.7	6.2	<1	iii
Use of UV curing inks containing N-VP in an automated process	1.7	21	<1	iii
Use of UV curing inks containing N-VP in a manual process	1.7	29	<1	iii
Use of UV lacquers containing N-VP	1.7	2.6	<1	iii
Manufacture of contact lenses	1.7	1.6	~1	iii

‡ based on inhalation of 5 ppm for 6 hours per day and assuming bodyweight of 0.5 kg and inhalation of 6 litres of air per hour.

4.1.3.2.6 Summary of the risk characterisation for workers

In all occupational situations involving the manufacture or use of N-VP, (other than those situations in which exposure may be only to residual levels of N-VP monomer in polymers) the predicted levels of exposure are close to concentrations at which tumours have occurred in rats. In the absence of evidence to the contrary it must be assumed that these tumours are of relevance to humans, hence these levels of occupational exposure give cause for concern. It is recommended that steps should be taken to prevent eye contact with liquid N-VP in any situation where this may occur.

4.1.3.3 Consumers

4.1.3.3.1 Introduction

N-VP monomer is not used directly in consumer products but may be present in trace amounts as a residue in products containing PVP. PVP is widely used in a variety of consumer products including pharmaceuticals and non-pharmaceutical tablets, foods and beverages, cosmetics and toiletries, adhesives, contact lenses, suspensions, dispersions and emulsions, denture fixatives and products coloured with UV curing inks and coatings. It has also been used in the past as a viscosity improver for lubricating oils.

The key adverse effects of concern are nasal cavity, laryngeal and liver tumours and the non-neoplastic lesions that occur in these tissues after repeated exposures to N-VP. As indicated in the risk characterisation for workers, the risks for nasal/laryngeal effects are only dependent on the levels of inhalation exposure. The only scenario that has been identified in which consumers are likely to inhale N-VP is the use of hairsprays. For all other scenarios, the risk assessment for consumers concentrates on the risks for effects in the liver. Effects produced by N-VP in the liver are dependent on the total body burden, and hence the combined body burden resulting from all relevant routes of exposure for each product is considered in the consumer risk characterisation. In addition, liquid N-VP has been identified as a severe eye irritant. It is

therefore also necessary to consider the risk of adverse effects in the eye arising from the presence of residual N-VP in consumer products intended to be applied to the eye.

4.1.3.3.2 Acute toxicity

There are no consumer exposure scenarios that involve single peak exposures and therefore a risk characterisation is not relevant for this endpoint. **Conclusion (ii)** applies.

4.1.3.3.3 Irritation

Eye irritation

Pharmaceuticals

Small quantities of N-VP may be present in eye drops at a concentration of 0.45 ppm. Although undiluted N-VP is severely irritating to the eye, no eye irritation is expected from such a dilute solution and therefore exposure via eye drops does not give cause for concern. **Conclusion (ii)** applies.

Contact lenses

Daily exposure to residual N-VP monomer in contact lenses is predicted to be less than 13 µg/day. This will be diluted by the fluid covering the surface of the eye and therefore is not expected to result in eye irritation. Therefore **conclusion (ii)** applies.

Shampoo

Total daily exposure to residual N-VP monomer in shampoos is estimated to be 1.2 µg from a daily application of 12 g of shampoo. As it can be assumed that not all the 12 g of shampoo will get into the eye, the daily exposure can be considered to be significantly less than 1.2 µg and is not expected to cause eye irritation. Therefore **conclusion (ii)** applies.

4.1.3.3.4 Repeated dose toxicity and carcinogenicity

The only consumer exposure scenario which involves repeated inhalation exposure is the use of hairsprays. A risk characterisation for nasal/laryngeal tumours as well as for liver tumours is therefore applicable for this scenario. For all other scenarios, inhalation exposure is not relevant and therefore there are no potential concerns for nasal/laryngeal tumours; the risk characterisation for these remaining scenarios will address only the potential for the development of liver tumours.

Pharmaceuticals

The total worst-case daily exposure to N-VP monomer in ingested or dermally applied pharmaceutical products (tablets, mouthwash or lotion) is estimated to be a maximum of 10 µg/day, giving a daily dose of 0.16 µg/kg/day. There are no long-term studies to investigate the dose response for N-VP induced carcinogenicity by the oral or dermal exposure routes. Therefore this estimated body burden is compared with the estimated body burden corresponding to the inhalation LOAEL in the rat i.e. 1.7 mg/kg/day. Consumer exposure is 4 orders of magnitude below the body burden producing liver tumours in rats. Therefore, the presence of

residual N-VP monomer in pharmaceuticals does not give cause for concern and **conclusion (ii)** applies.

Cosmetics

Total daily exposure to residual N-VP monomer in cosmetics and toiletries (shampoos, styling gels, hair sprays and pre-shave gels) is predicted to be around 9 µg/day. This would give rise to a body burden of 0.15 µg/kg/day for a 60 kg adult. This is over 11,000 times lower than the body burden in rats that would arise from inhaling 5 ppm N-VP for 6 hours per day and is not considered to pose a risk to human health. Therefore **conclusion (ii)** applies.

The use of hair sprays may give rise to repeated inhalation exposure and therefore a risk characterisation for nasal/laryngeal tumours is relevant for this scenario. The estimated exposure concentration to which a consumer could be exposed per event is 7 $\mu g \cdot m^{-3}$ ($1.5 \cdot 10^{-6}$ ppm). This is six orders of magnitude lower than the LOAEL for nasal cavity tumours therefore there are no concerns. **Conclusion (ii)** is reached.

Contact lenses

The daily wearing of contact lenses could result in exposure to 13 µg N-VP per day. This is equivalent to a body burden of 0.2 µg/kg/day for a 60 kg adult, assuming 100% absorption via the eyes. This results in a MOS of 8,500 when compared with the body burden producing effects in rats. An MOS of this magnitude does not give rise to concern, therefore **conclusion (ii)** is reached.

Suspensions, dispersions and emulsions

Residual N-VP monomer may be present in suspensions, dispersions and emulsions. One example is washing powder where a concentration of 8 µg/7 litres water is predicted to occur during the hand washing of clothes. Assuming that all of this 8 µg is available for absorption this would give rise to a body burden of 0.15 µg/kg/event for a 60 kg adult, four orders of magnitude below the body burden that would occur in rats inhaling 5 ppm N-VP, 6 hours per day. This does not give cause for concern. Therefore **conclusion (ii)** applies.

Dental fixatives

Residual N-VP monomer may be present in denture fixative. In this case, 6 µg/day is available for absorption giving a body burden of 0.1 µg/kg/day for a 60 kg adult assuming this dose was completely absorbed by the oral mucosa. In relation to the risk of developing liver tumours, this is four orders of magnitude below the body burden in rats inhaling 5 ppm N-VP and is not considered to represent a risk to human health. Therefore **conclusion (ii)** applies.

4.1.3.3.5 Total potential daily dose for consumers

It is possible that a consumer may receive exposure to residual N-VP monomer from a number of different sources. Taking as a worst case an adult exposed to N-VP from pharmaceuticals (10 µg/day), and denture fixative (6 µg/day), cosmetics (9 µg/day), washing powder (8 µg/event) and also from contact lenses (13 µg/day) on a daily basis this would give rise to a total daily exposure of 46 µg/day and a systemic body burden of 0.8 µg/kg/day for a 60 kg adult assuming 100% absorption by all routes. In relation to the risk of developing liver tumours, this is 2,000 times lower than the body burden that would arise in rats inhaling 5 ppm N-VP for 6 hours per day. This level of exposure does not give cause for concern. Therefore **conclusion (ii)** applies.

4.1.3.3.6 Summary of the risk characterisation for consumers

Overall, no concerns have been identified for the presence of residual N-VP monomer in PVP as it is used in consumer products, and therefore **conclusion (ii)** applies for all scenarios.

4.1.3.4 Humans exposed via the environment

Local scenarios

Individuals may also be exposed to N-VP monomer indirectly via the environment. Most is obtained from dietary sources such as drinking water, fish, leaf and root crops, meat and milk but N-VP may also be inhaled. The greatest source of indirect exposure arises from N-VP production and processing (a total daily intake of $4.28 \cdot 10^{-3}$ mg/kg/day was predicted). In relation to the risk of development of liver tumours, this daily intake is around 400 times lower than the body burden that would arise from inhaling 5 ppm N-VP for 6 hours per day (1.7 mg/kg/day). However, much of the N-VP that has been ingested would hydrolyse in the stomach prior to uptake, therefore the actual systemic body burdens arising from indirect exposure are likely to be very much lower than these figures suggest.

In relation to the risk of development of nasal cavity and laryngeal tumours, the greatest daily dose of inhaled N-VP, 0.13 µg/kg/day comes from N-VP production. This is 13,000 times lower than the body burden that would arise from inhaling 5 ppm N-VP for 6 hours per day. Overall therefore, for both dietary sources and by inhalation, indirect exposure to N-VP via the environment does not give cause for concern. Therefore **conclusion (ii)** applies for these scenarios.

Regional scenario

The regional exposure results in an intake of $1.5 \cdot 10^{-6}$ mg/kg/day, six orders of magnitude below that arising in rats inhaling 5 ppm N-VP for 6 hours per day (1.7 mg/kg/day). This does not give rise to concern and therefore **conclusion (ii)** applies.

In relation to the risk of development of nasal cavity and laryngeal tumours, the greatest daily dose of inhaled N-VP from regional exposures is estimated to be $7.5 \cdot 10^{-9}$ mg/kg/day. These results in a body burden six orders of magnitude below that arising in rats inhaling 5 ppm N-VP for 6 hours per day. Therefore **conclusion (ii)** applies.

4.1.3.5 Combined exposure to humans via all routes

It is possible for an individual to receive exposure to N-VP at work, from consumer products and indirectly via the environment. However, the levels of N-VP in consumer products and the levels that would be received indirectly from environmental sources are so low that they will not significantly add to the daily body burden received at work.

Therefore the conclusions reached for workers apply to combined exposure.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

The substance is of relatively low vapour pressure at ambient temperatures, and flammability and explosive properties of the substance are not a cause for concern as long as current safety measures are implemented.

During the manufacture, storage and use of this substance, the control measures that are used ensure that there are no concerns for workers arising from the physicochemical properties of N-VP. It should however be noted that care needs to be taken when using this substance in acid conditions, or if the shelf life or storage temperatures are greatly exceeded, due to the possibility of polymerisation, as significant evolution of heat can occur.

There is no cause for concern identified for consumers from any of the exposures with relation to physicochemical properties. There is also considered to be no cause for concern for humans exposed indirectly via the environment.

Therefore **conclusion (ii)** is reached.

5 RESULTS

5.1 INTRODUCTION

1-Vinyl-2-pyrrolidone is used mainly as a monomer to produce polyvinylpyrrolidone and copolymers. It is also used in some radiation-cured inks and coatings.

5.2 ENVIRONMENT

The production and use of 1-vinyl-2-pyrrolidone and the release of 1-vinyl-2-pyrrolidone during use of polymers that contain residual 1-vinyl-2-pyrrolidone monomer is not thought to present a risk to the environment. This conclusion is based on site-specific information for the main production and use sites, and generic "worst-case" scenarios to cover the other sites of use.

Result

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to all environmental compartments for production, processing and use of 1-vinyl-2-pyrrolidone and release of 1-vinyl-2-pyrrolidone during use of polymers that contain residual 1-vinyl-2-pyrrolidone monomer.

5.3 HUMAN HEALTH

5.3.1 Human health (toxicity)

5.3.1.1 Workers

Although the effects of exposure to N-VP have been extensively studied in experimental animals, there remains considerable uncertainty about the mechanisms underlying the development of tumours in rats inhaling N-VP. Consequently, although it is thought that a non-genotoxic mechanism underlies the development of these tumours it has not been possible to make any statements as to where the NOAEL might lie for carcinogenicity in rodents. In the absence of any evidence to the contrary it must be assumed that these tumours are of relevance to humans. On this basis, the following scenarios gave cause for concern: the production of N-VP and its use in the production of polymers, the use of N-VP in the manufacture of UV curing inks and UV curing lacquers, the use of UV curing inks containing N-VP, the use of UV curing lacquers containing N-VP and the use of N-VP in the manufacture of contact lenses. In addition, there are concerns for single exposure toxicity and respiratory tract irritation in exposure situations where there is the potential for peak exposures to occur. Such peak exposures can occur during the production of N-VP and its use in the production of polymers, the use of N-VP in the manufacture of UV curing inks and UV curing lacquers, the use of UV curing inks containing N-VP. It is recommended that steps should be taken to reduce exposures for these occupational uses. It is also recommended that steps should be taken to prevent eye contact with liquid N-VP in any situation where this may occur.

No concerns were identified for workers whose only form of exposure to N-VP was as a residue in N-VP based polymers owing to the very low level of N-VP to which these workers would be exposed.

Results

Conclusion (iii) There is a need for limiting the risks; risk reduction measure which are already being applied shall be taken into account

This conclusion applies to workers exposed to N-VP during its manufacture, during its use in the production of polymers, during manufacture of UV curing inks and lacquers and during use of UV curing inks, because of concerns for single exposure toxicity, respiratory tract irritation, repeated dose toxicity and carcinogenicity. In addition, it applies to the use of UV curing lacquers containing N-VP, and the use of N-VP in the manufacture of contact lenses because of concerns for repeated dose toxicity and carcinogenicity.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to workers exposed to residual N-VP monomer during use of its polymers. It also applies to all scenarios in relation to the eye irritation of the liquid substance, providing good occupational hygiene practices are in operation. However, if there is contact with the eye, which could occur accidentally, then local damage is possible.

5.3.1.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion is reached because the levels of residual N-VP monomer in consumer products are so low that there are no concerns for risks to human health.

5.3.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion is reached because the levels of N-VP monomer which individuals are likely to receive from environmental sources are very low and do not give cause for concern for human health.

5.3.1.4 Combined exposure

Conclusion (iii) There is a need for limiting the risks; risk reduction measure which are already being applied shall be taken into account.

This conclusion is reached because it is possible for an individual to receive exposure to N-VP at work, from consumer products and indirectly via the environment. However, the levels of N-VP in consumer products and the levels that would be received indirectly from environmental

sources are so low that they will not significantly add to the daily body burden received at work. Therefore the conclusions for combined exposure are the same as those for the worker.

5.3.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion is reached because there are no concerns associated with the physico-chemical properties of this substance, as long as current safety measures are implemented.

It should however be noted that care needs to be taken when using this substance in acid conditions, or if the shelf life or storage temperatures are greatly exceeded, due to the possibility of polymerisation, as significant evolution of heat can occur.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling

PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme

US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Appendix A: EUSES Calculations

This EUSES printout contains the calculations for the following generic scenarios contained in the main report:

Use pattern in EUSES		Scenario
1:	Processing	Small user – polymerisation – E
2:	Formulation	Small user – polymerisation – F (25 days)
	Processing	Small user – polymerisation – F (10 days)
3:	Formulation	Small user – polymerisation – G (17 days)
	Processing	Small user – polymerisation – G (7 days)
4:	Formulation	Small user – polymerisation – H (34 days)
	Processing	Small user – polymerisation – H (14 days)
5:	Formulation	Ink formulation
	Processing	Ink use

The EUSES printout for the site-specific information and small users Use A-D, is contained in the Confidential Annex.

European Commission

EUR 20846 EN **European Union Risk Assessment Report**
1-vinyl-2-pyrrolidone, Volume 39

Editors: S.J. Munn, R. Allanou, F. Berthault, J. de Bruijn, C. Musset, S. O'Connor, S. Pakalin, A. Paya-Perez, G. Pellegrini, S. Scheer, S. Vegro.

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Environment and quality of life series

The report provides the comprehensive risk assessment of the substance 1-vinyl-2-pyrrolidone. It has been prepared by The United Kingdom in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The environmental risk assessment for 1-vinyl-2-pyrrolidone concludes that there is no concern for the aquatic ecosystem, the terrestrial ecosystem, the atmosphere or for microorganisms in the sewage treatment plant as well as for secondary poisoning.

The human health risk assessment for 1-vinyl-2-pyrrolidone concludes that there is concern for workers. For consumers and humans exposed via the environment the risk assessment concludes that risks are not expected.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, private or national.

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