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1-VINYL-2-PYRROLIDONE

CAS No: 88-12-0

EINECS No: 201-800-4

Summary Risk Assessment Report

2003 **Special Publication I.03.151**

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SUMMARY RISK ASSESSMENT REPORT

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**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 1-vinyl-2-pyrrolidone that has been prepared by the United Kingdom in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 88-12-0
EINECS Number: 201-800-4
IUPAC Name: 1-vinyl-2-pyrrolidone (N-VP)
Synonyms: 1-Ethenylpyrrolidin-2-one; 1-vinyl-2-pyrrolidinone; 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 g/mole
Molecular formula: C_6H_9NO

1.2 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

Property	Value/remark
Physical state at ntp	Colourless to light yellow liquid - darkens in absence of stabilisers
Melting point	13-14°C
Boiling point	90-92°C at 13 hPa
Density	1.045 g/cm^3 at 20°C
Vapour density	3.8
Vapour pressure	0.12 hPa at 20°C
Water solubility	Miscible with water at 20°C
Log octanol-water partition coefficient (log Kow)	0.4 (measured value at 25°C) -0.37 (calculated value)
Flash point	95°C
Auto-flammability	240°C
Explosive properties	Explosive limits in air: 1.4-10% by volume
Oxidising properties	Not an oxidising agent
Other hazardous reactions	Can polymerise exothermically in the absence of stabilisers, particularly in acid conditions or if shelf life exceeded

1.3 CLASSIFICATION

The classification and labelling of N-VP 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

There is no classification for effects on the environment.

2 GENERAL INFORMATION ON EXPOSURE

There are understood to be only two producers of N-VP worldwide, one in the USA and one in the EU. The annual production volume in 1999 was 10,000-50,000 tonnes. The majority of N-VP that is sold within the EU is used in the production of polyvinyl pyrrolidone (PVP) or copolymers for a wide range of applications. It is also used as a reactive thinner in UV-cured inks and coatings.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

The major characteristics of N-VP relevant for the exposure assessment are:

- readily biodegradable,
- an estimated Henry's law constant of 0.0056 $Pa \cdot m^3 \cdot mole^{-1}$,
- a low log Kow value of 0.4,
- an estimated atmospheric half-life of 10.4 hours.

The low log Kow value indicates that the substance is not expected to adsorb strongly to soil, sediment or suspended matter, and so the substance is expected to leach from soil. The low log Kow also indicates that the substance is unlikely to bioconcentrate or bioaccumulate in the environment. The substance is expected to volatilise slowly from water, but once in the atmosphere will be quickly degraded.

In wastewater treatment plants it is estimated that 87.2% of any discharge of N-VP will be degraded, with 12.6% remaining in the water discharged from the plant. Minor amounts are predicted to be adsorbed onto sludge (0.16%) and to be directed to air (0.0024%).

Environmental releases

Site-specific information on releases from production and the main processing sites has been provided. These sites account for >90% of the total use of N-VP. Site-specific information has also been provided for some smaller sites, but this information may not be applicable to all sites using N-VP. For this reason a generic approach, using the default release estimates given in the EU Technical Guidance Document (TGD), has been used for the remaining smaller sites. In addition to these releases, the releases of residual N-VP present in the polymeric products is also accounted for in the assessment.

The methods in the TGD were used to estimate predicted environmental concentrations (PECs) for water, sediment, wastewater treatment plants, air and soil. **Table 3.1** shows the PECs calculated for the various stages of the lifecycle of N-VP. The calculated levels in air are very low for all lifecycle stages and so are not presented here. In addition, the substance has a low bioaccumulation potential and so the assessment for secondary poisoning through the food chain is not necessary. There are no measured data for N-VP and so it is not possible to compare the PECs with concentrations actually found in the environment.

3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. Sediment and wastewater treatment plants)

Results of short-term toxicity tests are available for fish, invertebrates and algae. The lowest value from these tests was a 48-hour EC_{50} of 45 mg/l for the invertebrate *Daphnia magna.* In accordance with the TGD, an assessment factor of 1,000 is applied to this value to give a predicted no effect concentration (PNEC) of 45 µg/l for the aquatic compartment.

There are no toxicity data for sediment-dwelling organisms and so a provisional PNEC has been calculated using the equilibrium partitioning method described in the TGD. This gives a tentative PNEC of 51.8 µg/kg wet weight for the sediment compartment.

N-VP showed low toxicity to microorganisms. The lowest NOEC reported was >1,995 mg/l for activated sludge respiration inhibition. Applying an assessment factor of 100 to this value gives a $PNEC_{microorganisms}$ of 19.95 mg/l for use in the assessment of effects on the functioning of wastewater treatment plants.

Terrestrial compartment

There are no toxicity studies available on soil-dwelling organisms and so a provisional PNEC for soil of 18.7 µg/kg has been calculated using the equilibrium partitioning method.

Atmosphere

No data are available to allow a PNEC to be derived for this compartment. However, atmospheric concentrations of N-VP are likely to be very small, and so adverse effects are unlikely.

Secondary poisoning

In line with the methods outlined in the TGD, the substance is of no immediate concern for secondary poisoning and so it is not necessary to derive a PNEC for this endpoint.

3.3 RISK CHARACTERISATION

The realistic worst-case PEC/PNEC ratios are summarised in **Table 3.1**. A ratio greater than 1 indicates a potential concern.

Table 3.1 Summary of PECs and PEC/PNEC ratios

Media	Release source	PEC	PEC/PNEC
Surface Water	Production/processing – site-specific information	0.085 µg/l	0.0019
	Processing at smaller sites (site-specific)	0.040 µg/l	0.0009
	Processing at smaller sites (worst case default)	0.21-44.3 µg/l	0.0047-0.98
	Ink/varnish formulation	3.20 µg/l	0.071
	Ink/varnish processing	1.93 µg/l	0.043
	Regional	0.0388 µg/l	0.00086
Sediment	Production/processing – site-specific information	0.098 µg/kg wet wt.	0.0019
	Processing at smaller sites (site-specific)	0.046 µg/kg wet wt.	0.0009
	Processing at smaller sites (worst case default)	0.24-50.9 µg/kg wet wt.	0.0047-0.98
	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.	0.00068
Waste water treatment plant	Production/processing – site-specific information	1.48 mg/l	0.074
	Processing at smaller sites (site-specific)	$8.8 \cdot 10^{-3}$ µg/l	$4.4 \cdot 10^{-7}$
	Processing at smaller sites (worst case default)	92.3-442 µg/l	0.0046-0.022
	Ink/varnish formulation	31.6 µg/l	0.0016
	Ink/varnish processing	19.0 µg/l	0.00095
Soil	Production/processing – site-specific information	0.13 µg/kg wet wt.	0.007
	Processing at smaller sites (site-specific)	$7 \cdot 10^{-3}$ µg/kg wet wt.	0.00037
	Processing at smaller sites (worst case default)	3.0-14.3 µg/kg wet wt.	0.16-0.76
	Ink/varnish formulation	1.03 µg/kg wet wt.	0.055
	Ink/varnish processing	0.62 µg/kg wet wt.	0.033
	Regional	$3.1 \cdot 10^{-3}$ µg/kg wet wt.	0.00017

Aquatic compartment (incl. sediment)

The PEC/PNEC ratios for surface water, sediment and sewage treatment are <1 for all scenarios considered, indicating that the risk to the aquatic compartment from the production and use of N-VP, and release of N-VP during use of polymers containing residual monomer, is low: **conclusion (ii)**.

Terrestrial compartment

The screening assessment for soil gives PEC/PNEC ratios <1 for all scenarios considered, indicating that the risk to the terrestrial compartment from the production and use of N-VP, and release of N-VP during use of polymers containing residual monomer, is low: **conclusion (ii)**.

Atmosphere

Effects on the atmosphere from production and use of N-VP, and release of N-VP during use of polymers containing residual monomer, are not expected to occur due to the relatively low release and the rapid degradation rate in air: **conclusion (ii)**.

Secondary poisoning

The log Kow for N-VP is low and there are no other indications of bioaccumulation potential. Therefore no assessment is necessary and it can be concluded that the risk of secondary poisoning from the production and use of N-VP, and release of N-VP during use of polymers containing residual monomer, is low: **conclusion (ii)**.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Occupational exposure

Occupational exposure to N-VP can potentially occur during its manufacture, during production and use of its polymers, during the manufacture and use of UV curing inks and lacquers, and during the manufacture of contact lenses.

For monomer and polymer manufacture, most exposures are less than 0.1 ppm (8-hour TWA); this value is taken as the reasonable worst-case exposure. The highest dermal exposures are likely to occur during filter changing, with an estimated reasonable worst-case value of 1 $mg \cdot cm^{-2} \cdot day^{-1}$.

Exposure during the manufacture of UV curing inks and lacquers may be up to 5 ppm (8-hour TWA), with dermal exposure predicted to be in the range 0.1-1 $mg \cdot cm^{-2} \cdot day^{-1}$, although most exposures are likely to be at the bottom of this range.

Occupational exposures of up to 14 ppm (8-hour TWA) are predicted for UV screen printers operating without LEV and manually printing. Dermal exposure for this scenario is estimated to be up to 0.7 $mg \cdot cm^{-2} \cdot day^{-1}$.

For users of UV lacquers and for manufacturers of contact lenses, 8-hour TWA exposures are estimated to be 0.045 ppm and 0.25 ppm, respectively. Dermal exposure is estimated to be up to 0.09 $mg \cdot cm^{-2} \cdot day^{-1}$ for the use of UV lacquers and up to 0.05 $mg \cdot cm^{-2} \cdot day^{-1}$ for the manufacture of contact lenses.

Exposure to residual N-VP monomer during the use of polymers is negligible.

Consumer exposure

N-VP monomer is not used directly in consumer products but may be present in trace amounts as a residue in products containing PVP. Consumer use of these products may result in exposure to residual monomer.

The maximum daily exposure to N-VP monomer in pharmaceutical products is estimated to be 10 μg. For N-VP present in cosmetics and toiletries, maximum daily exposure is estimated to be less than 9 μg, and for wearers of contact lenses, maximum daily exposure is 13 μg. PVP may also be used in certain types of washing powders, the use of which could lead to an exposure of up to 8 μg, as a very worst-case prediction. Exposure arising from the use of PVP in denture fixative is estimated to be up to 6 μg daily.

It is possible that a consumer could receive daily exposure to N-VP from each of these individual sources, resulting in a total combined daily exposure of 46 μg.

Humans exposed via the environment

The highest total daily intake of N-VP via the environment arises from N-VP production and processing and is estimated to be $4.28 \cdot 10^{-3}$ $mg \cdot kg^{-1} \cdot day^{-1}$. Exposures at a regional level result in an intake of $1.5 \cdot 10^{-6}$ $mg \cdot kg^{-1} \cdot day^{-1}$. Considering exposures via the inhalation route

alone, the highest daily inhalation exposure is 0.13 $\mu g \cdot kg^{-1} \cdot day^{-1}$ (from N-VP production), and $7.5 \cdot 10^{-9}$ $mg \cdot kg^{-1} \cdot day^{-1}$ for exposures at a regional level.

4.1.2 Effects assessment

No useful human data are available relating to the effects of exposure to N-VP and therefore the available information is based on studies in animals. 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. 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 extensively metabolised to form highly polar compounds, which are rapidly eliminated (within 24 hours), predominantly in the urine. However, the two major urinary metabolites of N-VP have not been characterised. Other routes of elimination include the faeces (via the bile), and as CO_2 in exhaled air, accounting for around 5-8% and 3% of the administered dose respectively. N-VP and its metabolites do not bind to plasma proteins nor to DNA to any great extent.

N-VP is moderately toxic following single exposure by all three exposure routes. The liver and kidneys have been identified as target organs by all three routes of exposure. Irritation of the mucous membranes lining the gastrointestinal or respiratory tracts commonly occurs following single oral or inhalation exposure. 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 eye were specifically investigated in repeated inhalation studies was only 20 ppm. It is predicted that N-VP has the potential to cause respiratory tract irritation. Based on observations from inhalation toxicity studies, the NOAEL for sensory irritation may lie around 15 ppm. N-VP is not a skin sensitiser, and is not predicted to cause respiratory tract 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. A NOAEL for lifetime exposure cannot be identified; a LOAEL of 5 ppm, identified from a 3-month study is used for risk characterisation. Signs of toxicity in rats at this exposure level included 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. Inhalation of concentrations of 15 ppm (69 $mg.m^{-3}$) 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 $mg \cdot kg^{-1} \cdot day^{-1}$ has been identified in a drinking water study. However, gavage doses of up to 60 $mg \cdot kg^{-1} \cdot day^{-1}$ 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 genotoxic. N-VP vapour is clearly carcinogenic in rats, causing tumours in the liver, nasal cavity and larynx. 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. This observation 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. However, it is unclear what toxicological process(es) underlie(s) 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.

The potential for adverse effects on fertility has not been specifically investigated in experimental animals. However, there were no indications from repeated dosing studies for an adverse effect on the reproductive organs and thus 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

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: **conclusion (iii).** There are also concerns for single exposure toxicity and for respiratory tract irritation in scenarios where there is the potential for high peak exposures, namely manufacture of N-VP and its polymers, manufacture of UV curing inks and lacquers and use of UV curing inks: **conclusion (iii).** It is also recommended that steps should be taken to prevent eye contact with liquid N-VP in any situation where this may occur.

There are no concerns for skin irritancy, skin sensitisation, asthmagenicity, mutagenicity and effects on fertility: **conclusion (ii)**.

Consumers

Exposure to N-VP via PVP (polymers) is very low, and none of the exposure scenarios give rise to concern for consumers, for any endpoint: **conclusion (ii)**.

Humans exposed via the environment

For both local and regional sources, exposure to N-VP does not give cause for concern for any of the identified human health effects: **conclusion (ii)**.

Combined exposure

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 the environment are so low that they will not add significantly to the body burden received at work. Therefore the conclusions reached for workers apply to combined exposure.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

There is no cause for concern identified from any of the exposures with relation to physico-chemical properties: **conclusion (ii)**.

5 RESULTS

5.1 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.

The production and use of N-VP, and the release of N-VP during use of polymers that contain residual N-VP 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.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

The key health effects of concern are single exposure toxicity, eye and respiratory tract irritation, repeated dose toxicity and carcinogenicity.

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.

Workers

Concerns for single exposure toxicity and respiratory tract irritation arise in those scenarios where there is the potential for high peak exposures, namely manufacture of N-VP and its polymers, manufacture of UV curing inks and lacquers and use of UV curing inks. In relation to repeated dose toxicity and carcinogenicity, there are concerns for the manufacture of N-VP and its polymers, the use of N-VP in the manufacture of UV curing inks and lacquers, the use of UV curing inks and lacquers containing N-VP, and the use of N-VP in the manufacture of contact lenses. 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.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures 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.

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.

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.

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.

5.2.2 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.

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.