N-VINYL-2-PYRROLIDONE AND POLYVINYL PYRROLIDONE

Data were last reviewed in IARC (1979) and the compounds were classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

1.1 Chemical and physical data

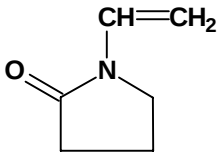
1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 88-12-0

Chem. Abstr. Name: 1-Ethenyl-2-pyrrolidinone

Synonyms: Vinylbutyrolactam; vinylpyrrolidinone; 1-vinylpyrrolidinone; *N*-vinyl-pyrrolidinone; 1-vinyl-2-pyrrolidinone; *N*-vinyl-2-pyrrolidinone; vinylpyrrolidone; *N*-vinylpyrrolidone; 1-vinyl-2-pyrrolidone

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_6H_9NO Relative molecular mass: 111.1

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (Lewis, 1993)

(*b*) *Boiling-point*: 193°C (at 53 kPa) (Lide, 1997)

(*c*) *Melting-point*: 13.5°C (Lide, 1997)

(*d*) *Solubility*: Miscible with water and most organic solvents; partially miscible with aliphatic hydrocarbons (Harreus, 1993)

(*e*) *Vapour pressure*: 12 Pa at 20°C (Harreus, 1993)

(*f*) *Stability*: Flash-point, 98.4°C; polymerizes readily in the presence of oxygen (Lewis, 1993)

(*g*) *Conversion factor*: $mg/m^3 = 4.54 \times ppm$

1.2 Production and use

Information available in 1995 indicated that *N*-vinyl-2-pyrrolidone was produced in four countries (China, Germany, United Kingdom, United States) (Chemical Information Services, 1995).

It is used in the manufacture of polyvinylpyrrolidone (PVP), in the manufacture of copolymers with, for example, acrylic acid, acrylates, vinyl acetate and acrylonitrile and in the synthesis of phenolic resins. About 10–15% of the monomer is used in the pharmaceutical industry for the production of PVP–iodine complex used as a disinfectant. It is also used as a reactive solvent of ultraviolet-curable resins for the production of printing inks and paints as paper and textile auxiliaries, and as an additive in the cosmetics industry (Harreus, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 6000 workers in the United States were potentially exposed to *N*-vinyl-2-pyrrolidone (see General Remarks).

1.3.2 *Environmental occurrence*

No data were available to the Working Group.

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not proposed any occupational exposure limit for *N*-vinyl-2-pyrrolidone in workplace air. Russia has a short-term exposure limit of 1 mg/m^3 for exposure in workplace air, with a skin notation (International Labour Office, 1991).

No international guideline for *N*-vinyl-2-pyrrolidone in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Polyvinyl pyrrolidone was tested in mice, rats and rabbits by several routes of administration, using materials of various molecular weights. Repeated subcutaneous injections of an aqueous solution of polyvinyl pyrrolidone to rats caused local sarcomas. Single or several subcutaneous or intraperitoneal implantations of polyvinyl pyrrolidone powder resulted in a low incidence of local tumours. After several intravenous injections

or after intraperitoneal implantation of polyvinyl pyrrolidone, tumours occurred in rats at distant sites, including the reticuloendothelial system; the results of these experiments do not permit an evaluation of a possible association of these distant tumours with the treatment (IARC, 1979).

3.1 Inhalation exposure

Rat: Groups of 60 male and 60 female Sprague-Dawley rats, 37–39 days of age, were administered *N*-vinyl-2-pyrrolidone (purity, 99.9%) by whole-body exposure at concentrations of 5, 10 or 20 ppm [22, 45 or 90 mg/m^3] vapour for 6 h per day on five days per week for 24 months. A group of 70 males and 70 females exposed to air alone served as controls. Macroscopic examination was carried out on all animals, and histopathological examination was performed on almost all organs and all gross lesions. Exposed animals displayed a significant reduction in body weight gain. No difference in survival was noted in any group. As shown in Table 1, adenomas and adenocarcinomas of the nasal cavity and hepatocellular carcinomas occurred with significantly positive dose-related trends in treated groups of each sex. In addition, squamous carcinomas of the larynx were found in rats of the high-dose group. Increased incidences of inflammation, atrophy of the olfactory epithelium, hyperplasia and metaplasia in the nasal cavity, focal hyperplasia, foci of cellular alteration and spongiosis hepatis in the liver, and epithelial hyperplasia in the larynx were also seen in the exposed groups (Klimisch *et al*., 1997a).

Groups of 30 male and 30 female Sprague-Dawley rats, 37–39 days of age, were administered *N*-vinyl-2-pyrrolidone (purity, 99.9%) by whole-body inhalation at concen-

Table 1. Incidence of neoplasms in *N*-vinyl-2-pyrrolidone-treated Sprague-Dawley rats

Sex	Male				Female			
Exposure concentration (ppm)	0	5	10	20	0	5	10	20
Number	70	60	60	60	70	60	60	60
Nasal cavity								
Adenoma	0	9	9	11*	0	2	8	14**
Adenocarcinoma	0	0	4	6**	0	0	0	4*
Liver								
Hepatocellular carcinoma	1	6	5	17**	1	3	6	26**
Larynx								
Squamous carcinoma	0	0	0	4	0	0	0	4

From Klimisch *et al*. (1997a)

* Peto's analysis for trend, $p < 0.001$

** Peto's analysis for trend, $p < 0.0001$

trations of 0, 5, 10 or 20 ppm [0, 22, 45 or 90 mg/m^3] vapour for 6 h per day on five days per week for 12 months; 10 males and 10 females of each group were killed after three months of treatment. Macroscopic examination was carried out on all animals, and histopathological examination was performed on the liver, nasal cavity and pancreas. Adenomas of the nasal cavity were seen in one male in the low-dose group and one male and one female in the high-dose group at 12 months of treatment. Foci of cellular alteration (clear cell areas) of the liver were observed in low-dose females at 12 months, and in mid- and high-dose males and females at three and 12 months [incidence and statistical significance unspecified]. Also increased liver weight, spongiosis hepatis and nasal lesions (inflammation, atrophy of the olfactory epithelium, hyperplasia of basal cells of the respiratory and olfactory epithelium, and hyperplasia of the submucosal glands) were observed in the treated groups (Klimisch *et al*., 1997b).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Polyvinyl pyrrolidone of molecular weight of less than 25 000 can be excreted via the kidneys. Following intravenous administration to terminal cancer patients of polyvinyl pyrrolidone (average molecular weight 40 000), approximately one-third was eliminated in urine in 6 h and another one-third in the following 18 h. At autopsy, accumulation was observed in the kidneys, lung, liver, spleen and lymph nodes (IARC, 1979).

4.1.2 *Experimental systems*

The disposition of *N*-[^{14}C]vinyl-2-pyrrolidone has been studied in male Sprague-Dawley rats following a single intravenous injection. The plasma half-life was 1.9 h. Up to 6 h after dosing, the highest tissue concentrations of radioactivity were found in the liver and small intestines. By that time, about 19% of the dose had been excreted in bile, yet, by 12 h, only about 0.4% had been excreted in faeces while about 75% had been excreted in urine. Thus, there appeared to be substantial enterohepatic recirculation of biliary metabolites. Very small quantities of the administered material were excreted unchanged. In a single rat, 12% of the urinary radioactivity was present as acetic acid. Other metabolites were not identified (McClanahan *et al*., 1984).

There was no significant metabolism of polyvinyl pyrrolidone injected intravenously into rats, rabbits or dogs. Retention is proportional to molecular weight (IARC, 1979).

4.2 Toxic effects

4.2.1 *Humans*

In liver biopsies from people who had received polyvinyl pyrrolidone intravenously, basophilic globular deposits were observed in Kupffer cells, occasionally accompanied by

mild inflammation. Thesaurismosis (a foam-cell storage phenomenon characterized by swollen cells with reticulated nuclei loaded with vacuoles or deposits of polyvinyl pyrrolidone) has been observed after inhalation of hair sprays containing polyvinyl pyrrolidone and may be accompanied by pulmonary fibrosis and pneumonia (IARC, 1979).

4.2.2 *Experimental systems*

A thesaurismotic reaction has been found in many organs, but particularly the spleen, in mice, rats, rabbits and dogs treated with polyvinyl pyrrolidone (IARC, 1979).

The toxicology of *N*-vinyl-2-pyrrolidone in rodents described in unpublished reports has been summarized (Klimisch *et al*., 1997a,b). Most of these studies involved inhalation exposure to concentrations of up to 120 ppm [545 mg/m^3] (a lethal concentration) for periods ranging from one week to one year. Oral administration studies (gavage and drinking-water) have also been conducted in rats at dose levels of up to 100 mg/kg bw per day. *N*-Vinyl-2-pyrrolidone is an irritant to skin and mucous membranes, causes hepatotoxicity in rats and mice, but not Syrian hamsters, and causes nasal damage upon inhalation. Nasal cavity inflammation, atrophy of olfactory epithelium and hyperplasia of the basal cells of the respiratory and olfactory epithelium were seen in Sprague-Dawley rats exposed to 5 ppm [23 mg/m^3] or more for 6 h per day on five days per week for three months. Haematological changes (reduced haemoglobin, erythrocyte count and haematocrit) and blood chemistry changes (reduced plasma protein and increased γ-glutamyltranspeptidase) were also observed.

4.3 Reproductive and developmental effects

No data were available to the Working Group on either substance.

4.4 Genetic and related effects

No data were available to the Working Group on either substance.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Little information was available to the Working Group regarding potential exposures to *N*-vinyl-2-pyrrolidone.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

N-Vinyl-2-pyrrolidone was tested for carcinogenicity in one experiment in rats by inhalation exposure. It produced adenomas and adenocarcinomas of the nasal cavity, squamous carcinomas of the larynx and hepatocellular carcinomas in both sexes.

Another 12-month inhalation experiment in rats of the same strain indicated occurrence of adenomas of the nasal cavity and foci of cellular alteration of the liver.

Polyvinyl pyrrolidone was tested for carcinogenicity in mice, rats and rabbits by several routes of administration, producing local tumours.

5.4 Other relevant data

N-Vinyl-2-pyrrolidone metabolites and polyvinyl pyrrolidone are excreted mainly in urine. Inhalation of low concentrations of *N*-vinyl-2-pyrrolidone by rats can cause nasal cavity inflammation, atrophy of olfactory epithelium and hyperplasia of the basal cells of the respiratory and olfactory epithelium. In humans and experimental animals, polyvinyl pyrrolidone accumulates in vacuoles of cells of many organs and, in humans, may be accompanied by pulmonary fibrosis and pneumonia. There have been no genetic toxicity studies with either compound.

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of *N*-vinyl-2-pyrrolidone or polyvinyl pyrrolidone were available.

There is *limited evidence* for the carcinogenicity of *N*-vinyl-2-pyrrolidone in experimental animals.

There is *limited evidence* for the carcinogenicity of polyvinyl pyrrolidone in experimental animals.

Overall evaluation

N-Vinyl-2-pyrrolidone is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Polyvinyl pyrrolidone is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

American Conference of Governmental Industrial Hygienists (ACGIH) (1997) *1997 TLVs® and BEIs®*, Cincinnati, OH

Chemical Information Services (1995) *Directory of World Chemical Producers 1995/96 Edition*, Dallas, TX

Harreus, A.L. (1993) 2-Pyrrolidone. In: Gerhartz, W. & Yamamoto, Y.S., eds, *Ullmann's Encyclopedia of Chemical Technology*, 5th rev. Ed., Vol. A22, Deerfield Beach, FL, VCH Publishers, pp. 457–463

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Lyon, pp. 461–477

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 70, 73

International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd Ed. (Occupational Safety and Health Series No. 37), Geneva, pp. 418–419

Klimisch, H.-J., Deckardt, K., Gembardt, C., Hildebrand, B., Küttler, K. & Roe, F.J.C. (1997a) Long-term inhalation toxicity of *N*-vinylpyrrolidone-2 vapours. Studies in rats. *Food chem. Toxicol.*, **35**, 1041–1060

Klimisch, H.-J., Deckardt, K., Gembardt, C., Hildebrand, B., Küttler, K. & Roe, F.J.C. (1997b) Subchronic inhalation and oral toxicity of *N*-vinylpyrrolidone-2. Studies in rodents. *Food chem. Toxicol.*, **35**, 1061–1074

Lewis, R.J., Jr (1993) *Hawley's Condensed Chemical Dictionary*, 12th Ed., New York, Van Nostrand Reinhold, p. 1218

Lide, D.R., ed. (1997) *CRC Handbook of Chemistry and Physics*, 78th Ed., Boca Raton, FL, CRC Press, p. 3-306

McClanahan, J.S., Lin, Y.C. & Digenis, G.A. (1984) Disposition of *N*-vinyl-2-pyrrolidinone in the rat. *Drug chem. Toxicol.*, **7**, 129–148

NOES (1997) *National Occupational Exposure Survey 1981-83*, Unpublished data as of November 1997, Cincinnati, United States Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health

WHO (1993) *Guidelines for Drinking Water Quality*, 2nd Ed., Vol. 1, *Recommendations*, Geneva