The MAK Collection for Occupational Health and Safety

N-Vinyl-2-pyrrolidone

MAK Value Documentation, addendum – Translation of the German version from 2014

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N-Vinyl-2-pyrrolidone / 1-Ethenylpyrrolidin-2-one

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated *N*-vinyl-2-pyrrolidone [88-12-0], considering all toxicological endpoints. Available publications and unpublished study reports are described in detail.

The main critical effects are the carcinogenic effects in the liver, nose and larynx after inhalation, with cell proliferation in the liver and degeneration and hyperplasia in the nasal epithelium starting at 0.5 ml/m³ being the most sensitive endpoints. The no observed adverse effect concentration (NOAEC) for both organs is 0.2 ml/m³. As a NOAEC was obtained and the substance is not genotoxic, *N*-vinyl-2-pyrrolidone is classified in Carcinogen Category 4.

As the NOAEC of 0.2 ml/m³ for cell proliferation in the liver after 28 days was lower than that after 7 days, a MAK value for *N*-vinyl-2-pyrrolidone of 0.02 ml/m³ has been established, taking into account the short study duration. As the MAK value is derived from a systemic effect, the substance is classified in Peak Limitation Category II with the default excursion factor of 2, because the half-life in humans is not known.

In a developmental toxicity study in rats, *N*-vinyl-2-pyrrolidone at 20 ml/m³ markedly reduced body weights in dams and foetuses and increased the incidence of variations in foetuses. As developmental toxicity occurred at a maternally toxic concentration, and the 250-fold difference between the NOAEC for developmental toxicity of 5 ml/m³ and the MAK value of 0.02 ml/m³ is sufficiently large, *N*-vinyl-2-pyrrolidone is classified in Pregnancy Risk Group C.

N-Vinyl-2-pyrrolidone is neither mutagenic nor clastogenic and therefore not classified in one of the categories for germ cell mutagens.

As the amount calculated to be absorbed through the skin is far above the amount absorbed daily by exposure at the level of the MAK value, *N*-vinyl-2-pyrrolidone is designated with an "H" (for substances that can be absorbed through the skin in systemically toxic amounts).

The substance is not regarded as a sensitizer, because there are no corresponding clinical findings in humans and a Buehler test in guinea pigs was negative.

Keywords

N-vinyl-2-pyrrolidone; N-vinylpyrrolidone; N-vinylpyrrolid-2-one; 1-vinyl-2-pyrrolidone; N-vinylpyrrolidinone; 1-vinyl-2-pyrrolidinone; 1-ethenyl-2-pyrrolidinone; vinylbutyrolactam; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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N-Vinyl-2-pyrrolidone

[88-12-0]

Supplement 2014

MAK value (2013)	**0.02 ml/m³ (ppm) ≙ 0.09 mg/m³**
Peak limitation (2013)	**Category II, excursion factor 2**
Absorption through the skin (2004)	**H**
Sensitization	**–**
Carcinogenicity (2013)	**Category 4**
Prenatal toxicity (2013)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
log K_{OW}[1)]	0.37–0.40 (Environment Canada, Health Canada 2010)
Solubility	108 g/l water (calculated) (Environment Canada, Health Canada 2010)

N-Vinyl-2-pyrrolidone is used in the production of polymers, and ultraviolet curing coatings and inks.

For *N*-vinyl-2-pyrrolidone, documentation is available from 1991 (documentation "N-Vinyl-2-pyrrolidone" 1993) regarding its classification in Carcinogen Category 2, and a supplement from 2004 (documentation "N-Vinyl-2-pyrrolidone" 2004) for its designation with an "H" (for substances which can be absorbed through the skin. In the meantime, new studies have become available for *N*-vinyl-2-pyrrolidone which make it necessary to reassess the classification of the substance.

1 Toxic Effects and Mode of Action

In rabbits, the irritating effects of *N*-vinyl-2-pyrrolidone on the skin are slight; in the eyes, irritation is more pronounced and leads to corneal opacity. The target or-

1) octanol/water partition coefficient.

gans after single and repeated administration are the liver, kidneys and haematopoietic system, and after inhalation also the nasal cavity and the nasal mucosa. *N*-Vinyl-2-pyrrolidone is not mutagenic or clastogenic. In a 4-week study with rats, *N*-vinyl-2-pyrrolidone caused cell proliferation in the liver and histopathological changes in the nasal epithelium at concentrations of 0.5 ml/m³ and above. At the low concentration of 5 ml/m³, no adverse effects on the liver were found in a 90-day study; cell proliferation was not specifically investigated, however. In a 2-year inhalation study with rats, *N*-vinyl-2-pyrrolidone produced carcinomas in the liver at the low concentration of 5 ml/m³ and above; the incidence increased in a concentration-dependent manner. At higher concentrations, these tumours were observed also in the nasal cavity and the larynx.

The results of a Buehler test in guinea pigs were negative. In a developmental toxicity study with rats, variations in the offspring were produced only after concentrations which were also toxic to the dams of 20 ml/m³.

2 Mechanism of Action

There are three conceivable causes for the initiation of the carcinogenic effects of *N*-vinyl-pyrrolidone: the formation of nitrosamine from pyrrolidone and nitrites contained in the food, genotoxic effects, for example of a main metabolite, or tissue toxicity with subsequent cell proliferation.

The pyrrolidone possibly released in the stomach (see Section 3.2) could, as a result of contamination of the food with nitrite, form a nitrosamide via nitrosation. However, the liver toxicity of *N*-vinyl-2-pyrrolidone (cell proliferation, foci) was more pronounced after inhalation than after ingestion, which makes this hypothesis unlikely. Also, the effects in the liver within an animal group are very homogeneous. This unlikely pattern would not be postulated for tumour formation after the ingestion of *N*-vinyl-2-pyrrolidone adhering to the fur of the animals and the accompanying contamination with nitrite or nitrosamide. This hypothesis is also contradicted by the fact that no tumours in the liver were found in a 2-year inhalation study (up to 150 ml/m³) with morpholine, which is readily nitrosated (supplement "Morpholin" 1996, available in German only), although nitrosomorpholine itself is a strong carcinogen. In addition, neither caprolactam (supplement "ε-Caprolactam" 1992), formamide (documentation "Formamide" 2013) or pyrrolidone (BASF AG 1998) were found to have a potential for liver toxicity. Unlike their *N*-vinyl derivatives, these substances can be administered in high doses without any effects on the liver. In contrast, the other *N*-vinyl compounds such as *N*-vinyl caprolactam (BASF AG 1995 a) and *N*-vinyl formamide (BASF AG 1995 b) caused liver toxicity similar to that of *N*-vinyl-2-pyrrolidone after medium-term inhalation exposure. Therefore the decisive toxophore is the vinyl group at the nitrogen. The overall evidence therefore speaks against the liver effects being produced by nitrite contamination or the formation of nitrosamides.

The acetaldehyde in the acidic gastric juices possibly cleaved from *N*-vinyl-2-pyrrolidone is genotoxic and, under specific conditions, has clastogenic properties (documentation "Acetaldehyde" 2013). In the stomach, however, even after long-term exposure to *N*-vinyl-2-pyrrolidone, no corresponding effects were found. To

date, it has not been investigated whether the release of acetaldehyde by enzymatic means is possible outside the stomach, such as is found in the case of vinyl acetate, which is cleaved by esterases in the extracellular space. As, however, all available genotoxicity tests with *N*-vinyl-2-pyrrolidone both in vitro and in vivo, including an in vivo DNA-binding study, yielded negative results, the amount of acetaldehyde possibly released is not sufficient to be the cause of the carcinogenicity of *N*-vinyl-2-pyrrolidone.

In the serum of rats, *N*-vinyl-2-pyrrolidone has a relatively long half-life of 1.9 hours so that, after inhalation, the substance can reach the liver as target organ. In a 28-day inhalation study with rats, cell proliferation in the liver was found at a concentration of 0.5 ml/m^3 in the inhaled air. The concentration–effects curve for *N*-vinyl-2-pyrrolidone is steep and rises consistently (cell proliferation at 0.5 ml/m^3, liver tumours at 5 ml/m^3 and above in the long-term study, tumours at 45 ml/m^3 in the stop-exposure protocol; BASF AG 1992; Klimisch et al. 1997); the concentration in the inhaled air is apparently more important than the duration of exposure. From the comparison of the dose–response relationship for carcinogenicity and for cell proliferation, it can be assumed that liver toxicity, followed by cell proliferation, is the relevant mechanism for tumour formation caused by *N*-vinyl-2-pyrrolidone.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

There are no studies in humans available.

Six hours after single intravenous injections of radioactively labelled *N*-vinyl-2-pyrrolidone, the highest ^{14}C activity occurs in rats in the liver and small intestine. The half-life of *N*-vinyl-2-pyrrolidone in the plasma of rats is 1.9 hours and that of dogs 20 to 40 minutes. Within 12 hours 75% of the radioactivity is eliminated with the urine, and within 6 hours 19% with the bile (documentation "N-Vinyl-2-pyrrolidone" 1993; EU 2003).

With the data for the solubility of the substance in water (108 g/l), dermal penetration rates of 0.075, 0.11 and 0.48 mg/cm^2 and hour following exposure to a saturated aqueous solution can be calculated according to the models of Guy and Potts (1993), Wilschut et al. (1995) and Fiserova-Bergerova et al. (1990), respectively. For a 2000 cm^2 area of skin (both hands and forearms) at least 150 mg can therefore be absorbed.

3.2 Metabolism

Less than 1% of the radioactivity eliminated with the urine or bile within 12 hours consisted of the unchanged substance. *N*-Vinyl-2-pyrrolidone is sensitive to acid and in the acidic environment of the stomach a certain amount might hydrolyze to acetaldehyde and pyrrolidine-2-one after oral administration (documentation "N-Vinyl-2-pyrrolidone" 1993), although this has not actually been demonstrated.

On the basis of its chemical structure, also the formation of an epoxide seems possible. However, DNA adducts would then be expected. This has not been confirmed experimentally (see Section 5.6.2).

4 Effects in Humans

Since the documentation of 1991 (documentation "N-Vinyl-2-pyrrolidone" 1993), there are still no reports available of clinical findings with *N*-vinyl-2-pyrrolidone in humans. In the EU Risk Assessment Report, a morbidity study is described, in which no substance-related health effects occurred in workers exposed to an unknown concentration of *N*-vinyl-2-pyrrolidone (EU 2003).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

There are no new studies available.

In rats, the lowest LC_{50} or LD_{50} values for *N*-vinyl-2-pyrrolidone were 3070 mg/m³ (667 ml/m³; 4 hours, aerosol) after inhalation exposure, between 834 and 1700 mg/kg body weight after oral administration, and about 2 ml pure substance (4 hours) after dermal application. An oral LD_{50} of 900 mg/kg body weight was obtained in mice, and an oral LD_{50} of more than 1 ml/kg body weight in rabbits. The dermal LD_{50} in rabbits was 4000 mg/animal or 560 mg/kg body weight after semi-occlusive application to the ear. After all three exposure routes, narcosis, balance disorders, nasal discharge, salivation, irritation of the skin and mucosa and damage to the liver, spleen and kidneys were observed as signs of intoxication. In addition, inhalation exposure led to pulmonary oedema. After dermal application, also systemic toxicity occurred (documentation "N-Vinyl-2-pyrrolidone" 1993; Environment Canada, Health Canada 2010; EU 2003).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

The documentation from 1991 (documentation "N-Vinyl-2-pyrrolidone" 1993) already described dysproteinaemia, haematological changes suggestive of anaemia and pathological changes in the liver, nasal cavity and larynx after repeated exposure of rats and mice to *N*-vinyl-2-pyrrolidone. Centrilobular necrosis was found in the liver, with an increase in glycogen in the hepatocytes, accumulation of fat and degenerative changes in the cell nucleus occurring in this region. In the nasal cavity, inflammation occurred in the olfactory and respiratory epithelium and, after prolonged exposure, also in the larynx. In rats, a NOAEC (no observed adverse effect concentration) of 1 ml/m³ (4.61 mg/m³) was obtained after exposure to *N*-vinyl-2-pyrrolidone vapour for 3 months. Clear signs of irritation in the nasal cavity

and dysproteinaemia occurred at concentrations of 5 ml/m³, although there were no histopathological changes in the liver. After exposure to concentrations of 5 ml/m³ for 2 years, an increased number of foci and hyperplasia were found in the liver. Exposure to 15 ml/m³ caused liver toxicity in rats within one week. Deaths occurred in mice at 45 ml/m³ and above, and in rats at 120 ml/m³ and above (documentation "N-Vinyl-2-pyrrolidone" 1993; BASF AG 1985; EU 2003).

Female rats were exposed to concentrations of 45 ml/m³ for 3 months. Groups of 15 animals were examined after 7 weeks, at the end of the 3-month exposure period and after recovery periods of 9 or 21 months. Marked regeneration of the liver was seen (after 12 months). However, at the end of the 24-month study period, liver carcinomas were found in 2 of 6 surviving exposed animals and nodules in the livers of another 2 animals. Four of the 15 control animals survived (documentation "N-Vinyl-2-pyrrolidone" 1993; BASF AG 1985; EU 2003).

After 3-month exposure of hamsters to *N*-vinyl-2-pyrrolidone concentrations of 45 ml/m³ with an interim examination after 7 weeks and an additional examination after 15 months, no liver toxicity occurred (documentation "N-Vinyl-2-pyrrolidone" 1993; BASF AG 1985; EU2003).

The complete report has meanwhile become available for the inhalation study already described on the basis of an interim report in the documentation of 1991 (documentation "N-Vinyl-2-pyrrolidone" 1993). Sprague Dawley rats were exposed to *N*-vinyl-2-pyrrolidone concentrations of 0, 5, 10 or 20 ml/m³ for 24 months. In addition, 3 satellite groups were included, which were examined after 3 months (group 1, 20 males and 20 females) and 12 months (group 2, 10 males and 10 females) or 18 months exposure with a 6-month recovery period (group 3, 10 males and 10 females). For each satellite group, control groups of 10 male and 10 female rats were included. The findings are shown in Table 1 (toxicity) and Table 4 (carcinogenicity). In this study, there were no effects on food consumption, clinical, ophthalmological and urine parameters, or mortality (BASF AG 1992).

In a 28-day inhalation study carried out according to OECD Test Guideline 412 (see Table 1), groups of 8 male Wistar rats were exposed to *N*-vinyl-2-pyrrolidone concentrations of 0, 0.5, 5 or 10 ml/m³ to investigate cell proliferation in the liver as the target organ. The nasal epithelium was examined histopathologically with haematoxylin-eosin (HE) staining. As a NOAEC was not obtained in this study, further groups of animals were exposed to concentrations of 0, 0.2 or 0.5 ml/m³. At concentrations of 0.5 ml/m³ and above, concentration-dependent proliferation was observed in the liver (see Table 2) and degeneration, hyperplasia and squamous metaplasia in the nasal epithelium (see Table 3); the NOAEC for both organs was 0.2 ml/m³. There were no substance-related clinical symptoms, no deaths, no changes in relative organ weights, nor gross-pathological or histopathological findings other than in the liver and nose (BASF SE 2011).

5.2.2 Oral administration

There are no new studies available.

The toxicity of orally administered *N*-vinyl-2-pyrrolidone is lower than that after inhalation exposure and the no observed adverse effect level (NOAEL) is consequently higher. This could be caused by partial hydrolysis of the *N*-vinyl-2-pyrroli-

done in the acidic environment of the stomach, which results in less *N*-vinyl-2-pyrrolidone being systemically available. In a 3-month drinking water study in Wistar rats, a NOAEL of 3.6 mg/kg body weight and day was obtained. The lowest observed adverse effect level (LOAEL) was the high dose of 8.3 mg/kg body weight and day, at which dysproteinaemia was observed. Gavage administration of up to 60 mg/kg body weight and day for 3 months produced neither dysproteinaemia nor any clear pathological changes in the liver of rats, and only slight changes in some biochemical and haematological parameters (documentation "N-Vinyl-2-pyrrolidone" 1993; BASF AG 1985, 1986; EU 2003).

5.2.3 Dermal application

There are no studies available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

There are no new studies available.

After semi-occlusive application of undiluted *N*-vinyl-2-pyrrolidone to the skin of rabbits for 20 hours, slight reddening and desquamation of the skin occurred, and 2 of 8 animals died within 2 days (documentation "N-Vinyl-2-pyrrolidone" 1993).

5.3.2 Eyes

There are no new studies available.

In two studies, *N*-vinyl-2-pyrrolidone was irritating to the eyes of rabbits and caused corneal opacity and lesions in the conjunctiva. These were not completely reversible by the end of the recovery period on day 8 (documentation "N-Vinyl-2-pyrrolidone" 1993).

5.4 Allergenic effects

In a Buehler test carried out according to OECD Test Guideline 406 (3 occlusive induction treatments lasting 6 hours once a week, followed by an occlusive challenge treatment 14 days later; the undiluted substance was used in each case), *N*-vinyl-2-pyrrolidone did not produce a skin reaction in any of the 20 guinea pigs (BASF AG 1996).

Table 1 Effects of *N*-vinyl-2-pyrrolidone after repeated inhalation exposure

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 8 ♂, purity > 99.6%	**28 days**, 0, 0.5, 1, 5, 10 ml/m^3, 6 hours/day, 5 days/week, 7 days satellite group	examinations: histopathology of nose (HE staining), cell proliferation in liver: BrdU mini-pumps implanted 7 days prior to examination **after 7 days**: **0.5 ml/m^3**: NOAEC; **1 ml/m^3 and above**: liver: concentration-dependent proliferation ↑ (see Table 2); **1 and 5 ml/m^3**: liver: apoptosis ↑; **after 28 days**: **0.5 ml/m^3 and above**: liver: concentration-dependent proliferation ↑ (see Table 2), (at 0.5 ml/m^3 especially in zone 2 ($p < 0.01$), at 1 ml/m^3 and above especially in zone 3 ($p < 0.01$)), nose (concentration-dependent increase in severity): degeneration, hyperplasia, squamous metaplasia (see Table 3); **1 ml/m^3 and above**: liver: apoptosis ↑; **10 ml/m^3**: body weight gains 22% ↓ ($p < 0.05$)	BASF SE 2011
rat, Wistar, 8 ♂, purity > 99.6%	**28 days**, 0, 0.2, 0.5 ml/m^3, 6 hours/day, 5 days/week	examinations: histopathology of nose (HE staining), cell proliferation in liver: BrdU mini-pumps implanted 7 days prior to examination these animals were not examined after 7 days **after 28 days**: **0.2 ml/m^3**: NOAEC liver and nose; **0.5 ml/m^3**: liver: proliferation ↑ (significant in zone 2, $p < 0.05$); nose: degeneration, hyperplasia, squamous metaplasia (see Table 3)	BASF SE 2011

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 20 ♂, 20 ♀, controls: 10 ♂, 10 ♀	**3 months**, 0, 5, 10, 20 ml/m³, 6 hours/day, 5 days/week	**after 3 months**: no NOAEC; **5 ml/m³ and above**: total plasma protein ↓ (liver damage), in liver: foci, in nose: focal hyperplasia also of basal cells in respiratory and olfactory epithelium, atrophy of the olfactory epithelium, inflammation, ♂: from week 2 body weights ↓ (month 3: 5.9%), ♀: from week 3 in some cases body weights ↓ (month 3: 3.4%); **10 ml/m³ and above**: concentration-dependent thrombocytes ↑, white blood cells ↑, ♂: absolute and relative liver weights ↑ from week 1, in liver homogenate: GSH ↑, ♀: from week 1 transient decrease in body weights (month 3: 5.6%); **20 ml/m³**: absolute and relative liver weights ↑, in liver homogenate: GSH ↑, ♂: from week 1 body weights ↓ (month 3: 11%), ♀: from week 1 transient decrease in body weights (month 3: 5%), γ-GT ↑	BASF AG 1992

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 10 ♂, 10 ♀	**12 months**, 0, 5, 10, 20 ml/m^3, 6 hours/day, 5 days/week	**after 12 months**: no NOAEC; **5 ml/m^3 and above**: in liver: concentration-dependent: spongiosis hepatis, foci, focal hyperplasia, in nose: focal hyperplasia also of basal cells in respiratory and olfactory epithelium, atrophy of the olfactory epithelium, inflammation, ♂: from week 2 body weights ↓, absolute liver weights ↑, ♀: from week 3 in some cases body weights ↓; **10 ml/m^3 and above**: total plasma protein ↓ (liver damage), ♂: from week 1 body weights ↓, ♀: from week 1 transient decrease in body weights, ALT activity ↓, absolute liver weights ↑; **20 ml/m^3**: in liver homogenate: GSH ↑, ALT activity ↓, γ-GT ↑, absolute and relative liver weights ↑, ♂: from week 1 body weights ↓, hepatocellular adenoma in 1 animal, ♀: from week 1 transient decrease in body weights, white blood cells ↑ (signs of inflammation), red blood cells ↓ (incipient anaemia), cholesterol ↑	BASF AG 1992
rat, Sprague Dawley, 10 ♂, 10 ♀	**18 months** +6 months recovery period, 0, 5, 10, 20 ml/m^3, 6 hours/day, 5 days/week	**after 18-month exposure with 6-month recovery period**: no effects on absolute or relative liver weights, **5 ml/m^3 and above**: in liver dose-dependent: spongiosis hepatis, foci, focal hyperplasia, in nose: focal hyperplasia also of basal cells in respiratory and olfactory epithelium, atrophy of the olfactory epithelium, inflammation; **10 ml/m^3 and above**: in liver homogenate: γ-GT ↑	BASF AG 1992

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 60 ♂, 60 ♀	**2 years**, 0, 5, 10, 20 ml/m³, 6 hours/day, 5 days/week	**after 24 months**: no NOAEC; **5 ml/m³ and above**: degeneration of hepatocytes, in liver dose-dependent: spongiosis hepatis, foci, focal hyperplasia, in nose: focal hyperplasia also of basal cells in respiratory and olfactory epithelium, atrophy of the olfactory epithelium, inflammation, ♂: from week 2 body weights ↓, ♀: from week 3 in some cases body weights ↓; **10 ml/m³**: ♂: from week 1 body weights ↓, focal epithelial hyperplasia in the larynx, ♀: from week 1 transient decrease in body weights, red blood cells (anisocytosis, microcytosis, macrocytosis) ↑; **20 ml/m³**: absolute and relative liver weights ↑, focal epithelial hyperplasia in the larynx, ♂: from week 1 body weights ↓, ♀: from week 1 transient decrease in body weights, red blood cells (anisocytosis, microcytosis, macrocytosis) ↑	BASF AG 1992

ALT: alanine aminotransferase, BrdU: bromodesoxyuridine, GSH: glutathione, γ-GT: gamma glutamyl transferase

Table 2 Investigation of proliferation in different zones of the liver in a 28-day inhalation study with male rats (two study groups) (BASF SE 2011)

Exposure [ml/m³]	0	0.2	0.5	1	5	10
labelling indices after 7 days, only group 1 examined						
zone 1	3.20 (100%)	n. d.	3.70 (116%)	3.57 (112%)	5.06 (158%)	**5.39* (168%)**
zone 2	3.51 (100%)	n. d.	4.46 (127%)	**6.29* (179%)**	**6.67** (190%)**	**7.49** (213%)**
zone 3	3.46 (100%)	n. d.	4.33 (125%)	4.61 (133%)	**10.29** (297%)**	**14.63** (423%)**
total	3.39 (100%)	n. d.	4.16 (123%)	4.83 (142%)	**7.34** (217%)**	**9.17** (271%)**
after 28 days, group 1						
zone 1	1.39 (100%)	n. d.	1.97 (142%)	1.39 (100%)	1.39 (100%)	1.45 (104%)
zone 2	0.90 (100%)	n. d.	**1.78** (198%)**	1.41 (157%)	**1.95* (217%)**	**1.66* (184%)**
zone 3	1.04 (100%)	n. d.	**1.52* (146%)**	**2.47** (238%)**	**2.48** (238%)**	**7.25** (697%)**
total	1.11 (100%)	n. d.	**1.76* (159%)**	**1.76* (159%)**	**1.94* (175%)**	**3.45* (311%)**
after 28 days, group 2						
zone 1	1.94 (100%)	0.83 (43%)	1.17 (60%)	n. d.	n. d.	n. d.
zone 2	1.21 (100%)	1.72 (142%)	**2.45* (202%)**	n. d.	n. d.	n. d.
zone 3	1.47 (100%)	1.02 (69%)	2.87 (195%)	n. d.	n. d.	n. d.
total	1.54 (100%)	1.19 (77%)	2.16 (140%)	n. d.	n. d.	n. d.

n. d.: not determined: the animals of group 1 or group 2 were not exposed to these concentrations; significance calculated with inclusion of corresponding range of variation: * $p \leq 0.05$; ** $p \leq 0.01$ (one-sided Wilcoxon test)

Table 3 Nasal findings in a 28-day inhalation study with male rats (two study groups) (BASF SE 2011)

Exposure [ml/m³]	0	0.2	0.5	0	0.5	1	5	10
number of animals	8	8	8	8	8	8	8	8
nasal cavity, section plane 1								
degeneration of respiratory epithelium	n.f.	n.f.	grade 1 (5/8)	n.f.	grade 1 (5/8)	grade 1 (7/8) grade 2 (1/8)	grade 1 (1/8) grade 2 (7/8)	grade 1 (5/8) grade 2 (3/8)
degeneration of olfactory epithelium	n.f.	n.f.	n.f.	n.f.	n.f.	grade 1 (1/8)	grade 1 (0/8) grade 2 (2/8)	grade 1 (1/8)
hyperplasia of respiratory epithelium, basal cells	n.f.	n.f.	grade 1 (4/8)	n.f.	grade 1 (4/8) grade 2 (2/8)	grade 1 (0/8) grade 2 (6/8) grade 3 (2/8)	grade 1 (0/8) grade 2 (1/8) grade 3 (6/8) grade 4 (1/8)	grade 1 (0/8) grade 2 (3/8) grade 3 (5/8)
hyperplasia of transitional epithelium	n.f.	n.f.	n.f.	n.f.	grade 1 (5/8) grade 2 (2/8)	grade 1 (1/8) grade 2 (6/8) grade 3 (1/8)	grade 1 (0/8) grade 2 (0/8) grade 3 (8/8)	grade 1 (0/8) grade 2 (6/8) grade 3 (2/8)
squamous metaplasia of respiratory epithelium	n.f.	n.f.	grade 1 (5/8)	n.f.	grade 1 (5/8)	grade 1 (8/8)	grade 1 (0/8) grade 2 (8/8)	grade 1 (6/8) grade 2 (1/8)
squamous metaplasia of transitional epithelium	n.f.	n.f.	n.f.	n.f.	n.f.	n.f.	n.f.	grade 1 (2/8)

grade 1: minimal findings; grade 2: slight; grade 3: marked; grade 4: severe; number of affected animals in parentheses;
n.f.: no findings

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

No specific studies with *N*-vinyl-2-pyrrolidone are available (documentation "N-Vinyl-2-pyrrolidone" 1993). Studies with repeated exposure provided no evidence of relevant effects.

5.5.2 Developmental toxicity

Groups of 25 mated Wistar rats were exposed in whole-animal chambers to *N*-vinyl-2-pyrrolidone concentrations of 0, 1, 5 or 20 ml/m^3 from gestation days 6 to 19. The NOAEC for maternal toxicity was 1 ml/m^3. At 5 ml/m^3, body weight gains were reduced, the corrected body weights were decreased by 31% and the carcass weights by 6%. For the offspring, the NOAEC was 5 ml/m^3. A reduced mean body weight and an increase in the incidence of variations (wavy ribs) and delayed ossification of the hyoid and occipital bone in the foetuses were found at 20 ml/m^3. At this concentration, marked maternal toxicity occurred with reduced body weight gains, corrected body weights reduced by 68% and salivation. There was no increase in the incidence of malformations (BASF AG 2001; EU 2003). The incidences of incomplete ossification of the skull (incidences of 0, 9.7, 1.9, 5.1 at concentrations of 0, 1, 5, 20 mg/m^3; range of historical controls 0–5.2), the basisphenoid bone (incidences of 3.8, 16.4, 9.5, 10.4 at concentrations of 0, 1, 5, 20 mg/m^3, range of historical controls 0–29.3) and the parietal bones (incidences of 12.6, 23.9, 22.7, 24.7 at concentrations of 0, 1, 5, 20 mg/m^3, range of historical controls 23.8–28.6) did not increase in a dose-dependent manner and were within the range of historical control data. They are therefore not regarded as treatment-related effects. The increase in the incidences of incomplete ossification of the supraoccipital bone (incidences of 6.3, 11.5, 11.8, 22.4 at concentrations of 0, 1, 5, 20 mg/m^3, range of historical controls 4.0–9.7) was not statistically significant until concentrations of 20 mg/m^3. *N*-Vinyl-2-pyrrolidone did not produce specific malformations in the offspring, and incomplete ossification did not occur until maternally toxic concentrations. The NOAEC for developmental toxicity is therefore 5 ml/m^3 (corresponding to 23 mg/m^3) and the NOAEC for maternal toxicity 1 ml/m^3 (corresponding to 4.6 mg/m^3).

5.6 Genotoxicity

5.6.1 In vitro

N-Vinyl-2-pyrrolidone was neither mutagenic nor clastogenic in valid studies with Salmonella typhimurium, nor was it found to be either mutagenic or clastogenic using the fluctuation test with Klebsiella pneumonia, HPRT and TK$^{+/-}$ locus tests in mouse lymphoma cells, the cell transformation test (BALB/3T3 mouse cells) and the UDS test with rat hepatocytes (documentation "N-Vinyl-2-pyrrolidone" 1993; BASF AG 1985; EU 2003).

Sister chromatid exchange (SCE) was not induced in human lymphocytes up to concentrations of 50 µg/ml in the presence of a metabolic activation system and up to 900 µg/ml in the absence of a metabolic activation system (BASF AG 1989; EU 2003).

5.6.2 In vivo

N-Vinyl-2-pyrrolidone was not mutagenic in Drosophila (sex-linked recessive lethal test) (documentation "N-Vinyl-2-pyrrolidone" 1993).

The results of a DNA binding study in the rat liver were negative after 1 hour and 5 hours following single or 5-day intraperitoneal injections of 150 or 300 mg/kg body weight with *N*-vinyl-2-pyrrolidone labelled at the ring or at the side chain (documentation "N-Vinyl-2-pyrrolidone" 1993; BASF AG 1985; EU 2003). The sensitivity of this study was, however, limited; the formation of 8-hydroxyguanosine by OH radicals or of a labile adduct with acetaldehyde during nucleoside analysis (Hecht et al. 2001) might not have been detected.

N-Vinyl-2-pyrrolidone did not lead to an increase in the incidence of SCE in human blood or isolated human lymphocytes (BASF AG 1993; EU 2003).

A valid micronucleus test with *N*-vinyl-2-pyrrolidone carried out in NMRI mice in accordance with OECD Test Guideline 474 yielded negative results. There was no increase in the number of micronuclei 16, 24 or 48 hours after single oral doses of up to 600 mg/kg body weight although signs of toxicity were observed (BASF AG 1987; EU 2003).

5.7 Carcinogenicity

In an inhalation study already described in the documentation of 1991 (documentation "N-Vinyl-2-pyrrolidone" 1993) on the basis of a preliminary report, Sprague Dawley rats were exposed to *N*-vinyl-2-pyrrolidone concentrations of 0, 5, 10 or 20 ml/m^3 for 24 months. Three satellite groups were investigated after 3 (20 male and 20 female animals) and 12 (10 males and 10 females) months of treatment, and after exposure for 18 months with a 6-month recovery period (10 males and 10 females). Each satellite group had a parallel control group made up of 10 male and 10 female rats. In the main study, concentration-dependent increases in the incidence of liver cell carcinomas and nasal cavity adenomas were found at concentrations of 5 ml/m^3 and above, and also adenocarcinomas of the nasal cavity at 10 ml/m^3 and above and squamous carcinomas of the larynx at 20 ml/m^3. The incidences are shown in Table 4. Non-neoplastic findings are listed above all in Table 1 under Section 5.2.1 (BASF AG 1992; Klimisch et al. 1997).

Table 4 Results of the carcinogenicity study with *N*-vinyl-2-pyrrolidone

Author:	BASF AG 1992
Substance:	*N*-vinyl-2-pyrrolidone (purity 99%)
Species:	**rat,** Sprague Dawley, main study groups of 60 exposed ♂ and 60 exposed ♀
Administration route:	inhalation
Concentration:	0, 5, 10, 20 ml/m^3
Duration:	2 years, 5 days/week, 6 hours/day
Toxicity:	5 ml/m^3 and above: liver and nasal toxicity (see Section 5.2.1)

		Exposure concentration (ml/m^3)			
		0	5	10	20
Survivors:	♂	39/70 (56%)	36/60 (60%)	29/60 (48%)	33/60 (55%)
	♀	29/70 (41%)	25/60 (42%)	26/60 (43%)	24/60 (40%)
Tumours and preneoplasms					
liver:					
liver cell carcinomas	♂	1/70 (1%)	6/60 (10%)*	5/60 (8%)*	17/60 (28%)***
	♀	1/70 (1%)	3/60 (5%)	6/60 (10%)*	26/60 (43%)***
nasal cavity:					
adenomas	♂	0/70 (0%)	9/60 (15%)***	10/60 (17%)***	13/60 (22%)***
	♀	0/70 (0%)	2/60 (3%)	8/60 (13%)**	15/60 (20%)***
adenocarcinomas	♂	0/70 (0%)	0/60 (0%)	4/60 (7%)*	6/60 (10%)*
	♀	0/70 (0%)	0/60 (0%)	0/60 (0%)	4/60 (7%)*
larynx:					
squamous carcinomas	♂	0/70 (0%)	0/60 (0%)	0/60 (0%)	4/60 (7%)*
	♀	0/70 (0%)	0/60 (0%)	0/60 (0%)	4/60 (7%)*
Non-neoplastic changes					
liver:					
hyperplasia of basophilic and eosinophilic cells, focal clear cells, otherwise not specified cells, total$^{\#)}$	♂	6/70$^{\#)}$	17/60$^{**\#)}$	33/60$^{***\#)}$	54/60$^{***\#)}$
	♀	11/70$^{\#)}$	31/60$^{***\#)}$	42/60$^{***\#)}$	58/60$^{***\#)}$
foci, eosinophilic	♂	3/70 (4%)	5/60 (8%)	10/60 (17%)*	17/60 (28%)***
	♀	1/70 (1%)	6/60 (10%)	13/60 (22%)**	22/60 (37%)***
spongiosis hepatis	♂	37/70 (53%)	36/60 (60%)	45/60 (75%)*	55/60 (92%)***
	♀	7/70 (10%)	19/60 (32%)**	28/60 (47%)***	42/60 (70%)***

Table 4 (continued)

nasal cavity:					
inflammation	♂	20/70 (29%)	36/60 (60%)***	47/60 (78%)***	52/60 (87%)***
	♀	9/70 (13%)	35/60 (58%)***	50/60 (83%)***	42/60 (70%)***
atrophy	♂	7/70 (10%)	21/60 (35%)***	48/60 (80%)***	58/60 (97%)***
	♀	0/70 (0%)	30/60 (50%)***	51/60 (85%)***	56/60 (93%)***
metaplasia in septum, lateral wall, total[#)]	♂	3/70[#)]	8/60[#)]	8/60[#)]	28/60[#)]
	♀	5/70[#)]	21/60[#)]	31/60[#)]	21/60[#)]
hyperplasia of basal cells, goblet cells, olfactory epithelium, glands, total[#)]	♂	11/70[#)]	37/60[#)]	100/60[#)]	119/60[#)]
	♀	10/70[#)]	77/60[#)]	107/60[#)]	127/60[#)]
larynx:					
inflammation	♂	6/70 (9%)	4/60 (7%)	4/60 (7%)	4/60 (7%)
	♀	0/70 (0%)	2/60 (3%)	2/60 (3%)	5/60 (8%)*
hyperplasia, epithelium	♂	0/70 (0%)	0/60 (0%)	3/60 (3%)	6/60 (10%)*
	♀	0/70 (0%)	0/60 (0%)	0/60 (0%)	4/60 (7%)**

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.005$

#) The various kinds of metaplasia and hyperplasia have been grouped together in this table; the incidences can therefore not be given as a percentage.

An additional group consisting of 10 female animals was exposed for 3 months to *N*-vinyl-2-pyrrolidone concentrations of 45 ml/m³ and subsequently observed for 21 months. By the end of the study, 6 animals had survived, 2 of which were found to have neoplastic nodules in the liver, and 2 a hepatocellular carcinoma. There were no neoplastic changes in the animals that had died during the study (Klimisch et al. 1997).

6 Manifesto (MAK value/classification)

The main critical effects are the non-genotoxic, carcinogenic effects in the liver, nose and larynx after inhalation. The most sensitive end points after inhalation are cell proliferation in the liver, and degeneration and hyperplasia in the nasal epithelium.

Carcinogenicity. In a 2-year inhalation study in rats, *N*-vinyl-2-pyrrolidone led to a concentration-dependent increase in the incidences of liver cell carcinomas and nasal cavity adenomas at the low concentration of 5 ml/m³ and above, nasal cavity adenocarcinomas at concentrations of 10 ml/m³ and above, and squamous carcinomas in the larynx at 20 ml/m³. Therefore, in 1991, *N*-vinyl-2-pyrrolidone was classified in Carcinogen Category 2. In a 28-day inhalation study carried out in the meantime with rats, cell-proliferating effects in the liver were observed even at

doses of as little as 0.5 ml/m³, with a NOAEC of 0.2 ml/m³ (BASF SE 2011). The results of in vitro and in vivo studies of genotoxicity were negative throughout. From a comparison of the dose–response relationships for carcinogenicity and cell proliferation, and in view of the negative results of genotoxicity studies, it can be assumed that the cell proliferation is the relevant mechanism underlying the tumour formation caused by *N*-vinyl-2-pyrrolidone. As a NOAEC was obtained for cell proliferation and a MAK value can therefore be derived, *N*-vinyl-2-pyrrolidone is classified in Carcinogen Category 4.

MAK value. Histopathological changes in the nasal epithelium occur only after inhalation exposure. In the liver, histopathological changes occur after inhalation at lower concentrations than after ingestion. This could be caused by the hydrolysis of some of the substance in the stomach. In a 28-day inhalation study with rats, cell proliferation in the liver and degeneration and hyperplasia in the nasal epithelium occurred at concentrations of 0.5 ml/m³ and above. The concentration of 0.2 ml/m³ was the NOAEC for both of these organs. On the basis of this NOAEC of 0.2 ml/m³ and taking into account the fact that the study lasted only 28 days, and that a lower NOAEC for cell proliferation in the liver was obtained after 28 days compared with after exposure for 7 days, a MAK value of 0.02 ml/m³ has been established in accordance with the procedures of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (see List of MAK and BAT Values, Section I).

Peak limitation. Both the liver and the nose were found to be equally sensitive with regard to initial effects after inhalation exposure. As the MAK value is derived from a systemic effect, the substance is classified in Peak Limitation Category II. The half-life of *N*-vinyl-2-pyrrolidone in the plasma is 1.9 hours in rats (documentation "N-Vinyl-2-pyrrolidone" 1993) and between 20 and 40 minutes in dogs. There are no data available for the toxicokinetics of the substance in humans. Therefore, a default excursion factor of 2 has been established for *N*-vinyl-2-pyrrolidone.

Prenatal toxicity. After the exposure of rats to *N*-vinyl-2-pyrrolidone concentrations of 20 ml/m³ in a valid developmental toxicity study, markedly reduced corrected body weights in the dams and reduced body weights in the foetuses with an increase in the incidence of skeletal variations in the form of wavy ribs and delayed ossification of the occipital bone and the hyoid were found. The increased incidence of findings in bone at the concentrations 1 and 5 ml/m³, which in some cases was statistically significant, was within the range of historical control data (with the exception of supraoccipital bones). None of the findings was dose-dependent, and they are therefore not regarded as substance-related. The NOAEC for the offspring was 5 ml/m³. At this concentration, the corrected body weights of the dams were significantly reduced, the NOAEC for maternal toxicity was 1 ml/m³. As the developmental toxicity occurred at maternally toxic doses, and the 250-fold difference between the NOAEC for developmental toxicity of 5 ml/m³ and the MAK value of 0.02 ml/m³ is sufficiently large, *N*-vinyl-2-pyrrolidone is classified in Pregnancy Risk Group C.

Germ cell mutagenicity. According to the available studies of the genotoxicity of the substance, *N*-vinyl-2-pyrrolidone is neither mutagenic nor clastogenic. The substance is therefore not classified in one of the categories for germ cell mutagens.

Absorption through the skin. According to model calculations, the absorption of at least 150 mg is to be expected after the exposure of a 2000 cm^2 area of skin for one hour to a saturated aqueous solution of *N*-vinyl-2-pyrrolidone. A total 0.92 mg *N*-vinyl-2-pyrrolidone is absorbed (100% retention, 10 m^3 respiratory volume) after inhalation exposure at the level of the MAK value of 0.02 ml/m^3. As the calculated amount absorbed through the skin is far above the amount absorbed daily by inhalation at the level of the MAK value, *N*-vinyl-2-pyrrolidone is designated with an "H" (for substances that can be absorbed through the skin).

Sensitization. There are still no clinical findings available for the sensitizing effects of the substance. The results of a Buehler test in guinea pigs with undiluted *N*-vinyl-2-pyrrolidone were negative. Experimental studies of respiratory sensitization are not available. *N*-Vinyl-2-pyrrolidone is therefore not designated with "Sh" or "Sa" (for substances that cause sensitization of the skin or airways).

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