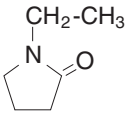
N-Ethyl-2-pyrrolidone**

MAK value (2013)	**2 ml/m³ (ppm) ≙ 9 mg/m³**
Peak limitation (2013)	**Category I, excursion factor 2**
Absorption through the skin (2013)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2013)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	1-ethylazacyclopentan-2-one
	1-ethylpyrrolidin-2-one
Chemical name	*N*-ethyl-2-pyrrolidone
CAS number	2687-91-4
Structural formula	
Molecular formula	$C_6H_{11}NO$
Molecular weight	113.16
Melting point	< –75°C (ECHA 2011)
Boiling point at 1013.25 hPa	212–213°C (ECHA 2011)
Density at 20°C	0.998 g/cm³ (ECHA 2011)
Vapour pressure at 20°C	0.18 hPa (IFA 2012)
log K_{OW}[1)]	–0.04 (SRC 2012)
Solubility at 25°C	115 g/l water (ECHA 2011)

1) octanol/water partition coefficient

** *NB: Please check The List of MAK and BAT Values 2016. This substance has been re-evaluated and in 2016 a German documentation was published changing the value to 5 PPM, thus superceding this documentation.*
An English translation of the new document is planned.

pH	10%: 9; 90%: 12 (ECHA 2012)
1 ml/m³ (ppm) ≙ 4.7 mg/m³	**1 mg/m³ ≙ 0.213 ml/m³ (ppm)**

A document was published by the Risk Assessment Committee of ECHA (2011); however, only reproductive toxicity was evaluated.

N-Ethyl-2-pyrrolidone is used as an industrial solvent, catalyst and cationic surfactant.

The vapour saturation of *N*-ethyl-2-pyrrolidone is about 180 ml/m³ (840 mg/m³) at room temperature.

1 Toxic Effects and Mode of Action

N-Ethyl-2-pyrrolidone caused slight irritation of the skin and, because of its alkalinity, led to severe irritation of the eyes and irreversible changes to the cornea.

The main effects observed after the inhalation exposure of rats included clinical symptoms of irritation at 200 mg/m³ and above and degeneration/regeneration of the olfactory epithelium at 80 mg/m³ and above.

The liver, kidneys and haematopoietic system were the target organs of *N*-ethyl-2-pyrrolidone after ingestion. Increased liver and kidney weights were the first effects observed after 3 months in rats fed 100 mg/kg body weight and above. Higher concentrations caused changes in liver enzymes and disturbed blood clotting.

Oral administration of *N*-ethyl-2-pyrrolidone during gestation induced decreased foetal weights, post-implantation losses and skeletal and cardiovascular malformations in rats and rabbits. These effects were observed also after dermal treatment in rabbits, whereas in rats only reduced foetal weights were found. Therefore, *N*-ethyl-2-pyrrolidone has foetotoxic and teratogenic effects, but only at maternally toxic doses. *N*-Ethyl-2-pyrrolidone had no sensitizing effects in a modified lymph node assay in guinea pigs.

N-Ethyl-2-pyrrolidone did not induce genotoxicity either in vitro in a bacterial mutagenicity assay or in HPRT tests in CHO cells (a cell line derived from Chinese hamster ovary) or in vivo in bone marrow cells in a chromosomal aberration test or micronucleus test.

There are no studies available for the carcinogenicity of the substance.

2 Mechanism of Action

The irritating effects of *N*-ethyl-2-pyrrolidone on the eyes and mucosa are to the result of its high alkalinity.

The toxic effects on the kidneys observed in male rats may be caused by alpha-2u-globulin nephropathy, which is not relevant to humans. The nephrotoxicity observed in female rats at high concentrations suggests another possible nephrotoxic mechanism (BASF AG 2006 b).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

There are no studies available for the absorption of *N*-ethyl-2-pyrrolidone after inhalation, ingestion or through the skin. The structurally homologous *N*-methyl-2-pyrrolidone is known to be readily absorbed after inhalation and ingestion as well as through the skin (supplement "N-Methyl-2-pyrrolidone" 2010 b).

In samples from 56 individuals of the general population, *N*-ethyl-2-pyrrolidone metabolites were found in 32% of the urine samples, whereas metabolites of the structurally related *N*-methyl-2-pyrrolidone were detected in 96% of the urine samples (Schindler et al. 2012).

For a saturated aqueous *N*-ethyl-2-pyrrolidone solution, a model calculation according to Guy and Potts (1993) and Wilschut et al. (1995) predicted the absorption of 80 mg and 132 mg, respectively, after exposure for 1 hour and an exposed skin area of 2000 cm^2. This yielded dermal flux values of 0.04 mg/cm^2 and hour and 0.066 mg/cm^2 and hour, respectively.

According to the model of Fiserova-Bergerova et al. (1990), the amount dermally absorbed is about 444 mg. For the structurally homologous *N*-methyl-2-pyrrolidone, the models predicted dermal flux values of 1.38 mg/cm^2 and hour (Fiserova-Bergerova et al. 1990), 0.24 mg/cm^2 and hour (Guy and Potts 1993) and 0.48 mg/cm^2 and hour (Wilschut et al. 1995) under standard conditions. However, experimental studies carried out with *N*-methyl-2-pyrrolidone by Bader et al. (2005) and Keener et al. (2007) demonstrated that in vivo exposure of human skin to undiluted *N*-methyl-2-pyrrolidone (duration: 30–120 minutes; area: 10–17.5 cm^2) results in a flux of about 5.5 to 6.5 mg/cm^2 and hour. Therefore, all models underestimate the dermal penetration of *N*-methyl-2-pyrrolidone and presumably also of *N*-ethyl-2-pyrrolidone; the model that most closely reflects the experimentally established values is that of Fiserova-Bergerova et al. (1990).

3.2 Metabolism

It was demonstrated that *N*-ethyl-2-pyrrolidone is metabolized to form the ring-hydroxylated compounds 5-hydroxy-*N*-ethyl-2-pyrrolidone and 2-hydroxy-*N*-ethylsuccinimide. Up to 70% of the tested dose is converted to these 2 compounds. Further metabolites have not been identified to date (Käfferlein 2013; Schindler et al. 2012). The major metabolites identified suggest that an attack on the ethyl group is not of prime importance in the metabolism of *N*-ethyl-2-pyrrolidone. The structurally homologous *N*-methyl-2-pyrrolidone is successively oxidized to 5-hydroxy-*N*-methyl-2-pyrrolidone, *N*-methylsuccinimide and 2-hydroxy-*N*-methylsuccinimide; here, too, 5-hydroxy-*N*-methyl-2-pyrrolidone and 2-hydroxy-*N*-methylsuccinimide are the major metabolites (supplement "N-Methyl-2-pyrrolidone" 2010 b; Akesson and Jönsson 1997).

4 Effects in Humans

There are no studies available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The 4-hour LC_{50} according to OECD Test Guideline 403 was higher than 5100 mg/m^3 in rats. Accelerated respiration, ruffled fur, squatting posture and soiled fur were described as symptoms (BASF AG 2005 a).

5.1.2 Oral administration

The oral LD_{50} of *N*-ethyl-2-pyrrolidone for rats was 1350 mg/kg body weight (Ansell and Fowler 1988). A different source reported an LD_{50} value of 3200 mg/kg for *N*-ethyl-2-pyrrolidone in rats. Symptoms included dyspnoea, apathy, paralysis and erythema. Necropsy revealed cardiac dilation and pulmonary oedema (BASF AG 1978 a).

Single *N*-ethyl-2-pyrrolidone doses of 2000 mg/kg body weight given to male CrI:NMRI mice in a micronucleus test led to squatting posture and abdominal positions in the animals 1 to 4 hours later (Section 5.6.2). These symptoms were transient, and no animal died up to necropsy after 48 hours (BASF AG 2006 a).

5.1.3 Dermal application

Single, 24-hour semi-occlusive applications of *N*-ethyl-2-pyrrolidone in doses of 2000 mg/kg body weight did not induce any symptoms in rats (BASF AG 2005 b).

5.1.4 Intravenous and intraperitoneal injection

After intravenous injection, the LD_{50} was 2600 mg/kg body weight (BASF AG 1978 b). The symptoms included dyspnoea, apathy, staggering and erythema.

Intraperitoneal injection yielded an LD_{50} value between 2200 and 2600 mg/kg body weight. Dyspnoea, apathy, staggering, tremor and exsiccosis were observed as symptoms (BASF AG 1978 c).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Groups of 10 male and 5 female Wistar rats were exposed nose-only to *N*-ethyl-2-pyrrolidone concentrations of 0, 82, 208 or 396 mg/m³. The exposure atmosphere consisted primarily (no other details) of vapour, and the aerosol fraction had a mass median aerodynamic diameter (MMAD) between 0.89 and 3.20 µm. The undiluted substance was used to generate the exposure atmosphere. Exposure took place for

Table 1 Degeneration/regeneration of the olfactory epithelium in the different planes of section of the nasal cavity of rats induced by *N*-ethyl-2-pyrrolidone (BASF AG 2011)

Sex	♂				♀			
Dose (mg/m³)	0	82	208	396	0	82	208	396
Number of animals	10	10	10	10	5	5	5	5
nasal cavity, plane of section I								
degeneration/regeneration of the olfactory epithelium (overall)	-	-	10	7	-	-	4	3
degree 1	-	-	8	5	-	-	4	3
degree 2	-	-	2	2	-	-	-	-
nasal cavity, plane of section II								
degeneration/regeneration of the olfactory epithelium (overall)	1	2	10	10	2	2	5	5
degree 1	1	2	1	1	2	1	2	1
degree 2	-	-	3	5	-	1	3	2
degree 3	-	-	6	3	-	-	-	2
degree 4	-	-	-	1	-	-	-	-
nasal cavity, plane of section III								
degeneration/regeneration of the olfactory epithelium (overall)	-	1	10	10	-	1	5	5
degree 1	-	1	2	2	-	-	-	2
degree 2	-	-	5	3	-	1	4	3
degree 3	-	-	3	5	-	-	1	-
nasal cavity, plane of section IV								
degeneration/regeneration of the olfactory epithelium (overall)	-	1	10	10	-	1	5	5
degree 1	-	1	2	1	-	1	1	3
degree 2	-	-	6	2	-	-	2	2
degree 3	-	-	2	4	-	-	2	-
degree 4	-	-	-	3	-	-	-	-

Table 2 Degeneration/regeneration of the olfactory epithelium of the nasal cavity of rats (only affected animals) induced by *N*-ethyl-2-pyrrolidone in the low dose group of 82 mg/m^3 compared with the incidence in control animals (BASF AG 2011)

	Controls			82 mg/m^3				
	animal 1 ♂	animal 2 ♀	animal 3 ♀	animal 1 ♂	animal 2 ♂	animal 3 ♂	animal 4 ♀	animal 5 ♀
plane of section II	degree 1	degree 1	degree 1		degree 1	degree 1	degree 1	degree 2
plane of section III						degree 1		degree 2
plane of section IV				degree 1				degree 1

6 hours a day, on 5 days a week, for a period of 4 weeks. Blood samples were taken immediately after the last exposure. Clinical symptoms observed at *N*-ethyl-2-pyrrolidone doses of 208 mg/m^3 and above included salivation, lacrimation, nasal discharge and noses encrusted with blood. Degeneration/regeneration of the olfactory epithelium in the nasal cavity was observed at the low dose of 82 mg/m^3 and above and also in some control animals. The severity and incidence of these findings increased with the exposure concentration. Table 1 shows the individual data. The incidences and degree of these effects in the individual animals of the low dose and control groups are shown in Table 2. The results were not evaluated statistically (BASF AG 2011). In the evaluation it is to be taken into account that 15% of the inhaled air reaches the olfactory epithelium in rats, whereas only 7% reaches the olfactory epithelium in humans (Frederick et al. 1998).

The respiratory tract (lungs, larynx, olfactory and respiratory epithelia), testes and liver were examined histopathologically. At 396 mg/m^3, reduced body weight gains were observed in male rats from days 4 to 8. This effect was transient. Feed consumption was not affected by exposure in any group. The haematological examination revealed individual differences compared with the values for the control animals, but these were not dose-dependent. The authors regarded these results as unrelated to the treatment. Further effects that were not dose-dependent included a decrease in alkaline phosphatase activity in the females of the group exposed to 208 mg/m^3, a decrease in the triglyceride concentration in the group exposed to 208 mg/m^3 and an increased triglyceride level in the males of the group exposed to 396 mg/m^3. Here, too, the authors ruled out a treatment-related effect because the observed effects were not dose-dependent and were regarded as marginal. The study was carried out according to OECD Test Guideline 412 (BASF AG 2011). The Commission regarded the concentration of 82 mg/m^3 (17 ml/m^3) to be the LOAEC (lowest observed adverse effect concentration) because the increased degeneration/regeneration observed in the olfactory epithelium is evidence of a beginning dose–response relationship.

5.2.2 Oral administration

The administration of *N*-ethyl-2-pyrrolidone to groups of 10 male and 10 female Wistar rats with the diet in doses of 0, 100, 300 or 1000 mg/kg body weight and day for a period of 90 days induced initial effects on the liver, kidneys and haematopoietic system even in the low dose group. The observed effects are described in Table 3.

The relative liver weights were increased in males and females in relation to the dose. The increase was 7% ($p \leq 0.05$) in the males and 5% (not significant) in the females even in the low dose group given *N*-ethyl-2-pyrrolidone doses of 100 mg/kg body weight. Centrilobular hypertrophy of the hepatocytes was found in the males of all dose groups, but not in the control animals. The effect size increased with the dose. In female rats, the increase in relative liver weights was statistically significant at 300 mg/kg body weight and above; centrilobular hypertrophy of the hepatocytes was observed only in the high dose group of 1000 mg/kg body weight. Enzyme induction in the liver was not investigated as a possible cause of the weight increases. There was no increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in blood as a sign of liver damage (BASF AG 2006 b). According to Hall et al. 2012, liver hypertrophy without histopathological liver changes and without any changes in clinico-chemical liver parameters is regarded as an adaptive effect.

The effects observed in the kidneys of male rats may be caused by alpha-2u-globulin nephropathy, which is not relevant to humans. As the relative kidney weights were increased in females at 300 mg/kg body weight and above depending on the dose, nephrotoxicity may also be involved. A significant increase in the platelet count was detected in the females of the low dose group. In addition, ALT activities were decreased in the females of this dose group. As no adverse effects were associated with the decreased ALT activity in this study, the authors did not consider this to be of toxicological relevance. The number of sperm with abnormal heads was increased in the males of the high dose group (see Section 5.5.1). The urine of the animals was a yellowy-orange at 100 mg/kg body weight and above. This is regarded as evidence of the bioavailability of the substance rather than as an adverse effect. The histopathological examination of the urinary sediment revealed an increased number of transitional epithelial cells, urinary casts and epithelial casts in all treated male rats at the end of the exposure period. Most of the transitional epithelial cells found in the sediment were degenerated. Thus, this study revealed beginning liver hypertrophy without any other histopathological or clinico-chemical changes at *N*-ethyl-2-pyrrolidone doses of 100 mg/kg body weight and increased liver weights and reduced body weight gains in the males and increased kidney weights in the females at 300 mg/kg body weight and above (BASF AG 2006 b).

Table 3 Effects after 90-day oral administration of *N*-ethyl-2-pyrrolidone to 10 ♂/10 ♀ Wistar rats (BASF AG 2006 b)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 10 ♂	**90 days**, 0, 100, 300, 1000 mg/kg body weight and day; diet	**100 mg/kg body weight**: LOEL, liver: relative liver weights increased by 7%*, centrilobular hypertrophy ↑, kidneys: relative kidney weights increased by 9%*, ALT activity ↑; **300 mg/kg body weight**: body weight gains ↓*, feed consumption –13.2%* (day 7), –7.2%* (day 91), liver: relative liver weights increased by 13%**, centrilobular hypertrophy ↑, kidneys: relative kidney weights increased by 14%**, ALT activity unchanged; **1000 mg/kg body weight**: body weight gains ↓**, feed consumption –21.1%** (day 7), –14.8%** (day 91), liver: relative liver weights increased by 53%**, centrilobular hypertrophy ↑, kidneys: relative kidney weights increased by 32%**, platelets ↑**, ALT activity ↓**, AST activity ↓*	BASF AG 2006 b
rat, Wistar, 10 ♀	**90 days**, 0, 100, 300, 1000 mg/kg body weight and day; diet	**100 mg/kg body weight**: liver: relative liver weights increased by 5% (not significant), ALT activity ↓*, platelets ↑**; **300 mg/kg body weight**: body weight gains ↓**, feed consumption –7.5%* (day 7), – (unchanged on day 91), liver: relative liver weights increased by 7%**, kidneys: relative kidney weights increased by 9%**, ALT activity ↓*, platelets ↑*; **1000 mg/kg body weight**: body weight gains ↓**, feed consumption –23.3%** (day 7), –18.4%** (day 91), liver: relative liver weights increased by 29%**, centrilobular hypertrophy ↑, kidneys: relative kidney weights increased by 22%**, platelets ↑**, ALT activity ↓**, AST activity ↓**	BASF AG 2006 b

ALT: alanine aminotransferase, AST: aspartate aminotransferase, LOEL: lowest observed effect level, * $p \leq 0.05$, ** $p \leq 0.01$ (statistically significant according to Kruskal-Wallis and Wilcoxon tests, two-sided)

5.2.3 Dermal application

In the local lymph node assay in mice (see Section 5.4), treatment of the ears with 25 µl of a 3%, 10% or 50% *N*-ethyl-2-pyrrolidone/acetone mixture (w/w) did not induce any signs of systemic toxicity (BASF AG 2005 c).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

The irritating effects of *N*-ethyl-2-pyrrolidone on the skin were investigated in 1 male and 2 female Vienna White rabbits according to OECD Test Guideline 404. About 0.5 ml of the undiluted test substance was applied semi-occlusively to the depilated intact dorsal skin of the animals (skin area: 2.5 × 2.5 cm) for 4 hours. After exposure, the patch was removed and the exposed site was washed with Lutrol and Lutrol/water (1:1). The animals were investigated after 30 to 60 minutes, 24, 48 and 72 hours and on day 8 after exposure. All animals were found to have slight to severe erythema, but after 8 days this was no longer visible. Oedema was not found (BASF AG 1986 b).

The primary irritating effects of *N*-ethyl-2-pyrrolidone on the skin were investigated in 6 albino rabbits. The abraded or intact skin was treated with 0.5 ml *N*-ethyl-2-pyrrolidone for 24 hours under occlusive conditions. Signs of irritation were not observed even after 72 hours (Ansell and Fowler 1988).

Treatment of the ears of mice with 25 µl of a 3%, 10% or 50% *N*-ethyl-2-pyrrolidone/acetone mixture (w/w) in a local lymph node assay (see Section 5.4) resulted in an increase in ear weight that was not dependent on the concentration, but attributed to irritation of the skin of the ear (BASF AG 2005 c).

N-Ethyl-2-pyrrolidone had no effects on the treated skin in a study of developmental toxicity in Wistar rats (see Section 5.5.2). The animals' skin was exposed semi-occlusively to *N*-ethyl-2-pyrrolidone doses of 0, 200, 400 or 800 mg/kg body weight, for 6 hours per day, for 14 days (BASF AG 2005 f).

In another study of developmental toxicity (see Section 5.5.2) in Himalayan rabbits, skin changes were not observed after semi-occlusive dermal exposure to *N*-ethyl-2-pyrrolidone doses of 0, 100, 300 or 1000 mg/kg body weight, for 6 hours per day, for a period of 22 days (BASF AG 2010).

5.3.2 Eyes

After the instillation of 0.1 ml *N*-ethyl-2-pyrrolidone (undiluted) into the conjunctival sac of one eye of 2 male and 1 female Vienna White rabbits, redness and swelling of the conjunctiva were observed 1, 24 and 48 hours after treatment. In addition, changes to the cornea and iritis were detected after 24 hours. While the con-

junctivitis and iritis had subsided after 8 days, the changes to the cornea were still found 15 days after treatment. The study was carried out according to OECD Test Guideline 405 (BASF AG 1986 a).

In a study of eye irritation, 0.1 ml *N*-ethyl-2-pyrrolidone was instilled into the conjunctival sac of one eye of 3 female and 3 male New Zealand White rabbits. The findings were read 24, 48 and 72 hours and 7 days after treatment. The authors regarded the primary irritating effects of *N*-ethyl-2-pyrrolidone as moderately to severely irritating according to Draize. While the corneal changes (no other details) persisted, conjunctivitis and iritis had subsided after 7 days (Ansell and Fowler 1988).

In another study carried out according to OECD Test Guideline 405, the instillation of 0.1 ml undiluted *N*-ethyl-2-pyrrolidone into the conjunctival sac of one eye of 2 female and 1 male New Zealand rabbits induced severe eye irritation. The eyes were rinsed with water 24 hours after the instillation. Moderate corneal opacity was observed in 2 animals, which persisted in 1 animal even after 28 days. Moderate iritis was also detected in 2 animals and had not subsided in 1 animal after 72 hours. All animals had moderate to severe conjunctival redness and chemosis (score 3), which had not yet subsided after 7 days. All animals were found to have a severe discharge (score 3), which still persisted in 1 animal after 7 days, although to a slighter extent. Additional effects included suppuration, contracted pupils, the discharge of blood, marginal neovascularization of the cornea and dilated scleral venous vessels (BASF AG 2005 d).

After the application of 0.3 ml of a solution of 0%, 10%, 20% or 30% *N*-ethyl-2-pyrrolidone in Pluronic PE 6200, a comparative HET-CAM test yielded an *N*-ethyl-2-pyrrolidone threshold concentration between 10% and 20% for effects that indicate severe eye damage (BASF AG 2006 c).

Conclusions

N-Ethyl-2-pyrrolidone causes severe irritation of the eyes and mild irritation of the skin.

5.4 Allergenic effects

In a modified local lymph node assay, in which the cell count and the weights of the lymph nodes, rather than [^{3}H]-methylthymidine incorporation, were determined, the authors did not observe any sensitization under the chosen conditions. Groups of 6 female CBA/Ca mice were treated with 0%, 3%, 10% or 50% *N*-ethyl-2-pyrrolidone in acetone (w/w). Both ears were treated with 25 µl of the respective solution on 3 consecutive days. The animals were sacrificed 3 days after the last exposure, and the auricular lymph nodes were removed for subsequent examination. As an indicator of skin irritation, ear biopsies at the application sites from previously sacrificed animals were weighed. A statistically significant difference was

found for the stimulation indices for lymph node weights and cell count (1.2 and 1.32, respectively) compared with the values for the controls at the high concentration. The authors concluded that the effects were caused by skin irritation detected at concentrations as low as 3% (increase in ear weights). In their opinion, the significant effects found in the high concentration group (lymph node weight index, cell count index and ear weight index) were too low to be of biological relevance (BASF AG 2005 c).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no specific studies available. Administration of *N*-ethyl-2-pyrrolidone doses of 0 to 1000 mg/kg body weight and day to groups of 10 male Wistar rats via their diet for a period of 90 days increased the number of sperm with abnormal heads to 11.4% ($p < 0.01$; controls: 2.0%) in the high dose group. *N*-Ethyl-2-pyrrolidone had no significant effects on the number of homogenization-resistant spermatids, sperm counts in the epididymis or sperm motility. No histopathological changes were found in the testes of the animals (BASF AG 2006 b).

5.5.2 Developmental toxicity

Table 4 shows the results of the studies for developmental toxicity.

The yellowy-orange discoloration of the urine, which was observed in all studies, is indicative of the systemic availability of *N*-ethyl-2-pyrrolidone rather than evidence of adverse effects. In all studies, reduced body weight gains were observed at the beginning of exposure from days 6 to 9 of gestation, even in the control animals. All studies were carried out in accordance with OECD Test Guideline 414. The purity of the *N*-Ethyl-2-pyrrolidone used was 99.8% (BASF AG 2005 f, 2007 a, b, 2010) or 99% (Saillenfait et al. 2007).

Rats

In a study of developmental toxicity with Sprague Dawley rats given gavage doses of 0, 50, 250, 500 or 750 mg/kg body weight and day, the low dose of 50 mg/kg body weight and day was the NOAEL (no observed adverse effect level) for the offspring; the body weights of the dams were still transiently reduced at this dose level. A dose-dependent decrease in the body weights of the offspring was observed at 250 mg/kg body weight and day and above. Post-implantation losses (resorptions and only a small, not significant increase in dead foetuses) were found at 500 mg/kg body weight and day and above and reached 83% at 750 mg/kg body weight and day. Maternal toxicity was observed in all dose groups (Saillenfait et al. 2007). Clinical parameters were not examined.

Table 4 Developmental toxicity studies after the administration of *N*-ethyl-2-pyrrolidone

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 25 ♀	**GD 6–20** gavage, 0, 50, 250, 500, 750 mg/kg body weight and day, examination on GD 21	**50 mg/kg body weight**: dams: GD 6–9: body weight gains (85%) ↓, feed consumption (21%) ↓, foetuses: **NOAEL**; **250 mg/kg body weight and above**: dams: GD 0–21: body weight gains (17%) ↓, corrected body weights unchanged, foetuses: foetal weights (7%) ↓, additional 14th rib ↑; **500 mg/kg body weight and above**: dams: feed consumption ↓, corrected body weights unchanged, resorptions and post-implantation losses significantly increased, foetuses: external and skeletal malformations significantly increased (anal atresia with absent tail, oedema, fused cervical arches), rare vascular malformations ↑ (cardiovascular defects higher than control values), incomplete ossification of sternebrae and skull; **750 mg/kg body weight**: foetuses: foetal mortality, visceral malformations significantly increased	Saillenfait et al. 2007
rat, Wistar, 25 ♀	**GD 6–19** dermal, semi-occlusive, 0, 200, 400, 800 mg/kg body weight and day, 6 hours/day, 33.3% aqueous solution, examination on GD 20	**200 mg/kg body weight**: dams: **NOAEL**; **400 mg/kg body weight and above**: dams: body weight gains (10%) ↓, feed consumption (GD 6–8) (13%) ↓, foetuses: **NOAEL**; **800 mg/kg body weight**: dams: placental weights (17%) ↓, foetuses: foetal weights (11%) ↓, skeletal variations (retarded ossification in skull and vertebrae; additional 14th rib) ↑	BASF AG 2005 f
rabbit, Himalayan, 25 ♀	**GD 6–28** gavage, 0, 20, 60, 200 mg/kg body weight and day, examination on GD 29	**60 mg/kg body weight**: **NOAEL** for developmental and maternal toxicity, foetuses: spontaneous, external malformation (spina bifida) 1 foetus; **200 mg/kg body weight**: dams: body weight gains (27%) ↓, feed consumption (46%) ↓, ALT ↑, relative liver weights ↑, Ca^{2+} ↑, PO_4^{3-} ↑, relative kidney weights ↑, γ-GT ↑, corrected body weights (21%) ↓,	BASF AG 2007 a

Table 4 (Continued)

Species, strain, number per group	Exposure	Findings	References
		foetuses: skeletal malformations significantly increased (higher than historical controls), spontaneous, external malformation (meningocoele) 1 foetus	
rabbit, Himalayan, 25 ♀	**GD 6–28** gavage, 0, 220 mg/kg body weight and day, examination on GD 29	**220 mg/kg body weight**: dams: body weight gains (38%) ↓, feed consumption (47%) ↓, absolute liver weights ↑, ALT ↑, γ-GT ↑, coagulation parameters ↓, AP ↓, PO_4^{3-} ↑, urea ↑, triglycerides ↑, cholesterol ↑, albumin ↓, Mg^{2+} ↓, corrected body weights (23%) ↓, foetuses: foetal weights ↓, severe multiple malformations (2 foetuses from 2 litters), visceral and skeletal malformations significantly increased (higher than control values), rare vascular malformations ↑	BASF AG 2007 b
rabbit, Himalayan, 25 ♀	**GD 6–28** dermal, semi-occlusive, 0, 100, 300, 1000 mg/kg body weight and day, 6 hours/day, 33.3% aqueous solution, examination on GD 29	**100 mg/kg body weight**: foetuses: rare cardiovascular malformations; (atresia of the aortic arch, defective ventricular septum of the heart, 2 animals in 1 litter), in the range of the historical control values; **300 mg/kg body weight**: dams: **NOAEL**, foetuses: **NOAEL**; **1000 mg/kg body weight**: dams: body weight gains (61%, GD 6–9) ↓, feed consumption (42%) ↓, corrected body weights unchanged, foetuses: additional 13th rib (variation) ↑, cardiovascular malformations (absent brachial artery, defective ventricular septum of the heart, dextrocardia, 5 foetuses in 3 litters)	BASF AG 2010

ALT: alanine aminotransferase, AP: alkaline phosphatase, GD: gestation day, γ-GT: γ-glutamyl transferase; NOAEL: no observed adverse effect level

A developmental toxicity study with Wistar rats given doses of 0, 200, 400 or 800 mg/kg body weight and day did not reveal any significant increase in malformations or post-implantation losses after semi-occlusive dermal exposure. Skeletal variations were observed in the foetuses of the high dose group. The decrease in foetal weights is not regarded as a foetotoxic effect caused by *N*-ethyl-2-pyrrolidone because of the maternal toxicity. In this study, maternal toxicity was first observed

at 400 mg/kg body weight and day (BASF AG 2005 f). The NOAEL was 200 mg/kg body weight and day for maternal toxicity and 400 mg/kg body weight and day for toxic effects on prenatal development.

Rabbits

In a study of developmental toxicity with pregnant Himalayan rabbits given gavage doses of 0, 20, 60 or 200 mg/kg body weight and day, the high dose induced maternal toxicity. In the dams of the high dose group, body weight gains and feed consumption were reduced, while liver weights and the activity of alanine aminotransferase in serum were increased, which is evidence of liver toxicity caused by *N*-ethyl-2-pyrrolidone. Reproductive parameters were not affected by the treatment and no visceral variations could be attributed to the exposure to *N*-ethyl-2-pyrrolidone. At 200 mg/kg body weight and day the incidence of non-specific skeletal malformations in the foetuses was significantly increased. External malformations (one case of spina bifida and of meningocele) were observed at 60 and 200 mg/kg body weight; in this rabbit strain low incidences of these malformations occur spontaneously and are not regarded as treatment-related (BASF AG 2007 a). The NOAEL for maternal toxicity and toxic effects on prenatal development was 60 mg/kg body weight in this study.

A follow-up study in which Himalayan rabbits were given gavage doses of 0 and 220 mg/kg body weight and day confirmed the maternal toxicity (reduced body weights and increased absolute and relative liver weights). The results of the blood analyses and the increased enzyme activities were attributed to phase II enzyme induction in the hepatocytes. Significant effects on reproductive parameters were not observed. Foetal weights were significantly reduced. The incidence of non-specific foetal malformations (skeletal and visceral) was significantly increased, and severe multiple malformations were observed in 2 foetuses (BASF AG 2007 b). The organs were not examined histopathologically in this study.

Another study with semi-occlusive dermal application of 0, 100, 300 or 1000 mg/kg body weight did not reveal any significant effects on reproductive parameters. The treatment with *N*-ethyl-2-pyrrolidone did not cause visceral variations. The observed skeletal variations were not dose-dependent. A dose-dependent increase in the incidence of an additional 13th rib was significant and in the high dose group was above the historical control values. At 100 mg/kg body weight and day, rare cardiovascular malformations occurred in 2 foetuses of 1 litter, but the incidence was still in the range of the historical control values; at 1000 mg/kg body weight and day, incidences that were outside the range of the historical control values occurred in 5 foetuses of 3 litters. The data are shown in Table 5. In the high dose group, the body weights and feed consumption of the dams were significantly reduced (in the initial phase). The NOAEL for maternal toxicity was 300 mg/kg body weight and day. The authors concluded that the NOAEL was 1000 mg/kg body weight for toxic effects on prenatal development because the cardiovascular malformations were not dose-dependent (BASF AG 2010). According to ECHA (2011),

Table 5 Foetal malformations and variations after dermal exposure in rabbits (BASF AG 2010; ECHA 2011)

	Dose (mg/kg body weight and day)				Historical control values[a)]
	0	100	300	1000	
number of foetuses examined (litters)	155 (23)	155 (23)	134 (21)	144 (23)	
% of foetuses with malformations	1.9	6.5	5.2	4.9	4.07 (1.27–7.64)
% per litter with malformations	13	29	24	22	23.40 (8.00–43.48)
% of foetuses with external malformations	0	0	0	0.7	0.3 (0–2.6)
% per litter with external malformations	0	0	0	4.3	2.0 (0–20.0)
% of foetuses with visceral malformations	0.6	3.9	4.5	3.5	2.6 (0–7.2)
% per litter with visceral malformations	4.3	13	19	13	15.5 (0–43.5)
% of foetuses with cardiovascular malformations	0	1.3	0.7	3.5	–
% of foetuses with absent brachial artery	0	0	0.7	0.7	0
% of foetuses with membranous ventricular septal defects	0	0.6	0	1.4	0.06 (0–0.7)
% of foetuses with dextrocardia	0	0	0	2.1	0
% of foetuses with aortic arch atresia	0	0.6	0	0	0.06 (0–0.7)
% of foetuses with skeletal malformations	1.3	2.6	0.7	0.7	1.9 (0.6–3.1)
% per litter with skeletal malformations	8.7	17	4.8	4.3	12.8 (4.0–21.7)
% of foetuses with skeletal variations	65	62	61	69	60 (51.5–77.8)
% per litter with skeletal variations	100	96	95	100	96.6 (80.0–100)
% of foetuses with additional 13th rib (without cartilage)	7.7	0.6	12	16	6.9 (2.5–13.9)

[a)] mean foetal incidence in historical control data from 24 studies carried out in the same laboratory from 2003–2009

the incidences of an absent brachial artery, ventricular septal defects (hole in the cardiac septum) and dextrocardia (heart on the right side of the body) observed in the high dose group were above the historical control incidences and were thus treatment-related. Based on these findings, the Commission derived a NOAEL of 300 mg/kg body weight and day for developmental toxicity and maternal toxicity in rabbits after dermal exposure.

Conclusions

In developmental toxicity studies in rats, *N*-ethyl-2-pyrrolidone induced decreased foetal weights, post-implantation losses and skeletal and cardiovascular malformations after oral administration, whereas only reduced foetal weights were observed after dermal application in rats. The developmental toxicity caused by *N*-ethyl-2-pyrrolidone was about the same as that observed in rats after oral administration of the structurally homologous *N*-methyl-2-pyrrolidone; however, because of the higher toxicity of *N*-ethyl-2-pyrrolidone compared with that of *N*-methyl-2-pyrrolidone, maternally toxic effects were reported even at the lowest tested dose of 50 mg/kg body weight (Saillenfait et al. 2007). The effects described were detected in the offspring of rabbits after both oral and dermal exposure. After oral administration, the NOAEL for the developmental toxicity of *N*-ethyl-2-pyrrolidone was 50 mg/kg body weight and day in rats and 60 mg/kg body weight and day in rabbits. Dermal application yielded NOAELs of 400 mg/kg body weight and day for developmental toxicity in rats and of 300 mg/kg body weight and day in rabbits. Developmental toxicity was observed in rats and rabbits only in association with maternal toxicity.

5.6 Genotoxicity

5.6.1 In vitro

In bacterial mutagenicity tests with the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli WP2 uvrA, *N*-ethyl-2-pyrrolidone was not found to be mutagenic in the concentration range of 20 to 5000 μg/plate in the standard test without activation or in the pre-incubation test in either the presence or absence of a metabolic activation system (S9 mix from rat liver induced by Aroclor 1254). Signs of cytotoxicity were not observed even at the high concentration. The tests were carried out according to OECD Test Guidelines 471 and 472 (BASF AG 1998).

In an HPRT gene mutation test carried out with CHO cells according to OECD Test Guideline 476, *N*-ethyl-2-pyrrolidone was not mutagenic in either the presence or absence of a metabolic activation system (S9 mix from rat liver induced by phenobarbital/β-naphtoflavone). The *N*-ethyl-2-pyrrolidone concentrations were 0, 125, 250, 500, 1000 or 1130 μg/ml in the tests without metabolic activation and 0,

125, 250, 400, 500, 600, 800, 1000 or 1130 µg/ml in the tests with metabolic activation (BASF AG 2008).

5.6.2 In vivo

A chromosomal aberration test carried out according to OECD Test Guideline 475 with bone marrow cells from male Clr:NMRI mice did not produce clastogenic or aneugenic effects after single oral doses. Groups of 5 animals were given single *N*-ethyl-2-pyrrolidone doses of 0, 500, 1000 or 2000 mg/kg body weight. For the microscopic examination, the bone marrow cells were prepared in all dose groups after 24 hours and in the control group and high dose group also after 48 hours. The microscopic examination revealed no difference in the incidence of chromosomal aberrations in the controls and treated groups. In view of the absence of effects on the number of chromosomes, the authors concluded that the substance is not aneugenic (BASF AG 2005 e).

In a micronucleus test according to OECD Test Guideline 474, male CrI:NMRI mice were given single gavage doses of *N*-ethyl-2-pyrrolidone of 0, 500, 1000 or 2000 mg/kg body weight. The test substance was dissolved in 10 ml water. In the bone marrow removed after 24 or 48 hours, the number of small or large micronuclei in polychromatic erythrocytes was not increased. The PCE/NCE ratio was unchanged. There is thus no evidence of cytotoxic effects on the bone marrow. Squatting posture and abdominal positions were observed in the animals 1 to 4 hours after single *N*-ethyl-2-pyrrolidone doses of 2000 mg. These symptoms were transient (BASF AG 2006 a).

Conclusions

The studies carried out yielded no evidence of mutagenic, clastogenic or aneugenic effects of *N*-ethyl-2-pyrrolidone.

5.7 Carcinogenicity

There are no studies available.

6 Manifesto (MAK value/classification)

The critical effects of *N*-ethyl-2-pyrrolidone are irritation and damage to the olfactory epithelium after inhalation, increased liver and kidney weights after oral administration and prenatal toxicity in association with maternal toxicity.

MAK value. There are no data available for humans. Therefore, the MAK value has been established on the basis of the results from animal studies.

A 28-day inhalation study in rats (BASF AG 2011) yielded a LOAEC of 82 mg/m³ ≙ 17 ml/m³. At this concentration, 5 of 15 animals were found to have minimal to mild degeneration/regeneration of the olfactory epithelium in the nasal cavity; however, minimal effects were observed also in 3 control animals. The severity and incidence of these findings increased with the exposure concentration.

In a 90-day feeding study in rats (BASF AG 2006 b), *N*-ethyl-2-pyrrolidone led to a dose-dependent increase in relative liver weights. This effect was significant in males at the low dose of 100 mg/kg body weight and day and above and in both sexes in the 2 higher dose groups of 300 and 1000 mg/kg body weight and day.

The relative kidney weights were significantly increased in male rats even at the low dose level. The α2u-globulin-mediated nephropathy that was observed in the males of all dose groups is species-specific and sex-specific and is not considered to be of relevance to humans. However, as the increase in the relative kidney weights was dose-dependent also in the females and was significant at 300 mg/kg body weight and above ($p \leq 0.01$), this may be evidence of additional nephrotoxicity.

The following toxicokinetic data are used to extrapolate the dose of 100 mg/kg body weight to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction value for the rat determined on the basis of the toxicokinetic data (1:4), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 245 mg/m³.

Initial effects on the olfactory epithelium were observed in rats in the 28-day inhalation study at 82 mg/m³ ≙ 17 ml/m³; in view of these minimal effects, a NAEC (no adverse effect concentration) of about 8 ml/m³ is assumed. It must be borne in mind, however, that in the absence of a 90-day study it cannot be excluded that the NAEC may be lower after long-term exposure, and on the other hand that the human olfactory epithelium is exposed to a lesser extent than the olfactory epithelium of rats (Frederick et al. 1998). Therefore, a MAK value of 2 ml/m³ ≙ 9 mg/m³ has been established for *N*-ethyl-2-pyrrolidone.

Peak limitation. The local effects on the nasal epithelium of rats is the decisive critical effect for the derivation of the MAK value. *N*-Ethyl-2-pyrrolidone has therefore been classified in Peak Limitation Category I. As there are no data available for sensory irritation in humans and the effects were only minimal at the lowest tested concentration of 82 mg/m³ (BASF AG 2011), an excursion factor of 2 has been established.

Carcinogenicity and germ cell mutagenicity. There are no studies available for the carcinogenicity of the substance. *N*-Ethyl-2-pyrrolidone did not induce genotoxic effects either in vitro in a bacterial mutagenicity assay and an HPRT gene mutation test or in vivo in a chromosomal aberration test and a micronucleus test. Therefore, *N*-ethyl-2-pyrrolidone has not been classified in any of the categories for carcinogens or germ cell mutagens.

Prenatal toxicity. In rats, *N*-ethyl-2-pyrrolidone induced decreased foetal weights, post-implantation losses and skeletal and cardiovascular malformations after oral administration during gestation, whereas only reduced foetal weights were observed after dermal application of the substance. The described effects were detected in the offspring of rabbits after both oral and dermal exposure. The toxic effects on development caused by *N*-ethyl-2-pyrrolidone resembled those observed in rats after oral administration of *N*-methyl-2-pyrrolidone. After oral administration, the lowest NOAEL for the developmental toxicity of *N*-ethyl-2-pyrrolidone was 50 mg/kg body weight and day in rats and 60 mg/kg body weight and day in rabbits. Dermal application yielded a NOAEL of 400 mg/kg body weight and day for developmental toxicity in rats and 300 mg/kg body weight and day in rabbits. Developmental toxicity was observed in rats and rabbits only in association with maternal toxicity.

The NOAELs from the oral studies in rats and rabbits are used for the toxicokinetic extrapolation to a concentration in workplace air. The following differences are taken into account: the corresponding species-specific correction value for the rat and rabbit determined on the basis of the toxicokinetic data (1:4 or 1:2.4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. This results in the respective concentrations of 87.5 and 175 mg/m^3, which are 9.7 and 19.4 times higher than the MAK value of 9 mg/m^3. As *N*-ethyl-2-pyrrolidone caused developmental toxicity in rats and rabbits only at maternally toxic doses and the difference between the calculated NAEC and the MAK value is sufficiently high, *N*-ethyl-2-pyrrolidone has been classified in Pregnancy Risk Group C.

Absorption through the skin. There are no quantitative data available for the absorption of *N*-ethyl-2-pyrrolidone through the skin. Model calculations for the exposure of both hands and forearms for 1 hour to a saturated aqueous solution yielded the dermal absorption of between 80 and 444 mg (1.1 and 6.3 mg/kg body weight at a body weight of 70 kg; see Section 3.1). An extrapolated dose of 17.5 mg/kg body weight was obtained for humans on the basis of the dose of 100 mg/kg body weight from the 90-day feeding study in rats (toxicokinetic species-specific correction value (1:4), daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5) and extrapolation from animal studies to humans). As the estimated dermal absorption is more than 25% of the extrapolated oral dose for humans, the dermal route of exposure may significantly contribute to the total body burden. Therefore, *N*-ethyl-2-pyrrolidone has been designated with an "H" (for substances which can be absorbed through the skin).

Sensitization. There are no findings available from humans for the sensitizing effects of *N*-ethyl-2-pyrrolidone on the skin or respiratory tract. Marginal effects that were found in a local lymph node assay in mice were probably caused by the irritating effects of *N*-ethyl-2-pyrrolidone (BASF AG 2005 c). *N*-Ethyl-2-pyrroli-

done has therefore not been designated with “Sh” or “Sa” (for substances which cause sensitization of the skin or airways).

References

Akesson B, Jönsson BA (1997) Major metabolic pathway for N-methyl-2-pyrrolidone in humans. *Drug Metab Dispos* 25: 267–269

Ansell JM, Fowler JA (1988) The acute oral toxicity and primary ocular and dermal irritation of selected N-alkyl-2-pyrrolidones. *Food Chem Toxicol* 26: 475–479

Bader M, Keener SA, Wrbitzky R (2005) Dermal absorption and urinary elimination of N-methyl-2-pyrrolidone. *Int Arch Occup Environ Health* 78: 673–676

BASF AG (1978 a) Bericht über die Prüfung der akuten oralen Toxizität von Äthylpyrrolidon an der Ratte (Investigation of the acute oral toxicity of ethyl pyrrolidone in the rat) (German). Report from 24.10.1978, BASF AG, Ludwigshafen, unpublished

BASF AG (1978 b) Bericht über die Prüfung der akuten intravenösen Toxizität von Äthylpyrrolidon an der Ratte (Investigation of the acute intravenous toxicity of ethyl pyrrolidone in the rat) (German). Report from 24.10.1978, BASF AG, Ludwigshafen, unpublished

BASF AG (1978 c) Bericht über die Prüfung der akuten intraperitonealen Toxizität von Äthylpyrrolidon an der Maus (Investigation of the acute intraperitoneal toxicity of ethyl pyrrolidone in the mouse) (German). Report from 24.10.1978, BASF AG, Ludwigshafen, unpublished

BASF AG (1986 a) N-Ethyl-2-pyrrolidon – Report on the acute irradiation to the eye of the white rabbit based on OECD. Report from 21.02.1986, BASF AG, Ludwigshafen, unpublished

BASF AG (1986 b) N-Ethyl-2-pyrrolidon – Report on the acute dermal irritation/corrosivity to the intact dorsal skin of the white rabbit based on OECD. Report from 21.2.1986, BASF AG, Ludwigshafen, unpublished

BASF AG (1998) Report on the study of N-Ethyl-2-pyrrolidon (ZHT test substance No.: 96/390) in the ames salmonella/mammalian-microsome mutagenicity test and escherichia coli/mammalian-microsome reverse mutation assay (standard plate test and preincubation test). Report No. 40M0390/964206, BASF AG, Ludwigshafen, unpublished

BASF AG (2005 a) N-Ethyl-2-pyrrolidon – acute inhalation toxicity study in Wistar rats 4-hour exposure to a mixture of liquid aerosol and vapor. Report No. 1310033/047017, BASF AG, Ludwigshafen, unpublished

BASF AG (2005 b) N-Ethyl-2-pyrrolidon – Acute dermal toxicity study in rats. Report No. 11 A0033/041092, BASF AG, Ludwigshafen, unpublished

BASF AG (2005 c) N-Ethyl-2-pyrrolidon – Murine local lymph node assay (LLNA). Report No. 45H0033/042269, BASF AG, Ludwigshafen, unpublished

BASF AG (2005 d) N-Ethyl-2-pyrrolidon – Acute eye irritation in rabbits. Report No. 11H0033/042268, BASF AG, Ludwigshafen, unpublished

BASF AG (2005 e) Bone marrow chromosome analysis in vivo with N-Ethyl-2-pyrrolidon in mice – single oral administration. Report No. 20M0033/044172, BASF AG, Ludwigshafen, unpublished

BASF AG (2005 f) N-Ethyl-2-pyrrolidone – Prenatal developmental toxicity study in Wistar rats – dermal application. Report No. 34R0033/04006, BASF AG, Ludwigshafen, unpublished

BASF AG (2006 a) Cytogenetic study in vivo with N-Ethyl-2-pyrrolidon in the mouse micronucleus test – single oral administration. Report No. 26M0033/044178, BASF AG, Ludwigshafen, unpublished

BASF AG (2006 b) N-Ethyl-2-pyrrolidon – Repeated dose 90-day oral toxicity study in Wistar rats; administration in the diet. Report No. 50S0033/04072, BASF AG, Ludwigshafen, unpublished

BASF AG (2006 c) Acetophenone, Agnique KE 3658, gamma-Butyrolacton, DMSO, Cyclohexanone, Benzylalcohol, Propylencarbonate, 1,2-Propylenglycole, Rhodiasolv RPDE, N-octylpyrrolidone, Tributylphosphate, N-ethyl-2-pyrrolidone, Purasolv EHL, 2-Heptanon, 2-Ethylhexanole – Comparative HET-CAM test. Alternative method to study the potential of serious damage to the eyes/mucous membranes in incubated hen eggs. Report No. 60H0617/052113, BASF AG, Ludwigshafen, unpublished

BASF AG (2007 a) N-Ethyl-2-pyrrolidone – Prenatal developmental toxicity study in Himalayan rabbits – oral administration (gavage). Report No. 40R0033/04058, BASF AG, Ludwigshafen, unpublished

BASF AG (2007 b) N-Ethyl-2-pyrrolidone – Supplementary prenatal developmental toxicity study in Himalayan rabbits – oral administration (gavage). Report No. 40R0033/04075, BASF AG, Ludwigshafen, unpublished

BASF AG (2008) N-Ethyl-2-pyrrolidone – In vitro gene mutation test in CHO cells (HPRT locus assay). Report No. 50M0033/044204, BASF AG, Ludwigshafen, unpublished

BASF AG (2010) N-Ethyl-2-pyrrolidone – Prenatal developmental toxicity study in Himalayan rabbits dermal application. Report No. 44R0033/04110, BASF AG, Ludwigshafen, unpublished

BASF AG (2011) N-Ethyl-2-pyrrolidone – Subacute 28-day inhalation lung toxicity in Wistar rats – liquid aerosol with vapor fraction. Report No. 40I0033/04I021, BASF AG, Ludwigshafen, unpublished

ECHA (European Chemicals Agency) (2011) Committee for risk assessment. Annex 1. Background document to the opinion proposing harmonised classification and labelling at community level of N-ethyl-2-pyrrolidone (NEP), http://echa.europa.eu/documents/10162/dd84e8c9-6f29-452a-8738-61055379ba48

ECHA (2012) Information on registered-substances. Dataset on N-ethyl-2-pyrrolidone (CAS Number 2687-91-4) http://echa.europa.eu/information-on-chemicals

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. *Am J Ind Med* 17: 617–635

Frederick CB, Bush ML, Lomax LG, Black KA, Finch L, Kimbell JS, Morgan KT, Subramaniam RP, Morris JB, Ultman JS (1998) Application of a hybrid computational fluid dynamics and physiologically based inhalation model for interspecies dosimetry extrapolation of acidic vapors in the upper airways. *Toxicol Appl Pharmacol* 152: 211–231

Guy RH, Potts RO (1993) Penetration of industrial chemicals across the skin: a predictive model. *Am J Ind Med* 23: 711–719

Hall AP, Ellcombe CR, Foster JR, Harada T, Kaufmann W, Knippel A, Küttler K, Malarkey DE, Maronpot RR, Nishikawa A, Nolte T, Schulte A, Strauss V, York MJ (2012) Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes – conclusions from the 3rd International ESTP Expert Workshop. *Toxicol Pathol* 40: 971–994

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) (2012) GESTIS-Stoffdatenbank, N-Ethyl-2-pyrrolidone (CAS Nummer 2687-91-4), www.dguv.de/ifa/de/gestis/stoffdb/index.jsp www.dguv.de/ifa/GESTIS/GESTIS-Stoffdatenbank/index-2.jsp

Käfferlein HU (2013) Mitteilung an das Kommissionssekretariat zu toxikokinetischen Studien mit N-Ethyl-2-pyrrolidon (Communication to the Commission regarding toxicokinetic studies with N-ethyl-2-pyrrolidone) (German) 14.02.2013

Keener SA, Wrbitzky R, Bader M (2007) Human volunteer study on the influence of exposure duration and dilution of dermally applied N-methyl-2-pyrrolidone (NMP) on the urinary elimination of NMP metabolites. *Int Arch Occup Environ Health* 80: 327–334

Saillenfait AM, Gallisot F, Sabaté JP (2007) Developmental toxic effects of N-ethyl-2-pyrrolidone administered orally to rats. *J Appl Toxicol* 27: 491–497

Schindler BK, Koslitz S, Meier S, Belov VN, Koch HM, Weiss T, Brüning T, Käfferlein HU (2012) Quantification of four major metabolites of embryotoxic N-Methyl- and N-Ethyl-2-pyrrolidone in human urine by cooled-injection gas chromatography and isotope dilution mass spectrometry. *Anal Chem* 84: 3787–3794

SRC (Syracuse Research Corporation) (2012) PhysProp database, dataset on N-ethyl-2-pyrrolidone (CAS Number 2687-91-4), http://www.srcinc.com/what-we-do/databaseforms.aspx?id=386

Wilschut A, ten Berge WF, Robinson PJ, McKone TE (1995) Estimating skin permeation. The validation of five mathematical skin permeation models. *Chemosphere* 30: 1275–1296

completed 27.02.2013