The MAK Collection for Occupational Health and Safety

N-Ethyl-2-pyrrolidone (vapour)

MAK Value Documentation, addendum – Translation of the German version from 2016

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Keywords: N-ethyl-2-pyrrolidone; irritation; olfactory epithelium; MAK value; maximum workplace concentration; peak limitation; developmental toxicity

Citation Note: Hartwig A, MAK Commission. N-Ethyl-2-pyrrolidone (vapour). MAK Value Documentation, addendum – Translation of the German version from 2016. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2017 Apr;2(2):357-368]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2026. https://doi.org/10.34865/mb268791e5617_w

Republished (online): 07 Aug 2026

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb268791e5617

Addendum completed: 11 Dec 2014

Published (online): 25 Apr 2017

The commission established rules and measures to avoid conflicts of interest.

N-Ethyl-2-pyrrolidone[1)]/ 1-Ethylpyrrolidin-2-one

MAK Value Documentation

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DOI: 10.1002/3527600418.mb268791e5617

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the work place (MAK value) of N-ethyl-2-pyrrolidone [2687-91-4] of 2 ml/m³, considering the endpoints irritation of the respiratory tract and developmental toxicity.
The critical effect of N-ethyl-2-pyrrolidone is degeneration of the olfactory epithelia in rats in a new 13-week-inhalation study. Since 2014, the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. According to these proposals, the NOAEC of 62.6 mg/m³ (13.3 ml/m³ vapour) corresponds to a work place air concentration of 31 mg/m³ (6.6 ml/m³). The irritating response in the 13 week study is not more pronounced than after shorter exposition times. Therefore the MAK-value is increased to 5 ml/m³ for the vapour phase only. Local effects are critical and only minimal irritation occurs at the LOAEC, therefore the assignment of N-ethyl-2-pyrrolidone to Peak Limitation Category I and excursion factor 2 established in 2014 are retained. Also with the increased MAK value, damage to the embryo or foetus is unlikely when the MAK value is observed. Therefore, classification of N-ethyl-2-pyrrolidone in Pregnancy Risk Group C is confirmed.

Keywords

N-ethyl-2-pyrrolidone; 1-ethylazacyclopentan-2-one; 1-ethylpyrrolidin-2-one; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; reproductive toxicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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1) The substance can be present simultaneously in vapour and aerosol form

N-Ethyl-2-pyrrolidone[1)] (vapour)

[2687-91-4]

Supplement 2016

MAK value (2015)	**5 ml/m³ (ppm) ≙ 23.5 mg/m³ (vapour)**
Peak limitation (2015)	**Category I, excursion factor 2**
Absorption through the skin (2014)	**H**
Sensitization (2014)	**–**
Carcinogenicity (2014)	**–**
Prenatal toxicity (2015)	**Pregnancy Risk Group C**
Germ cell mutagenicity (2014)	**–**
BAT value (2015)	**–**
pH	8 – 9 (100 g/l) at 20°C (IFA 2014)
1 ml/m³ (ppm) ≙ 4.695 mg/m³	**1 mg/m³ ≙ 0.213 ml/m³ (ppm)**

Since the documentation from 2014 (documentation "N-Ethyl-2-pyrrolidone" 2014), a new 13-week inhalation study has been carried out in accordance with OECD Test Guideline 413. There are also two new biological monitoring studies available.

As *N*-ethyl-2-pyrrolidone is used as a solvent, aerosols can occur, for example, as a result of paint spraying.

Toxicokinetics and Metabolism

Absorption, distribution, elimination

Three volunteers ingested a defined amount of *N*-ethyl-2-pyrrolidone of 20.9 mg (about 250 µg/kg body weight; 80 kg/person). The elimination of the metabolites

1) The substance can be present simultaneously in vapour and aerosol form

5-hydroxy-*N*-ethyl-2-pyrrolidone and 2-hydroxy-*N*-ethylsuccinimide with the urine was investigated over the subsequent 96 hours. The maximum amount of 5-hydroxy-*N*-ethyl-2-pyrrolidone was eliminated three hours after absorption and that of 2-hydroxy-*N*-ethylsuccinimide after 30 hours. The elimination half-times were around 7 hours for 5-hydroxy-*N*-ethyl-2-pyrrolidone and 22 to 27 hours for 2-hydroxy-*N*-ethylsuccinimide. After 4 days, 50.7% of the dose was recovered in urine as these two metabolites (29.1% as 5-hydroxy-*N*-ethyl-2-pyrrolidone and 21.6% as 2-hydroxy-*N*-ethylsuccinimide) (Koch et al. 2014).

Analysis of the post-shift urine of 12 employees in the paint shop of an automobile manufacturer yielded median values of 0.15 mg/l urine (maximum 5.6 mg/l urine) for 5-hydroxy-*N*-ethyl-2-pyrrolidone and of 0.19 mg/l urine (maximum 6.4 mg/l urine) for 2-hydroxy-*N*-ethylsuccinimide. These values were five times higher than the metabolite concentrations in the urine of control persons (9 employees from the company from work areas not exposed). Two of the employees had carried out cleaning work on the paint-spraying cabin using solvents containing *N*-alkyl-pyrrolidone. The maximum metabolite concentrations the next morning were 31.1 mg/l urine for 5-hydroxy-*N*-ethyl-2-pyrrolidone and 8.45 mg/l urine for 2-hydroxy-*N*-ethylsuccinimide. The authors attribute the high values to the additional dermal exposure resulting from the cleaning work. In order to follow the course of the metabolite concentrations, urine samples were collected in the middle of the week before the beginning of the shift, after the shift and on the following morning before the beginning of the shift. A continuous increase in the metabolite concentrations in urine was observed in the more highly exposed cleaning workers. All the determinations were related to the level of creatinine. They revealed the same pattern of exposure as the volume-based data. No details were given regarding the exposure concentration, the duration of exposure or adverse effects (Koslitz et al. 2014).

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

In a 13-week study carried out according to OECD Test Guideline 413, groups of 10 female and 10 male Wistar rats were exposed via the head and nose to *N*-ethyl-2-pyrrolidone concentrations of 0, 29.8, 62.6 or 197.5 mg/m^3 for 6 hours a day, on five days a week. The exposure atmosphere, generated from the undiluted substance, was made up of vapour. Aerosols could not be detected.

The observed effects are shown in Table 1. Histopathological examination of the larynx, nasal cavity (olfactory and respiratory epithelium), epididymis and testes (in each case only the left organ) was carried out in all concentration groups. Degeneration/regeneration of the olfactory epithelium took place in all animals of the high concentration group, but in none of the animals of the two lower concentration groups or the control group. The data are shown in Table 2. The changes in the creatinine and potassium values and the aspartate aminotransferase (AST) activity in

the female animals were not dose-dependent. The dose-dependent decrease in the globulin values in the female animals was within the range of that of the historical controls. The haematological investigation and urinalysis did not reveal any differences compared with the values for the controls. The neurofunctional behavioral tests likewise did not reveal any effects. The neurofunctional tests were carried out with 5 male and 5 female animals after the end of the 13-week exposure period. Significantly increased values were found for motor activity in the female animals at one interval (interval 10 of 12) in all three concentration groups. In the middle concentration group the activity was highest, in the high concentration group the activity was lowest. As the increase was not concentration-dependent and occurred only once during the 12 determination intervals, these findings were not regarded as substance-related. As there was no histopathological correlation and the findings were not concentration-dependent, the significant changes in the relative organ weights were likewise not regarded as substance-related. Deposits and oligospermia were found in the epididymis at concentrations of 29.8 mg/m³ and above. Multifocal tubular degeneration of minimally increased severity occurred in the testes at 29.8 mg/m³ and above. The data are shown in Table 3. The effects in the testes and the epididymis were not concentration-dependent. The data from the sperm analyses with the parameters motility, number of sperms in the testes, number of sperms in the epididymis and number of abnormal sperms are shown in Table 4. The number of sperms in the 62.6 mg/m³ group was significantly decreased and the incidence of abnormal sperms in the 29.8 mg/m³ group was significantly increased.

Table 1 Effects of *N*-ethyl-2-pyrrolidone after inhalation exposure for 13 weeks (BASF SE 2013)

Species, strain number per group	Exposure	Findings	References
rat, Wistar, 10 ♂, 10 ♀	**13 weeks**, 0, 29.8, 62.6, 197.5 mg/m³ 6 hours/day, 5 days/week, head/nose, **vapour**	**29.8 mg/m³ and above**: ♀: serum: creatinine ↓, K^+ ↑, AST ↓; ♂: relative weights of epididymis and testes ↓, abnormal sperms ↑* (only at 29.8 mg/m³, see Table 3); **62.6 mg/m³**: **NOAEC** ♀: serum: globulin ↓, relative liver weights ↓ (96%), relative ovary weights ↓ (87%)*; ♂: number of sperms ↓*; **197.5 mg/m³**: degeneration of the olfactory epithelium 20/20** (see Table 2) ♀: serum: globulin ↓, relative liver weights ↓ (94%)*, relative ovary weights ↑ (110%)*	BASF SE 2013

*$p \leq 0.05$; **$p \leq 0.01$; AST: aspartate aminotransferase; NOAEC: no observed adverse effect concentration

Table 2 Histological changes in the nasal cavity after inhalation exposure for 13 weeks to *N*-ethyl-2-pyrrolidone concentrations of 197.5 mg/m³ (BASF SE 2013)

Sex	♂		♀	
Concentration (mg/m³)	0	197.5	0	197.5
Number of animals investigated	10	10	10	10
Nasal cavity (section I)				
degeneration/regeneration, olfactory epithelium (total)	–	–	–	3
grade 1	–	–	–	2
grade 2	–	–	–	1
Nasal cavity (section II)				
degeneration/regeneration, olfactory epithelium (total)	–	7	–	7
grade 1	–	5	–	4
grade 2	–	2	–	2
grade 3	–	–	–	1
Nasal cavity (section III)				
degeneration/regeneration, olfactory epithelium (total)	–	8	–	10
grade 1	–	4	–	4
grade 2	–	3	–	4
grade 3	–	1	–	2
Nasal cavity (section IV)				
degeneration/regeneration, olfactory epithelium (total)	–	10	–	10
grade 1	–	3	–	5
grade 2	–	4	–	4
grade 3	–	3	–	1

The observed effects were within the range of the findings for the historical controls as regards incidence and severity and were not concentration-dependent. In addition, such effects on the testes and epididymis are often observed in inhalation studies with head and nose exposure. The incidence of these findings in historical control data (21 studies in the period January 2008–February 2013) ranges from 0% to 100% of the animals with a severity of minimal (grade 1) to high (grade 4). The histopathological findings in the testes and epididymis and the resulting findings in the sperm analyses were therefore regarded in this study as not substance-related by the authors (BASF SE 2013).

Table 3 Results of the histopathological investigation of the left epididymis and the left testicle after inhalation exposure to *N*-ethyl-2-pyrrolidone for 13 weeks (BASF SE 2013)

Concentration (mg/m³)		0	29.8	62.6	197.5
Number of animals investigated		10	10	10	10
Epididymis					
cell debris		3	5	5	6
oligospermia		–	2	2	2
spermagranuloma		–	–	1	–
Testicle					
degeneration, tubular, multifocal		6	8	6	8
	grade 1	4	4	–	3
	grade 2	1	1	5	3
	grade 3	1	2	1	2
	grade 4	–	1	–	–

Table 4 Parameters of the sperm analysis after inhalation exposure to *N*-ethyl-2-pyrrolidone for 13 weeks (BASF SE 2013)

Concentration (mg/m³)		0	29.8	62.6	197.5
Number of animals		10	10	10	10
sperm motility (%), day 92	mean value	86x–	70	73	79
	S.D.	7	27	26	15
	median	86	80	82	80
number of sperms in the testes (million/g), day 92	mean value	118x–	105	97*	101
	S.D.	18	28	19	29
	median	117	109	99	104
number of sperms in the epididymis (million/g), day 92	mean value	485x–	351	513	376
	S.D.	141	194	143	116
	median	500	340	533	410
abnormal sperms (%), ("cut off" 6%)[a], day 92	mean value	6.3x+	16.6*	14.5	7.0
	S.D.	1.1	13.9	16.9	2.3
	median	6.0	11.2	6.5	6.0

**$p \leq 0.05$; x+: Wilcoxon with Bonferroni-Holm (one-sided +);
x–: Wilcoxon with Bonferroni-Holm (one-sided –); S.D. standard deviation;
[a] values < 6% are given as 6%

Conclusions

In the 13-week inhalation study with rats (BASF SE 2013), the substance-related finding of degeneration/regeneration of the olfactory epithelium occurred at the high concentration of 197.5 mg/m³ with a NOAEC (no observed adverse effect concentration) of 62.6 mg/m³. Effects in the lower concentration groups that were not concentration-dependent are not regarded as relevant to the evaluation.

Comparison of the irritative effects in the 13-week and 28-day inhalation studies

The irritative effects described in the 28-day study (see documentation "N-Ethyl-2-pyrrolidone" 2014) from day 19 onwards of salivation, lacrimation, nasal discharge and red encrustation around the nose, were not observed in the 13-week study in the 208 mg/m³ group. A comparison of the irritative effects observed in the 28-day study and the 13-week study is shown in Table 5.

In the 13-week study the exposure atmosphere consisted only of vapour; an aerosol fraction could not be detected. Determination of the daily exposure levels showed that up to the 16th exposure, concentrations above 200 mg/m³ were present in the high exposure group, and from the 8th to 16th exposure, even concentrations of above 240 mg/m³ were present. From the 29th exposure onwards, all concentrations were about 180 mg/m³. The standard deviation was 23.6 mg/m³ and the nominal concentration 216 mg/m³ (BASF SE 2013).

The exposure atmosphere in the 28-day study consisted mainly of vapour (no other details); the aerosol fraction had a mass median aerodynamic diameter (MMAD)

Table 5 Comparison of the effects of inhalation exposure to *N*-ethyl-2-pyrrolidone for 28 days and 13 weeks (BASF SE 2011, 2013)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 10 ♂, 5 ♀	**28 days**, 0, 82, 208, 396 mg/m³, 6 hours/day, 5 days/week, nose-only exposure, **vapour/aerosol**	**0 mg/m³**: degeneration of the olfactory epithelium 3/15, minimal; **82 mg/m³**: LOAEC; degeneration of the olfactory epithelium 5/15, minimal–slight; **208 mg/m³**: degeneration of the olfactory epithelium 15/15, day 19 onwards: salivation, lacrimation, nasal discharge, red encrustation around the nose	BASF SE 2011
rat, Wistar, 10 ♂, 10 ♀	**13 weeks**, 0, 29.8, 62.6, 197.5 mg/m³, 6 hours/day, 5 days/week, head/nose exposure, **vapour**	**62.6 mg/m³**: **NOAEC**; **197.5 mg/m³**: degeneration of the olfactory epithelium 20/20; **no** other clinical signs of irritation	BASF SE 2013

LOAEC: lowest observed adverse effect concentration;
NOAEC: no observed adverse effect concentration

of between 0.89 and 3.20 µm. The exact amount of the aerosol fraction was not determined, but was described as "small". Daily determination of the exposure concentrations in the 208 mg/m³ group showed that in the first half of the study, up to the 11th exposure, the concentrations were markedly below 200 mg/m³ (about 150 mg/m³) and in the second half of the study were markedly above 200 mg/m³ (about 250 mg/m³). The standard deviation was 54.9 mg/m³ and the nominal concentration 303 mg/m³. The efficiency with which the atmosphere was generated in the 208 mg/m³ group was calculated to be only 69%. Compared with 80% efficiency in the other two concentration groups, this value is low. The authors suspect there was a systematic error here during sampling (BASF SE 2011; BASF SE 2014 a, b).

Conclusions

The findings observed in the 28-day study at 82 mg/m³, which were regarded as the beginning of the dose–response relationship and thus as the LOAEC (documentation "N-Ethyl-2-pyrrolidone" 2014), could not yet be found in the 13-week study at the slightly lower concentration of 62.6 mg/m³. The weaker irritative effects in the 13-week study, compared with those in the 28-day study, could be attributed to the fact that the exposure atmosphere did not contain an aerosol fraction. In addition, in the new 13-week study the nominal concentrations were better adhered to than in the 28-day study.

The 13-week study showed, however, that the local effects do not increase markedly over time. A MAK value can be derived from the 13-week study only for vapour.

Relative organ weights

In order to be able to evaluate the marked fluctuations in the relative organ weights (> 10%) in the inhalation studies, which were not clearly dose-dependent, Table 6 shows a comparison of the relative organ weights of the uterus, ovaries, testes and epididymis under different exposure conditions. The toxicokinetic extrapolation of the *N*-ethyl-2-pyrrolidone doses of 100, 300 and 1000 mg/kg body weight and day to a concentration in workplace air yields values of 245, 735 and 2450 mg/m³ (see also documentation "N-Ethyl-2-pyrrolidone" 2014; BASF SE 2013).

Conclusions

The fluctuations in the relative organ weights in the inhalation studies are not concentration-dependent. The study of oral toxicity shows that there is an increase in relative organ weights only at very high concentrations.

Developmental toxicity

In rats, *N*-ethyl-2-pyrrolidone caused a decrease in foetal weights and non-specific variations (additional 14th rib) after oral administration during the gestation period at 250 mg/kg body weight and day, and post-implantation losses and malformations of the skeleton and cardiovascular system at 500 mg/kg body weight and day

Table 6 Comparison of the relative organ weights after the inhalation or oral administration of *N*-ethyl-2-pyrrolidone (BASF AG 2006; BASF SE 2011, 2013)

28 days, inhalation, Wistar rats, groups of 10 ♀, 5 ♂				
	N-ethyl-2-pyrrolidone concentration (mg/m³)			
	0	80	200	400
body weights ♂ (in g)	276.88	275.07	286.63	276.50
body weights ♀ (in g)	186.64	185.20	178.28	186.22
relative organ weights in %				
testes	100	109	107	106
epididymis	100	106	100	103
ovaries	100	not investigated	not investigated	not investigated
uterus	100	not investigated	not investigated	not investigated
13 weeks, inhalation, Wistar rats, groups of 10 ♀, 10 ♂				
	N-ethyl-2-pyrrolidone concentration (mg/m³)			
	0	29.8	62.6	197.52
body weights ♂ (in g)	292.07	298.99	282.14	285.00
body weights ♀ (in g)	197.69	200.90	194.06	198.22
relative organ weights in %				
testes	100	91	96	94
epididymis	100	89	89	90
ovaries	100	100	87*	110*
uterus	100	87	93	105
13 weeks, oral, Wistar rats, groups of 10 ♀, 10 ♂				
	N-ethyl-2-pyrrolidone dose (mg/kg body weight and day)			
	0	100	300	1000
body weights ♂ (in g)	360.52	362.93	330.68*	295.71**
body weights ♀ (in g)	217.29	213.9	198.24**	177.43**
relative organ weights in %				
testes	100	101	108*	126**
epididymis	100	100	109**	118**
ovaries	100	105	110*	119*
uterus[a)]	100	75	98	93

[a)] Uterus: high standard deviation, therefore not significant;
*$p < 0.05$; **$p < 0.01$

and above. After dermal application, however, only reduced foetal weights were observed. In rabbits, the above-named effects occurred in the offspring both after oral administration at 200 mg/kg body weight and day and after dermal application at 1000 mg/kg body weight and day. The lowest NOAEL (no observed adverse effect level) for the developmental toxicity of *N*-ethyl-2-pyrrolidone after oral administration was 50 mg/kg body weight and day for rats and 60 mg/kg body weight and day for rabbits. After dermal application, a NOAEL for developmental toxicity of 400 mg/kg body weight and day for rats and of 300 mg/kg body weight and day for rabbits was obtained. Toxic effects on development occurred in rats and rabbits only with simultaneous maternal toxicity (see documentation "N-Ethyl-2-pyrrolidone" 2014).

Manifesto (MAK value/classification)

The critical effects are degeneration/regeneration of the olfactory epithelium after the inhalation exposure of rats.

MAK value. There are no suitable data from humans for the derivation of a MAK value.

In a 13-week inhalation study with rats (BASF SE 2013), *N*-ethyl-2-pyrrolidone was present only in the form of vapour. Under these conditions a NOAEC of 62.6 mg/m³ (13.3 ml/m³) for the degeneration/regeneration of the olfactory epithelium can be derived. In the documentation from 2014 (documentation "N-Ethyl-2-pyrrolidone" 2014) a NAEC (no adverse effect concentration) of 8 ml/m³ for effects on the olfactory epithelium was derived from the LOAEC of 17.5 ml/m³ from the 28-day study; it can therefore be expected that the NOAEC, even with long-term exposure, will not decrease to any great extent. The 28-day study was carried out, however, with an exposure atmosphere with a "small" aerosol fraction, and unlike in the 13-week study, clinical signs of irritation were observed from day 19 onwards of the study at 208 mg/m³. A possible reason for the stronger irritative effects might be the stronger effects of the aerosol than of the vapour; as a result of the occurrence of droplets, the local concentration in the target tissue might be higher, while the vapour is distributed evenly. Also, it is possible that the irritation was caused by the increased exposure concentration in the second half of the 28-day study (about 250 mg/m³ instead of 200 mg/m³). Therefore, a MAK value can be derived from the 13-week study only for *N*-ethyl-2-pyrrolidone vapour.

An empirical comparison showed that the long-term NOAEC for histologically detectable adverse effects in the olfactory epithelium of rats is, at most, twice as high as the short-term NOAEC for sensory irritation of the eyes and respiratory tract of humans (Brüning et al. 2014). It can be concluded from the 13-week inhalation study that an increase in the severity of the irritative effects of *N*-ethyl-2-pyrrolidone is not to be expected after long-term exposure. From the NOAEC of 62.6 mg/m³ for humans, a corresponding concentration of 31 mg/m³ (6.6 ml/m³) can

therefore be derived, and in accordance with the preferred value approach, a MAK value for *N*-ethyl-2-pyrrolidone vapour of 5 ml/m³ can be established.

Peak limitation. The local effect on the nasal epithelium of rats is the critical effect which is decisive for the derivation of the MAK value.

N-Ethyl-2-pyrrolidone is therefore classified in Peak Limitation Category I.

An excursion factor of 2 would lead to a peak *N*-ethyl-2-pyrrolidone concentration of 10 ml/m³ (47 mg/m³). This value is below the NOAEC from the 90-day inhalation study which is relevant to the evaluation (BASF SE 2013). As the effects at the LOAEC of 82 mg/m³ in the 28-day inhalation study (BASF SE 2011) are only minimal, even in the presence of aerosol, the Commission regards an excursion factor of 2 as justified.

Prenatal toxicity. *N*-Ethyl-2-pyrrolidone was classified in 2014 in Pregnancy Risk Group C (documentation "N-Ethyl-2-pyrrolidone" 2014).

The NOAELs from the oral studies with rats and rabbits were 50 and 60 mg/kg body weight and day, respectively. The following toxicokinetic data are taken into consideration for the extrapolation to a concentration in workplace air: the corresponding species-specific correction values for the rat and rabbit (1:4 and 1:2.4), 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 concentrations calculated from this are 87.5 mg/m³ (18.6 ml/m³) and 175 mg/m³ (37.2 ml/m³), which are, respectively, 4 and 8 times higher than the MAK value of 23.5 mg/m³ (5 ml/m³) and thus not high enough for Pregnancy Risk Group C. In rats and rabbits, at the LOAEL (lowest observed adverse effect level) of 250 and 200 mg/kg body weight and day (438 and 583 mg/m³), respectively, variations and non-specific malformations of the skeleton occurred. The concentrations in air calculated from the rat and rabbit data are 19 and 24 times higher, respectively, than the MAK value. Maternal toxicity at these concentrations is severe, as the body weights and food consumption were reduced by up to 15% and 21% in the rat and 27% and 46% in the rabbit. As at the LOAEL only non-specific effects occurred in the rat and rabbit and, in addition, severe maternal toxicity was simultaneously observed, the 19-fold and 24-fold difference between the calculated concentration for the LOAEC and the MAK value of 23.5 mg/m³ (5 ml/m³) would seem to be sufficient. *N*-Ethyl-2-pyrrolidone therefore remains in Pregnancy Risk Group C.

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completed 11.12.2014