Formamide

MAK value	**not yet established; see Section IIb of the *List of MAK and BAT Values***
Peak limitation	–
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–
Synonyms	formic acid amide
	methanamide
Chemical name (CAS)	formamide
CAS Number	75-12-7
Structural formula	NH_2–CHO
Molecular formula	CH_3NO
Molecular weight	45.05
Melting point	2–3°C
Boiling point	210°C
	partial decomposition into CO and NH_3 from 180°C
Density at 20°C	1.130 g/cm^3
Vapour pressure at 20°C	0.08 hPa
log P_{ow}[1)]	–0.82
1 ml/m^3(ppm) ≙ 1.8 mg/m^3	**1 mg/m^3 ≙ 0.56 ml/m^3 (ppm)**

1) *n*-octanol/water partition coefficient

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1 Toxic Effects and Mode of Action

Formamide has a low acute toxicity to rodents. The kidneys and blood are the target organs of toxicity after repeated inhalation exposure. In rats, ingestion led to apathy and loss of reflexes as well as changes in the stomach region, blood count, kidney, adrenal gland, spleen, thyroid and testes. Damage to the testes and thyroid was not reversible. Dermal application over a prolonged period caused slight erythema and apathy as well as erythrocythaemia in all males and in the females of the highest dose group. The substance induced irritation to the skin in rats and guinea pigs and eye irritation in rabbits. Formamide led to reduced fertility and a prolonged oestrus cycle in female mice. A reduced number of liveborn foetuses, an increased number of resorptions and malformations were observed in mice and rats after ingestion or dermal application as well as in rabbits after ingestion. The substance showed no adverse effects in mutagenicity studies.

2 Mechanism of Action

In rats, dermal application induced polycythaemia, which is attributed to the carbon monoxide and carboxyhaemoglobin that form in the metabolism of formamide (BASF 1985).

3 Toxicokinetics and Metabolism

Formamide was excreted unchanged by dogs or cats after ingestion (no other details) (Kennedy 1986). About 27% of the dose was excreted unchanged in the urine after ingestion of 1500 or 5000 mg by rats (no other details) (Bray et al. 1950). Doses of 2000, 3000 and 4000 mg formamide were administered to rabbits by gavage. After 24 hours, about 39% of the substance was excreted unchanged. The authors concluded that about 61% of the administered dose was hydrolyzed in the body. *In vitro*, 4% and 10% were hydrolyzed by rabbit liver extracts and rabbit liver slices, respectively, after 5 hours (Bray et al. 1949). No information is available on the absorption, metabolism and excretion in humans (Fail et al. 1998; NTP 1992 a, b). Calculations according to the formulae of Fiserova-Bergerova et al. (1990) and Guy and Potts (1993) yielded absorbed amounts of 3044 and 146 mg, respectively, for a saturated aqueous formamide solution after 1-hour epicutaneous exposure of 2000 cm^2 (area of hands and forearms).

4 Effects in Humans

There are no data available on the effects of formamide in humans.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

No toxicity was observed in rats that had been exposed to formamide concentrations of 188, 2357, 3720 or 3921 ml/m³ (338, 4243, 6696 or 7058 mg/m³) for 6 hours. The animals were observed for 2 weeks after treatment and showed normal weight gain (no other details) (Du Pont 1982). All 12 rats survived after exposure to an atmosphere saturated with formamide vapour at 20°C for 8 hours; 1 of 12 animals died when exposed to an atmosphere saturated with formamide at 150°C (no reaction to hydrogen cyanide using Draeger detector tubes). Under the latter test conditions, 6 guinea pigs survived. Rats and guinea pigs showed attempts to escape and irritation to the mucous membranes. Dyspnoea, which persisted for days in some animals, apathy, loss of weight and 2 cases of slight pneumonia were observed in the rats. The guinea pigs exhibited no abnormalities (BASF 1963 a). Table 1 lists the LD_{50} values for mice, rats and guinea pigs.

Table 1 LD_{50} of formamide in various species

Type of administration	Species	LD_{50} (mg/kg body weight)	References
oral	mouse	3200	Kennedy 1986
	mouse (female)	2000	BASF 1973
	rat	6000	Thiersch 1962
intravenous	mouse	5100	Kennedy 1986
	rat	5600	Kennedy 1986
intraperitoneal	mouse	4600–7400	Kennedy 1986
	mouse	2700	BASF 1963 a
	mouse	2060	BASF 1974 d
	rat	5700–5900	Kennedy 1986
	guinea pig	1250	Kennedy 1986
dermal	rat	>13500	Kennedy 1986
	rabbit	6000 (lethal dose)	Czajkowska 1981
	rabbit	17000 (lethal dose)	Du Pont 1982

Formamide was injected intraperitoneally into male CBA/CA mice at 400 mg/kg body weight. Sorbitol dehydrogenase and alanine and aspartate aminotransferase enzyme activities were determined in the plasma 24 hours after administration to determine the degree of possible hepatotoxicity. According to the authors, the hepatotoxic effect of formamide was slight. The administered dose led to weight loss in the animals of about 6% (Kestell et al. 1987). Marked leukopenia was caused

in mice by 1 or 2 injections of formamide at 1500 mg/kg body weight. The liver and spleen were reduced in size. The hepatocytes revealed hydropic degeneration with enlarged nuclei and an increased number of Kupffer's cells. The cellularity of the spleen was decreased (Morrison and Higgins 1956). Transient anorexia was observed in 2 cats after a single ingestion of formamide at 100 µl/kg body weight (113 mg/kg body weight). The blood, liver and kidney functions and the urinary finding were normal (BASF 1964). Administration of formamide at 100 µl/kg body weight (113 mg/kg body weight) caused slight diarrhoea and loss of appetite in 3 rabbits as well as just perceptible atonia in 1 animal. Polychromasia, anisocytosis and an increased incidence of normoblasts and macroblasts occurred in the blood, and another rabbit was found to have erythrocytes in the urine (BASF 1964).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

The results of studies with inhalation exposure are listed in Table 2.

Exposure of 6 rats 5 times for 8 hours to a stream of air saturated with formamide vapour (volatile at 150°C) caused severe irritation to the mucous membranes and dyspnoea. The snouts of some of the animals were encrusted with blood. Three rats died within the first week of observation. Necropsy revealed focal

Table 2 Effects after prolonged inhalation exposure of test animals to formamide

Species	Exposure conditions	Effects	References
rat,	**2 weeks**	**1500 ml/m³:** no changes	Du Pont 1982
2 ♂	(5 d/w) 1500 ml/m³		
rat,	**2 weeks**	no signs of toxicity	Du Pont 1982
2 ♂	(5 d/w)		
	air at room temperature saturated with formamide		
rat,	**2 weeks**	**100 ml/m³:** NOAEL	Warheit et al. 1989
Crl:CD BR,	(6 h/d, 5 d/w)	**0 to 1500 ml/m³:** signs of diarrhoea	
10 ♂ per group	0, 100, 500, 1500 ml/m³	**500 and 1500 ml/m³:** thrombocytopenia	
		1500 ml/m³: weakness, bent posture,	
		reduced body weights, increased relative kidney weight, nephrosis and decrease in circulating leukocytes	

pneumonia in 1 of the animals that died. The surviving animals had not yet recovered after another 2 weeks. The amounts of hydrogen cyanide analytically detected in the formamide vapours were too low to be involved in causing the effects (BASF 1963 b).

Two male rats were exposed to a formamide concentration of 1500 ml/m³ 10 times within 2 weeks for 6 hours per day. No abnormalities were observed in the animals during treatment. The pathological examination revealed no organ lesions (no other details). No signs of toxicity were observed after inhalation of air saturated with formamide at room temperature (Du Pont 1982).

Three groups of 10 randomized male rats (Crl:CD BR) (9 weeks old at the beginning of exposure) were exposed nose-only by inhalation to technical formamide at 0, 100, 500 or 1500 ml/m³ (purity: 99%) for 6 hours per day on 5 days per week for 2 weeks. A control group of 10 animals was also exposed nose-only to air. Diarrhoea was sometimes observed in animals of all groups during treatment. Weakness and bent posture occurred in the animals exposed to formamide at 1500 ml/m³. One animal of this group died on day 3 and another on day 9 of treatment. A third animal had to be sacrificed on day 11. Discharge from the nose and eyes and diarrhoea were clinical signs that often occurred immediately after treatment, but also in the control animals. According to the authors, this is observed in rats that are restrained. After 10-day exposure and in the following 14 days of the post-exposure observation period, lymphopenia was seen in the animals of the high exposure group, and thrombocytopenia in the animals of the middle and high exposure groups, which was statistically significant in relation to the values determined in the control group. The biological significance of thrombocytopenia was considered to be ambiguous. The findings of the treatment-related microscopic lesions in the kidney and a simultaneous increase in the kidney/body weight ratio indicated that the kidney was the target organ of toxicity. Based on the haematological and clinicochemical parameters determined in the animals exposed to 500 ml/m³, the authors considered a value of 100 ml/m³ to be the no observed adverse effect level (NOAEL) for repeated inhalation of formamide. It should be pointed out that a significant increase in atypical lymphocytes was observed during the observation period in the animals treated with 100 ml/m³ (Warheit et al. 1989). In the report on which this publication is based (Du Pont 1988), the authors classified a number of changes found in the microscopic tissue examinations as being not related to the substance administered. This referred to the depletion of lymphocytes in the spleen, thymus and lymph nodes, gastric erosion, degeneration of the testicular epithelium and bone marrow (sternum) atrophy. Specific findings are listed in detail in Table 3.

Table 3 Incidence of findings of tissue examination in rats after inhalation exposure to formamide for 2 weeks and a 2-week observation period (Du Pont 1988)

Organ	Days 1–12 treatment				Days 24–26 observation period			
	concentration (ml/m³)				concentration (ml/m³)			
	0	100	500	1500	0	100	500	1500
liver: hepatitis	5/5	5/5	5/5	3/5	3/5	5/5	5/5	3/4
kidney: ectasia	0/5	1/5	0/5	0/5	0/5	0/5	0/5	0/4
kidney: hydronephrosis	0/5	0/5	1/5	0/5	1/5	0/5	0/5	0/4
kidney: nephrosis	0/5	0/5	0/5	5/5	0/5	0/5	0/5	4/4
bladder: cystic	0/5	0/5	0/5	0/5	1/4	0/5	0/5	0/4
lung: pneumonia	1/5	1/5	0/5	1/5	1/5	0/5	0/5	1/4
heart: myocarditis	0/5	0/5	1/5	0/5	0/5	0/5	0/5	0/4
spleen: depletion of lymphocytes	0/5	0/5	0/5	2/5	0/5	0/5	0/5	0/4
thymus: depletion of lymphocytes	0/5	0/5	0/5	3/5	0/5	0/5	0/5	0/4
pancreas: pancreatitis	0/5	0/5	0/5	0/5	0/5	1/5	0/5	0/4
gastric erosion	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/4
mesenteric lymph nodes: depletion of lymphocytes	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/4
testes: degeneration of the epithelium	0/5	1/5	0/5	3/5	1/5	1/5	0/5	1/4
sternum: atrophy	0/5	0/5	0/5	1/5	0/5	0/5	0/5	0/5
epididymides: reduction of sperm	0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/4
eyes: retina	1/5	0/5	0/5	1/5	0/5	1/5	0/5	0/4
nose: rhinitis	0/5	0/5	0/5	0/5	1/5	0/5	0/5	1/4
nose: metaplasia	0/5	0/5	0/5	0/5	1/5	0/5	0/5	1/4

5.2.2 Ingestion

Studies with oral administration of formamide are shown in Table 4.

In a multi-generation study (0, 100, 350 or 750 mg/l administered in the drinking water; see Section 5.5.1), increased feed and water consumption were observed in the males of the high dose group (corresponding to 172 mg/kg body weight). There were no differences in the body or organ weights or the weights of the male reproductive organs and ovaries. No morphological alterations were detected microscopically (Fail et al. 1998; Heindel et al. 1997; NTP 1992 a, b).

Table 4 Effects after prolonged oral exposure of test animals to formamide

Species	Exposure conditions	Effects	References
rat, 6	**2 weeks** 1500 mg/kg b.w. (diet)	**1500 mg/kg b.w.:** b.w. ↓; malnutrition; mortality (3/6)	Du Pont 1982
rat, Sprague Dawley, groups of 20 ♂ and 20 ♀, 6 weeks old	**4 weeks** (5 d/w) 0, 40, 113, 400, 1130 mg/kg b.w. (gavage) 2 weeks recovery period	**40 mg/kg b.w.:** no changes in b.w. **113 mg/kg b.w.:** b.w. ↓; ♂: relative organ weights of heart, liver, testes and kidney ↑; ♀: relative organ weights of heart ↑ **400 mg/kg b.w.:** b.w. ↓; ruffled coat, hunched posture and paraphimosis; mortality (10/20 ♂/♀); animals that died: erosions in the mucous membranes of gastric glands, oedema of stomach wall and gastritis; fibrous spleen and thymus; nephrosis; degeneration of the testicular epithelium; surviving animals: ♂: % relative organ weights of the kidney, adrenal gland, thyroid, heart and liver ↑; ♀: % relative organ weights of kidney, adrenal gland, thyroid and heart ↑, of spleen ↓; no changes in the gastrointestinal tract; fibrous spleen and thymus **1130 mg/kg b.w.:** feed consumption ↓, apathy and loss of general reflexes. All animals died or were sacrificed after the 1st week. Erosions in the gastric gland mucosa, stomach wall oedema and gastritis; nephrosis and fibrous spleen and thymus; epithelial changes in the thyroid and testes **40 mg/kg b.w. (2 weeks recovery period):** no decrease of body weight or feed consumption; ♂: relative organ weight of heart and thyroid ↑ **113 mg/kg b.w. (2 weeks recovery period):** no decrease of body weight; ♂: relative organ weight of heart and thyroid ↑; liver ↑ **400 mg/kg b.w. (2 weeks recovery period):** significant decrease of body weight; ♂: relative organ weight of adrenal gland ↑ and testes ↓; ♂ and ♀: relative organ weights of heart, liver, spleen, kidney and thyroid ↑	BASF 1976 a, 1978

Table 4 (Continued)

Species	Exposure conditions	Effects	References
mouse, Swiss, groups of 10 ♂ and 10 ♀	**2-generation study** 7 days before, 14 days during and 6 weeks after mating about 19, 62 and 172 mg/kg b.w. in ♂ and 29, 98 and 218 mg/kg b.w. in ♀ (drinking water)	**62 mg/kg b.w.:** no effects **172 mg/kg b.w. (♂):** increased feed and water consumption; no developmental toxicity **all doses:** no effects on body weights, organ weights or weights of ♂ reproductive organs and ovaries; no histopathological alterations detected	Fail et al. 1998; NTP 1992 a, b

b.w.: body weight;

Formamide was administered via the diet to 6 rats at 1500 mg/kg body weight 5 times per week for 2 weeks. Three animals died after the 5th treatment and 1 animal each after the 7th, 9th and 10th treatments. A distinct weight reduction was observed in all animals during treatment. The pathological examination revealed changes characteristic of gastritis, which led to malnutrition (Du Pont 1982).

Groups of 20 male or female Sprague-Dawley rats (aged 6 weeks) received formamide concentrations of 0, 30, 100, 300 or 1000 µl/kg body weight and day (corresponding to formamide doses of 0, 40, 113, 339 or 1130 mg/kg body weight and day) over a period of 4 weeks. The substance was dissolved in bidistilled water and administered by gavage on 5 days per week. At the end of the administration period, 10 animals were sacrificed per group; the remaining animals were sacrificed after an observation period of 2 weeks. In addition to a deterioration of the general state of the animals of the 2 highest dose groups and decreased body weight gain together with reduced feed consumption, effects were found on the kidney, adrenal gland, blood count, spleen, liver, heart, thyroid, thymus, testes and stomach. According to the authors of the report, it is questionable whether the increased relative weights of the heart and thyroid recorded in the males of the 2 lower dose groups at the end of the observation period were caused by the substance. No such findings were obtained in the animals that were sacrificed at the end of administration. The gross-pathological examination of the organs removed from the animals treated with 300 µl/kg body weight at the end of administration and after the

observation period demonstrated the reversibility of gastric ulcer formation, atrophy in the spleen and liver and discolouration of the adrenals. The testes were still small and the general nutritional state was poor. Comparison of the histopathological examinations showed reversibility in the spleen, thymus and adrenals, whereas the lesions of the testes and thyroid were not reversible. Based on the authors' interpretation, according to which the weight increases of the heart and thyroid in the low dose groups were not to be regarded as substance-induced, this study revealed a no observed effect level (NOEL) of 40 mg/kg body weight for formamide. However, it should be pointed out that changes of clinicochemical parameters determined in the blood and urine were apparently not included in the interpretation of the findings. It was stated that no pathological relevance was attributed to the increased levels of urea, inorganic phosphate and haemoglobin or to the reduced levels of glucose and creatinine on the basis of the plausibility criteria and the slight deviation from the control group. According to the authors, the remaining changes (decrease of potassium, calcium, total protein, total lipids, alanine aminotransferase, alkaline phosphatase and plasma cholinesterase during the treatment period; decrease of total protein and plasma cholinesterase and increase of sodium and chloride during the observation period) are probably directly or indirectly (see reduced body weight gain) related to the substance administered (BASF 1976 a, 1978).

Groups of 3 or 4 rabbits were given different numbers of formamide doses of 0, 100, 200 or 500 µl/kg body weight (113, 230 or 570 mg/kg body weight) by gavage on consecutive days. Doses of 500 µl/kg body weight and 200 µl/kg body weight led to the death of the test animals after 2 or 3 administrations and 7 or 16 administrations, respectively. One rabbit survived after 25 administrations of 200 µl/kg body weight. The animals tolerated up to 25 doses of 100 µl/kg body weight without any signs or symptoms. Two animals of the dose group that received 200 µl/kg body weight were found to have polychromasia and 1 animal additionally had anisocytosis. Necropsy of the rabbits that died revealed haemorrhages in a large number of organs (no other details), the trachea being regularly affected (BASF 1964). Hardly any signs or symptoms were recorded in 2 cats after 26 ingestions of formamide at 100 µl/kg body weight. Transient loss of appetite was observed in 1 animal (BASF 1964).

5.2.3 Dermal absorption

Dermal application studies are shown in Table 5.

In a range-finding study for a mid-term dermal study, 5 male and 5 female Wistar rats (3 months old) were given formamide doses of 100, 300, 1000 or 3000 mg/kg body weight. The substance was applied semi-occlusively to the shaved skin for about 6 hours per day on 5 days of the week for 14 days. At the end of the study, the spleen and testes were weighed and putative target organs were examined histopathologically. No marked toxicity was found at concentrations of up to

Table 5 Effects after prolonged dermal exposure of test animals to formamide

Species	Exposure conditions	Effects	References
rat,	**2 weeks**	**0 to 3000 mg/kg b.w.:** no marked toxicity	BASF 1983
Wistar,	(6 h/d, 5 d/w)	**3000 mg/kg b.w.:** slight anaemic effect	
groups of 5 ♂ and 5 ♀	0, 100, 300, 1000, 3000 mg/kg b.w. semi-occlusively, shaved skin		
rat,	**90 days**	**300 to 3000 mg/kg b.w.:** ♂: erythrocythaemia (increase in haemoglobin level and erythrocyte count)	BASF 1984
Wistar,	(6 h/d, 5 d/w)	**3000 mg/kg b.w.:** decrease of feed consumption and body weight gain; erythema on days 55–58; apathy and dyspnoea 6–27 days after first occurrence of erythema; 3 animals died; relative liver and kidney weights increased; ♀: erythrocythaemia (increase in haemoglobin level and erythrocyte count)	
groups of 10 ♂ and 10 ♀	0, 300, 1000, 3000 mg/kg b.w. intact skin		
rat,	**90 days**	**100 mg/kg b.w.:** NOAEL	BASF 1985
Wistar,	(6 h/d, 5 d/w)	**3000 mg/kg b.w.:** feed consumption and body weight gain reduced; erythema on days 55–58; apathy and dyspnoea 6–27 days after first occurrence of erythema; 3 animals died;	
groups of 10 ♂ and 10 ♀	0, 30, 100, 3000 mg/kg b.w. intact skin	haemoglobin, erythrocytes, haematocrit and mean corpuscular volume increased in ♂ and ♀; increase in number of reticulocytes and carboxyhaemoglobin concentration in ♂ and ♀; reduction of leukocyte and lymphocyte counts in ♂; ♂: absolute organ weights of liver, kidney, spleen, testes and adrenal gland decreased and relative adrenal weight increased; ♂ and ♀: relative organ weights of liver and kidney increased;	
		number of animals with bilateral testicular tubular atrophy increased	

3000 mg/kg body weight. A slightly anaemic effect was observed in the high dose group. No changes in behaviour were observed (BASF 1983).

In the subsequent 90-day study, formamide was applied to the intact skin of groups of 10 male and 10 female Wistar rats at 300, 1000 or 3000 mg/kg body

weight (no other details about the form of application). Groups of 10 male or female sham-treated rats were used as controls. Polycythaemia was the main finding in the males of all dose groups and the females of the highest dose group. In the blood samples of the treated rats, no increase in the carboxyhaemoglobin level over 10% could be detected by the method of determination used. In spite of these results, the authors stated that the formation of carboxyhaemoglobin could not be ruled out as the cause of polycythaemia (BASF 1984; BASF Wyandotte 1983; Monsanto 1985).

Another 90-day follow-up study was carried out to determine the non-toxic dose of formamide after dermal application. Formamide was applied to the intact skin of groups of 10 male and 10 female Wistar rats at concentrations of 0, 30 or 100 mg/kg body weight and to 20 male and 20 female rats at 3000 mg/kg body weight (no other details about the form of application). Groups of 10 male and 10 female untreated rats were used as controls. The animals of the control group and highest dose group were subjected to ophthalmoscopy at the beginning of the study and at the end of treatment. Haematological examinations were carried out during weeks 5 and 8 and at the end of the study. Compensatory polycythaemia at a formamide dose of 3000 mg/kg body weight was the main finding of the haematological examinations (BASF 1985). A range between 100 and 300 mg/kg body weight for males and between 300 and 1000 mg/kg body weight for females was established by the authors of the study as the NOAEL for formamide, considering that no substance-induced effects occurred at 30 and 100 mg/kg body weight and including the results obtained at doses of 300 and 1000 mg/kg body weight in the earlier dermal study (BASF 1985). Therefore, based on these studies, the NOAEL for formamide is 100 mg/kg body weight.

5.2.4 Intraperitoneal injection

After 36 intraperitoneal injections of 150 mg formamide (no other details), rats revealed reduced body weight gain, but there were no clinical abnormalities or any histopathological changes (Kennedy 1986). The intraperitoneal injection of formamide at 200 mg/kg body weight or of higher doses of formamide daily for 7 days led to toxic or lethal effects in mice. Hardly any toxic effects occurred at the low dose, but were more marked with increasing doses. Loss of weight, weakness and a poor general state were observed as well as a staggering gait at very high doses (no other details) (Morrison and Higgins 1956).

5.3 Local effects on skin and mucous membranes

Formamide was slightly irritating to the skin and eyes (DECOS 1995; Kennedy 1986). Skin irritation rapidly subsided (Du Pont 1982). Erythema was also observed in the 90-day dermal study in male and female rats treated with 3000 mg/kg body

weight on days 55 to 58 after the beginning of treatment (BASF 1984) (see Section 5.2). Undiluted formamide led to severe erythema on the dorsal skin of rabbits after 24 hours, which turned into slight scaling after 8 days (no other details) (BASF 1963 a).

Aqueous solutions of 20% or 80% formamide that were instilled into the conjunctival sac of rabbits led to purulent conjunctivitis, which healed 4 days after treatment (Kennedy 1986). Amounts of 100 µl and 50 µl of undiluted formamide were introduced into the conjunctival sac of 4 male albino rabbits and 1 rabbit, respectively. The eyes were not rinsed after treatment. Following treatment with 100 µl, the examinations carried out after 1 and 4 hours and after 1, 2, 3, 6 and 7 days revealed slight damage to the cornea in 1 animal, iritis in 2 animals and conjunctivitis that was slight in 1 animal and slight to moderate in 3 animals. Treatment with 50 µl caused damage to the cornea, iritis and conjunctivitis, all of which were slight. The corneal lesions had healed after 24 hours. On day 7, only 1 animal still had slight conjunctivitis (Du Pont 1982).

An amount of 50 µl undiluted formamide caused slight erythema and slight oedema in the rabbit eye after 1 hour, slight oedema and opacity in addition to severe erythema after 24 hours. Irritation was no longer observed after 8 days (BASF 1963 a).

5.4 Allergenic effect

Formamide did not lead to any allergic skin reactions in guinea pigs (no other details) (Du Pont 1982).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

A multi-generation study was carried out in mice according to the RACB (Reproductive Assessment by Continuous Breeding) protocol to evaluate the reproductive toxicity of formamide. Formamide was administered in drinking water at concentrations of 0, 100, 350 or 750 mg/l. Based on the mean body weight and average water consumption, this corresponds to an estimated daily dose of 19, 62 and 172 mg/kg body weight in males and 29, 98 and 218 mg/kg body weight in females. These doses were administered to the animals 1 week before mating, 14 days during mating and 6 weeks after mating. There were no differences in the body or organ weights or the weights of the male reproductive organs and ovaries. No morphological alterations were detected microscopically (Fail et al. 1993, 1998; Heindel et al. 1997; NTP 1992 a, b). A decrease in litter size of 8% per pair and a reduced number of live offspring of 28% per litter as compared with the control

were observed as effects of reproductive toxicity in the animals of the highest dose group. Gestation was 5 to 10 days longer in the animals of this dose group. The NOAEL for an adverse effect on fertility was established at 350 mg/l, corresponding to 62 mg/kg body weight and day in males and 98 mg/kg body weight in females (Fail et al. 1998; Heindel et al. 1997; NTP 1992 a, b).

A subsequent crossover test demonstrated that a reduced number of females became pregnant in the highest dose group (750 mg/l; estimated dose: 218 mg/kg body weight) after they had been mated with untreated males. No other end points, such as the number of live offspring per litter, survival rate of the offspring or adjusted live weight of the offspring, were affected. Mating of treated males with female control animals was not different from that of the control animals.

The offspring of the last litter of each dose group were reared until weaning to investigate a potential effect of formamide on the fertility of this generation. The animals of this study were also treated with the 3 doses. Only 2/3 of the animals became pregnant in the high dose group; the number of liveborn offspring per litter was reduced by 27%. The examination of the males after sacrifice showed that the weight of the seminal vesicles was decreased by 22%. No differences in sperm indices were detected in the epididymides. The body weight of the females that were given the high dose was reduced by 10%, and the ovarian weight was decreased by 25% in this group and the middle dose group. The oestrus cycle was also prolonged in the animals of the high dose group from 4.8 days (controls) to 6.5 days. The NOAEL for reproductive toxicity was 350 mg/l, corresponding to 62 mg/kg body weight and day in males and 98 mg/kg body weight in females (Fail et al. 1998; Heindel et al. 1997; NTP 1992 a, b).

5.5.2 Developmental toxicity

The results of studies on the developmental toxicity of formamide are listed in Table 6.

Table 6 Developmental toxicity of formamide in test animals after various administration routes

Species	Exposure conditions	Effects	References
Ingestion			
mouse, groups of 22–24 animals	**GD 6–15** **at single days** 132, 198, 396, 989 mg/kg oral	**132 mg/kg b.w.:** no embryolethal, foetotoxic or teratogenic effects (exp. GD 8) **198 mg/kg b.w.:** no embryolethal, foetotoxic or teratogenic effects (exp. GD 6, 9, 11, 13, 14); (slightly) foetotoxic (exp. GD 8) **396 mg/kg b.w.:** no foetotoxicity (exp. GD 10, 13); (slightly) foetotoxic (exp. GD 6, 7, 8, 9, 11, 12, 14, 15); teratogenic (exp. GD 8, 9)	BASF 1973

Table 6 (Continued)

Species	Exposure conditions	Effects	References
		989 mg/kg b.w.: (slightly) foetotoxic (exp. GD 6); foetotoxic (exp. GD 7, 9, 10, 11, 14, 15); (severely) foetotoxic (exp. GD 8, 12); (slightly) embryolethal (exp. GD 7 and 8); (slightly) teratogenic (exp. GD 7 and 13); teratogenic (exp. GD 10); (severely) teratogenic (exp. GD 8 and 9)	
mouse,	**GD 6–15**	**152 mg/kg b.w.:** NOAEL	BASF 1974 b
groups of 18–28 animals depending on the dose	44, 79, 152, 198 and 396 mg/kg b.w.	**198 mg/kg b.w.:** malformations of the head, spinal column, ribs and extremities in 25 foetuses (11%); malformations of the head in 2% of the foetuses of the control group	
	oral	**396 mg/kg b.w.:** treatment discontinued after 8th treatment because of vaginal haemorrhages in some of the animals and because of a poor general state; number of live foetuses ↓, resorptions ↑ and weight and average length of foetuses ↓; malformations of the head, spinal column, ribs and extremities in 75 foetuses (78%); malformations of the head in 1% of foetuses	
rat,	**GD 7**	**2000 mg/kg b.w.:** 50% resorptions and dwarfism in 26% of the surviving offspring; no malformations	Thiersch 1962
(no other details)	2000, 6000 mg/kg b.w.	**6000 mg/kg b.w.:** administration of the LD_{50} in 3 doses (no other details); 100% resorptions	
	oral		
rat,	**GD 7or 11**	**4000 mg/kg b.w.:** 100% resorptions	Thiersch 1971
(no other details)	4000 mg/kg b.w.		
	oral		
	GD 7 and 8	**2000 mg/kg b.w.:** 100% resorptions	
	2000 mg/kg b.w.		
	oral		
	GD 7–12	**total dose of 1000 mg/kg b.w.:** 90% resorptions, dwarfism and malformations of extremities and palate in 26% of the offspring	
	total dose of 1000 mg/kg b.w.		
	oral		

Table 6 (Continued)

Species	Exposure conditions	Effects	References
	GD 11–16 total dose of 1000 mg/kg b.w. oral	**total dose of 1000 mg/kg b.w.:** fewer resorptions, but also dwarfism and malformations	
	GD (n.s.) administered repeatedly during gestation, total dose of 400 mg/kg b.w. oral	**total dose of 400 mg/kg b.w.:** incidence of resorptions, dwarfism and malformations lower than at 1000 mg/kg b.w.	
rat, ♀, 17–27	**GD 6–9, 11–15** 3950 or 1579 mg/kg b.w. oral	**3950 mg/kg b.w.:** GD 6–8: severe embryolethality; GD 9–13: foetotoxic and teratogenic effects **1579 mg/kg b.w.:** no maternal toxicity or any adverse effects on the offspring	Bayer 1975
	GD 7, 10 3950, 1579 or 790 mg/kg b.w. oral	**790 mg/kg b.w.:** no maternal toxicity or any adverse effects on the offspring	
rat, ♀	**GD 6–15** 176, 316, 522, 790, 1579 mg/kg b.w. oral	**176 mg/kg b.w.:** foetal NOAEL **from 176 to 1579 mg/kg:** reduced maternal weight **from 316 mg/kg b.w.:** malformations and growth retardation **790 mg/kg b.w.:** maternal toxicity; embryolethality, malformations, low birth rate, growth retardation **1579 mg/kg b.w.:** maternal toxicity; embryolethality (99%)	BASF 1974 a
rat, CD, 25 ♂ per group	**GD 6–19** 0, 50, 100, 200 mg/kg b.w.	**50 mg/kg b.w.:** foetal NOAEL **100 mg/kg b.w.:** reduced foetal body weight; maternal NOAEL	George et al. 2000; NTP 1998

Table 6 (Continued)

Species	Exposure conditions	Effects	References
	oral	**200 mg/kg b.w.:** reduced body weight and body weight gain	
rabbit, Himalayan, 10–12 ♀ per group	**GD 6–18** 0, 23, 79, 226 mg/kg b.w. oral	**23 mg/kg b.w.:** maternal and foetal NOAEL **79 mg/kg b.w.:** reduced feed consumption, lower body weight gain and 1 spontaneous birth on day 27; foetuses significantly lighter and 7 foetuses of 6 litters with malformations (anasarca, cystic dilatations in the cerebellum, cleft lips and palates and 6 misshapen clavicles) **226 mg/kg b.w.:** discontinuation after 9 doses because of signs of toxicity	BASF 1976 b; Merkle and Zeller
Epicutaneous application; intraperitoneal injection			
mouse, 25♀ per group	**GD 11** 100 µl(1×, 2×) epicutaneous	**100 µl, single application:** 50% resorptions; cleft palates and disturbances in development of extremities in 50% of the foetuses **2 applications:** 80% resorptions; cleft palates and disturbances in development of extremities in the foetuses	Oettel and Frohberg 1964
mouse	**GD 8** 2500 µl/kg b.w. epicutaneous	**2500 µl/kg b.w.:** embryolethal (about 85% dead foetuses), embryotoxic (decrease in length and weight of foetuses) and teratogenic effects (malformations in 9 of the 25 live foetuses)	BASF Wyandotte 1982
mouse, NMRI (no other details)	**GD 10 and 11** 8, 76µl/kg b.w. epicutaneous **GD 6–15** 76, 190 µl/kg b.w. intraperitoneal	**8 µl/kg b.w.:** malformation rate: 0%; proportion of foetal loss: 8% **76 µl/kg b.w.:** malformation rate: 36%; proportion of foetal loss: 61% **76 µl/kg b.w.:** malformation rate: 4%; proportion of foetal loss: 13% **190 µl/kg b.w.:** malformation rate: 25%; proportion of foetal loss: 27%	Gleich 1974
rat, 6–7 per group	**GD 9; 10 and 11; 11 and 12; 12 and 13** 150 µlepicutaneous (shaved skin)	**150 µl:** slight embryotoxicity; no teratogenic effects	Du Pont 1967

Table 6 (Continued)

Species	Exposure conditions	Effects	References
rat, 6–7 per group	**GD 9; 10 and 11; 11 and 12; 12 and 13** 600 mg epicutaneous (shaved skin)	**600 mg/kg b.w. (GD 9):** slight increase in embryolethality; no malformations **600 mg/kg b.w. (GD 10 and 11):** no increase in embryolethality; distortions in the head region in 1 of the 53 offspring **600 mg/kg b.w. (GD 11 and 12):** 13% increase in embryolethality; no malformations **600 mg/kg b.w. (GD 12 and 13):** no increase in embryolethality; subcutaneous blood clots in 4 of the 60 offspring	Stula and Krauss 1977

b.w.: body weight; exp.: exposure; GD: day of gestation; n.s.: not specified

5.5.2.1 Oral administration

Formamide dissolved in bidistilled water was administered by gavage to pregnant NMRI mice (22 to 24 animals depending on the dose group) on a single day of gestation. The animals were given formamide doses of 875 or 350 µl/kg body weight (989 or 396 mg/kg body weight) once on day 7, 10, 12 or 15 of gestation. On day 6, 9, 11, 13 or 14 of gestation, the animals were given formamide doses of 875, 350 or 175 µl/kg body weight (198 mg/kg body weight); on day 8, 117 µl/kg body weight (132 mg/kg body weight) was administered. The dams tolerated the doses administered on the single days without any clinically evident signs of toxicity. Gross pathology revealed no pathological organ changes that could be attributed to the administered substance. Foetotoxicity was the main adverse effect of formamide on the offspring of treated pregnant mice. After formamide doses of 989 mg/kg body weight given orally on days 7, 8, 9, 10 or 13 of gestation, teratogenic effects were observed in the form of malformations of the head and, according to the dosage day, of the spinal column, ribs or extremities. Teratogenic effects were also observed after a formamide dose of 396 mg/kg body weight on day 9 (BASF 1973).

Formamide was administered daily by gavage to pregnant mice (18 to 26 animals depending on the dose group) from days 6 to 15 at 39, 70, 117, 175 or 350 µl/kg body weight (44, 79, 152, 198 or 396 mg/kg body weight), that is maximally 1/5 of the LD_{50}. Treatment with 396 mg/kg body weight was discontinued after the 8th treatment because of vaginal haemorrhages in some of the animals and because of a poor general state. The number of resorptions was increased, and the number of live foetuses as well as their weight and length were reduced. Malformations of the head, spinal column, ribs and extremities were observed in 75 foetuses (78%). The

control group revealed malformations of the head in 1%. After administration of 198 mg/kg body weight, 25 foetuses (11%) exhibited malformations of the head, spinal column and ribs. In the corresponding control group, malformations of the head were observed in 4 foetuses (2%). Malformations of the head were observed in 7 foetuses of the dose group that received 152 mg/kg body weight, but there was no significant difference from the foetuses of the specific control group. Nor were there significant differences found between the foetuses of the corresponding control group and the 11 foetuses affected of the 79 mg/kg body weight dose group or the 7 foetuses of the 44 mg/kg body weight dose group. Therefore, a NOAEL of 152 mg/kg body weight was established (BASF 1974 b).

A single formamide dose of 2000 mg/kg body weight was administered orally to pregnant rats on day 7 of gestation. This led to resorptions in 50% of the dams and to dwarfism in 26% of the surviving offspring. Administration of the LD_{50} in 3 doses each of 2000 mg/kg body weight on day 7 led to the resorption of all litters (Thiersch 1962). In further studies, Thiersch found that an oral dose of 4000 µl/kg body weight (4500 mg/kg body weight) administered on days 7 or 11 of gestation led to a resorption rate of 55%. A dose of 2000 mg/kg body weight administered twice on days 7 and 8 had the same effect (60% resorptions); this dose additionally administered on day 9 induced total resorption. Fewer effects were found if the dose was administered on days 2, 4 or 11. Repeated administration of 1000 µl/kg body weight (1100 mg/kg body weight) from days 7 to 12 of gestation led to 90% resorptions with dwarfism and malformations. This dose administered on days 11 to 16 of gestation induced fewer resorptions (36%), but also led to dwarfism and malformations. These effects were even less marked after repeated administration of a lower dose of 400 µl/kg body weight (450 mg/kg body weight) from days 7 to 15 or days 11 to 18 (Thiersch 1971).

Groups of 17 to 27 pregnant Sprague-Dawley rats were given formamide doses of 1400 or 3500 µl/kg body weight (3950 or 1579 mg/kg body weight) on days 6 to 15 of gestation and additionally 700 µl/kg body weight (790 mg/kg body weight) on days 7 and 10. Administration of formamide from days 6 to 8 *post coitum* caused severe embryolethality; foetotoxic and teratogenic effects predominated after administration from days 9 to 13 *post coitum*. No toxic effects to the dams or adverse effects on the offspring were observed at the lowest dose on the individual days of gestation. Foetotoxicity induced by formamide could not definitely be ruled out at the low doses on days 8, 9 and 14 (Bayer 1975).

Rats (number not specified) were given formamide doses of 156, 280, 463, 700 and 1400 µl/kg body weight (176, 316, 522, 790 and 1579 mg/kg body weight) from days 6 to 15 of gestation. The maternal weight was reduced at all doses. Embryolethality (99%) was observed at 1579 mg/kg body weight. In addition, malformations, low birth rates and growth retardation of the foetal skeletons occurred at 790 mg/kg body weight. Growth retardation and malformations were also observed in the foetuses at 316, but not at 176 mg/kg body weight. Therefore, the NOAEL for developmental toxicity was 176 mg/kg body weight in this study (BASF 1974 a).

Groups of 25 pregnant CD rats were administered formamide doses of 0, 50, 100 or 200 mg/kg body weight by gavage daily from days 6 to 19 of gestation. Reduced body weight gain was recorded in the highest dose group. A NOAEL of 100 mg/kg body weight per day was established for the maternal toxicity of formamide. Foetal body weight was reduced from a formamide dose of 100 mg/kg body weight per day. This resulted in a NOAEL of 50 mg/kg body weight per day. It was pointed out that the few malformations recorded in this study revealed no relation to the dose, but were similar to the results obtained in earlier studies carried out with higher doses. These earlier studies reported a LOAEL (lowest observed adverse effect level) of 318 mg/kg body weight and day and a NOAEL of 177 mg/kg body weight and day for developmental toxicity after a shorter treatment period (days 6 to 15 of gestation) (George et al. 2000; NTP 1998).

Technical formamide was administered orally as an aqueous solution by gavage to 11 or 12 pregnant Himalayan rabbits (strain: Chbb:HM) at doses of 20, 70 or 200 µl/kg body weight (23, 79 or 226 mg/kg body weight). The control group consisted of 25 animals. The doses were administered from days 6 to 18 post insemination. On day 28 post insemination, the foetuses were delivered by caesarean section. Administration of 79 mg/kg body weight led to reduced feed consumption and lower body weight gain. One animal of this dose group had a spontaneous birth of immature foetuses on day 27 of gestation. Treatment was discontinued after 9 administrations because of severe signs of toxicity among the dams that received a dose of 226 mg/kg body weight. No maternal parameters were evaluated here. The dams of the 2 lower dose groups revealed no gross-pathological changes. Malformations (anasarca, cystic dilatations in the cerebellum, cleft lips and palates and 6 cases of misshapen clavicles) were observed in 7 foetuses of 6 litters. The percentage of malformed foetuses per litter was significantly increased. The foetuses of untreated dams showed no malformations. The dams and the offspring tolerated the dose of 23 mg/kg body weight without symptoms (BASF 1976 b; Merkle and Zeller 1980). This value can be regarded as the (foetal and maternal) NOAEL.

5.5.2.2 Dermal application

In mice, a single application of 100 µl formamide on day 11 of gestation caused 50% foetal resorptions as well as cleft palates and disturbances in development of extremities (phocomelia) in 50% of the foetuses; 2 percutaneous applications led to disturbances in development of extremities (amelia) and a foetal resorption of about 80% (Oettel and Frohberg 1964).

A formamide dose of 2500 µl/kg body weight was applied to mice percutaneously once on day 8 *post coitum*. Caesarean section was carried out on day 18 of gestation. The dose of 2500 µl/kg body weight caused considerably reduced body weight gain in the dams; at necropsy, liver damage was suspected in 2 animals. Formamide had embryolethal (about 85% dead foetuses), embryotoxic (reduced

weight and length of the foetuses) and teratogenic (malformations in 9 of the 25 live foetuses) effects (BASF Wyandotte 1982).

Formamide was intraperitoneally injected into NMRI mice (number not specified) at a dose of 76 µl/kg body weight 10 times from days 6 to 15 of gestation or epicutaneously applied on days 10 and 11. After 10 intraperitoneal injections, the malformation rate was 4% and the percentage of dead foetuses was 13%. After 2 epicutaneous applications of 76 µl/kg body weight per animal, 36% of the foetuses showed malformations and the percentage of dead foetuses was 61%. Ten intraperitoneal injections of 190 µl/kg body weight led to a malformation rate of 25% and a percentage of dead foetuses of 27%. After 2 epicutaneous applications of 8 µl/kg body weight per animal, no malformations were observed and the percentage of dead foetuses was 8% (no other details) (Gleich 1974).

Application of 150 µl of formamide to the shaved skin (about 1.5 cm^2) of groups of 6 or 7 pregnant rats on days 9, 10 and 11, 11 and 12 or 12 and 13 of gestation induced slight embryotoxicity. No teratogenic effects were observed (Du Pont 1967).

Formamide was applied to the shaved skin of 6 or 7 pregnant albino rats at doses of 600 mg/kg body weight on days 9, 10 and 11, 11 and 12 or 12 and 13 of gestation. The animals were sacrificed on day 20 of gestation. A slight increase in embryolethality was observed in the offspring of the animals treated on day 9. A 13% increase in embryolethality as compared with that of the controls was recorded in the animals treated on days 11 and 12 of gestation. Embryolethality was not elevated in the animals treated on days 10 and 11 or 12 and 13 as compared with the control animals. No foetal malformations were observed in the offspring of the animals treated on day 9 or days 11 and 12. A misshapen head was observed in 1 of the 53 offspring of the animals treated on days 10 and 11; 4 of the 60 offspring of the animals treated on days 12 and 13 had subcutaneous blood clots (Stula and Krauss 1977).

Rats were percutaneously treated with doses of 310, 630 or 1250 ml/kg body weight ("ml" in the report should probably be "µl") repeatedly during workdays from days 1 to 3, 6 to 10 or 13 to 17 of gestation and were sacrificed on day 18. Maternal toxicity, maternal lethality, embryolethality, teratogenicity and foetotoxic effects were observed in the highest dose group. The dose of 630 "ml"/kg body weight was foetotoxic; the incidence of inhibited development of skeletons and organs was increased. Reduced foetal weights were also found in the dose group of 310 "ml"/kg body weight (BASF 1974 c).

5.5.3 In vitro studies

Young chick embryos were incubated *in vitro* with formamide concentrations of 0.1 to 0.5 mol/l. The formamide concentration of 0.1 mol/l had no effect in the neuroepithelium of the embryos; 0.25 mol/l blocked mitosis in the metaphase, 0.31 mol/l totally inhibited the nuclear migration that normally occurs before mito-

sis, 0.37 mol/l reduced the amount of cytoplasmic microtubules and caused rounding of the cells. At the formamide concentration of 0.43 mol/l, no microtubules were detected and all cells were spherical; all cells were detached from one another at 0.5 mol/l. The observed effects were reversible up to 0.43 mol/l. The authors postulated a direct effect of formamide on microtubules (ECB 1996; Messier 1976).

5.6 Genotoxicity

5.6.1 In vitro

Formamide (purity: 98%) was tested in the *S. typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 in an aqueous solution range of 0 to 10000 µg/plate. No mutagenicity was detected either with or without S-9 liver fraction of male Sprague-Dawley rats and male Syrian hamsters pre-treated with Aroclor 1254 (Mortelmans et al. 1986). Formamide is often used as a negative control in genotoxicity studies of substances (Kennedy 1986).

5.6.2 In vivo

The dominant lethal test was carried out to investigate the mutagenicity of formamide on male germ cells. Male NMRI mice that were 12 to 14 weeks old were used. Formamide was injected intraperitoneally into the 20 animals of the test group at a concentration of 364 µl/kg body weight (411 mg/kg body weight); the positive control was injected intraperitoneally with a Trenimon® (2,3,5-tris(ethyleneimino)-1,4-benzoquinone) dose of 0.125 mg/kg body weight. An untreated control group was included in the study. The treated and untreated males were mated with virgin females at a mating ratio of 3:1 at weekly intervals for 8 weeks. The uteri of the females were examined on day 18 after the beginning of the specific mating week. No significant increase of dead implantations as compared with the control was found in the formamide groups at any of the mating intervals. As expected, the results obtained with Trenimon® were positive. At the end of mating week 8, all males were sacrificed and examined for gross-pathological alterations. The males revealed no clinically evident signs of toxicity or changes in body weight gain during the treatment period. No gross-pathological alterations were observed either in the control animals or in the treated animals (BASF 1974 d).

Wallon et al. (1960) found chromosome lesions in various rat cells (bone marrow, liver, spleen, testes and ileum). In this study, which was cited in (ECB 1996), 1 rat each was injected subcutaneously with 5000 mg/kg body weight (18 h) or 10000 mg/kg body weight (8 h). Eosinophilic and neutrophilic cells and erythrocytes were investigated; a slight increase in cell counts was observed at the high dose. This study cannot be assessed because it was inadequately documented.

5.7 Carcinogenicity

5.7.1 Short-term studies

A negative result was obtained in the cell transformation assay after treatment of embryonic rat cells (1706 P88) with formamide concentrations of 0.01, 0.1, 0.5, 1, 10 or 100 µg/ml (Freeman et al. 1973). No clear result was obtained in hamster cells (ECB 1996).

5.7.2 Long-term studies

There are no data available for long-term studies.

5.8 Other effects

In vitro, a blockage of the cell membranes of mammalian muscles was demonstrated for formamide. After several-minute exposure, which led to paralysis, decreased membrane potentials and damage to the fibres of various muscles (tibia, toes and diaphragm) were detected in rats. Formamide also inhibited the potassium-mediated contraction of the mammalian ileum. It was postulated that structural proteins were modified by formamide and this inhibited the influx of potassium into the sarcoplasm (ECB 1996; Kennedy 1986).

6 Manifesto (MAK value/classification)

No studies in humans are available that are suitable for deriving a MAK value. The systemic effects as well as the irritation to the respiratory tract and eyes observed in humans cannot be assessed. Nor are there any data from animals on effects after inhalation over a prolonged period. A NOAEL of 100 ml/m^3 (180 mg/m^3) was derived from a 2-week inhalation study on the basis of haematological and clinicochemical parameters in rats; a significant increase of atypical lymphocytes was observed during the observation period. A NOAEL of 40 mg/kg body weight was established in rats after ingestion for 2 weeks. After 90-day dermal application, a NOAEL of 100 mg/kg body weight can be assumed for haematological parameters; however, erythema was observed and only body and organ weights were determined in addition to the haematological parameters. Administration of formamide via the drinking water in a multi-generation study in mice led to a prolonged oestrus cycle (NOEL: 350 ml/m^3; corresponding to 98 mg/kg body weight in females) and reduced seminal vesicle weight (NOEL: 350 ml/m^3; corresponding to 62 mg/

kg body weight in males) in this dose range. The studies were carried out for relatively short periods. Therefore, a MAK value cannot be derived from the available data. For this reason, formamide is classified in Section IIb of the *List of MAK and BAT Values*.

The animal studies yielded relatively low dermal toxicity. There are no quantitative data available for absorption through the skin. Very good penetration can be predicted from the theoretical models. Formamide is designated with an "H" because of the risk of developmental toxicity.

The substance is not designated with an "S" due to the lack of data. No classification in any of the germ cell mutagen categories is required on the basis of the available data.

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