The MAK Collection for Occupational Health and Safety

Nitroethane

MAK Value Documentation, addendum – Translation of the German version from 2017

A. Hartwig[1,*], MAK Commission[2,*]

[1] *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

[2] *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

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Nitroethane / 1-Nitroethane

MAK value documentation

A. Hartwig[1, *], MAK Commission[2, *]

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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 workplace (MAK value) for nitroethane [79-24-3], considering the endpoints local and systemic toxicity as well as developmental toxicity. Nitroethane acts locally as well as systemically. A 13-week study in rats and mice found significantly increased methaemoglobin levels accompanied by changes in the spleen as critical effects. A NOAEC was not obtained. Based on the LOAEC of 100 ml/m^3 and taking into consideration the higher sensitivity of humans and the possibility of effects increasing with time, the MAK value for nitroethane is lowered to 10 ml/m^3. Degeneration, inflammation and hyperplasia of the olfactory epithelium occur at higher exposure concentrations. As the critical effect is systemic, the assignment to Peak Limitation Category II is retained as well as the excursion factor of 4. Because there are no studies on developmental toxicity with pure nitroethane, the assignment to Pregnancy Risk Group D is also confirmed. Skin contact may contribute significantly to systemic toxicity and nitroethane is designated with an "H". Sensitization is not expected from the limited data.

Keywords

nitroethane; 1-nitroethane; mononitroethane; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

Author Information

[1] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute of Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany

[2] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

[*] Email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

Nitroethane

[79-24-3]

Supplement 2017

MAK value (2016)	**10 ml/m³ ≙ 31 mg/m³**
Peak limitation (2016)	**Category II, excursion factor 4**
Absorption through the skin (2016)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2016)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
Vapour pressure	27.9 hPa (ECHA 2015)
log K_{OW}[1)]	0.162 (ECHA 2015)
Solubility in water at 25 °C	48 g/l (ECHA 2015)
1 ml/m³ (ppm) ≙ 3.11 mg/m³	**1 mg/m³ ≙ 0.321 ml/m³ (ppm)**

For nitroethane, there is documentation available (documentation "Nitroethane" 2003).

This supplement is based on a review of the toxicological data by the European Commission (2012) and on the publicly available registration data under REACH (ECHA 2015).

1 Toxic Effects and Mode of Action

Nitroethane causes slight irritation of the skin and eyes of rabbits. In humans, sensory irritation begins at a concentration of 100 ml/m³.

After inhalation and ingestion, nitroethane is metabolized to acetaldehyde and nitrite.

The ingestion of single doses of nitroethane caused increased methaemoglobin formation in the blood of infants.

1) octanol/water partition coefficient

Inhalation exposure to a concentration of 84 ml/m³ for two years resulted in delayed body weight gains in rats.

Also in rats, increased blood methaemoglobin levels accompanied by increasing dose-dependent histopathological changes in the spleen and in the liver were found after inhalation exposure to nitroethane concentrations of 100 ml/m³ and above for 13 weeks. Similar effects occurred at 350 ml/m³ in mice.

Nitroethane was not found to have skin-sensitizing, genotoxic or carcinogenic potential.

2 Mechanism of Action

The metabolite nitrite is co-responsible for the toxicity of nitroethane. The nitrite oxidizes the Fe^{2+} in the haemoglobin to Fe^{3+} to form methaemoglobin (metHb) (Curry 1982).

The effect of nitroethane is manifest in the dose-dependent formation of metHb, which is reversible via the activity of metHb reductase. Massive oxidation of the iron can, however, result in oxidative stress with impaired redox equilibrium, membrane changes and disturbances in the interactions in the erythrocytes. The presence of Heinz bodies after nitroethane exposure indicates the formation of haemichromes from metHb. Histopathological changes in the spleen and extramedullary haematopoiesis are further effects of erythrocyte toxicity. The spleen of the rat is able to carry out erythropoiesis, whereas the human spleen does not possess this ability (Jarolim et al. 1990; Pauluhn 2004; Rockwood et al. 2003; Srivastava et al. 2002; see also supplement "Aniline" 2010).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

After inhalation in rats, about 50% of the nitroethane in the respiratory tract is absorbed (documentation "Nitroethane" 2003).

The absence of systemic toxicity after skin irritation tests indicates, in the authors' opinion, that nitroethane is not absorbed by the skin (no other details; Dow Chemical Company 1982 a).

Two rhesus monkeys were subjected to the occlusive application of 300 or 230 µl of an ethanolic/etheric solution containing about 4.9% ^{14}C-labelled nitroethane to a 20 cm² area of skin for 12 hours. Blood, faeces and urine were collected for 72 hours. In the faeces and urine, as well as in the skin at the site of application, 0.2% of the applied dose was found. The authors assume that most evaporated as a result of the high vapour pressure; in addition, the exhaled air was not analyzed (ECHA 2015). The absorbed amount corresponds to a flux of 0.12 µg/cm² and hour (300 mg × 0.049/20 cm²/12 ho urs × 0.002). This flux is probably an underestimation of the amount absorbed through the skin, as radioactivity was not analyzed in the animals' bodies and in the exhaled air.

In contrast to this, for a saturated aqueous solution, very much higher fluxes of 250, 39 or 81 µg/cm² and hour are obtained using the models of Fiserova-Bergerova

et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), respectively. Assuming the exposure of 2000 cm^2 of skin for one hour, this would correspond to absorbed amounts of 500, 78 and 162 mg, respectively.

A similar study with nitromethane was carried out in rhesus monkeys; dermal absorption was found to be 0.1% of the applied dose, a value similar to that for nitroethane. According to Fiserova-Bergerova et al. (1990), the amount absorbed under standard conditions is 1200 mg. Nitromethane was therefore designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts) and classified in Carcinogen Category 3B (documentation "Nitromethane" 2003). Absorbed quantities of 660, 108 and 286 mg, respectively, are calculated according to the three models cited if determined instead of extrapolated values for the physico-chemical data are used.

In the case of 1-nitropropane, there is relatively good agreement between the absorbed amounts of 472, 56 and 88 mg calculated according to the models with those determined in an in vitro study (358 mg) (supplement "1-Nitropropane" 2017). Therefore, the maximum absorbed amount of 500 mg nitroethane obtained from the model calculation (see above) is used for estimating the dermal penetration of the substance instead of the usually preferred in vivo data.

After intravenous injection, nitroethane was rapidly metabolized in rabbits. Elimination took place in part with the exhaled air and was complete within 30 hours (documentation "Nitroethane" 2003).

The oral administration of 1260 mg/kg body weight to rabbits resulted in nitroethane levels of up to 1.1 mg/ml in the blood. After inhalation exposure to 13 500 ml/m^3, blood nitroethane levels of up to 2.7 mg/ml were obtained after 360 minutes; levels of up to 0.36 mg/ml were obtained 500 minutes after exposure to 2700 ml/m^3. The nitrite and nitrate levels in the blood increased during the exposure (no other details; Cossum et al. 1990).

In rats, the metHb half-life, as a surrogate for the haem-oxidizing metabolites of nitroethane, is certainly shorter than that in humans. In rats, a metHb level of about 62% had decreased to 1.9% after 19 hours (half-life about 4 hours), while in children, after ingestion of nitroethane, a metHb level of 53% was merely reduced to 5.5% (half-life about 6 hours) during the same period, under treatment with methylene blue. In both cases, the doses were very high and the detoxification capacity presumably overloaded.

3.2 Metabolism

For the oxidative metabolic degradation of nitroethane the following pathway has been suggested, see Figure 1 (Lai et al. 1982):

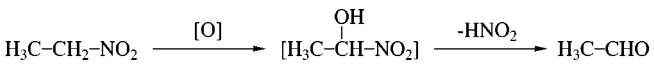

Figure 1 Degradation pathway of nitroethane

The tautomeric property of nitroethane produces an acid compound, which constitutes the basis of important chemical reactions (Figure 2, Stokinger 1982).

Figure 2 Tautomerism of nitroethane

In rats and rabbits it was demonstrated that nitroethane is metabolized to acetaldehyde and nitrite both after inhalation and ingestion. Nitrite is then oxidized to nitrate and this can subsequently be reduced to nitrite again in the liver or by nitrite-producing bacteria in the gastrointestinal tract. This oxidative denitrification of nitroethane with its product nitrite possibly takes place via the microsomal cytochrome P450 monooxygenase system. The formation of nitrite can be considered the cause of metHb formation (see Section 4; European Commission 2012; Lai et al. 1982; Scott 1943; Shugalei et al. 2012). The acetaldehyde produced is oxidized by acetaldehyde dehydrogenase to form acetate, which serves as substrate in the citric acid cycle (Smith and Anderson 2013).

The reduction of oxyhaemoglobin is accompanied by the formation of nitrogen dioxide and possibly also the formation of peroxynitrite and active oxygen species (see also Section 2; Shugalei et al. 2012).

The delayed development of methaemoglobinaemia in humans after swallowing nitroethane indicates, however, that the biotransformation of the substance more probably results in the formation of metabolites other than nitrite, as metHb formation via nitrite takes place more rapidly than that via nitroethane (Hornfeldt and Rabe 1994; Osterhoudt et al. 1995).

It was furthermore found in in vitro studies that nitroalkanes can be denitrified via two mechanisms: via the microsomal cytochrome P450 monooxygenase system and via various flavoenzymes (Davis 1993).

In vitro, it was observed that isolated nitroalkane oxidases from streptomyces and filamentous fungi catalyze the oxidation of nitroethane to acetaldehyde while simultaneously forming nitrite and hydrogen peroxide. Nitroethane is furthermore transformed in vitro by glucose oxidase into acetaldehyde, nitrite, hydrogen peroxide and in small amounts also nitrate and dinitroethane (Porter and Bright 1977). The role of oxidases in the metabolism of nitroethane in vivo is, however, not known (Cossum et al. 1990).

4 Effects in Humans

There are no data available for the end points repeated exposure, allergenic effects, reproductive toxicity, genotoxicity and carcinogenicity.

4.1 Single exposures

In children, swallowing nitroethane (no details of dose, a few drops up to 90 ml) resulted in six cases in methaemoglobinaemia with the slow accumulation of metHb during the first four hours. High metHb levels were not found until after 10 to 22 hours. The maximum metHb levels in the affected children were 39% to 56%

(Osterhoudt et al. 1995). A metHb level of more than 70% is lethal (Curry 1982). Further symptoms such as vomiting, shortness of breath and cyanosis, were caused by methaemoglobinaemia. All children were free of symptoms, with a metHb level of about 1.5%, around one day after the administration of one to three doses of methylene blue. Although oxygen was given in some cases, it was, however, not found to have any effect on the course of methaemoglobinaemia, and these data are neither used for the evaluation nor described. The case descriptions are given in Table 1.

Table 1 Cases of nitroethane poisoning

Child sex, age	Assumed uptake[a] amount and substance	MetHb level, symptoms	Medication	References
♀, 2 years	a "few drops" of nitroethane and acetone, no other details (about 500 mg/kg body weight)	9 hours: pale, vomiting 22 hours: 56.1% metHb 28 hours: 15.5% metHb	MB (1.5 mg/kg body weight, i. v.)	Shepherd et al. 1998
♂, 2 years	10 ml 98% nitroethane (about 830 mg/kg body weight)	after admission to hospital: 1 hour: 14.5% metHb 4.5 hours: 33% metHb hypoxic, vomiting 9.5 hours: 23.7% metHb disturbed consciousness 13.5 hours: 34% metHb 16 hours: 25.9% metHb 24 hours: 40% metHb, hypoxic 32 hours: 11% metHb 38 hours: 1.7% metHb	active carbon[b] MB (2 mg/kg body weight) MB (2 mg/kg body weight), intubation ascorbic acid intubation, blood transfusion intubation	Wells and Anderson 1996 abstract
♂, 27 months	15–30 ml 98% nitroethane (about 1250–2500 mg/kg body weight)	1 hour: asymptomatic 4 hours: 12% metHb 7 hours: 19.3% metHb, blue lips 9.5 hours: 18.2% metHb 11.5 hours: 17% metHb no details: 35.7%, cyanosis no details: 13.4% metHb no details: (18 hours later): 7.1% metHb	active carbon[b] MB (1 mg/kg body weight, infusion)	Shepherd et al. 1998
♂, 20 months with respiratory disease	< 30 ml (ounce) 100% nitroethane (about 2000 mg/kg body weight)	1 hour: asymptomatic 10 hours: sleepy, vomiting 11 hours: 39% metHb, cyanosis, shortness of breath 12 hours: 5.7% metHb	MB (15 mg, i. v.)	Hornfeldt and Rabe 1994

Table 1 (continued)

Child sex, age	Assumed uptake[a] amount and substance	MetHb level, symptoms	Medication	References
♂, 24 months	~30 ml nitroethane and acetone, no other details (about 2500 mg/kg body weight)	30 minutes 5 hours: pale, lethargic 7 hours: 27% metHb 8 hours: 8.2% metHb 15 hours: 14.4% metHb 19 hours: 12.7% metHb	active carbon[b] and gastric irrigation MB (1 mg/kg body weight, i. v.) MB (1 mg/kg body weight, i. v.) MB (1 mg/kg body weight, i. v.)	Shepherd et al. 1998
♀, 13 months	< 90 ml 100% nitroethane (about 9700 mg/kg body weight)	7 hours: 48% metHb, lethargic, vomiting, tachypnoea, cyanosis 17 hours: 19% metHb 23 hours: 53% metHb 35 hours: 24% metHb 42 hours: 5.5% metHb 60 hours: 0.4% metHb	MB (3.5 mg/kg body weight, i. v.) MB (2 mg/kg body weight, i. v.)	Osterhoudt et al. 1995

i. v.: intravenous; MB: methylene blue

[a] The absorbed amount obtained from information given by the parents. Extrapolation was carried out assuming that 13-month-old children weigh 9.3 kg and 2-year-old children about 12 kg.

[b] The administration of active carbon does not affect the course of methaemoglobinaemia.

The half-life of nitroethane can indirectly be estimated from the time course of the formation of metHb after single ingested doses. Assuming that a decrease in the metHb level to below 5% corresponds to about four half-lives, the half-life of nitroethane or its haem-oxidizing metabolites is at least 8 hours according to the available data. Medication with methylene blue reduced the metHb concentration in blood. The renewed increase in the metHb level in the blood observed in a number of cases after previous reduction by methylene blue could indicate a half-life of more than 8 hours (documentation "Nitroethane" 2003; European Commission 2012; Grover et al. 1996; Shepherd et al. 1998; Wells and Anderson 1996). In one case, the authors derived from the course of intoxication that nitroethane is eliminated from the blood within 30 hours (Wells and Anderson 1996). As to how the authors reached this conclusion is, however, unclear.

4.2 Local effects on skin and mucous membranes

Sensory irritation is observed at nitroethane concentrations of 100 ml/m³ (310 mg/m³) and above (no other details; Ruth 1986). In a study from 1946, conjunctival irritation occurred in volunteers with 1-nitropropane, which is to be considered as structurally analogous, at and above concentrations of 100 ml/m³ (no other details; Silverman et al. 1946; Zitting 1988).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

From inhalation studies in rabbits and guinea pigs, a NOEC (no observed effect concentration) for acute irritation of 480 ml/m^3 can be derived (documentation "Nitroethane" 2003).

LC_{50} values > 2200 ml/m^3 (6800 mg/m^3) were obtained after inhalation for 6 hours in Wistar rats (ECHA 2015).

5.1.2 Oral administration

The oral LD_{50} for rats was between 1000 and 1428 mg nitroethane/kg body weight (Dow Chemical Company 1982 a; ECHA 2015).

The oral LD_{50} was 860 mg/kg body weight for mice (NTP 2014).

After oral administration of 275 mg nitroethane/kg body weight, an accelerated turnover of the neurotransmitters noradrenalin and serotonin was observed in rats (documentation "Nitroethane" 2003).

5.1.3 Dermal application

Occlusive application of 2000 mg/kg body weight to the abraded skin for 24 hours did not produce any effects in 5 male and 5 female New Zealand White rabbits, even after a 14-day recovery period (ECHA 2015).

5.1.4 Intraperitoneal injection

The intraperitoneal LD_{50} for mice was 310 mg/kg body weight (NTP 2014).

In albino rats, intraperitoneal injection of 0.58 mmol/kg body weight (44 mg/kg body weight) resulted in a metHb increase of about 10% after one hour and a slight further increase over the following three hours (no other details; Matsumoto et al. 1961).

In rats, the application of nitroethane produced an increase in the enzyme activity of a protein kinase in the brain and proliferation of the smooth endoplasmic reticulum as well as degranulation and disorganization of the rough endoplasmic reticulum in the liver. This was accompanied by an increase in the activity of epoxide hydrolase and UDP glucuronosyl transferase, and a decrease in the activity of 7-ethoxycoumarin O-deethylase (cytochrome P450 1A1, 1A2 and 2B). No hepatotoxic effects were found in mice (documentation "Nitroethane" 2003; Yamazaki et al. 1996).

5.1.5 Intravenous injection

In albino rats, intravenous injection of 0.44 mmol nitroethane/kg body weight (33 mg/kg body weight) resulted in a metHb increase of 10% after one hour and a slight further increase over the following 3 hours (no other details; Matsumoto et al. 1961).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

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

In a 13-week study carried out according to OECD Test Guideline 413, groups of 15 female and 15 male F344 rats and B6C3F1 mice were exposed whole-body to nitroethane vapour concentrations of 0, 100, 350 or 1000 ml/m³ for 6 hours a day on 5 days per week. The purity of the nitroethane was 97% (1.5% 2-nitropropane, 1% nitromethane). Interim necropsy was carried out in 5 animals killed after 29 and 30 days (20 exposures). In a range-finding study to determine the exposure concentrations for the 13-week inhalation study, groups of 5 female and 5 male F344 rats and B6C3F1 mice were exposed to nitroethane concentrations of 0, 350, 1000, 2000 or 4000 ml/m³ on 6 hours a day for 4 days. The data of the range-finding study and the 13-week study are given in Table 2. In rats, increased, dose-dependent metHb levels, accompanied by histopathological changes in the spleen, were found at nitroethane concentrations of 100 ml/m³ and above. In mice, increased metHb levels were not found until the concentration of 350 ml/m³. The demonstrated increase in the number of reticulocytes and Heinz bodies was associated with a dose-dependent increase in metHb formation. However, 15 hours after the 20th exposure, no increased metHb levels were detected, which indicates the reversibility of this process. The metHb levels directly after the 20th exposure were not determined. Urinalysis did not reveal any unusual findings. There was no decrease in body weight in the mice. The non-dose-dependent, significant decrease in the relative kidney weights of the male mice after 4 weeks and the increase in the relative kidney weights of the females after 13 weeks in the animals of the 100 ml/m³ group were regarded by the authors as being within the normal range. The swelling of the salivary glands in some of the rats observed at concentrations of 100 ml/m³ and above was attributed to a mild virus infection (sialodacryoadenitis), as no histopathological changes in the salivary glands were found after 4 weeks (Dow Chemical Company 1982 a).

In a carcinogenicity study, groups of 40 female and 40 male Long Evans rats were exposed for 2 years to nitroethane vapour concentrations of about 0, 84 or 168 ml/m³ (0, 263 and 525 mg/m³, as corresponds to the values 100 ml/m³ and 200 ml/m³ at 1350 meters above sea level given in the publication). The animals were exposed for 7 hours a day, on 5 days per week. Nitroethane with a purity of 98% was used (2% 2-nitropropane, 0.01% nitromethane). The tumour incidence was not increased. Table 3 shows the body weight gains in the surviving rats at 4-week intervals. In rats given 84 ml/m³, slightly delayed body weight gains of up to about 10% occurred occasionally. Body weights were dose-dependently reduced in the females and the reduction was more than 10% at the concentration 200 ml/m³. No further treatment-related effects were found. MetHb formation was not determined, the haemoglobin level was unaffected. The LOAEC (lowest observed adverse effect concentration) was therefore 84 ml nitroethane/m³ (Griffin et al. 1988; documentation "Nitroethane" 2003).

Table 2 Effects of nitroethane after repeated inhalation exposure

Species, strain, number per group	Exposure	Findings	References
rat, F344, 5 ♀, 5 ♂	**4 days**, 0, 100, 350, 1000, 2000, 4000 ml/m³ 6 hours/day	**350 ml/m³: NOAEC;** **1000 ml/m³**: body weights ↓, drowsiness, eyes: reddened, surrounded by porphyrin accumulations, nasal turbinates: reddened; **2000 ml/m³ and above**: drowsiness, eyes: irritated and reddened, porphyrin pigment around eyes and nose, nasal turbinates: irritated and reddened, hyperaemia, thymus: atrophy; **4000 ml/m³**: cyanosis, after 2 exposures: all animals died	Dow Chemical Company 1982 a; Gushow et al. 1982
rat, F344, 5 ♀, 5 ♂	**4 weeks**, 0, 100, 350, 1000 ml/m³ 6 hours/day, 5 days/week	**100 ml/m³**: olfactory epithelium: inflammation 1/5 ♀; **350 ml/m³ and above**: olfactory epithelium: degeneration 8/10, inflammation 6/10, blood: reticulocytes and Heinz bodies ↑, ♀: body weights ↓, heart: relative weights ↑ 111%*, ♂: spleen: weights ↑, dark discoloration, congestion, extramedullary haematopoiesis, red pulp ↑; **1000 ml/m³**: body weights ↓, indications of cyanosis, nasal turbinates: chronic inflammation, adipose tissue: reduced, olfactory epithelium: degeneration 10/10, inflammation 10/10, spleen: weights ↑, red pulp of spleen ↑, dark discoloration, extramedullary haematopoiesis, ♀: stomach: submucosal oedema ♂: blood: haemoglobin ↓*, liver: inflammation and necrosis (1/5), increased vacuolization, kidneys: granularity in proximal tubular cells ↓	

Table 2 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 5 ♀, 5 ♂	**6 weeks**, 0, 100, 350, 1000 ml/m³ 6 hours/day, 5 days/week	**controls**: metHb ♀: 0.4%, ♂: 0.6%; **100 ml/m³**: metHb ↑ ♀: 4.7%*, ♂: 2.3%; **350 ml/m³**: metHb ↑* ♀: 26.9%*, ♂: 10.7%*, only blood examined: no further examinations	
rat, F344, 10 ♀, 10 ♂ histopathology 5 ♀, 5 ♂	**13 weeks**, 0, 100, 350, 1000 ml/m³ 6 hours/day, 5 days/week	**controls**: metHb ♀: 0.5%, ♂: 0.4%; **100 ml/m³**: **LOAEC** mild effects on salivary glands, blood: metHb ↑ ♀: 5.3%, ♂: 2.4%, after 19 hours ♀: 0.8%, ♂: 0.4%, spleen: histopathological changes (10/10, congestion), extramedullary haematopoiesis (6/10), ♀: body weights ↓, coat care ↓, liver: degenerated hepatocytes with increased vacuolization (1/10, minimal), blood: haemoglobin ↓*; **350 ml/m³ and above**: cyanosis level 1, eyes: dull, dark red, blood: metHb ↑* ♀: 30.7%*, ♂: 12.9%*, after 19 hours ♀: 0.8%, ♂: 0.6%, reticulocytes and Heinz bodies ↑, glucose ↓*, olfactory epithelium: slight degeneration (4/10), inflammation (4/10), spleen: histopathological changes, extramedullary haematopoiesis (7/10), liver: increased vacuolization, ♀: body weights ↓*; **1000 ml/m³**: body weights ↓*, cyanosis grade 2, nasal turbinates: inflammation, blood: metHb ↑ ♀: 61.8%* (after 4 hours: 64.1%; after 19 hours: 1.9%*), ♂: 50.7%* (after 4 hours: 58.6%; after 19 hours: 1.5%*), olfactory epithelium: inflammation (9/10), moderate degeneration (10/10), liver: relative weights ↑*, kidneys: granularity in proximal tubular cells ↓, ♀: blood: haematocrit ↑*, AP ↑*, bilirubin ↑*, erythrocytes ↓, ♂: blood: haemoglobin ↓*, erythrocytes ↓*	

Table 2 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Long Evans, 40 ♀, 40 ♂	**2 years**, 0, 84, 168 ml/m³ 7 hours/day, 5 days/week	**84 ml/m³**: **LOAEC**, body weight gains ↓ (≈ 10%), no other examinations	Griffin et al. 1988
mouse, B6C3F1, 5 ♀, 5 ♂	**4 days**, 0, 100, 350, 1000, 2000, 4000 ml/m³ 6 hours/day	**350 ml/m³**: lungs: dark foci (2/10); **1000 ml/m³**: **NOAEC**; **2000 ml/m³ and above**: body fat ↓, thymus atrophy, difficult breathing, bile or blood in the gastrointestinal tract, drowsiness, coordination disturbances, after 3 exposures: 2 animals died; **4000 ml/m³**: difficult breathing, unconsciousness, after 2 exposures: all animals died	Dow Chemical Company 1982 a; Gushow et al. 1982
mouse, B6C3F1, 5 ♀, 5 ♂	**4 weeks**, 0, 100, 350, 1000 ml/m³ 6 hours/day, 5 days	**100 ml/m³ and above**: **LOAEC** blood: urea-nitrogen ↓*, AP ↓, ♀: salivary gland: granularity ↓ (5/5), eosinophilic staining ↓ (5/5), thymus: relative weights ↓* 78%, ♂: kidneys: relative weights ↓*; **350 ml/m³ and above**: blood: reticulocytes and Heinz bodies ↑, olfactory epithelium: degeneration (8/8), hyperplasia (6/8), ♀: hepatocytes: degeneration with vacuolization (1/5); **1000 ml/m³**: blood: urea-nitrogen ↓*, olfactory epithelium: degeneration (9/9), hyperplasia (9/9), liver: increased vacuolization, ♀: liver: relative weights ↑ 117%*, heart: relative weights ↓*, ♂: blood: haemoglobin ↑*, haematocrit ↑*, erythrocytes ↑*	

Table 2 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 10 ♀, 10 ♂ histopathology 5 ♀, 5 ♂	**13 weeks**, 0, 100, 350, 1000 ml/m³ 6 hours/day, 5 days/week	**100 ml/m³ and above**: **LOAEC** ♀: olfactory epithelium: glandular hyperplasia (1/5), kidneys: relative weights ↑*; **350 ml/m³ and above**: blood: metHb ↑* ♀: 5.8%*, ♂: 6.6%*, reticulocytes and Heinz bodies ↑, olfactory epithelium: degeneration (9/10), hyperplasia (10/10), liver: cytoplasmic homogeneity in the centrilobular area ↑, ♀: heart: relative weights ↓*, ♂: testis: relative weights ↑*; **1000 ml/m³**: blood: metHb ↑* ♀: 20.8%*, ♂: 36.4%*, olfactory epithelium: degeneration (10/10), hyperplasia (10/10), ♂: multinucleated spermatids	

*$p < 0.05$; AP: alkaline phosphatase, metHb: methaemoglobin

Table 3 Body weights in rats at four-week intervals after inhalation (Griffin et al. 1988)

Exposure week	Male					Female				
	0 ml/m³	84 ml/m³		168 ml/m³		0 ml/m³	84 ml/m³		168 ml/m³	
	BW	BW	% CV	BW	% CV	BW	BW	% CV	BW	% CV
0	191	188	98.4	195	102.1	164	167	101.8	161	98.2
4	344	319	92.7	330	95.9	225	224	99.6	217	96.4
8	415	384	92.5	393	94.7	250	249	99.6	240	96.4
12	464	423	91.2	437	94.2	265	259	97.7	256	96.6
16	490	457	93.3	467	95.3	274	269	98.2	259	94.5
20	517	490	94.8	498	96.3	286	283	99.0	273	95.5
24	537	508	94.6	522	97.2	294	291	99.0	280	95.2
31	586	546	93.2	553	94.4	311	306	98.4	291	93.6
35	592	559	94.4	565	95.4	323	310	96.0	294	91.0
39	600	563	93.6	576	96.0	326	314	96.3	297	91.1
43	610	577	94.6	587	96.2	335	324	96.7	306	91.3
47	634	592	93.4	598	94.3	349	336	96.3	316	90.5
51	660	614	93.0	631	95.6	367	347	94.6	326	88.8
55	670	631	94.2	648	96.7	375	358	95.5	330	88.0
59	660	614	93.0	641	97.1	365	344	94.2	320	87.7
64	692	645	93.2	674	97.4	393	373	94.9	342	87.0
68	703	644	91.6	669	95.2	402	378	94.0	347	84.4
72	712	644	90.4	676	94.9	411	386	93.9	357	86.9
76	708	646	91.2	679	95.9	412	385	93.4	358	86.9
80	662	644	97.3	664	100.3	395	385	97.5	355	89.9
84	669	606	90.6	626	93.4	402	375	93.3	352	87.6
88	688	643	93.5	649	94.3	414	385	93.1	367	88.6
92	686	642	93.6	650	94.8	418	379	90.7	374	89.5
96	700	654	93.4	644	92.0	424	390	92.0	387	91.3
100	703	657	93.5	656	93.3	424	397	93.6	381	89.5
104	686	645	94.0	653	95.2	439	386	87.9	382	87.0

BW: body weight in grams; % CV: percentage of the control value

In an inhalation study (see Section 5.7), groups of 18 female and 25 male Long Evans rats were exposed for 2.5 years to 0 or 10 ± 1 ml nitroethane/m³ together with 9 ± 1 ml diethylhydroxylamine/m³. Exposure was on 6 days per week for 12 hours per day. The animals were also exposed to an unknown quantity of diethylamine hydrogen sulfite vapour (7 days/week, 24 hours/day). Control animals were exposed to filtered room air. Examination of two animals of each sex after three months revealed a non-significant decrease in the haemoglobin levels of the female and male rats, as well as a minimal reduction in the haematocrit in the male rats. Further haematological examinations did not reveal any effects (DuPont Chem 1976).

The continuation of the study (see Section 5.7) did not reveal clearly significant changes in body weights and haematological parameters after two years (Heicklen et al. 1981).

Summary

In rats, increased metHb values were found in the 13-week study at nitroethane concentrations of 100 ml/m³ and above, which were accompanied by dose-dependent histopathological changes in the spleen. In mice, no increased metHb levels were found until 350 ml/m³. Degeneration and hyperplasia of the olfactory epithelium were found in both species at nitroethane concentrations of 350 ml/m³ and above, although without amplification of the effects over time. Effects on the olfactory epithelium at 100 ml/m³ were found only in one female rat after 4 weeks and in one female mouse after 13 weeks. The observed liver effects were only minimal at the low concentration in one male rat, but increased dose-dependently. The LOAEC for effects on the spleen and metHb formation, was 100 ml/m³. In the 2-year carcinogenicity study in rats, body weight gains were reduced; the LOAEC was 84 ml/m³.

5.2.2 Oral administration

There are no studies available for nitroethane.

5.2.3 Dermal application

There are no studies available for nitroethane.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Nitroethane (0.5 ml; 96.52% nitroethane; 0.01% nitromethane; 3.38% 2-nitropropane; 0.022% water, all specifications in % by weight) was applied for 24 hours in undiluted form under occlusive conditions to the shaved intact and abraded skin of 6 albino rabbits. No effects were found (irritation score 0) on the intact skin. Mild erythema and oedema were observed in the abraded skin (irritation score 0.1; no maximum score given) of one rabbit. After a recovery period of 48 hours these effects had fully subsided (Dow Chemical Company 1982 b).

Repeated semi-occlusive application of nitroethane to the ear of one rabbit resulted in very slight, transient hyperaemia, repeated application on the abraded skin led to slight redness and scab formation. The effects disappeared after the final application (ECHA 2015).

5.3.2 Eyes

In a study from 1940, nitroethane caused mild irritation in the rabbit eye (documentation "Nitroethane" 2003).

No irritation occurred in 6 albino rabbits after the instillation of 0.1 ml nitroethane into the conjunctival sac of the right eye after 24, 48 or 72 hours (Dow Chemical Company 1974).

In 2 of 6 New Zealand White rabbits, the application of 0.1 ml nitroethane was slightly irritating to the eye after 24 hours (irritation score 6.2 of 110 according to Draize). The effect had subsided 72 hours after the treatment (ECHA 2015).

The instillation of 0.1 ml undiluted nitroethane into the conjunctival sac of the eye resulted in moderate lacrimation after 48 hours only in one of six albino rabbits. No other irritant effects occurred (NTP 2014).

In another study with 6 albino rabbits, 0.1 ml nitroethane was instilled into one eye and the eye was held closed for one second. Slight eye irritation was found after 2 hours (irritation score 12 of a maximum 110 according to Draize), which was fully reversible within 24 hours (no other details; ECHA 2015).

Direct contact of undiluted nitroethane with the eyes produced minor pain and minimal, transient irritation in the conjunctival sac of rats and mice (no other details; Dow Chemical Company 1982 a).

Summary

Nitroethane is slightly irritating to the skin and the eyes of rabbits (see also documentation "Nitroethane" 2003).

5.4 Allergenic effects

In a study also described as a Draize test, 10 male guinea pigs (no other details) first received two intradermal injections of a 10% nitroethane solution (97.7% nitroethane; 0.13% nitromethane; 1.8% 2-nitropropane and 0.024% water) in physiological saline (0.05 ml for the first and 0.1 ml for the second injection). As irritant reactions occurred, the third injection was carried out with 0.1 ml of a 5% preparation and the following seven injections with 0.1 ml of a 1% preparation. Two weeks after the final injection, intradermal challenge treatment with a 1% preparation did not produce skin reactions in any of the animals (ECHA 2015).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a two-generation study with 40 male and 40 female animals per group, no differences to the control values were found as regards the number of live pups and the number of pups per litter after inhalation exposure (whole-body) to nitroethane concentrations of 11.5 ± 2.9 m/m^3 together with 7.8 ± 1.2 ml diethylhydroxylamine/m^3 and diethylamine hydrogensulfite vapour on 5 days per week and for 6 to 10 hours per day (Heicklen et al. 1979).

There are no studies available with exposure to nitroethane alone.

5.5.2 Developmental toxicity

No unusual findings were obtained on microscopic examination of the offspring in a two-generation study with exposure to a mixture containing nitroethane (see also Section 5.5.1; Heicklen et al. 1979). Teratogenicity was not investigated.

There are no studies available with exposure to nitroethane alone.

5.6 Genotoxicity

In vitro, nitroethane was not found to have genotoxic potential in bacteria. Negative results were obtained also in the HPRT (hypoxanthine-guanine phosphoribosyltransferase) test with CHO (Chinese hamster ovary) cells. In vivo, nitroethane did not induce micronucleus formation in bone marrow erythrocytes of mice after single oral doses of 0, 250, 500 or 1000 mg/kg body weight (documentation "Nitroethane" 2003; Dow Chemical Company 1980; ECHA 2015; Warner et al. 1988).

5.7 Carcinogenicity

In a 2-year inhalation study in which Long Evans rats were exposed to nitroethane concentrations of 0, 84 or 168 ml/m^3, no increased tumor incidences were found (Griffin et al. 1988; documentation "Nitroethane" 2003).

In a 2.5-year inhalation study, groups of 18 female and 25 male Long Evans rats were exposed to nitroethane concentrations of 0 or 9 ± 2 ml/m^3 together with 9 ± 1 ml diethylhydroxylamine/m^3 and diethylamine hydrogen sulfite vapour (concentration not specified). The animals were exposed for 12 hours daily on 6 days per week. The occurrence of one skin tumour (haemangioendothelioma, with metastases in the lymph vessels) in one exposed male animal after three months was not regarded as substance-related. Testicular interstitial cell tumours (post mortem, no other details) were found in 2 of 10 examined male animals. In the concurrent groups exposed to 16 ± 3 ml diethylhydroxylamine/m^3 or 12–27 ml diethylhydroxylamine/m^3 and diethylamine hydrogensulfite vapour, testicular tumours were likewise found (1/7 and 1/12, respectively) (DuPont Chem 1976; Heicklen et al. 1981).

In a 2-year inhalation study with exposure of Swiss mice to nitroethane concentrations of 0 or 10 ± 4 ml/m³ together with 10 ± 4 ml diethylhydroxylamine/m³ and diethylhydrogen sulfite vapour (< 1 ml/m³), a significant increase in the incidence of primary skin tumours (fibrosarcomas) in the males (exposed animals 24%, controls 8%) was found, but not in the female animals (Heicklen et al. 1982).

Summary

Nitroethane was not carcinogenic in rats. The occurrence of skin tumours and testicular tumours from a mixture containing nitroethane was not confirmed in the study with markedly higher nitroethane concentrations.

6 Manifesto (MAK value/classification)

The critical effects are sensory irritation, metHb formation accompanied by changes in the spleen and delayed body weight gains after inhalation exposure of rats to nitroethane.

MAK value. There are no adequate data in humans for nitroethane. The available data for the acute toxicity of nitroethane in children do not allow any conclusions to be made as regards long-term exposure to nitroethane. Therefore, for the derivation of the MAK value, animal studies are used.

From a 2-year carcinogenicity study in rats with inhalation exposure (Griffin et al. 1988), a LOAEC of 84 ml/m³ ≙ 261 mg/m³ is obtained. At this concentration, delayed body weights gains of up to 10% in the male and the female animals occurred occasionally, which were dose-dependent only in the female animals. MetHb formation was not determined in this study.

In a 13-week inhalation study with rats and mice (Dow Chemical Company 1982 a), nitroethane exposure caused a dose-dependent increase in the formation of metHb, which was accompanied by histopathological changes in the spleen and in the liver. MetHb formation was about 5.3% in female rats at the low nitroethane concentration of 100 ml/m³ and in male rats about 2.4%. Even at the low concentration of 100 ml/m³, congestion of the spleen was observed in all rats and extramedullary haematopoiesis in all male rats and in one female. A benchmark calculation is therefore not possible. Effects on the liver were not evident in either species until concentrations of 350 ml/m³ and above. In the mice, irritation of the olfactory epithelium occurred which, however, was not yet significant at the lowest concentration tested of 100 ml/m³. Significant increases in relative kidney weights were found in the female mice at concentrations of 100 ml/m³ and above, although this effect was not more pronounced at higher concentrations. In the mice, metHb formation was not increased until concentrations of 350 ml/m³ and above.

From the effects observed in the spleen, on the metHb level and on body weight gains, the MAK value can be derived in the following ways.

A NAEC (no adverse effect concentration) can be derived from the LOAEC of 100 ml/m³ in rats for systemic effects in the spleen in the 13-week study (1:3). Taking into consideration a possible amplification of the effects during long-term exposure (1:2), a concentration of about 20 ml/m³ is obtained. As effects in the spleen of rats are more pronounced than in humans, as shown in studies with the metHb

former aniline (supplement "Aniline" 2010), a NAEC at the same level is assumed for systemic toxicity in humans. According to the formula of Buist et al. (2012) a blood:air partition coefficient of about 800 is obtained from the molar mass of 75.07 g/mol, the vapour pressure of 20.8 hPa and the log K_{OW} of 0.18. Therefore, the increased respiratory volume at the workplace compared with that in animal experiments has to be taken into account and this results in a MAK value of 10 ml/m³ (see List of MAK and BAT Values 2016).

An increase in the metHb level in humans beyond the value of 1.5% is to be considered as an exposure marker; it indicates exposure to metHb formers. Adverse effects are not to be expected up to a metHb level of 5% (Leng and Bolt 2016). However, it is known that humans are more sensitive to the formation of metHb than rats. There are no human data for nitroethane available which allow the quantification of this difference in sensitivity. The formation of metHb after the inhalation of aniline can be used as a comparison, however. In humans, 6-hour exposure to 2 ml aniline/m³ produces an increase in the metHb level from 0.7% to 1.2%, that is an increment of 0.5% (Käfferlein et al. 2014). After linear extrapolation, the increment in the metHb level in humans would be 6% for exposure to aniline at 24 ml/m³. In rats, 6-hour exposure to 24 ml aniline/m³ produces a measurable metHb level increment of about 1.2% compared with the basal level of metHb (Pauluhn 2004). The increase in the metHb level in humans after exposure to aniline is therefore higher than that in rats by a factor of 5 (6:1.2). If this species difference observed with aniline is applied to nitroethane, the metHb level of a maximum 5.3% occurring in rats at a nitroethane concentration of 100 ml/m³ would correspond to a nitroethane concentration of 20 ml/m³ (100:5) for metHb formation in humans. As adverse effects are not to be expected in humans at metHb levels up to 5%, a two-fold margin to a MAK value of 10 ml/m³, as derived above, is considered to be sufficiently large.

A LOAEC of 84 ml/m³ was obtained in the carcinogenicity study for reduced body weight gains in rats. For extrapolation to a NAEC, a factor of 2 is considered sufficient as the effect was marginal. If, according to the established procedure of the Commission, the corresponding concentration for humans is taken to be half the NAEC and the increased respiratory volume at the workplace compared with that in animal experiments is taken into account for the extrapolation, a MAK value of 10 ml nitroethane/m³ is likewise derived from this effect.

A MAK value of 10 ml/m³ has therefore been established for nitroethane.

Peak limitation. As irritation of the olfactory epithelium after inhalation exposure of rats and mice is only minimal at the nitroethane concentration of 100 ml/m³ and not significant until 350 ml/m³, it is not crucial for the determination of the threshold limit value. An empirical comparison revealed that the chronic NOAEC (no observed adverse effect concentration) for histologically determinable adverse effects in the olfactory epithelium of rats was at most two times higher than the acute NOAEC for sensory irritation of the eyes and respiratory tract of humans (Brüning et al. 2014). From the minimal effects found at 100 ml nitroethane/m³ in the animal studies, it is concluded that a value of 50 ml/m³ would be sufficient to avoid irritation in humans. In humans, sensory irritation is not observed until nitroethane concentrations of 100 ml/m³ (310 mg/m³) and above (no other details; Ruth 1986).

The derivation of the MAK value is therefore based on the significant spleen effects, the increase in metHb up to adverse levels and the reduced body weight gains caused

by nitroethane in rats. Nitroethane is therefore assigned to Peak Limitation Category II. The available human data indicate the delayed initiation of metHb formation after the ingestion of nitroethane and a half-life for the substance of at least 8 hours, from which an excursion factor of 8 would result. As sensory irritation in humans is found at 100 ml nitroethane/m^3, however, an excursion factor of 4 has been set.

Prenatal toxicity. There are no data available for the effects of nitroethane alone on prenatal development. A nitroethane mixture had no effects in a two-generation study; the study is, however, not suitable for the evaluation, as no investigations of teratogenicity were carried out.

Assignment to Pregnancy Risk Group D is therefore confirmed.

Carcinogenicity and germ cell mutagenicity. There was no evidence of carcinogenicity in a study with rats. The occurrence of skin tumours and testicular tumours observed in a study with exposure of rats to a mixture containing nitroethane was not confirmed in the study with markedly higher nitroethane concentrations.

Nitroethane is not mutagenic in bacteria and not genotoxic in mammalian cells. In mice, nitroethane did not induce micronucleus formation in the bone marrow. There is therefore no evidence of a genotoxic potential. This agrees with the results of a large number of studies demonstrating that primary nitroalkanes, unlike secondary nitroalkanes, are generally not genotoxic and not carcinogenic.

As before, the substance is therefore not classified in one of the categories for carcinogens or germ cell mutagens.

Absorption through the skin. Assuming the exposure of 2000 cm^2 of skin to a saturated aqueous solution for one hour, a dermal absorption of 500 mg can be estimated for humans from a model calculation (Section 3.1). From the systemic NAEC of 31 mg/m^3 extrapolated to humans, a systemically tolerable amount of 310 mg is obtained at a respiratory volume of 10 m^3. Therefore, the amount absorbed through the skin is above the systemically tolerable amount, and the substance has been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. As no findings of skin and respiratory sensitization in humans and no positive results in animal studies are available, and a study described as a Draize test yielded negative results, the substance is not designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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