



# Recommendation from the Scientific Committee on Occupational Exposure Limits for Nitroethane

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8-hour TWA:	20 ppm (62 mg/m <sup>3</sup> )
STEL (15 minutes):	100 ppm (312 mg/m <sup>3</sup> )
Notation:	"Skin"

### Substance identification

Chemical name:	Nitroethane
Structural formula:	$\text{H}_3\text{C}-\text{CH}_2-\text{NO}_2$
Synonyms:	1-Nitroethane
EC No.:	201-188-9
Annex I Index No.:	609-035-00-1
CAS No.:	79-24-3
Molecular formula:	C <sub>2</sub> H <sub>5</sub> NO <sub>2</sub>
Molecular weight:	75.07
Conversion factor	1 ppm = 3.12 mg/m <sup>3</sup> ;
(20 °C, 101 kPa):	1 mg/m <sup>3</sup> = 0.320 ppm

#### EU classification:

Flam. Liq. 3	H226	Flammable liquid and vapour
Acute Tox. 4 *	H332	Harmful if inhaled
Acute Tox. 4 *	H302	Harmful if swallowed

This evaluation is based on ACGIH (2001a), DFG (2000a), HCN (2004), Zitting (1988), the references cited in these reviews, and additional references from a literature search performed by SCOEL in February 2011.

### Physico-chemical properties

Nitroethane is an organic compound and a colourless oily liquid with a mild, fruity odour. The boiling point of the substance is 114 °C and the vapour pressure 2.1 kPa at 20 °C (DFG 2000a, Zitting 1988) and 2.9 kPa at 25 °C (ACGIH 2001a, HCN 2004). The vapour pressure 2.9 kPa was used for estimating sensory irritation in humans. The water solubility of nitroethane is 47 g/l at 20 °C and the log P<sub>OW</sub> is 0.18. The substance has a flash point of 41 °C (open cup) and a density of 1.051 g/cm<sup>3</sup> at 20 °C (ACGIH 2001a, DFG 2000a, HCN 2004).

## 1. Occurrence/use and occupational exposure

Nitroethane is used as a fuel additive, as a solvent for cellulose esters, vinyl, alkyd and other resins and waxes and as a precursor to explosives. It is also used in chemical synthesis (ACGIH 2001a, HCN 2004).

## 2. Health significance

### 2.1. Toxicokinetics

#### 2.1.1. Human data

Oral intoxications in children show a slow accumulation of methaemoglobin (MHb) during the first 4 hours post-ingestion. In the next 20 hours, it may reach high levels. This pattern may be explained by delayed gastrointestinal absorption and/or enterohepatic recirculation and metabolic activation. MHb formation may be explained by oxidation of nitroethane with formation of acetaldehyde and nitrite, which can cause MHb formation. Most children who had ingested nitroethane were discharged about two days after the ingestion when MHb levels were low (Hornfeldt and Rabe 1994, Osterhoudt *et al* 1995, Shepherd *et al* 1998). If considering four half-lives being necessary to reach low MHb levels and thus low nitroethane levels, the biological half-life of nitroethane would crudely be about 10 hours in young children. Taking into account a delayed absorption from the gastrointestinal tract, the value can be considered an upper boundary in humans.

#### 2.1.2. Animal data

In anaesthetised rats exposed to 1 000 ppm (3 120 mg/m<sup>3</sup>), absorption of nitroethane was 58 % and absorption in the upper respiratory tract was substantial compared to that in the lower respiratory tract, i.e. the nose functioned as a “scrubbing tower”. However, bypassing the upper airways showed approximately the same absorption fraction in the isolated upper and lower airways. Taking into account the different surface areas in the upper and the lower airways suggests that the dose per unit area is > 1 000 times greater in the upper airways than in the lower airways (Stott and McKenna 1984). No quantitative data on absorption by the oral or dermal route were available. After oral and inhalation exposure, nitroethane was metabolised to ethanal and nitrite, and the latter possibly to nitrate. *In vitro* studies showed that nitroethane was metabolised by oxidative denitrification through microsomal cytochrome P450 monooxygenases and flavoenzyme oxidases (HCN 2004). After i.v. application, nitroethane was rapidly metabolised and mostly excreted within 30 hours. The compound was partly excreted in expired air (Machle *et al* 1942). No further information about the toxicokinetics of nitroethane was available.

#### 2.1.3. Skin absorption

No relevant data on skin absorption was retrieved on nitroethane in a PubMed search (“CAS No. AND skin AND absorption”) that also comprised the closely related nitromethane, 1-nitropropane and 2-nitropropane. Neither were relevant data on nitroethane retrieved from the ACGIH (2001a), the German (DFG 2000a), the Dutch (HCN 2004) or the Nordic (Zitting 1988) occupational exposure limit (OEL) documentations.

For nitromethane, ACGIH (2001b) did not assign a skin notation as “skin application to animals gave no evidence of sufficient absorption to result in systemic injury”. In contrast, the German DFG (DFG 2000b) assigned a skin notation based on two

studies. In a non-published study in two female Rhesus monkeys, 47.1 mg nitromethane was applied occlusively for 12 hours in a 5.5 % (v/v) solution on the shaved skin. Metabolites in urine and faeces were collected. After 72 hours, 15.4 µg nitromethane had been excreted and only little nitromethane (3.5 µg) was detected in the skin. As only an extremely small amount of the applied dose was accounted for, this study cannot be used to evaluate skin absorption; nitromethane may have been exhaled unchanged and may have been metabolised by denitrification that would result in formation of nitrite and formaldehyde, which is metabolised to carbon dioxide. Exhalation could be a major route of excretion. The German DFG assigned a skin notation to nitromethane, based on the other study, an elder quantitative structure activity relationship (QSAR) study from the Fiserova-Bergerova group, which estimated the dermal penetration to 0.6 mg/(cm<sup>2</sup> x hour). Assuming a 1-hour exposure of a skin area of 2 000 cm<sup>2</sup>, this corresponds to a predicted absorbed dose of 1 200 mg.

No skin notation was assigned to 1-nitropropane and 2-nitropropane by ACGIH (2001c, 2001d) due to lack of relevant data. Neither did the German DFG (DFG 1997) assign a skin notation to 1-nitropropane. In contrast, a skin notation was assigned to 2-nitropropane (DFG 2006), based on two QSAR estimates. One estimate was derived from a model from the Fiserova-Bergerova group that suggested a skin penetration rate of 0.365 mg/(cm<sup>2</sup> x hour), which corresponds to a predicted absorbed dose of 730 mg if 2 000 cm<sup>2</sup> of skin is exposed during one hour. An additional estimate was obtained from another QSAR model of Guy and Potts, suggesting a penetration rate of 0.04 mg/(cm<sup>2</sup> x hour) and an absorbed dose of 80 mg at a 1-hour exposure of 2 000 cm<sup>2</sup> of skin. An additional cause of the added skin notation may be that 2-nitropropane is a genotoxic liver carcinogen, and even a small absorption may possess an increased cancer risk.

In conclusion, no relevant experimental data is available about skin absorption for nitroethane. Skin notations assigned to compounds closely related to nitroethane are not due to experimental data but due to estimates from QSARs. The predicted 1-hour absorption through 2 000 cm<sup>2</sup> skin ranged from 80 to 1 200 mg in nitroalkanes bracketing the molecular size of nitroethane and its octanol-water partition coefficient. This suggests that the absorption of nitroethane might be considerable compared to the inhaled dose at the recommended OEL during an 8-hour working day (10 m<sup>3</sup> x 62 mg/m<sup>3</sup> = 620 mg).

#### 2.1.4. Upper boundary estimates of methaemoglobin in humans

MHb (HbFe<sup>3+</sup>) formation from nitrite is a complex process in which nitrite is oxidised to nitrate by haemoglobin in the red blood cell cells. In humans, the half times of blood nitrite and MHb are about 35 min and 16 min, respectively. MHb is formed by two processes (Hon *et al* 2010), from deoxyhaemoglobin (HbFe<sup>2+</sup>) and from oxyhaemoglobin (Hb(FeO<sub>2</sub>)<sup>2+</sup>).

In the experimental study by Barker *et al* (2006), 10 healthy volunteers were administered sodium nitrite (molar weight 69.00) by intravenous infusion at a dose rate of 6 mg/min (5.2 mmol/h) for about 50 min. This infusion resulted in MHb levels between 5 % and 12 %.

A more recent study was performed by Hon *et al* (2010). Sodium nitrite was infused at doubling rates of 100, 200, 400, 800 and 1 600 nmol/(min x kg) every 5 min for a total of 25 min; the majority (77 %) of the infused dose was administered during the last 10 min of the period, thus the dose was minimally influenced by elimination. The total infused dose was 0.0155 mmol/kg, corresponding to a dose rate of 5.0 mmol/h

in a 70-kg man. The infusion resulted in 3 % MHB in the blood (Hon *et al* 2010, Figure 1).

Assuming a one-compartment model, the steady-state level of MHB ( $C_{ss}$ ) can be calculated by solving the equation:

$$C = C_{ss} \times (1 - \text{EXP}(\text{LN}2 / T_{1/2} \times T)),$$

where C is 5–12 %,  $T_{1/2}$  is 35 min and T is 50 min in the Barker *et al* (2006) study. The resulting steady-state range is 8–19 % MHB. From the Hon *et al* (2010) study, a steady-state level of 17 % can be calculated

The generation of nitrite from exposure to 62 mg/m<sup>3</sup> nitroethane (the recommended OEL) in humans can be estimated assuming as a worst case that all absorbed nitroethane is metabolised to nitrite, i.e. that one mole nitroethane generates one mole nitrite. Using the same relative respiratory uptake as in rats (58 %; Stott and McKenna 1984), a lung ventilation of 10 m<sup>3</sup> in 8 hours and a molar weight of 75.07, the resulting maximum formation rate of nitrite is:

$$62 \text{ mg/m}^3 \times 0.58 \times 10 \text{ m}^3 / (8 \text{ h} \times 75.07 \text{ g/mol}) = 0.6 \text{ mmol/h}$$

Assuming a linear relation between nitrite dose rate and MHB concentration at steady-state, the calculated MHB levels at the 62 mg/m<sup>3</sup> nitroethane condition are:

$$\text{Barker } et \text{ al (2006): } 8 \% \times 0.6 \text{ mmol/h} / (5.2 \text{ mmol/h}) = 0.9 \%$$

$$\text{Barker } et \text{ al (2006): } 19 \% \times 0.6 \text{ mmol/h} / (5.2 \text{ mmol/h}) = 2.2 \%$$

$$\text{Hon } et \text{ al (2010): } 17 \% \times 0.6 \text{ mmol/h} / (5.0 \text{ mmol/h}) = 2.0 \%$$

These estimates do not take into account the local metabolism of nitroethane that potentially may cause high local tissue concentrations. The main metabolic organ is the liver, but no liver toxicity was observed from nitroethane neither in humans nor at the repeated dose toxicity testing in animals. This suggests delivery of nitrite to the blood compartment that is similar to those in the above mentioned estimates. Taken together, the two independent studies give similar results and suggest that even if all nitroethane is converted to nitrite, the MHB level will be around 2 %. Thus, it appears that with respect to MHB formation, no extra uncertainty factor for species difference is needed when extrapolating from rats to humans.

### 2.1.5. Biological monitoring

There were no data available.

## 2.2. Acute toxicity

### 2.2.1. Human data

Ingestion of nitroethane containing artificial nail removers in children has caused severe MHB-aemia, requiring one or more treatments with methylene blue. Except for the MHB-aemia related symptoms, no other symptoms were reported. In all cases, MHB-aemia had a delayed onset.

A 20-month-old boy ingested less than one ounce (31 g) of an artificial nail remover containing 100 % nitroethane. The child cried initially, which was proposed to be due to oral irritation, but he was asymptomatic when the poison control centre was contacted. Ten hours later, the child appeared warm, very sleepy, with spontaneous emesis and respiratory symptoms (type not reported). His MHB concentration was 39 %, which decreased to 5.7 % one hour after methylene blue treatment. He was

discharged the next day with a MHB concentration of 1.5 %. Some of his presenting respiratory symptoms persisted a few days (Hornfeldt and Rabe 1994).

A 13-month-old girl weighing 10.2 kg ingested an unknown amount of a nitroethane containing artificial nail remover. She was symptom-free when seen in the emergency department. However, emesis, lethargy, tachypnoea, tachycardia, cyanosis and a MHB level of 48 % appeared 7 hours after the ingestion, which was decreased after methylene blue treatment. A rebound was observed 23 hours after the ingestion when the MHB level was 53 %, which was treated with another dose of methylene blue. The MHB level decreased to 5.5 % 42 hours after the ingestion, at which time no symptoms were observed. Serum liver enzyme levels were within laboratory standard values (Osterhoudt *et al* 1995).

Two cases were reported with MHB-aemia in children who had ingested nitroalkane-containing nail glue removers (Grover *et al* 1996). The 2-year-old male was asymptomatic a half hour after the ingestion. He was lavaged and given activated charcoal. Nevertheless, 5 hours later he had a grey appearance, which required a total of three doses of methylene blue treatments to be controlled. He was discharged after two days. A 2-year-old female was cyanotic and tachypnoeic 22 hours after the ingestion and had a MHB concentration of 56 %. One methylene blue dose was sufficient for treatment and she was discharged fully recovered the next day.

A 2-year-old boy with a body weight of 9.5 kg ingested 10 ml of a 98 % nitroethane-containing artificial nail remover. He received activated charcoal at admission. One hour later, the MHB-aemia was 14.5 % and 4.5 hours later 33 %. He was treated with methylene blue and the level decreased to 24 % at 9.5 hours post-hospitalisation. However, it increased to 34 % at 13.5 hours post-hospitalisation. At that time he was treated with another dose of methylene blue. It decreased the level to 25.9 % at 16 hours, but a rebound was seen 24 hours post-hospitalisation, when the level was 40 %. Exchange transfusion was initiated. The child was asymptomatic 38 hours post-hospitalisation with a MHB level of 1.7 % (Wells and Anderson 1996).

Three additional cases were described by Shepherd *et al* (1998). A 27-month-old boy ingested 0.5–1 ounce of a nail remover with 98 % nitroethane. Immediately after ingestion, the child was crying, but asymptomatic at arrival at the emergency department where charcoal was given. At 4 hours post-ingestion, no symptom was apparent, but the MHB level was 12 %. In the period 7–12 hours post-ingestion, the MHB level was about 18 % and lips were more or less blue. The MHB level increased to 35.7 % over the next several hours, requiring methylene blue treatment. The child was discharged the next day with a MHB level of 7.1 %. A 2-year-old-boy ingested less than 1 ounce of a nail remover containing nitroethane and acetone; gastric lavage was performed and charcoal was administered. About 5 hours after the ingestion, the boy appeared grey and lethargic and 7 hours after the ingestion the MHB level was 27 %; this dropped to 8.2 % after methylene blue administration. After 15 hours, the level increased to 14.4 % and a second dose of methylene blue was administered. The child was discharged 48 hours after the ingestion. Finally, a 2-year-old girl ingested a “few drops” of a nail remover containing nitroethane and acetone. She vomited and was pale 9 hours post-ingestion. At 22 hours post-ingestion, the MHB level was 56 %, which decreased after methylene blue administration. She was discharged two days after the ingestion.

### 2.2.2. Animal data

A single inhalation exposure (6–7 h) of rats to 13 000 ppm (40 560 mg/m<sup>3</sup>) caused the death of all animals. The MHB level of the animals was 2.8 %. No signs of toxicity were observed after inhalation exposure (5 × 6 h) of rats to 2 200 ppm (6 864 mg/m<sup>3</sup>)

(Dequidt *et al* 1972). Rabbits and guinea pigs were exposed by inhalation to concentrations of 480–28 850 ppm (1 500–90 000 mg/m<sup>3</sup>) for 0.5–12 hours. Increased mortality was observed in rabbits after exposure to 90 000 mg/m<sup>3</sup> (0.5 h), 15 000 mg/m<sup>3</sup> (3 h) or 3 000 mg/m<sup>3</sup> (12 h). Exposure to 3 000 mg/m<sup>3</sup> (5–6 h), 30 000 mg/m<sup>3</sup> (3 h) or 90 000 mg/m<sup>3</sup> (1 h) caused stupor and narcosis (Machle *et al* 1940).

The oral LD<sub>50</sub> was 1 625 mg/kg in rats, 2 159 mg/kg in mice, and 500–750 mg/kg were lethal for rabbits (DFG 2000a).

A single intraperitoneal (i.p.) administration of 9 mmol/kg (676 mg/kg) nitroethane in male BALB/c mice caused no liver toxicity as observed from blood sorbitol dehydrogenase, from alanine and aspartate aminotransferase, and from liver histopathology (Dayal *et al* 1989). It should be noted that serum liver enzyme levels were still within laboratory standard values in a 1-year-old child with severe MHB-aemia (see Section 2.2.1).

Wistar rats were treated with a single i.p. dose of 200 mg/kg of nitroethane and the animals were studied from 4 to 48 hours after the administration (Zitting *et al* 1982). The liver glutathione level decreased significantly (4 h post-treatment), which was followed by a significant increase (24 and 48 h post-treatment). The NADPH cytochrome c reductase decreased significantly (48 h post-treatment) as did 7-ethoxycoumarin *O*-deethylase (24 and 48 h post-treatment). The UDP-glucuronosyl-transferase increased (4–48 h post-treatment) as did epoxide hydrolase (24 and 48 h post-treatment). Electron microscopy showed progressing diffuse accumulation of lipid material in hepatocytes and in Kupffer cells. The rough endoplasmic reticulum showed degranulation (4 h post-treatment) and later disorganisation. Brain glutathione increased (4 h post-treatment) as did acid phosphatase (4–48 h post-treatment) and acetylcholine esterase (4–48 h post-treatment). In relation to liver toxicity, it is noted that rats seem to be more sensitive than mice.

## 2.3. Irritation and corrosivity

### 2.3.1. Human data

Amoore and Hautala (1983) reported an odour threshold of 2.1 ppm (6.6 mg/m<sup>3</sup>).

In a review by Ruth (1986), 100 ppm (310 mg/m<sup>3</sup>) was reported to be the threshold for sensory irritation, but no further details were given (“any reported threshold of irritation to humans”). The related substance 1-nitropropane caused conjunctival irritation in the majority of volunteers exposed to 100 ppm (Zitting 1988). Taking into account the weakness of the sensory irritation database, an estimate has also been derived from a QSAR relating the vapour pressure (P) at room temperature for non-reactive volatile compounds and the concentration depressing the respiratory rate in mice by 50 % due to sensory irritation ( $\log RD_{50} \text{ (ppm)} = 2.54 + (0.872 \times \log P \text{ (mm Hg)})$ ,  $N = 75$ ,  $r^2 = 0.84$  (Alarie *et al* 1995)); this relation suggests an RD<sub>50</sub> of 5 085 ppm. RD<sub>50</sub> values have been correlated with the Threshold Limit Values (TLV) and the relation  $TLV \sim 0.03 \times RD_{50}$  has been established for sensory irritants (Schaper 1993, Nielsen *et al* 2007). This relation suggests a TLV at 153 ppm if sensory irritation is the critical effect. Although each data set has limitations, the overall concordance between the sensory irritation estimates supports that a threshold for sensory irritation can be set at 100 ppm, which is used for recommending the STEL.

## 2.3.2. Animal data

### *Skin*

According to ACGIH (2001a), nitroethane is slightly irritating to the skin of rabbits (no further details given). No skin irritation was observed after 5 daily dermal (non-occlusive) exposures of rabbits (Machle *et al* 1940).

### *Eyes*

The exposed animals in the inhalation study by Machle *et al* (1940) showed signs of irritation of the eyes (conjunctival irritation, reddened lids, eye discharge, eye closure). According to the authors ("0.05 % were found to be safe and tolerable"), the concentration of 0.05 % (500 ppm, approx. 1 500 mg/m<sup>3</sup>) can be interpreted as an acute no observed adverse effect level (NOAEL) for eye irritation (ACGIH 2001a, DFG 2000a). This is consistent with the results of Gushov (1982a,b) indicating a NOAEL of 350 ppm and a lowest observed adverse effect level (LOAEL of) 1 000 ppm for eye irritation after repeated exposures.

### *Respiratory tract*

The exposed animals in the inhalation study by Machle *et al* (1940) showed signs of irritation of the respiratory tract (dyspnoea, occasionally audible rales). According to the authors ("0.05 % were found to be safe and tolerable"), the concentration of 0.05 % (500 ppm, approx. 1 500 mg/m<sup>3</sup>) can also be interpreted as an acute NOAEL for respiratory irritation (ACGIH 2001a, DFG 2000a).

Repeated inhalation exposure of rats to 100, 350 and 1 000 ppm (312, 1 092 and 3 120 mg/m<sup>3</sup>; 6 h/day, 5 days/week for 90 days) produced dose-related degenerative and inflammatory changes in the olfactory epithelium of the nose at concentrations of 350 ppm and above. The lowest concentration of 100 ppm caused no signs of irritation (Gushov *et al* 1982a, b). Mice exposed similarly showed minimal changes in the nasal turbinates and transient effects on salivary gland epithelium. Thus, the 100 ppm exposure concentration was judged to be a minimal effect level (Gushov *et al* 1982b).

## 2.4. Sensitisation

### 2.4.1. Human data

Human studies on sensitisation were not available.

### 2.4.2. Animal data

Studies on sensitisation in animals were not available.

## 2.5. Repeated dose toxicity

### 2.5.1. Human data

Human data on the effects of repeated exposure were not available.

### 2.5.2. Animal data

#### *Inhalation*

In a preliminary 4-day rat study by Gushov (1982a), no effects were observed at 350 ppm except thymus atrophy in females. However, this effect was not confirmed in the 90-day study. At 1 000 ppm, clinical signs (drowsiness (only after the first exposure),

dull dark-red eyes, slight amount of porphyrin around the eyes) occurred, which were more pronounced at 2 000 ppm (additional slight amount of porphyrin around the nares). All animals of the 4 000-ppm group died.

In the main study by Gushov *et al* (1982a, b), F344 rats and B6C3F1 mice (15 animals per sex and group) were exposed by inhalation to 100, 350 and 1 000 ppm (312, 1 092 and 3 120 mg/m<sup>3</sup>; 6 h/day, 5 days/week for 90 days). Five animals of each group were sacrificed after 20–30 exposures. In rats of the 1 000-ppm group, a decreased body weight gain was observed at the end of the study. Other effects at this concentration were MHB-aemia (51 % MHB for males and 62 % MHB for females immediately after the last exposure) associated with cyanosis, increased reticulocytes, formation of Heinz bodies and enlargement, congestion as well as extramedullary haematopoiesis of the spleen. Furthermore, moderate degenerative and inflammatory changes in the olfactory epithelium of the nose, slight hepatocellular vacuolisation and slightly decreased cytoplasmic granularity of the renal cortical tubular epithelium as well as of the ductal epithelial cells of the salivary glands were observed. In the 350-ppm group, similar effects were noted, which were less severe than those at the highest exposure level. The MHB concentrations were 13 % for males and 31 % for females immediately after the last exposure. At 100 ppm, very slight non-significant changes in MHB levels (5.3 % for females and 2.4 % for males) and slight histopathological alterations in the spleen and salivary glands were evident in rats. The MHB concentration (100-ppm group) was significantly increased in female rats at the interim sacrifices (4.7 % vs. 0.4 % in controls), but did not reach statistical significance at the terminal sacrifice (5.3 % vs. 0.5 % in controls). The histopathological changes occurred in the spleen (congestion: 5 males and 5 females, extramedullary haematopoiesis: 5 males and 1 female) and salivary glands (cytoplasmic granularity: 5 males and 5 females, and very slight tinctorial properties: 5 males and 1 female). For rats, it was concluded that 100 ppm was a “minimal effect level”. Mice showed similar effects, which, however, were less severe than those in rats. Granular hyperplasia of the olfactory epithelium was apparent at 1 000 ppm (1 female (slight), 4 females (moderate) and 5 males (moderate)), at 350 ppm (4 females (moderate), 5 males (moderate)) and at 100 ppm (1 female (slight)), but no effect was observed in unexposed controls. A transient effect was observed in the salivary gland at 29 days (interim kill). At 1 000 ppm, effects were: 1 female (slight) and 4 females (moderate); at 350 ppm effects were: 5 females (moderate); at 100 ppm: 5 females (very slight to slight); no effect was observed in males and neither was any effect observed at the end of the 13-week study. According to the authors (Gushov *et al* 1982a,b), the minimal effect level (LOAEL) was 100 ppm both for the rat (spleen and salivary glands) and for the mouse (nasal turbinates and transient effects to the salivary gland epithelium).

Long Evans rats (40 animals per sex and group) were exposed to 0, 100 and 200 ppm (263 and 525 mg/m<sup>3</sup>) by inhalation on 7 h/day, 5 days/week for 2 years (Griffin *et al* 1988). An extensive examination (body weight, organ weights and histology, haematological and clinical-chemistry parameters) revealed slightly reduced body weights in exposed animals. The critical endpoint of the subchronic study (Gushov *et al* 1982a, b), MHB-aemia, was not addressed in this chronic study neither were nasal histopathology. For further description, see Section 2.7.

#### Oral

Studies on repeated oral exposure in animals were not available.

### Dermal

No systemic effects were observed after 5 daily dermal (non-occlusive) exposures of rabbits to nitroethane (Machle *et al* 1940).

## 2.6. Genotoxicity

### 2.6.1. In vitro

Nitroethane was not mutagenic in several Ames tests with *Salmonella Typhimurium* strains TA92, TA98, TA100, TA102, TA1535, TA1537 and TA1538 when tested with and without metabolic activation (DFG 2000a, HCN 2004).

### 2.6.2. In vivo – Human data

Human data on genotoxic effects *in vivo* were not available.

### 2.6.3. In vivo – Animal data

A negative result was reported in a micronucleus test in Charles-River mice. The animals were exposed for two consecutive days to oral doses at 0.26, 0.53 and 1.05 g/kg and the bone marrow was examined 6 hours after the last dose. Thus, the protocol represents sampling both at 6 and 30 hours post-treatment and the highest dose was about the LD<sub>50</sub>. The positive control agent, methyl methanesulphonate (90 mg/kg/day i.p.) induced a highly positive response ( $p \leq 0.001$ ), which increased the micronucleus formation to about 10 times the background level (Hite and Skeggs 1979). Sampling at 24, 48 and 72 hours post-treatment has been recommended by a US EPA working group to detect slowly metabolised compounds. Ethyl methane-sulphonate (closely related to the positive control substance used in this study) is an appropriate control compound for an early response and 7,12-dimethylbenzanthracene for later sampling times (Heddle *et al* 1983). Taking into account the dose levels, the adequate positive control response and the fact that nitroethane is rapidly metabolised, the negative response may rather represent a real finding than a false negative result.

A dominant lethal test in Long-Evans rats gave a negative result in a mixed exposure study with combined inhalation exposure of male animals to 10 ppm nitroethane, 9 ppm diethylhydroxylamine (both about 7 h/day, 5 days/week) and a low level of diethylamine hydrogen sulphide (24 h/day, 7 days/week) for several months and afterwards mated with untreated females. The fertility rate of the animals was low, 59 % in the treated and 39 % in the unexposed controls (Legator *et al* 1979). The study has several limitations, including the low exposure level.

Multinucleated spermatids were observed in 2/5 mice exposed by inhalation to 1 000 ppm (3 120 mg/m<sup>3</sup>) on 6 h/day, 5 days/week for 13 weeks (Gushov *et al* 1982a). This effect is indicative of chromosomal damage (HCN 2004).

## 2.7. Carcinogenicity

### 2.7.1. Human data

Human data on carcinogenic effects were not available.

### 2.7.2. Animal data

A 2-year low-dose mixed exposure was conducted in Swiss mice (Heicklen *et al* 1982). Exposures were to diethylhydroxylamine (10 ppm, 6–8 h/day, 5 days/week), nitroethane (10 ppm, 6–8 h/day, 5 days/week) and diethylamine hydrogen sulphide ( $\leq 1$  ppm, 24 h/day, 7 days/week). The controls were exposed to filtered air. Groups contained 40 males (M) and 40 females (F). Survival in the combined control group (M+F) was 79 % and in the combined exposed group (M+F) 93 %. Extensive histopathology was conducted and the authors only noted two notable findings. In male controls and male exposed mice, the incidence of all kinds of tumours was 0.41 and 0.63 ( $p = 0.12$ ), respectively, whereas the trend in females was opposite (0.68 versus 0.36 ( $p < 0.0005$ )). The incidence of primary skin tumours (malign and benign combined) was 8 % in the male controls and 24 % in the exposed males ( $p = 0.048$ ). There were no neoplastic skin lesions in either control or exposed females except for one adenoma in an exposed female mouse. This study suggests no exposure-dependent neoplastic lesions in mice at 10 ppm nitroethane; excess skin tumours were not detected in other studies.

Long-Evans rats were exposed for up to 2½ year with interim sacrifice. Exposed rats (27 males and 18 females) received about 9 ppm diethylhydroxylamine (7–12 h/day, 5–6 days/week), about 9 ppm nitroethane (7–12 h/day, 5–6 days/week) and a low-level diethylamine hydrogen sulphite level (24 h/day, 7 days/week). Controls (25 males and 18 females) received filtered air. There was no significant difference between body weight, haematology and blood biochemistry parameters. Histopathology was comprehensive. The only noticeable exposure-dependent finding was two testis tumours in the exposed group, whereas none was observed in the controls (Heicklen *et al* 1981). This finding was not confirmed in the below described study where much higher concentrations were used.

Male (M) and female (F) Long-Evans rats were exposed to 0 (50 M and 40 F controls), 263 (40 M and 40 F) and 525 mg/m<sup>3</sup> (41 M and 39 F) of nitroethane 7h/day, 5 days/week for 2 years (Griffin *et al* 1988); the study was conducted at Alamogordo, New Mexico, which is situated 1.3 km above sea level and thus the appropriate exposure metrics is the mg/m<sup>3</sup> level, whereas the ppm cannot be readily interpreted. The percentage of surviving rats at 2 years of exposure was 50.0, 47.5, and 58.5 (M) and 42.5, 42.5 and 64.1 (F), respectively, and thus, nitroethane did not affect the survival. No pharmacological or no other overt effect of exposure was observed. The mean body weights (g) were generally less in the nitroethane groups. Thus, at the end of the 2-year period, the mean male body weight was 686, 645 (94 % of controls) and 653 (95 % of controls), respectively, and mean female body weight was 439, 386 (88 % of controls) and 382 (87 % of controls), respectively. In the males, a statistically significant decrease was observed in the low-dose group and occasionally in the top-dose group, where the decrease was statistically significant in the weeks 6–15 and occasionally thereafter. In the females, a significant decrease was always observed in the top-dose group and occasionally in the low-dose group. No effect appeared on the haematological parameters, erythrocyte count, packed cell volume, mean corpuscular volume, haemoglobin and leukocyte counts. Serum chemistry comprised aspartate and alanine aminotransferase, total bilirubin, total protein, creatinine, sodium and potassium, and blood urea nitrogen. Exposure-dependent effects were increased total protein and blood urea nitrogen in the female top-dose group. There was no consistent exposure-dependent effect on relative and absolute weights of the liver, kidney, brain, heart and lungs. The microscopic examinations comprised numerous tissues, but only age-dependent degenerations were observed, which showed neither exposure-dependent nor carcinogenic effects. Thus, the total number of tumours in male and female controls was 46 and 46, respectively. In the low-dose group there were 44 tumours in males and 56 in females, and in the top-

dose group there were 33 and 45, respectively. Taking the body weight as the critical effect (significantly reduced in the low-dose males and occasionally in the females) suggests a LOAEL at 263 mg/m<sup>3</sup>. The MHb level was not reported, neither was nasal histopathology performed.

## 2.8. Reproductive toxicity

### 2.8.1. Human data

Human data on reproductive or developmental effects were not available.

### 2.8.2. Animal data

#### *Fertility*

No significant exposure-dependent effects on reproduction were detected in a 3-generation study in Swiss mice by Heicklen *et al* (1979). The animals were exposed by inhalation to concentrations of 11 ppm (34.3 mg/m<sup>3</sup>) nitroethane in combination with 8 ppm diethylhydroxylamine for about 8 h/day, 5 days/week. An additional continuous exposure (24 h/day for 7 days/week) was to an unknown concentration of diethylamine hydrogen sulphite. Controls were exposed to filtered air. There was no statistical difference between litter size in controls and exposed mice. The number of pups that were stillborn or died soon after birth was significantly higher in the controls (2.86 % vs. 1.73 %). Microscopic examination of the second and the third generation showed an extremely small number of lesions, which were considered incidental findings. It is noted that the nitroethane exposure concentration was low.

There were no lesions of reproductive organs in Long-Evans rats, which inhaled 263 or 525 mg/m<sup>3</sup>, 7 h/day, 5 days/week for 2 years; the studied organs in males were testes, prostate, epididymis and seminal vesicles, and in females, the ovaries, uterus, cervix and oviduct (Griffin *et al* 1988).

#### *Developmental toxicity*

Developmental toxicity was studied in pregnant Swiss mice, which were exposed by inhalation to a nitroethane concentration of 14.3 ppm (44.6 mg/m<sup>3</sup>) for about 8 h/day on gestation days 6–17 in combination with 9 ppm diethylhydroxylamine and continuous exposure to an unknown concentration of diethylamine hydrogen sulphite. Control animals received filtered air. On day 18 of gestation, the females were sacrificed and fetuses were removed by caesarean section. In controls and the exposed group, pregnancy ratios (pregnant/bred) was 23/25 and 24/25, respectively, implantation sites (left horn/right horn) 126/125 and 144/137, respectively, resorptions/live fetuses 0/251 and 2/279, respectively, the average foetal weight was 1.03 and 1.06 g, respectively, and the mean live litter size was 11 and 12 pups, respectively. Neither significant maternal nor developmental effects were observed, nor were unusually skeletal variations in the fetuses observed (Beliles *et al* 1978). It is noted that the nitroethane exposure concentration was low.

#### *Nitrite*

As nitrite is an important metabolite of nitroethane, its reproductive effects were evaluated in relation to exposure at the proposed OEL; the evaluations showed that reproductive toxicity is not expected from this metabolite.

Several studies with high doses (about 200 mg/kg/day or more) of sodium nitrite (NaNO<sub>2</sub>) in pregnant rats indicated that nitrite can pass the placenta, increase mortality, cause liver damage and decrease haematopoiesis among pups. A drinking-

water study with  $\text{NaNO}_2$  suggested a no observed effect level (NOEL) of about 50 mg/kg/day (0.72 mmol/kg/day) and a 2-generation reproductive toxicity study showed no effect on litter size, postnatal mortality, growth rate or life span at 23 mg/kg/day (0.33 mmol/kg/day), which was the top-dose (JECFA 1996).

A reproduction and fertility study in Swiss CD-1 mice was reported by JECFA (2003), in which the  $F_0$  generation was exposed to drinking-water containing 0.06 %, 0.12 % and 0.24 % (w/v) of  $\text{NaNO}_2$  for the continuous cohabitation phase; the corresponding doses were 120, 260 and 420 mg/kg bw/day. A control group was also included. As no effects on reproduction were noted during this phase, only the controls and the highest dose group were retained after weaning and examination for potential reproductive toxicity in the  $F_1$  and  $F_2$  generations. No adverse effect on reproduction or reproductive performance was observed at 420 mg/kg/day (6.1 mmol/kg/day), which was considered the NOEL for reproductive toxicity.

At the recommended OEL, a 70-kg man is exposed to less than 0.07 mmol/kg nitrite.

### 3. Recommendation

In humans, the sensory irritation threshold may be about 100 ppm (312 mg/m<sup>3</sup>). Acute oral overexposure caused MHB-aemia and related symptoms.

Nitroethane was not found to be mutagenic. Long-term inhalation studies in mice and rats showed no consistent carcinogenic effect with exposures up to 525 mg/m<sup>3</sup>. In rats, 10 ppm (31 mg/m<sup>3</sup>) caused neither developmental toxicity nor reproductive effects in mice. No histopathological effect was observed on reproductive organs at exposures up to 525 mg/m<sup>3</sup> in rats.

In rats,  $\geq 350$  ppm (1 092 mg/m<sup>3</sup>) caused MHB-aemia and associated symptoms, degeneration and inflammation in the olfactory epithelium, and hepatic, renal and salivary gland effects. At 100 ppm (312 mg/m<sup>3</sup>), the MHB concentration was slightly increased ( $\sim 5$  %) with minimal histopathological effects in the spleen and the salivary gland. At 263 mg/m<sup>3</sup> (84 ppm), the only observed effect was a decreased body weight; the MHB concentration was not reported and nasal histopathology was not performed. Due to this limitation of the study, this level is considered the LOAEL, although the level may be close to the NOAEL, and used as the point of departure for recommending an OEL.

Due to the marginal effect, an uncertainty factor of two is considered sufficient for the extrapolation from the LOAEL to the NOAEL and due to the mild adverse effect, an additional uncertainty factor of two is considered sufficient for extrapolation from the NOAEL to the recommended OEL. SCOEL considers these uncertainty factors to include also the uncertainties in the database. Due to the preferred value principles, the value is rounded off to 20 ppm (62 mg/m<sup>3</sup>) and proposed as the 8-hour OEL for nitroethane.

From a separate analysis of nitrite effects in humans, the OEL is considered to protect against MHB-aemia in humans where a level of 5 % is considered tolerable (Bolt *et al* 1985). Also not addressed in the key study was the nasal effect. However, at a slightly higher exposure level (312 mg/m<sup>3</sup>) the effect was minimal. The margin-of-exposure between the recommended OEL and the minimal local effect is 5, which is considered sufficient.

Informative studies on reproductive toxicity is limited to no effect on sex organs at 525 mg/m<sup>3</sup> in a 2-year study in rats. At the recommended OEL, the exposure to the nitrite metabolite is below the NOELs in rat and mouse studies and thus no

reproductive toxicity is expected from this metabolite. Additionally, there is little concern about genotoxicity.

A STEL at 100 ppm is proposed to prevent sensory irritation. No relevant experimental data is available about skin absorption for nitroethane. Skin notations assigned to nitroalkanes closely related to nitroethane are not due to experimental data but due to estimates from QSARs. The predicted 1-hour absorption through 2 000 cm<sup>2</sup> skin ranged from 80 to 1 200 mg in nitroalkanes, bracketing the molecular size of nitroethane and its octanol-water partition coefficient. This suggests that the absorption of nitroethane might be considerable compared to the inhaled dose at the recommended OEL during an 8-hour working day (10 m<sup>3</sup> x 62 mg/m<sup>3</sup> = 620 mg). All together, a skin notation is proposed for nitroethane.

There were no data concerning the sensitising properties of nitroethane.

There were no data for biological monitoring available.

At the recommended TWA, no analytical difficulties are expected as much lower concentrations of the closely related compound, nitromethane, can be determined (Takeuchi *et al* 2010).

The present Recommendation was adopted by SCOEL on 26 September, 2012.

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