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N-(2-Hydroxyethyl)piperidine

MAK Value Documentation – Translation of the German version from 2022

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Keywords

N-(2-hydroxyethyl)piperidine; irritation; analogy; MAK value; workplace concentration; momentary value; screening developmental toxicity study; skin sensitization

Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and evaluated the data for *N*-(2-hydroxyethyl)piperidine [3040-44-6] to derive an occupational exposure limit value (maximum concentration at the workplace, MAK value), considering all toxicological end points. Relevant studies were identified from a literature search and also unpublished study reports were used. There are no data for human exposure and no inhalation studies in animals. *N*-(2-Hydroxyethyl)piperidine is a strong skin irritant and is therefore suspected of causing irritation in the upper respiratory tract when inhaled. A 9-week gavage study in female rats carried out according to OECD Test Guideline 422 established a NOAEL for *N*-(2-hydroxyethyl)piperidine of 75 mg/kg body weight and day, which corresponds to a concentration in workplace air of 23 mg/m^3. This value seems excessive because of the severe irritation induced by *N*-(2-hydroxyethyl)piperidine. Therefore, an analogy is drawn between this substance and 2-diethylaminoethanol, another tertiary amine with similar chemical properties. A maximum concentration at the workplace (MAK value) of 2 ml/m^3 was derived for 2-diethylaminoethanol on the basis of the NOAEC of 11 ml/m^3 established in a 13-week inhalation study in rats. By analogy, the MAK value for *N*-(2-hydroxyethyl)piperidine has been set at 2 ml/m^3. As the critical effect is local, the substance has been assigned to Peak Limitation Category I. As there are no data in humans, an excursion factor of 1 has been set and, in analogy to other aliphatic amines with the same MAK value, a momentary value of 5 ml/m^3. The only available developmental toxicity study is a screening study in rats carried out according to OECD Test Guideline 422. Therefore, *N*-(2-hydroxyethyl)piperidine has been assigned to Pregnancy Risk Group D. There are no studies on carcinogenicity and on genotoxicity in vivo. *N*-(2-Hydroxyethyl)piperidine is not genotoxic in vitro and the structural properties indicate no potential hazard. According to skin absorption models, *N*-(2-hydroxyethyl)piperidine is not expected to be taken up via the skin in toxicologically relevant amounts. Animal studies and in vitro tests show a skin sensitizing potential for *N*-(2-hydroxyethyl)piperidine, which is therefore designated with “Sh”. There are no data for respiratory tract sensitization.

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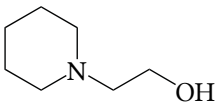
MAK value (2021)	**2 ml/m³ (ppm) ≙ 11 mg/m³**
Peak limitation (2021)	**Category I, excursion factor 1**
Momentary value (2021)	**5 ml/m³ (ppm) ≙ 27 mg/m³**
Absorption through the skin	–
Sensitization (2021)	**Sh**
Carcinogenicity	–
Prenatal toxicity (2021)	**Pregnancy Risk Group D**
Germ cell mutagenicity	–
BAT value	–
Synonyms	2-hydroxyethyl-1-piperidine 2-piperidinoethanol
Chemical name (IUPAC)	2-piperidin-1-ylethanol
CAS number	3040-44-6
Structural formula	
Molecular formula	$C_7H_{15}NO$
Molar mass	129.2 g/mol
Melting point	13 °C (ECHA 2020)
Boiling point at 1013 hPa	200 °C (ECHA 2020)
Density at 20 °C	0.973 g/cm³ (ECHA 2020)
Vapour pressure at 20 °C	0.217 hPa (ECHA 2020)
log K_{OW} at 25 °C and pH 10.5	0.62 (ECHA 2020)
Solubility	miscible with water (ECHA 2020)
pH at 20 °C	11.4 for 1% solution (ECHA 2020) 12.4 at 100 g/l (IFA 2020)
pKa at 25 °C	9.54 (ECHA 2020)
1 ml/m³ (ppm) ≙ 5.361 mg/m³	**1 mg/m³ ≙ 0.187 ml/m³ (ppm)**
Hydrolytic stability	no data
Stability	“stable under normal conditions” (Loba Chemie 2019)
Production	reaction of triethanolamine with ammonia in the presence of hydrogen at temperatures from 100 to 500 °C and pressures from 10 to 500 bar on heterogeneous catalysts (BASF AG 1995)
Purity	100% (Loba Chemie 2019) 99.8% (ECHA 2020)
Impurities	no data

Uses	for synthesis (Loba Chemie 2019) as a laboratory reagent or as a non-reactive process aid in industry (ECHA 2020)
Concentration used in metal-working fluids and lubricants	no data

Note: The substance can occur simultaneously as vapour and aerosol.

Cited unpublished toxicological studies from companies have been made available to the Commission.

It is not known at what concentration an *N*-(2-hydroxyethyl)piperidine solution no longer causes irritation. For substances that are corrosive to the skin, according to the Regulation on Classification, Labelling and Packaging, skin irritation is to be assumed at concentrations of 1% or more, that means 0.5% should no longer have an irritant effect (ECHA 2020).

1 Toxic Effects and Mode of Action

An aqueous solution of *N*-(2-hydroxyethyl)piperidine is strongly alkaline. The substance is corrosive to the skin of rabbits.

In a combined repeated dose toxicity study and reproductive/developmental toxicity screening test with daily gavage administration of up to 250 mg *N*-(2-hydroxyethyl)piperidine/kg body weight and day in Wistar rats, decreased food and water intake and decreased body weight gains were observed only in females at the highest dose tested. At this dose, there was also an increased number of postimplantation losses. Specific studies of fertility and developmental toxicity with histopathological examination of the offspring are not available.

N-(2-Hydroxyethyl)piperidine caused skin sensitization in the local lymph node assay in mice. In vitro studies likewise indicate skin sensitizing potential.

The substance is not genotoxic in vitro. Data for its genotoxicity in vivo and carcinogenicity studies are not available. There are also no data for effects in humans, no inhalation studies and no toxicokinetic studies.

2 Mechanism of Action

There are no mechanistic studies available. From the available data it can be concluded that local irritation is the main effect caused by the basicity.

3 Toxicokinetics and Metabolism

There are no experimental data available for the toxicokinetics and metabolism of the substance. Based on the chemical structure and the physicochemical data, it is assumed that *N*-(2-hydroxyethyl)piperidine is completely absorbed orally. As it is corrosive to the skin, ingestion of the substance can be expected to have an effect on the mucous membranes. *N*-(2-Hydroxyethyl)piperidine does not contain a labile functional group. Therefore, it is assumed that it is neither hydrolysed in the gastrointestinal tract nor in the body. Furthermore, it is postulated that the substance dissolves in the upper respiratory tract after inhalation exposure due to its good water solubility and leads to local effects and can also be absorbed there, possibly to 100%. Since the vapour pressure of the substance is low, exposure to the vapour is assumed to be minimal (ECHA 2020). Aerosol exposure during use in metal-working fluids is, however, possible.

To take into account the pH value of the skin, the log K_{OW} of 0.62 (pH value 10.5; 25 °C) is provisionally converted into a log D_{OW} of −3.42 at a skin pH value of 5.5 for the calculation of dermal absorption with the mathematical models (ECETOC 2013). Assuming a non-irritant 0.5% *N*-(2-hydroxyethyl)piperidine solution and the log D_{OW} of −3.42, fluxes of 1.6 and 0.3 µg/cm² and hour, respectively, are calculated using the models of Fiserova-Bergerova et al. (1990) and IH SkinPerm (Tibaldi et al. 2014). Assuming the exposure of 2000 cm² of skin for 1 hour, this would correspond to absorbed amounts of 3.2 and 0.6 mg, respectively.

For the log K_{OW} of 0.62 (pH 10.5), fluxes of 28.5 (Fiserova-Bergerova et al. 1990) or, using the IH SkinPerm model (Tibaldi et al. 2014), of 5.1 µg/cm² and hour and absorbed amounts of 57.0 and 10.1 mg, respectively, are calculated.

4 Effects in Humans

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

According to current test guidelines, acute inhalation studies do not need to be performed because the substance is regarded as corrosive to the skin (ECHA 2020).

In a "hazard test" that does not meet today's requirements, a total of 12 male and female rats were exposed to *N*-(2-hydroxyethyl)piperidine vapour for 7 hours. The test concentration, which was not determined analytically, was prepared by passing 200 l of air per hour through a 5 cm layer of the test substance. No deaths occurred. The animals wiped their snout, and secretion from the nose was observed. The animals' fur was ruffled and lagophthalmos (incomplete eyelid closure) was reported (ECHA 2020). This test cannot be used for the evaluation because the concentration was not determined analytically and the test description is imprecise. However, it does show that an atmosphere saturated with *N*-(2-hydroxyethyl)piperidine vapour has an irritant effect.

5.1.2 Oral administration

Groups of 5 male and 5 female Sprague Dawley rats were given single gavage doses of *N*-(2-hydroxyethyl)piperidine of 464, 1000, 1470, 2150 or 3160 mg/kg body weight. The calculated LD_{50} was 1100 mg/kg body weight. At and above 1000 mg/kg body weight, dyspnoea, apathy, tremor, staggering gait and poor general condition were observed and deaths occurred. At 464 mg/kg body weight, one female died within 24 hours and salivation was observed in some animals (BASF SE 2019 a).

Another LD_{50} in rats is given as 1500 mg/kg body weight (no other details; IFA 2020).

5.1.3 Dermal application

In a study in male and female Sprague Dawley rats carried out in 1981, the LD_{50} of a 50% or 100% *N*-(2-hydroxyethyl)-piperidine solution applied to an area of 50 cm² of dorsal skin for 24 hours under occlusive conditions was in the range of 1000 to 2000 mg/kg body weight. At the dose level of 1000 mg/kg body weight, no animals died, at 2000 mg/kg body weight 9 of 10 animals died within 14 days (ECHA 2020).

5.1.4 Intravenous injection

An LD_{50} of 166 mg/kg body weight was reported after intravenous injection in rats (no other details; NCBI 2020).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

In a 2-week range-finding study, *N*-(2-hydroxyethyl)piperidine doses of 0, 150 or 500 mg/kg body weight and day were administered by gavage to male and female Wistar rats. The NOAEL (no observed adverse effect level) was 150 mg/kg body weight and day (Table 1). At 500 mg/kg body weight and day, salivation, mortality, reduced food and water intake, reduced body weight gains, altered blood parameters and thickened walls of the stomach and duodenum were observed (BASF SE 2019 a).

In the combined repeated dose toxicity study and reproductive/developmental toxicity screening test carried out according to OECD Test Guideline 422 in Wistar rats (Table 1), the female parents were given gavage doses of *N*-(2-hydroxyethyl)piperidine at levels of 0, 25, 75 or 250 mg/kg body weight and day for 56 days and the males for 30 days. The NOAEL for the offspring and female parents was 75 mg/kg body weight and day, and that for male parents was the highest dose tested of 250 mg/kg body weight and day. At this dose, reduced food and water consumption and reduced body weight gains were observed in the dams (BASF SE 2019 a).

Tab. 1 Effects of *N*-(2-hydroxyethyl)piperidine after repeated oral administration in rats (BASF SE 2019 a)

Species, strain, number per group	Exposure	Findings
rat, Wistar, 4 ♂ and 4 ♀	14 days, 0, 150, 500 mg/kg body weight and day, 7 days/week, gavage, purity 99.8%	**150 mg/kg body weight**: NOAEL; **500 mg/kg body weight**: day 10: 1 ♂ died, 1 ♂ killed in moribund condition, other animals: salivation and piloerection, food intake ↓ (♂ on days 1–3: −36%; ♀ at the end of the study: −16%), body weight gains ↓ (♂ on days 1–3: −17.3 g, control group: 5.1 g; ♀ at the end of the study: −1.1 g, control group: 13.0 g), erythrocytes ♂ ↓ 7%, haemoglobin ♂ ↓ 7%, haematocrit ♂ ↓ 8%, reticulocyte count ↑ ♂ 45% and ♀ 36%, polymorphonuclear neutrophils ↑ ♂ 78% and ♀ 227%, eosinophils ↑ ♂ 256% and ♀ 155%, triglycerides ↑ ♀ 128%, relative liver weights ↑ ♀ 14%, thickened wall of stomach and duodenum, "foci" in forestomach and glandular stomach
rat, Wistar, 10 ♂ and 10 ♀	♂ 30 days, ♀ 56 days, 0, 25, 75, 250 mg/kg body weight and day, 7 days/week, gavage, purity 99.8%, OECD Test Guideline 422	on day 28: ♂ FOB test, no findings, on day 55: ♀ FOB test, no findings; **75 mg/kg body weight**: F0: ♀: NOAEL; F1: NOAEL; **250 mg/kg body weight**: F0: ♂: NOAEL; ♀: water consumption ↓ 18% before mating, 21% during mating period, 23% during lactation, food consumption ↓ (10% before mating, 9% during mating period, 23% during lactation), body weights ↓ PND 1–4: −1.5 g; body weight gains ↓ (PND 1–13: 19.4 g, control group: 32.9 g), TSH ♂ (day 13: +78%, day 30: −30%), F1: postimplantation losses ↑ 19.7%

FOB: functional observational battery (behavioural tests); PND: postnatal day; TSH thyroid stimulating hormone

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study from 1981, 2 Vienna White rabbits were exposed occlusively to 0.5 ml of undiluted *N*-(2-hydroxyethyl)piperidine on 2.5 × 2.5 cm of shaved dorsal skin for 1 hour (patch) and the substance was washed off afterwards. After 24 and 48 hours, the score for erythema at each reading was 2 on a scale up to 4 in 1 animal and 3 in the second, and the scores for oedema were 0.5 and 1 out of 4, respectively. Both findings were not reversible within 8 days and the animals displayed parchment-like and leathery-like necrosis on the treated skin. The substance was regarded as corrosive based on these findings (ECHA 2020).

An analogous study in 2 animals of the same species and strain with occlusive exposure of the shaved dorsal skin for 4 hours and subsequent washing of the skin site resulted in a score of 3 and 4 on a scale up to 4, respectively, for erythema and 2 out of 4 in both animals for oedema. The findings were not reversible within 8 days and the skin site displayed parchment-like and leather-like necrosis. The substance was regarded as corrosive based on these findings (ECHA 2020).

When exposure was carried out for only 3 minutes and followed by washing of the skin site under otherwise analogous conditions, the erythema score was 0.5 on a scale up to 4 and the oedema score was 0 out of 4 in both animals. All findings were reversible (ECHA 2020). Due to the short exposure time, this study cannot be used for the evaluation.

5.3.2 Eyes

As the substance is classified as corrosive to the skin according to CLP criteria, no eye irritation studies have been carried out (ECHA 2020).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

5.4.1.1 In vivo studies

Skin sensitization was tested in a local lymph node assay carried out according to OECD Test Guideline 429 in CBA/Ca mice. Solutions in 3 concentrations of 1%–10% (w/w) *N*-(2-hydroxyethyl)piperidine (purity ≥ 99.8%) in propylene glycol were used. The stimulation indices (SI) were determined by the incorporation of ^{3}H-thymidine as well as by cell count, the lymph node weights and the ear weights (Table 2). The 10% solution of the test substance led to an SI for ^{3}H-thymidine uptake of ≥ 3 and an SI for the cell count of ≥ 1.5. The test result can thus be regarded as positive. The EC3 value for ^{3}H-thymidine incorporation and the EC1.5 value for the increase in the cell count were determined to be 9.3% and 7.7%, respectively (BASF SE 2019 c).

Tab. 2 Effects of *N*-(2-hydroxyethyl)piperidine in the local lymph node assay in mice (BASF SE 2019 c)

Test group	^{3}H-Thymidine incorporation stimulation index	Cell count stimulation index	Lymph node weight stimulation index	Ear weight stimulation index
vehicle control	1.00	1.00	1.00	1.00
1%	1.15	1.16	1.13	1.06*
5%	1.75*	1.29	1.10	1.11*
10%	3.21**	1.68*	1.49*	1.07
biologically relevant at	≥ 3	≥ 1.5	no data	≥ 1.25

Propylene glycol served as the vehicle.
*$p \leq 0.05$; **$p \leq 0.01$ (Wilcoxon test)

5.4.1.2 In vitro studies

To estimate the sensitizing potential of *N*-(2-hydroxyethyl)piperidine, tests for protein reactivity ("direct peptide reactivity assay", DPRA), for the activation of keratinocytes (LuSens) and for the activation of dendritic cells ("human cell line activation test", h-CLAT) were carried out.

In the DPRA according to OECD Test Guideline 442C, the reactivity of the test substance towards cysteine and lysine peptides is tested. The mean depletion of the cysteine and lysine peptide caused by *N*-(2-hydroxyethyl)piperidine was 4.24% and 0.42%, respectively. Thus, the threshold values for a positive DPRA prediction (> 6.38% for the cysteine peptide and > 13.89% for the lysine peptide) were not reached and the test result was regarded as negative (BASF SE 2018 a).

Eight concentrations were tested in a LuSens assay according to OECD Test Guideline 442D. The calculated concentration needed to increase luciferase activity by 50% (EC1.5) was 206 µM and 530 µM, respectively, in two of three experiments performed, and met the criteria for a positive result (BASF SE 2018 a).

Eight concentrations were tested in an h-CLAT according to OECD Test Guideline 442E. A 100% increase in CD54 was achieved in 2 experiments at concentrations of 482 and 710 µg/ml and a 50% increase in CD86 was achieved in 1 experiment at a concentration of 1032 µg/ml. Thus, the result for *N*-(2-hydroxyethyl)piperidine is to be regarded as positive (BASF SE 2018 a).

5.4.2 Sensitizing effects on the airways

There are no studies available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In the study with the reproductive/developmental toxicity screening test described in Section 5.2.2, which was carried out according to OECD Test Guideline 422 in Wistar rats given daily gavage doses of *N*-(2-hydroxyethyl)piperidine, there were no effects on fertility up to 250 mg/kg body weight and day. This is therefore the NOAEL for fertility (BASF SE 2018 a).

5.5.2 Developmental toxicity

In the study described in Section 5.2.2 which was carried out according to OECD Test Guideline 422 in Wistar rats given daily gavage doses of *N*-(2-hydroxyethyl)piperidine, an increased number of postimplantation losses and, in the dams, decreased food and water intake and delayed body weight gains were observed at the highest dose tested of 250 mg/kg body weight and day. The NOAEL for maternal and developmental toxicity was the middle dose of 75 mg/kg body weight and day (BASF SE 2019 a). Since this type of study does not fully investigate teratogenicity, this study is not sufficient to assess the developmental toxicity of the substance.

5.6 Genotoxicity

5.6.1 In vitro

In a study carried out according to OECD Test Guideline 471, the potential of *N*-(2-hydroxyethyl)piperidine (purity ≥ 99.8%) to induce point mutations was investigated in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 as well as in Escherichia coli WP2 uvrA using the plate incorporation and the preincubation method at concentrations of 33 to 5000 µg/plate with and without metabolic activation by rat liver S9 mix. No precipitation of the substance occurred in the preparations and cytotoxicity was observed only in the preincubation test at and above 1000 µg/plate. No significantly increased mutation frequencies (at least factor 2 in the strains TA98, TA100, Escherichia coli or factor 3

in the strains TA1535, TA1537) were observed. *N*-(2-Hydroxyethyl)piperidine was not mutagenic in this test system, the positive controls yielded the expected results (BASF SE 2018 b).

In an in vitro micronucleus test carried out according to OECD Test Guideline 487 in human lymphocytes in the presence and absence of a metabolic activation system, *N*-(2-hydroxyethyl)piperidine (purity ≥ 99.8%) did not lead to a statistically significant increase in the incidence of micronuclei at concentrations up to 1300 µg/ml (corresponding to about 10 mM) after incubation for 4 hours. The result after incubation for 20 hours in the absence of a metabolic activation system was likewise negative. No cytotoxicity occurred. The positive control confirmed an intact test system (Envigo 2018).

In an HPRT (hypoxanthine guanine phosphoribosyl transferase) assay in CHO cells (a cell line derived from Chinese hamster ovary) carried out according to OECD Test Guideline 476, *N*-(2-hydroxyethyl)piperidine (purity ≥ 99.8%) did not increase the mutation frequency after incubation for 4 hours with concentrations up to 1300 µg/ml (corresponding to about 10 mM) with and without metabolic activation by rat liver S9 mix. The weakly positive result in the first test with metabolic activation was not confirmed in a second test. Only slight cytotoxicity occurred with a minimum level of survival of at least 65% of the cells. The positive controls yielded the expected results (BASF SE 2019 b).

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

There are no data available.

6 Manifesto (MAK value/classification)

There are no data in humans and no inhalation studies in animals. *N*-(2-Hydroxyethyl)piperidine is corrosive to the skin of rabbits. Therefore, local irritation of the respiratory tract is likely to be the main effect after inhalation exposure.

MAK value. In a study in Wistar rats according to OECD Test Guideline 422, daily administration of 250 mg/kg body weight and day by gavage for 9 weeks resulted in decreased food and water intake and decreased body weight gains in the females. There were no signs of irritation in the forestomach. This was the highest dose used and the NOAEL for males, the NOAEL for females was 75 mg/kg body weight and day (BASF SE 2019 a).

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 75 mg/kg body weight and day to a concentration in workplace air: the daily exposure of the animals compared with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The resulting concentration is 184 mg/m^3. Taking into consideration extrapolation to chronic exposure (1:4; study duration between subacute and subchronic) and extrapolation of the data from an animal experiment to humans (1:2), a corresponding concentration of 23 mg/m^3 (4.3 ml/m^3) is calculated. However, this calculated concentration appears to be too high as a MAK value because *N*-(2-hydroxyethyl)piperidine is corrosive to the skin. As there are no inhalation studies available, the MAK value has been derived in analogy to that for 2-diethylaminoethanol:

Both substances are tertiary amines, are liquid at room temperature and miscible with water, and have vapour pressures of similar magnitude (0.217 hPa for *N*-(2-hydroxyethyl)piperidine, 1.9 hPa for 2-diethylaminoethanol) and a similar pKa value at 25 °C (9.54 for *N*-(2-hydroxyethyl)piperidine, 10.1 for 2-diethylaminoethanol). In skin irritation studies according to OECD Test Guideline 404, 2-diethylaminoethanol had a slightly stronger effect than *N*-(2-hydroxyethyl)piperidine, although this does not necessarily allow a conclusion to be drawn about the effect on the respiratory tract. However, a 13-week inhalation study with 2-diethylaminoethanol in F344 rats is available, in which a NOAEC (no observed adverse effect concentration) of 11 ml/m^3 was obtained for local effects on the respiratory tract. From this, a MAK value of

2 ml/m³ was derived for 2-diethylaminoethanol (Hartwig and MAK Commission 2024), which has been adopted for *N*-(2-hydroxyethyl)piperidine. At a MAK value of 2 ml *N*-(2-hydroxyethyl)piperidine/m³, irritant effects on the respiratory tract should therefore not occur.

Diethylamine likewise has a MAK value of 2 ml/m³, derived from a 2-year inhalation study with a calculated NAEC (no adverse effect concentration) ($BMDL_{05}$) of 4 ml/m³ for mice (Hartwig and MAK Commission 2018).

Peak limitation. As *N*-(2-hydroxyethyl)piperidine is an irritant substance, it is assigned to Peak Limitation Category I. There is no information available on irritant effects in humans, therefore the default excursion factor of 1 has been set for peak limitation. In analogy to that for other aliphatic amines with a MAK value of 2 ml/m³ (for example *n*-butylamine, cyclohexylamine), a momentary value of 5 ml *N*-(2-hydroxyethyl)piperidine/m³ has been set.

Prenatal toxicity. In a screening study for reproductive/developmental toxicity according to OECD Test Guideline 422 with daily gavage administration of *N*-(2-hydroxyethyl)piperidine to Wistar rats, the highest dose tested of 250 mg/kg body weight and day resulted in an increased number of postimplantation losses and in reduced food and water intake and delayed body weight gains in the dams (BASF SE 2019 a). As this study did not fully investigate teratogenicity, it is insufficient to assess developmental toxicity. *N*-(2-Hydroxyethyl)piperidine is therefore assigned to Pregnancy Risk Group D.

Carcinogenicity. No carcinogenicity studies have been conducted with *N*-(2-hydroxyethyl)piperidine. The available data do not suggest the substance has carcinogenic effects and *N*-(2-hydroxyethyl)piperidine is not classified in one of the categories for carcinogens.

Germ cell mutagenicity. The studies of genotoxicity in vitro yielded negative results, studies in vivo are not available. Genotoxic effects are not expected from the structure of the substance. *N*-(2-Hydroxyethyl)piperidine is therefore not classified in one of the categories for germ cell mutagens.

Absorption through the skin. For humans, using mathematical models (Section 3), dermal absorption of 3.2 or 0.6 mg were calculated (with consideration of skin pH value) and of 57.0 or 10.1 mg (without consideration) for the exposure of 2000 cm² of skin to a 0.5% non-irritant solution for 1 hour.

To assess the calculated dermal absorption, the systemic NOAEL of 75 mg/kg body weight and day, which was determined after the administration of daily oral doses to rats for 8 weeks, is used. From this, a concentration at the workplace of 23 mg/m³ is extrapolated for humans (see "MAK value"). From this value, a systemically tolerable amount of 230 mg can be derived for a respiratory volume of 10 m³ and 100% absorption.

Within the skin barrier (corneal layer) with its acidic environment in some parts, the substance may be protonated, thereby decreasing the amount of absorbable non-protonated substance and thus reducing its absorption through the skin. Thus, the 57 mg calculated with the model of Fiserova-Bergerova could be an overestimation.

Absorption through the skin thus contributes less than 25% of the systemically tolerable amount. *N*-(2-Hydroxyethyl)piperidine is therefore not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. A positive result from a local lymph node assay in mice and positive results in two in vitro test procedures indicate that *N*-(2-hydroxyethyl)piperidine has skin sensitizing potential. The substance has therefore been designated with "Sh" (for substances which cause sensitization of the skin). There are no studies for respiratory sensitization; therefore, the substance has not been designated with "Sa" (for substances which cause sensitization of the airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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