The MAK Collection for Occupational Health and Safety

1,2,4-Triethylbenzene

MAK Value Documentation – Translation of the German version from 2018

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1,2,4-Triethylbenzene[1)]

MAK value documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated 1,2,4-triethylbenzene [877-44-1], considering all toxicological endpoints. Available publications are described in detail. In subchronic oral studies 1,2,4-triethylbenzene causes axonopathy of peripheral nerves in rats and mice. A NOAEL was not obtained. The structurally related 1,2-diethylbenzene leads to the same neurotoxic effects which are determined by oxidation of the 1,2-diethyl groups to a gamma-diketone. The formation of a gamma-diketone is possible and indirectly shown with 1,2,4-triethylbenzene and the mechanism of neurotoxicity is assumed to be the same for both compounds. Due to the limited data with 1,2,4-triethylbenzene, the better investigated 1,2-diethylbenzene, which is about 5 times as toxic, is used as a read-across. As a maximum concentration at the work place (MAK value) of 1 ml/m^3 has been set for 1,2-diethylbenzene, a MAK value of 5 ml/m^3 for 1,2,4-triethylbenzene is established.

Since a systemic effect is critical, Peak Limitation Category II is designated. Peripheral neurotoxicity is a cumulative effect and an excursion factor of 8 would be adequate. However, the NOEAC for airway and eye irritation is not known and therefore an excursion factor of 2 is set. Thus, the allowable peak exposures are lower than those of other alkyl benzenes.

There are no developmental toxicity studies. Therefore, 1,2,4-triethylbenzene is assigned to Pregnancy Risk Group D. There are no data on genotoxicity, carcinogenicity and sensitization. According to skin absorption models, percutaneous absorption can contribute significantly to systemic toxicity and 1,2,4-triethylbenzene is designated with an "H" notation.

Keywords

1,2,4-triethylbenzene; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance; peripheral neurotoxicity; axonopathy

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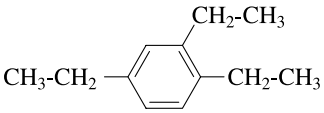
1) The substance can occur simultaneously as vapour and aerosol.

1,2,4-Triethylbenzene[1)]

MAK value (2017)	**5 ml/m³ (ppm) ≙ 34 mg/m³**
Peak limitation (2017)	**Category II, excursion factor 2**
Absorption through the skin (2017)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2017)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	–
Chemical name	1,2,4-triethylbenzene
CAS number	877-44-1
Structural formula	
Molecular formula	$C_{12}H_{18}$
Molar mass	162.28 g/mol
Melting point	–78 °C (Reagent World 2016)
Boiling point at 1004 hPa	217.5 °C (NLM 2016)
Density at 20 °C	0.872 g/cm³ (Reagent World 2016)
Vapour pressure at 25 °C	0.193 hPa (calculated; SRC 2016)
log K_{OW}[2)]	5.11 (calculated; SRC 2016)
Solubility at 25 °C	2.9 mg/l water (calculated; SRC 2016)
1 ml/m³ (ppm) ≙ 6.734 mg/m³	**1 mg/m³ ≙ 0.149 ml/m³ (ppm)**

Triethylbenzenes (all isomers) (CAS number 25340-18-5) are used as laboratory chemicals (NLM 2016). This documentation evaluates 1,2,4-triethylbenzene because it is a constituent of kerosene and aromatic solvents. The military fuel Jet

1) The substance can occur simultaneously as vapour and aerosol.

2) octanol/water partition coefficient

Fuel JP5 contains a fraction of 0.72% by weight of 1,2,4-triethylbenzene, the Jet Fuel JP8 a fraction of 0.99% by weight. Assuming that the density of the two fuels is about 0.8 kg/l (ATSDR 2016), this would be equivalent to 5.8 g and 7.9 g of 1,2,4-triethylbenzene per litre of fuel.

1 Toxic Effects and Mode of Action

1,2,4-Triethylbenzene induced axonopathy of the peripheral nerves in rats and mice after subchronic oral exposure to doses of 200 and 300 mg/kg body weight and day and above. Other effects have not been investigated.

2 Mechanism of Action

The neurotoxic effects of 1,2,4-triethylbenzene are probably caused by a reaction between the gamma-diketone metabolite 1,2-diacetyl-4-ethylbenzene and the epsilon-amino groups or sulfhydryl groups of neuroproteins of the axonal cytoskeleton. This leads to the segregation of cytoskeletal elements with clustering of microtubules and organelles and to the accumulation of maloriented neurofilaments in the proximal part of the axon by cross-linkage. Axonal swelling is thereby induced, resulting in decreased nerve conduction velocity and reduced sensory action potential amplitudes. This mechanism corresponds to that of the gamma-diketones of hexane and 1,2-diethylbenzene. The histological picture after administration of 1,2,4-triethylbenzene is similar to that after administration of 1,2-diethylbenzene (documentation "Diethylbenzene (all isomers)" 2018). The cause of the electrophysiological findings remains unclear. The isomer 1,3,5-triethylbenzene is not neurotoxic because it does not form a gamma-diketone (Tshala-Katumbay et al. 2006).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

No data are available for 1,2,4-triethylbenzene.

Oral absorption of 90% is assumed by analogy with diethylbenzene (documentation "Diethylbenzene (all isomers)" 2018). As no data are available for the absorption of diethylbenzene by inhalation, 60% absorption by inhalation is assumed for 1,2,4-triethylbenzene by analogy with ethylbenzene (supplement "Ethylbenzene" 2012).

Flux values of 284, 2.3 and 0.36 µg/cm^2 and hour, respectively, were calculated for a saturated aqueous solution using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995). Assuming the exposure of 2000 cm^2 of skin for one hour, dermal absorption was estimated to be 568, 4.6 and 0.72 mg.

3.2 Metabolism

The metabolism of 1,2,4-triethylbenzene has not been investigated. 1,2,4-Triethylbenzene can be metabolized at all three ethyl groups. A likely scenario would be the oxidation of the two ortho-positioned ethyl groups at the omega-1 position to form a gamma-diketone such as 1,2-diacetyl-4-ethylbenzene. Although this metabolite has not been identified, 1,2-diethylbenzene is known to be metabolized to the gamma-diketone 1,2-diacetylbenzene. This reacts with lysine in proteins, forming blue pigments which lead to blue discoloration of the skin and organs of animals (documentation "Diethylbenzene (all isomers)" 2018). This was observed also after exposure of rats and mice to 1,2,4-triethylbenzene and can be considered to be indirect proof of the metabolism of 1,2,4-triethylbenzene to the gamma-diketone. No gamma-diketone is formed from 1,3,5-triethylbenzene. Therefore, the substance does not lead to blue discoloration of the skin and neurotoxic effects (Gagnaire et al. 1993; Tshala-Katumbay et al. 2006).

4 Effects in Humans

A case study described a 35-year-old man with occupational exposure to lead carboxylate, triethylbenzene (no other details of the isomer), xylene and dichloromethane (no other details) who developed subacute sensory neuropathy. A biopsy of the peripheral nerves found axonal degeneration and unusual myelin lesions, but not the axonal swelling typical for gamma-diketones. The authors suggested that the findings could have been induced by any of the solvents used (Vital et al. 2006). Thus, the role triethylbenzene played in inducing the effects is unclear.

5 Animal Experiments and in vitro Studies

There are no data available for the end points sensitization, reproductive toxicity, genotoxicity and carcinogenicity.

5.1 Acute toxicity

There are no data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

Groups of 10 to 12 Sprague Dawley rats (sex not specified) were given gavage doses of 1,2,4-triethylbenzene of 0, 200 or 400 mg/kg body weight and day, on 4 days a week, for 8 weeks, beginning at 11 weeks of age and were then observed for a period of 8 weeks after the end of exposure. After 2 days, the skin turned a bluish colour and the urine greyish-green. A dose-dependent decrease in body weight gains was observed. Gait disorders developed after 6 weeks. Tail motor and sensory nerve conduction velocities and the sensory action potential amplitude and muscle action potential amplitude were reduced in comparison with the values for the control animals. These effects were not completely reversible after a recovery period of 8 weeks. A NOAEL (no observed adverse effect level) was not determined, the LOAEL (lowest observed adverse effect level) was 200 mg/kg body weight and day. Investigated under the same conditions, 1,3,5-triethylbenzene caused neither this kind of discoloration nor neurotoxic effects; also the development of body weights was normal. The NOAEL for 1,3,5-triethylbenzene was 400 mg/kg body weight and day (Gagnaire et al. 1993).

The neurotoxicity of the structurally similar 1,2-diethylbenzene is more pronounced; an oral dose of 100 mg/kg body weight and day given to rats of the same strain on 4 days a week for 8 weeks induced hind leg weakness and, in individual animals, complete paralysis and mortality (Gagnaire et al. 1990, 1993).

Groups of 3 C57Bl/6 mice were given gavage doses of 1,2,4-triethylbenzene of 0, 300, 600 or 900 mg/kg body weight and day, on 3 days a week for 12 weeks. Histopathological examination of the central and peripheral nervous systems was carried out. Bluish-green discoloration of the urine, the brain, the spinal medulla and the peripheral nerves was observed. At 600 mg/kg body weight and day, the weight gain of the animals was almost negligible, at 900 mg/kg body weight and day, a loss of body weight was observed during the study period. Dose-dependent muscle spasms, limb weakness and gait disorders were observed in all treated animals. At 300 mg/kg body weight, the first signs were observed after 8 weeks; they occurred earlier at higher doses. At 300 mg/kg body weight and day and above, disorganization of the axonal cytoskeleton with clustering of microtubules and organelles were observed in the distal sciatic nerves. The development of giant axonal swellings in lumbar ventral roots, dorsal root ganglia and, at 900 mg/kg body weight, also in the anterior horns, was dependent upon time and the dose. Intraspinal swollen axons were tightly packed with maloriented 10-nm neurofilaments. Axonal swellings were observed also in the cervical anterior horns and the lower medulla oblongata, proximal to the hypoglossal nucleus. No changes were found in the cerebellum, hippocampus, basal ganglia and frontal cortex. A NOAEL was not determined, the LOAEL was 300 mg/kg body weight and day. Investigated under the same conditions, 1,3,5-triethylbenzene induced neither discoloration nor any of the above-mentioned findings; the NOAEL was 900 mg/kg body weight and day (Tshala-Katumbay et al. 2006).

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

The structurally similar diethylbenzenes cause severe irritation of the skin (documentation "Diethylbenzene (all isomers)" 2018); similar effects are therefore assumed also for 1,2,4-triethylbenzene.

5.3.2 Eyes

The structurally similar diethylbenzenes do not cause irritation of the eyes (documentation "Diethylbenzene (all isomers)" 2018); therefore, this is assumed also for 1,2,4-triethylbenzene.

6 Manifesto (MAK value/classification)

No systemic toxic end points other than peripheral neurotoxicity were examined. As has been shown for 1,2-diethylbenzene, peripheral neurotoxicity is assumed to be the critical effect also for 1,2,4-triethylbenzene. This effect is very probably caused by a gamma-diketone that is formed during metabolism, such as 1,2-diacetyl-4-ethylbenzene.

MAK value. The LOAEL for neurotoxic effects (clinical and electrophysiological) was 200 mg/kg body weight and day after 1,2,4-triethylbenzene was given to rats by gavage for 8 weeks. A NOAEL was not determined. In comparison with 1,2-diethylbenzene, 1,2,4-triethylbenzene induces less severe neurotoxic effects in rats; exposure to a 1,2-diethylbenzene dose of 100 mg/kg body weight and day caused effects ranging from hind limb weakness to complete paralysis, but after exposure to a 1,2,4-triethylbenzene dose of 400 mg/kg body weight and day only gait disorders were observed (Gagnaire et al. 1990, 1993). It can be concluded from this that 1,2-diethylbenzene is at least 5 times as toxic as 1,2,4-triethylbenzene after oral administration. This difference may be due to the presence of the third ethyl group in 1,2,4-triethylbenzene with an additional possibility of metabolization and thus detoxification.

A MAK value of 1 ml/m^3 (documentation "Diethylbenzene (all isomers)" 2018) was derived for 1,2-diethylbenzene on the basis of its neurotoxic effects. As the substance is 5 times as toxic as 1,2,4-triethylbenzene, a MAK value of 5 ml/m^3 has been established for 1,2,4-triethylbenzene. Since neurotoxicity is expected to be the most sensitive effect, as is the case for 1,2-diethylbenzene, the MAK value thus provides protection also against other systemic effects.

Peak limitation. In view of the systemic effects, 1,2,4-triethylbenzene is assigned to Peak Limitation Category II. Its critical effect is a cumulative long-term effect; therefore, it would be possible to assign an excursion factor of 8 by analogy with 1,2-diethylbenzene. However, as it has not been established whether irritant effects are induced at the corresponding concentration of 40 ml/m^3, the substance has been assigned the default excursion factor of 2. The permissible peak concentration of

10 ml/m³ is below the permissible peak concentrations of other alkyl aromatics such as ethylbenzene, styrene and trimethylbenzene.

Prenatal toxicity. There are no developmental toxicity studies available for 1,2,4-triethylbenzene.

The following factors are taken into account to determine whether a read-across can be applied to the diethylbenzene isomers: studies have not been carried out to investigate the metabolism of 1,2,4-triethylbenzene; there is indirect evidence that the gamma-diketone 1,2-diacetyl-4-ethylbenzene may be a possible metabolite (Section 3.2); in addition, the diethylbenzene isomers have different target organs. The primary effect induced by 1,2-diethylbenzene is peripheral neurotoxicity, while the primary effects of 1,3-diethylbenzene are an increase in liver and thyroid weights and in thyroid-stimulating hormone levels and the primary effects of 1,4-diethylbenzene are an increase in the level of urea nitrogen found in the blood, in alanine aminotransferase activity and in the kidney weights (documentation "Diethylbenzene (all isomers)" 2018). It is not possible to draw any conclusions by analogy with the diethylbenzene isomers because no data are available for the metabolism of 1,2,4-triethylbenzene and the three diethylbenzene isomers have different toxicological end points. 1,2,4-Triethylbenzene has therefore been classified in Pregnancy Risk Group D.

Germ cell mutagenicity and carcinogenicity. There are no data available; therefore, no classification has been made.

Absorption through the skin. Due to the lack of data in vitro or in vivo, the absorption of the substance through the skin is estimated on the basis of mathematical models. As the results for other alkyl aromatics obtained using the model of Fiserova-Bergerova et al. (1990) coincide better with the in vivo data available for these substances, this model is used to assess this group of substances. According to this model (Section 3.1), a maximum dermal absorption of 568 mg has been estimated for humans after exposure to a saturated aqueous solution and assuming exposure to 2000 cm² of skin for one hour.

Therefore, the uptake via the skin as calculated with the Fiserova-Bergerova model is higher than the 204 mg of 1,2,4-triethylbenzene that is absorbed after exposure at the level of the MAK value at a respiratory volume of 10 m³ and 60% absorption by inhalation. 1,2,4-Triethylbenzene has therefore been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data available. For this reason, 1,2,4-triethylbenzene has not been designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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