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TOXICOLOGICAL EVALUATIONS

BG RCI

Kurfürsten-Anlage 62 · D-69115 Heidelberg, Germany
Telefon: +49 6221 5108-28451
E-Mail: toxikologischebewertungen@bgrci.de
Internet: www.bgrci.de/toxicologicalevaluations

TOXICOLOGICAL EVALUATION

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Vinyl ethyl ether

No. 263

CAS No. 109-92-2

BG Chemie
Berufsgenossenschaft der chemischen Industrie

BG Chemie
P.O.B. 10 14 80, 69004 Heidelberg, Germany
Telephone: +49 (0) 6221 523 400
E-Mail: praevention@bgchemie.de
Internet: www.bgchemie.de

Vinyl ethyl ether

A Toxicological Evaluation of the structural homologue of vinyl ethyl ether, methoxyethene (vinyl methyl ether), has previously been published in volume 5 of the book series “Toxicological Evaluations” published by Springer.

1 Summary and assessment

On acute oral administration, dermal application and inhalation exposure, vinyl ethyl ether is found to be of low toxicity (LD_{50} rat oral 6153 mg/kg body weight; LD_{50} rabbit dermal > 15000 mg/kg body weight; LC_{50} rat, 4 hours, > 21200 mg/m³). The clinical signs of intoxication are characterised by the narcotic effect of the substance.

In rabbits, vinyl ethyl ether causes no or only very mild irritation to the skin and eye.

In the Salmonella/microsome assay, vinyl ethyl ether is found to test negative both with and without metabolic activation. In the SCE assay in Chinese hamster ovary cells, the chemical causes a significant increase in sister chromatid exchange rate. From a mouse micronucleus test carried out with the structurally related chemical methoxyethene (vinyl methyl ether) after 5-day inhalation exposure, there was no indication of a mutagenic effect in vivo.

In the 1950s, vinyl ethyl ether was studied in clinical trials to investigate whether it was suitable as an anaesthetic. Some patients participating in these studies suffered complications (generalised convulsions due to hypercarbia and respiratory and circulatory depression as well as respiratory and cardiac arrest), which were attributed to overdosage. The degree of muscle relaxation obtained with this type of anaesthesia was considered to be inadequate. Liver function tests conducted after several hours of anaesthesia showed that hepatic function was not affected. Urinalyses, blood counts and electrocardiograms obtained after anaesthesia revealed slight, reversible changes in some cases.

2 Name of substance

2.1	Usual name	Vinyl ethyl ether
2.2	IUPAC name	Ethoxyethene
2.3	CAS No.	109-92-2
2.4	EINECS No.	203-718-4

3 Synonyms, common and trade names

Agrisynth EVE
Ethene, ethoxy- (9CI)
Ether, ethyl vinyl (8CI)
Ethoxyethen
1-Ethoxyethene
Ethoxyethylen
Ethoxyethylene
1-Ethoxyethylene
Ethyloxyethene
Ethylvinylether
Ethyl vinyl ether
EVE
Vinamar
Vinyläthyläther
Vinylethylether

4 Structural and molecular formulae

4.1	Structural formula	$CH_3CH_2–O–CH=CH_2$
4.2	Molecular formula	C_4H_8O

5 Physical and chemical properties

5.1	Molecular mass, g/mol	72.11

5.2	Melting point, °C	Ca. –115 (EC, 1996) –115.4 (Hort and Taylor, 1991) –115.8 (Lide and Frederikse, 1996)
5.3	Boiling point, °C	36 (at 1013 hPa) (EC, 1996) 35.5 (Lide and Frederikse, 1996) 35.7 (Hort and Taylor, 1991)
5.4	Vapour pressure, hPa	62.3 (at –25 °C) (Lide and Frederikse, 1996) 231 (at 0 °C) (Lide and Frederikse, 1996) 560 (at 20 °C) (EC, 1996) 570 (at 20 °C) (Hort and Taylor, 1991) 688 (at 25 °C) (Lide and Frederikse, 1996) 813 (at 30 °C) (EC, 1996)
5.5	Density, g/cm³	0.754 (at 20 °C) (EC, 1996) 0.7541 (Hort and Taylor, 1991) 0.7589 (at 20 °C) (Lide and Frederikse, 1996)
5.6	Solubility in water	8.3 g/l (at 15 °C) (EC, 1996) Low (Lide and Frederikse, 1996) 0.9% (w/w) (Hort and Taylor, 1991)
5.7	Solubility in organic solvents	Soluble in ethanol and tetrachloromethane, miscible with ethyl ether (Lide and Frederikse, 1996) Miscible with most organic solvents (Hort and Taylor, 1991)
5.8	Solubility in fat	Partition coefficient n-octanol/water, log P_{ow}: 1.63 (at 25 °C) (EC, 1996)
5.9	pH value	No information available
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 2.94 mg/m³ 1 mg/m³ ≙ 0.34 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

As an intermediate; monomer for synthesis of polymers (adhesives; BASF, 1992 a).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

Oral administration

For vinyl ethyl ether, an oral LD_{50} of 8.16 ml/kg body weight (equivalent to 6153 mg/kg body weight) was ascertained in male rats (Carworth-Wistar, body weight 90 to 120 g) within a 14-day observation period (no further details; Smyth et al., 1969).

Dermal application

The dermal LD_{50} for rabbits found after a 14-day observation period was given as > 20 ml/kg body weight (equivalent to > 15000 mg/kg body weight; Smyth et al., 1969).

A further LD_{50} value for rats was reported as > 20000 mg/kg body weight following dermal application (no further details; GAF, year not given).

Inhalation administration

The acute inhalation toxicity data for vinyl ethyl ether are summarised in Table 1 below. The data show the chemical to be of low toxicity.

Beginning of Table 1

Table 1. Acute inhalation toxicity of vinyl ethyl ether

Species, strain*	Sex	Duration of exposure	Observation period	LC_{50}	Effects	Reference
Rat, SPF-Wistar	male/ female	4 hours	14 days	> 21200 mg/m³		BASF, 1988 a
Rat, Sherman	male/ female	4 hours	14 days		at 16000 ppm (equivalent to 47000 mg/m³) 2 to 4 out of 6 animals died	Carpenter et al., 1949

Table 1. Acute inhalation toxicity of vinyl ethyl ether						
Species, strain*	Sex	Duration of exposure	Observation period	LC_{50}	Effects	Reference
Rat	no information	4 hours	14 days	> 188000 mg/m³	at 64000 ppm (equivalent to 188000 mg/m³) 0 out of 6 animals died	Smyth et al., 1969
Mouse	no information	15 minutes	no information	4.5 mmol/l (≙ 325000 mg/m³) LC_{1-5} 3.5 mmol/l (≙ 252000 mg/m³)	concentration at which 9 to 11 out of 20 animals died concentration at which 1 out of 20 animals died	Marsh and Leake, 1950
Mouse	no information	10 minutes	no information		16% (v/v): lowest concentration which caused respiratory arrest; 6% (v/v): narcosis	Mörch et al., 1956
Mouse	no information	10 minutes	no information		16.5% (v/v): concentration which caused respiratory arrest in 50% of animals within 5 minutes	Park et al., 1957
Rabbit	no information	22 minutes	–		500000 mg/m³ lethal after 22 minutes	I.G. Farben, 1930
Guinea pig	no information	17 minutes	–		663000 mg/m³ lethal after 17 minutes	I.G. Farben, 1930
Cat	no information	17 minutes	–		663000 mg/m³ lethal after 17 minutes	I.G. Farben, 1930
Rhesus monkey	male/ female	no information	no information		1.29 ml/kg body weight (given by the authors as ml/kg body weight): mean dose to result in respiratory arrest	Park et al., 1957
Dog	male/ female	no information	no information		1.7 ml/kg body weight (given by the authors as ml/kg body weight): respiratory arrest	Krantz et al., 1947
* where indicated						

End of Table 1

7.3 Skin and mucous membrane effects

Vinyl ethyl ether (no indication of purity) was tested for acute skin irritation in 3 rabbits (“Weiße Wiener”; 2 males, 1 female) in accordance with OECD guideline No. 404. The animals had 0.5 ml of the undiluted test substance semi-occlusively applied to the dorsal and flank skin for 4 hours. The effects were assessed 30 to 60 minutes upon removal of the patch as well as 24, 48 and 72 hours after the beginning of exposure. No skin changes were observed at any time point of inspection (BASF, 1988 b). The chemical thus proved not to be irritating to the skin (BASF, 1992 a).

When applied to the shorn abdominal skin of 5 albino rabbits, a 24-hour uncovered application of 0.01 ml undiluted vinyl ethyl ether produced no irritant effects within 24 hours (no further details; Smyth et al., 1969).

A 500 mg application of vinyl ethyl ether to the uncovered rabbit skin caused mild irritation (no further details; UCC, 1971).

The eye irritancy of vinyl ethyl ether (no indication of purity) was investigated in 3 rabbits ("Weiße Wiener"; 2 males, 1 female) in accordance with OECD guideline No. 405. The animals had 0.1 ml of the undiluted substance instilled into the conjunctival sac of one eye. The effects were assessed 1, 24, 48 and 72 hours following instillation. The conjunctivae showed mild to moderate reddening and slight swelling after 1 to 24 hours. Furthermore, there was a slight to moderate increase in secretion. The findings cleared up after 48 hours (BASF, 1988 c). The chemical was evaluated as non-irritating to the eye (BASF, 1992 a).

Instillation of 0.5 ml undiluted vinyl ethyl ether into the rabbit eye produced mild irritation (grade 1 on an ascending 10-point irritancy scale; no further details; Smyth et al., 1969).

7.4 Sensitisation

No information available.

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

In the Salmonella/microsome assay (standard-plate incorporation test and preincubation test) using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537, vinyl ethyl ether (99.8% pure; dissolved in distilled water) gave negative results at concentration levels of 20 to 5000 µg/plate, both with and without metabolic activation (S9 mix from Aroclor 1254-indu-

ced livers of male Sprague-Dawley rats). No bacteriotoxic effect was observed (BASF, 1992 b).

In a further Salmonella/microsome assay, vinyl ethyl ether (99.8% pure; dissolved in distilled water) was tested on the *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 in a desiccator. The test was carried out in the presence and absence of metabolic activation (S9 mix from Aroclor 1254-induced livers of male Sprague-Dawley rats). The test concentrations used were 2500 and 5000 µg/plate. In addition, 6 ml vinyl ethyl ether were introduced into the desiccator in order to produce a saturated atmosphere. No bacteriotoxic effect was observed and there was no increase in revertant counts. Vinyl ethyl ether thus also proved to be devoid of mutagenic activity under these experimental conditions (BASF, 1993).

A solution of vinyl ethyl ether in DMSO was tested in the Salmonella/microsome assay with preincubation for its mutagenic potential in *Salmonella typhimurium* strain TA 100. In the presence of a metabolic activation system (S9 mix from the livers of male Wistar rats induced with polychlorinated biphenyls), no significant increase in revertant counts was observed (no details as to the concentrations employed; Sone et al., 1989).

Furthermore, vinyl ethyl ether was tested for mutagenicity in Chinese hamster ovary cells (CHO) in the sister chromatid exchange (SCE) assay. Vinyl ethyl ether was delivered to CHO cells in their culture flasks for 2 minutes at a concentration level of 1.79% (v/v) in a gas mixture containing 5% carbon dioxide and 19% oxygen, the balance being nitrogen. Subsequently, the flasks were capped and incubated at 37 °C for one hour. Vinyl ethyl ether increased sister chromatid exchanges to significantly above the levels of the controls (vinyl ethyl ether 1.338 ± 0.031 SCEs/chromosome, control 0.536 ± 0.018 SCEs/chromosome). The authors suggested that this effect might be attributable to the reactivity of the vinyl group (White et al., 1979).

7.6.2 In vivo

No information available.

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

No information available.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

In order to investigate the biotransformation-dependent toxicity of vinyl ethyl ether, groups of male Swiss-Webster mice (15 to 18 mice/group, body weight range 25 to 30 g) received 0.25 mg phenobarbital/ml in their drinking water for 5 days to induce their microsomal enzymes, or they were pretreated with a subcutaneous injection of 0.2 ml of a 20-percent oily tetrachloromethane solution 24 hours prior to anaesthesia to inhibit the microsomal enzymes. The mice were placed under light anaesthesia by inhalation of vinyl ethyl ether (no details of the concentration administered). Even after 6 hours of anaesthesia, there were no deaths in either pretreatment group within 30 hours of awakening from anaesthesia (Cascorbi et al., 1974).

Two-hour anaesthesia with vinyl ethyl ether (no details of the concentration administered) was survived by all male rats in another study (no details of strain or number; body weight range 175 to 300 g). Histological examination of the animals which were sacrificed 24 hours after anaesthesia revealed unspecific hydropic changes in the hepatocytes, such as those that were also observed in the controls. Following 3-day pretreatment with phenobarbital at 80 mg/kg body weight/day, which was injected intraperitoneally, all 9 rats in the study survived the vinyl ethyl ether anaesthesia. Histologi-

cally, 2 out of 9 rats were found to have unspecific periportal hydropic degeneration of the hepatocytes. There was no necrosis. According to the investigators, vinyl ethyl ether was no more toxic in phenobarbital-induced rat livers than it was in livers without pretreatment, a finding which was contrary to the results obtained for trifluoroethyl vinyl ether and trifluoroethyl ethyl ether, which were investigated in parallel (Marsh et al., 1975).

Two 3-hour inhalation exposures to vinyl ethyl ether at concentration levels capable of inducing anaesthesia (no further details) were survived without clinical manifestations of toxicity by both untreated and pretreated male Sprague-Dawley rats (body weight range 200 to 300 g, 10 untreated rats, 9 rats intraperitoneally pretreated with 80 mg phenobarbital/kg body weight/day for 3 days). In 2 pretreated rats and in 5 rats without enzyme induction, periportal hydropic degeneration in the hepatocytes occurred (Harrison et al., 1976). In this study, again, vinyl ethyl ether was no more toxic in phenobarbital-induced rat livers than it was in livers without pretreatment, a finding which was contrary to the results obtained for trifluoroethyl vinyl ether and trifluoroethyl ethyl ether, which were investigated in parallel.

In mice, inhalation of vinyl ethyl ether at concentration levels of and above 3.6% (v/v) for a period of 10 minutes induced anaesthesia (Marsh and Leake, 1950).

For *Macacus rhesus* monkeys, the mean anaesthetic index for induction of anaesthesia was determined as 0.37 ± 0.12 ml/kg body weight (Park et al., 1957).

In order to assess liver function in 2 dogs and 2 monkeys *(Macacus rhesus)* 24 hours after 60-minute anaesthesia with vinyl ethyl ether (no details of the concentration administered), a bromosulphthalein test was carried out. The dye excretion was not significantly different from the preanaesthetic control rate (Krantz et al., 1947).

Three dogs (no further details) and 2 monkeys *(Macacus rhesus)* were anaesthetised with vinyl ethyl ether for 60 minutes each on 3 alternate days. On the fifth day after the first anaesthesia, liver biopsies were performed. No significant histopathological changes were observed in the liver (Krantz et al., 1947).

Two dogs (no further details) and 2 monkeys *(Macacus rhesus)* had blood samples taken for analysis prior to and 24 hours after 60-minute anaesthesia with vinyl ethyl ether. The CO_2 binding capacity and blood urea concentration were not significantly altered by the anaesthesia in either species (Krantz et al., 1947).

The clotting time of blood was ascertained in 2 monkeys *(Macacus rhesus)* by the capillary tube method. Under anaesthesia with vinyl ethyl ether (no details of the concentration administered), it was found that in both animals the clotting time increased 10 to 15% as compared with a clotting time of approx. one minute observed in untreated animals (Krantz et al., 1947).

In female Sheffield rats (body weight range 190 to 210 g) which were anaesthetised with ethyl carbamate (1250 mg/kg body weight, intraperitoneal injection), inhalation of vinyl ethyl ether (no details of the concentration administered) resulted in a dose-dependent increase in the latency and a decrease in the amplitudes of evoked cortical responses during anaesthesia (Angel and Gratton, 1982).

In an electroencephalographical study performed in one dog, anaesthesia with vinyl ethyl ether produced the same changes in recordings from various areas of the brain as those seen under anaesthesia with diethyl ether (no further details; Krantz et al., 1947).

In order to investigate the induction of drug-metabolising enzymes by vinyl ethyl ether, male Sprague-Dawley rats (body weight range 40 to 60 g) underwent one 7-hour exposure to a subnarcotic vinyl ethyl ether concentration of 0.9% or two such exposures on consecutive days. Twenty to 22 hours after the last exposure, hexobarbital sleeping time was determined (125 mg hexobarbital/kg body weight, intraperitoneal injection). Following single exposure, vinyl ethyl ether did not significantly reduce hexobarbital sleeping time, whereas reduction was significant after two days' exposure. The investigators concluded from these results that drug-metabolising enzymes are stimulated by vinyl ethyl ether (Linde and Berman, 1971).

In an in situ preparation of the gastrocnemius muscle of the dog, vinyl ethyl ether was studied with regard to its muscle-relaxing action. Under anaesthesia with vinyl ethyl ether (no details of the concentration administered), a reduction in contraction amplitudes occurred under electrical stimulation of the muscle via the sciatic nerve. The degree of the curarimime-

tic action of vinyl ethyl ether was judged as being limited in comparison with diethyl ether (Park et al., 1957).

When cardiac monitoring was carried out in 2 dogs and 2 rhesus monkeys under various levels of anaesthesia with vinyl ethyl ether, no significant abnormalities were observed. During anaesthesia of 20 minutes' duration, the ECG tracings which are typical of anaesthesia were seen (no further details; Krantz et al., 1947).

To assess the haemolytic action of vinyl ethyl ether, the chemical was added in varying concentrations in normal salt solution to defibrinated dog's blood and incubated at 25 °C for 24 hours. Concentrations of 10, 25 and 50 mg% (mg/100 ml) did not produce haemolysis. A saturated solution of vinyl ethyl ether in normal salt solution resulted in haemolysis and methaemoglobin formation (no further details; Krantz et al., 1947).

In the isolated guinea pig ileum suspended in aerated Tyrode physiological solution at 37 °C, the agonist carbachol elicited a submaximal response. Vinyl ethyl ether inhibited the carbachol-induced response at an ID_{50} (inhibitory dose) of $62.2 \pm 0.7 \times 10^{-3}$ mol/l, a finding which was interpreted as a carminative effect (Evans et al., 1978).

When studied in phenobarbital-induced microsomes from livers of male Wistar rats (body weight 180 to 220 g, 80 mg phenobarbital/kg body weight/day, 3-day intraperitoneal administration, microsomes isolated by gel filtration), vinyl ethyl ether (no details of the concentration used) caused no destruction of cytochrome P-450 following a 30-minute incubation period at 30 °C (Ivanetich et al., 1977).

In in vitro studies, 42 mM vinyl ethyl ether caused no destruction of microsomal cytochrome P-450 which had been isolated from livers of pretreated male Sprague-Dawley rats (body weight range 100 to 125 g, 0.1% phenobarbital administered in the drinking water for 5 days; Murphy et al., 1981).

8 Experience in humans

In the 1950s, vinyl ethyl ether (registered trademark Vinamar®) was studied in the following clinical trials as an inhalation anaesthetic (Dornette and Orth, 1955; Sadove et al., 1955).

A study encompassing 220 anaesthesias with vinyl ethyl ether alone (120 instances) or in combination with other anaesthetics (100 instances) described the course of vinyl ethyl ether anaesthesia and its concomitant effects. Anaesthesia was induced in 120 male and 100 female patients, ranging in age from several days to over 80 years, via the open technique or via semiclosed or closed circle absorption. The induction of anaesthesia with vinyl ethyl ether was adjudged to be satisfactory in 95.9% of all instances. Undesirable effects included one instance each of laryngospasm and salivation. In 12 instances, there were complications such as generalised convulsions due to hypercarbia, respiratory and circulatory depression as well as respiratory and cardiac arrest. The complications were attributed to overdosage with vinyl ethyl ether. The degree of muscle relaxation obtained with this type of anaesthesia, particularly in adults, was considered inadequate. Postanaesthetic complications primarily included nausea/vomiting (26.7%), circulatory depression (4.1%), excitement (1.6%) and hypoxia (0.8%). In 9 patients (28 to 74 years old) several liver function tests were carried out before and after anaesthesia (duration of anaesthesia 1 to 3 hours): prothrombin time, bromosulphthalein test, thymol turbidity, icteric index, cephalin-cholesterol flocculation test (Hanger's test). The results showed that vinyl ethyl ether did not impair hepatic function (Dornette and Orth, 1955).

Twenty-nine patients (ranging in age from 14 to 58 years; 22 women, 7 men) undergoing gynaecological or orthopaedic operations were anaesthetised with vinyl ethyl ether, combined with other anaesthetics such as nitrous oxide, diethyl ether, cyclopropane, sodium nembutal and procaine hydrochloride, and liver function was studied by means of the bromosulphthalein test before as well as 24 hours and 7 days after anaesthesia. Blood counts were performed before and at several intervals after anaesthesia. Urine specimens were also investigated for changes. Electrocardiograms were recorded before, during and immediately after administration of vinyl ethyl ether. In 17 of the patients (58%), bromosulphthalein excretion was unchanged after operation, one patient had increased excretion whereas 10 patients (34%) showed delayed excretion which was normal again on the seventh day after anaesthesia. The bromosulphthalein excretion data were incomplete on one patient. Urinalysis showed no changes in 20 patients (68%). Six patients had traces of acetone, 3 had traces of albumin and 2 were found to have sugar. In 3 patients, urine studies could not be

completed because of infections. Except in one patient, the readings had returned to the normal ranges 5 days after operation. Twenty-four patients (82%) revealed no changes in the blood picture, while the remaining 5 patients showed mild to moderate leukocytosis. The electrocardiogram was found to be unchanged in 14 patients (48%). In 5 cases, mild degrees of myocardial depression were noted (no information on the remaining 10 patients). Irregularities of pulse seemed to be related to depth of anaesthesia (Sadove et al., 1955).

There is a report of one case of transient damage to the human cornea, which was reversible after 48 hours (no further details; McLaughlin, 1946).

There have been no health complaints attributable to the handling of vinyl ethyl ether among the workers employed at a chemical production plant in recent years. In the period from 1989 to June 1996, no cases of acute exposure to, or accidents with, vinyl ethyl ether have been registered in the manufacturer's outpatient database (BASF, 1996).

9 Classifications and threshold limit values

No information available.

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