Substance Name: 1, 2-dimethoxyethane (EGDME)

EC Number: 203-794-9

CAS Number: 110-71-4

SUPPORT DOCUMENT FOR IDENTIFICATION OF

1, 2-DIMETHOXYETHANE (EGDME)

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR PROPERTIES

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TABLES AND FIGURES

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ABBREVIATIONS

AFSSET French Agency for Environmental and Occupational Health Safety, now "ANSES", Agence nationale de sécurité sanitaire

CAS Chemical Abstracts Service

CLP Classification, Labelling and Packaging

CMR Carcinogenic, Mutagenic and toxic to Reproduction

CSR Chemical Safety Report

DEGBE Diethylene glycol monobutyl ether

DEGDME Diethylene glycol dimethyl ether (Diglyme)

DEGEE Diethylene glycol monoethyl ether

DEGME Diethylene glycol monomethyl ether

DGCCRF Direction Générale de la Concurrence, de la Consommation, et de la Répression des Fraudes

DNEL Derived No Effect Level

DPGME Dipropylene glycol monomethyl ether

ECHA European Chemicals Agency

ECETOC European Centre for Ecotoxicology and Toxicology of Chemicals

EEC European Economic Community

EGBE Ethylene glycol monobutyl ether

EGDEE Ethylene glycol diethyl ether

EGDME Ethylene glycol dimethyl ether

EGEE Ethylene glycol monoethyl ether

EGME Ethylene glycol monomethyl ether

EGPE Propylene Glycol Monopropyl Ether

EGPhE Ethylene glycol phenyl ether

ERC Environmental release category

HPV High Production Volume

HSDB Hazardous Substances Data Bank

INERIS Institut National de l'Environnement industriel et des risques (French National Institute for Industrial Environment and Risks)

INRS Institut National de Recherche et de Sécurité (French National Institute for Research and Safety)

IUR Inventory Update Reporting

LOAEL Lowest Observed Adverse Effect Level

NACE European Classification of Economic Activities

NOAEC No Observed Adverse Effect Concentration

NOAEL No Observed Adverse Effect Level

OECD Organisation for Economic Co-operation and Development

OSPA Oxygenated Solvents Producers Association

PBT Persistent, Bioaccumulative and Toxic

2PG1BE 2-Propylene glycol 1-butyl ether

2PG1EE Propylene glycol monoethyl ether

PGME Propylene glycol monomethyl ether

PROC Process category

REACH Registration, Evaluation, Authorisation and Restriction of Chemical substances

SIN Substitute it now

SPIN Substances in Preparations in the Nordic countries

STEL Short Term Exposure Limit

SVHC Substance of Very High Concern

TEGDME Triethylene glycol dimethyl ether

TLV Threshold Limit Value

US EPA U.S. Environmental Protection Agency

VOC Volatile organic compounds

vPvB Very Persistent and very Bioaccumulative

Substance Name: 1, 2-dimethoxyethane (Ethylene glycol dimethyl ether, EGDME)

EC Number: 203-794-9

CAS number: 110-71-4

The substance is identified as a substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction 1B[1].

Summary of how the substance meets the criteria as category 1B reproductive toxicant.

1, 2-dimethoxyethane (EGDME) is listed as entry 603-031-00-3 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 as Repr. 1B, H360FD ("May damage fertility. May damage the unborn child"). This corresponds to a classification as toxic for reproduction Repr. Cat. 2; R60 R61 ("May impair fertility. May cause harm to the unborn child") in Annex VI, part 3, Table 3.2 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

Registration dossiers submitted for the substance? Yes

[1] Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances.

JUSTIFICATION

1 Identity of the substance and physical and chemical properties

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	203-794-9
EC name:	1,2-dimethoxyethane
CAS number (in the EC inventory):	110-71-4
CAS number:	110-71-4
Deleted CAS number:	173201-80-4
CAS name:	Ethane, 1,2-dimethoxy-
IUPAC name:	1,2-dimethoxyethane
Index number in Annex VI of the CLP Regulation	603-031-00-3
Molecular formula:	$C_4H_{10}O_2$
Molecular weight range:	90.121 g/mol
Synonyms:	EGDME; Ethylene glycol dimethyl ether; 1,2-Dimethoxyethane; 1,2-Ethanediol, dimethyl ether; 2,5-Dioxahexane; DME; DME (glycol ether); Dimethyl Cellosolve; Ethylene dimethyl ether; Glycol dimethyl ether; Glyme; Hisolve MMM; Monoethylene glycol dimethyl ether; Monoglyme; NSC 60542; α,β-Dimethoxyethane.

Structural formula:

1.2 Composition of the substance

Name: 1, 2- dimethoxyethane

Description: -

Degree of purity: *see confidential Annex*

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
1,2-dimethoxyethane EC-No 203-794-9	*See confidential Annex*		

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
See confidential Annex			

Additional confidential information from registrations is included in Annex II, Chapter 1.

1.3 Physico-chemical properties

Table 4: Overview of physico-chemical properties

Property	Value	Remarks
Physical state at 20°C and 1013 hPa	colourless liquid with ethereal odor	*from registration**
Melting/freezing point at 1013 hPa	-58°C	*from registration*
Boiling point at 1013 hPa	82-84,8 °C	*from registration*
Relative density	0.87 g/cm³at 20°C	*from registration*
Vapour pressure	66 hPa at 20°C	*from registration*
Surface tension	70.7 mN/m (23°C, 1g/L)	*from registration*
Water solubility	1000g/L at 25°C	*from registration*
Partition coefficient n-octanol/water (log P_{OW}) at 25°C	-0,21	*from registration*
Flashpoint	-0.3°C at 1013 hPa	*from registration*
Flammability at -0.3°C (flash point)	Lower explosion limit: 1.6% (v/v), Upper explostion limit:10.4% (v/v), No pyrophoricity. No flammability on contact with water.	
Autoflammability	205°C at 1008hPa	
Reactivity	Highly flammable. Slightly soluble in water.	*Chemical Book*[2]

*From dissemination database according to Regulation (EC) No.1907/2006, article 119

Conversion factors (25°C, 1013hPa) (Ecetoc, 1995): 1mg/m³ = 0.267ppm

1ppm = 3.74mg/m³

[2] http://www.chemicalbook.com/Search_EN.aspx?keyword=110-71-4

2 Harmonised classification and labelling

EGDME is covered by index number 603-031-00-3 in Annex VI, part 3 of Reg. (EC) No 1272/2008 as follows:

Table 5: Harmonised Classification and Labelling of EGDME according to part 3 of Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement code(s)		
603-031-00-3	1,2-dimethoxyethane, ethylene glycol dimethyl ether, EGDME	203-794-9	110-71-4	Flam. Liq. 2 Repr. 1B Acute Tox. 4 *	H225 H360FD H332	GHS02 GHS08 GHS07 Dgr	H225 H360FD H332	EUH019		

Table 6: Harmonised Classification and Labelling of EGDME according to part 3 of Annex VI, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
603-031-00-3	1,2-dimethoxyethane, ethylene glycol dimethyl ether, EGDME	203-794-9	110-71-4	F;R11 R19 Repr.Cat.2; R60 Repr.Cat. 2; R61 Xn;R20.	F;T R:60-61-11-19-20 S:53-45		E

3 Environmental fate properties

Not relevant

4 Human health hazard assessment

See section 2 Harmonised Classification and Labelling and Supplementary Information in Annex I.

5 Environmental hazard assessment

Not relevant

6 Conclusions oN the SVHC Properties

6.1 PBT, vPvB assessment

Not relevant

6.2 CMR assessment

EGDME is listed as entry 603-031-00-3 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008[3] as Repr. 1B, H360FD ("May damage fertility. May damage the unborn child"). This corresponds to a classification as toxic for reproduction Repr. Cat. 2; R60 R61 ("May impair fertility. May cause harm to the unborn child") in Annex VI, part 3, Table 3.2 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

6.3 Substances of equivalent level of concern assessment

Not relevant.

[3] Regulation (Ec) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

7 References

ECETOC, 1995. Technical Report No. 64. The Toxicology of Glycol Ethers and its Relevance to Man. August 1995.

ECETOC, 2005. Technical Report No. 95. The Toxicology of Glycol Ethers and its Relevance to Man (Fourth Edition). February 2005.

Hays SM, Elwswick BA, Blumehthal GM, Welsch F, Connolly RB, and Gargas, ML (2000). Development of a Physiologically Based Pharmacokinetic Model of 2-Methoxyethanol and 2Methoxyacetic Acid Disposition in the Rat. Toxicol. Appl. Pharmacol. 163:67-74.

Larson Filon F., Fiorito A., Adami G., Barbieri P., Coceani N., Bussani R., Reisenhofer E. (1999). *Skin absorption in vitro of glycol ethers.* Int Arch Occup Environ Health 72:480-484.

Leonhardt DE,Coleman LW and Bradshaw WS (1991). *Perinatal toxicity of ethylene glycol dimethyl ether in rat.* Reprod. Toxicol. 5:157-162

Ferro Corporation (2001) 1,2-dimethoxyethane US EPA HPV Challenge Program Submission. P 7-8 of 93

Klassen CD (2001) Casarett and Doull's toxicology, the basis science of poisons. MCGraw Hill, 6th,page 899

NTP (1993). Technical Report TOX-26. Toxicity Studies of Ethylen Glycol Ethers: 2-Methoxyethanol, 2-Ethanol, 2-Butoxyethanol (CAS Nos. 109-86-4, 110-80-5, 111-76-2) Administered in Drinking Water to F344/N Rats and B6C3F1 Mice

ANNEX I TOXICOKINETICS, TOXICITY FOR REPRODUCTION AND NON-CLASSIFICATION FOR THE ENVIRONMENT

1 Toxicokinetics (absorption, metabolism, distribution and elimination)

It has been demonstrated that most of the toxic effects of the monoalkyl glycol ethers arise as a result of the metabolic conversion of the glycol ether into a substituted acetic acid derivative. The metabolic pathway is shown in Figure 1. The competing reaction, demethylation of 2-Methoxyethanol to ethylene glycol is comparatively slow as it is accomplished by the mixed-function oxidase system. The pharmacokinetics of these transformations have been determined in the rat and the approximate ratio of production for 2methoxyacetic acid:ethylene is 5:1. The relative first-order rate constants have been determined to be 31 L/h/kg liver for conversion of 2-Methoxyethanol to 2-methoxyacetic acid and 5.6 L/h/kg liver for conversion of 2-Methoxyethanol to ethylene glycol (Hays *et al.* 2000).

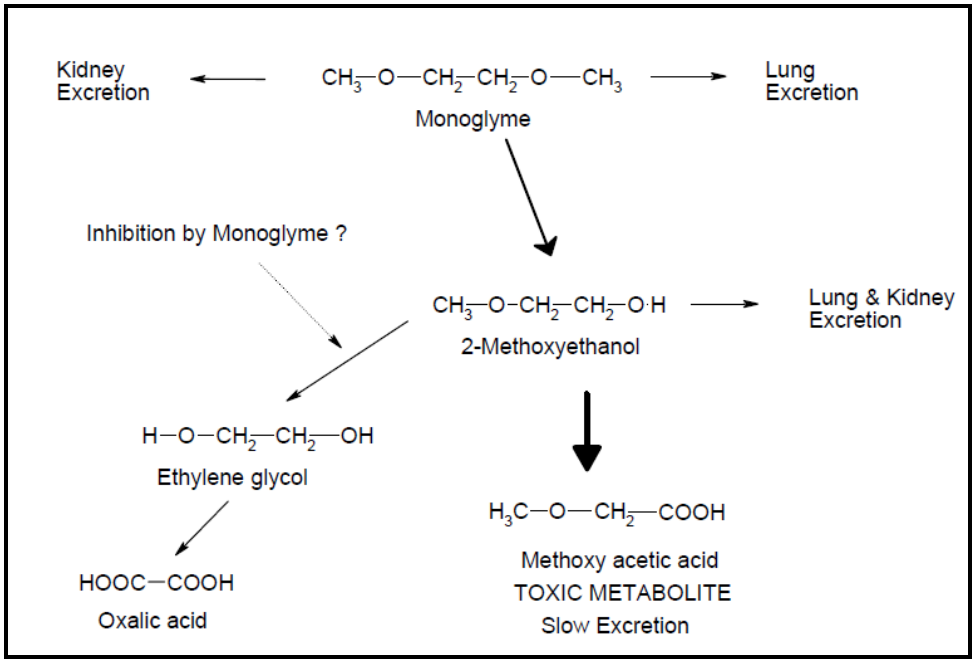

Figure 1: Metabolism and disposition of EGDME (US EPA 2001)

The main metabolite is 2-methoxyacetic acid.

Larson et al. (1999) confirmed the high percutaneous absorption of EGDME: 3.4 mg/cm²/h. It is the fastest solvent (followed by DEGDME, EGMEE and PGMME with values between 0.470 and 0.952 mg/cm²/h).

Glycol ethers in general are readily distributed throughout the body and eliminated through the urine. No substantial accumulation of the parent compound has been observed (ECETOC, 2005).

2 Toxicity for reproduction

It has been demonstrated that most of the toxic effects of the monoalkyl glycol ethers arise as a result of the metabolic conversion of the glycol ether into a substituted acetic acid derivative (Klassen 2001).

The reproductive toxicity of EGDME is attributed to the metabolite 2-methoxyacetic acid, which is generated from 2-methoxyethanol (EGME). The metabolite 2-methoxyacetic acid has shown evidence of accumulation in animals and humans (Ferro Corporation 2001).

Information about the metabolic pathways and nearly identical developmental effects at similar dose levels indicates that the repeated-dose, reproductive, and developmental toxicity of EGDME can be ascertained from the results of studies on EGME. The similarity in effects and dose levels for the perinatal toxicity in rats (Leonhardt *et al*. 1991) argue that EGME is an excellent surrogate for repeated dose toxic effects of EGDME.

2.1.1.1 Effects on fertility

The reproductive toxicity of EGDME is allocated to EGME. NTP Technical Report TOX-26 carried out investigations on rats and mice. Table 14 summed up the fertility toxicity in mice and in rat exposed to 2-Methoxyethanol.

In rat

Oral exposure for 2 weeks at **200 mg/kg bw/day** indicates no adverse effects on testis degeneration. Degeneration was clearly present in the testis of male rats in all but the lowest dose group.

In oral exposure for 13 weeks, degeneration was noticed **> 750 ppm**. Histopathologic changes in the testes consisted of a minimal to marked degeneration of germinal epithelium in the seminiferous tubules.

In mice

Oral exposure for 2 weeks carried out indicates **$NOEL_{male}$= 200 mg/kg bw/day** based on reduction of relative testis weight.

Oral exposure for 13 weeks indicates **NOAEL** <2000 ppm induced by reduction of testes in the 3 highest-dose groups.

2.1.1.2 Developmental toxicity

Table 15 indicates findings of the exposure to EGDME by inhalation in rabbits and rats.

Inhalation exposure of rats to EGDME produced no adverse maternal effects at any dose level. Body weight gain, food consumption and the organ weights were within the control range. No macroscopic changes occurred at any dose level.

Above **10 ppm (0.037 mg/L air)** developmental effects were recorded.

Conclusion:

Regarding fertility, the literature on 2-methoxyethanol and the metabolic data indicating that EGDME's oxidative metabolism to 2-methoxyacetic acid indicates a clear and significant reproductive hazard from overexposure to EGDME.

Regarding development, EGDME indicates that it has the potential to be teratogenic and fetotoxic. The studies show a dose-response relationship and indicate the potency range for EGDME as a developmental toxin.

An overview of different studies from dissemination site is presented in Table 16.

3 Environment

EGDME is not classified as hazardous to the environment.

The available registration data support the non-classification for environmental effects.

Table 14: Oral exposure toxicity, 2-Metoxyethanol (NTP Technical Report TOX-26)

Species	Route of exposure	Dose/ Concentration	Observations, effects	NO(A)EL
			1st study	
5/sex/species OECD guideline 407	Drinking water *Ad libitum* for 2 weeks	0, 200, 400, 600,1000, or 1200 mg/kg bw	**Rats**: Absolute and relative thymus weights decreased in a dose-related fashion for males and females as did absolute and relative testis weights for males. In addition to chemical-related gross lesions, the testis and epididymis from all dosed and control rats were examined microscopically. Degeneration was clearly present in the testis of male rats in all but the lowest dose group (200mg/kgbw/d) : moderate to marked loss of germinal epithelium and the presence of multinucleated Spermatid giant cells and cell debris in the lumen of seminiferous tubules. In male rats in the three highest dose groups, the lumen of the epididymis contained necrotic cells and cell debris and only a few spermatozoa. **Mice :** For male mice, absolute and relative testis and thymus weights decreased in a dose-related fashion, and for female mice in the two highest dose groups (1000 and 1200 mg/kg), absolute and relative thymus weights were lower than those of the control group.	**Rats**: **NOAEL:** 200 mg/kg bw/day based on testes degeneration **Mice :** **$NOEL_{male}$:** 200 mg/kg bw/day based on reduction of relative testis weight **$NOEL_{female}$**:600 mg/kg bw/day based on reduced relative thymus weight

2nd study				
10/sex/species OECD guideline 408	Drinking water *Ad libitum* for 13 weeks	**rats** : 0, 750, 1500, 3000, 4500, or 6000 ppm **mice**: 0, 2000, 4000, 6000, 8000, or 10,000 ppm.	**Rats:** Dose-related decreases were noted for the absolute and relative testis weights of male rats. Degeneration was present at all dose levels but was only minimal in 7 of 10 rats in the 750 ppm group. Histopathologic changes in the testes consisted of a minimal to marked degeneration of germinal epithelium in the seminiferous tubules. in more severely affected rats, the atrophic seminiferous tubules contained only Sertoli cells and a few spermatogonia. Also, spermatozoal measurements were significantly decreased for males in the two highest dose groups (1500 or 3000 ppm). For females, there was evidence to suggest that animals in the 1500 and 3000 ppm groups differed from the control animals in the relative frequency of time spent in estrous stages. **Mice :** Dose-related decreases were noted for the absolute and relative testis weights of male mice and the absolute and relative thymus weights of male and female mice. In male mice, degeneration of the testis was characterized microscopically by a dose related. Sperm morphology evaluations showed significant decreases in epididymal and cauda epididymal weights and in testicular weight. The values for sperm motility were significantly less than controls and spermatid measurements were significantly lower than controls. For females, all dose groups differed significantly from controls in the relative frequency of time spent in estrous stages.	**Rats:** **NOAEL**:< 750 ppm based on testicular degeneration in males and decreased thymus weight in males and females **Mice:** **NOAEL:**<2000 ppm based on reduced sperm motility and concentration in males and histopathological changes in the spleen and adrenal gland incl. increases hematopoesis in female mice

Table 15: Developmental toxicity, key studies, overview of exposure to EGDME (according to dissemination site)

Species	Route of exposure	Dose/ Concentration	Observations, effects	Maternal NOAEL	Fetal NOAEL/LOAEL	Reference
Rabbits (SPF Wiga) Pregnant Female 15 animals/group OECD 414	Inhalation: Vapour (whole body) 6h/day Daily Days 6-18 Recovery period: 10 days	0, 5ppm (0.019 mg/L), 16ppm (0.06 mg/L), 50ppm (0.187 mg/L)	**Maternal observations***:* All animals survived, no serious clinical signs were noted at any dose level. (only one abortion in the 16 ppm dose group). During the first week of treatment the body weight of the animals of the 50 ppm dose group was decreased. Within the second week of treatment this effect disappeared. There were no effects upon the mean daily food consumption observed at the 5 ppm dose level. The food consumption of the animals of the 50 ppm and 16 ppm dose level was slightly decreased during the exposure period. **Litter examinations:** There was no effect on foetal development and body weight observed at any dose level. The vitality of the litters within the first 24 hours after Caesarean section at 50 ppm exposure was considerably decreased. In the 50 ppm dose group 10 foetuses had an abnormal orientation of one or both fore-paws. Two foetuses showed skull malformations. Irregularity of the skull ossification 8 foetuses of the high dose group. 2 foetuses of the high dose group had red-bordered spots on the skin (mandible, neck and below the eyes).	NOAEC: **0.06 mg/L air (16 ppm)** Based on slightly decreased food consumption	NOEC : **0.06 mg/L air (16 ppm)** Based on decreased vitality within the first 24 hours at 0.187mg/L	Key study (1988)

Rats (APF71) Pregnant Female 20 animals/group OECD 414	Inhalation: Vapour (whole body) Days 7- 16 Recovery period: 10 days	10 ppm (0.037 mg/L), 32 ppm (0.12 mg/L) , 100 ppm (0.374 mg/L)	**<u>Maternal observations:</u>** All animals survived. No clinical signs were noted at any dose level. **<u>Litter examinations:</u>** There was a slight decrease of fetal weight observed in middle dose group and the body weight of the fetuses of the highest dose group was considerably decreased. The fetuses of the high dose group showed a retarded development. Resorptions as well as dead fetuses were found in this dose group. The number of resorptions at the high dose level was increased compared to the others. The number of viable fetuses was considerably decreased in the highest dose group. In this group 11 fetuses had malformations of the extremities and scapula (crooked, shortened). One fetus group had a shortened tail and 4 fetuses showed subcutaneous oedema. The ossification of the fetuses of the two higher dose groups was considerably retarded. In these dose groups fragmented thoracic and lumbar vertebrae were observed. The number of fetuses showing malformations of ribs was significantly increased at exposure to 32 ppm and 100 ppm of the test substance. Blood in the pericardium and enlarged ureter were observed in fetuses of the 32 ppm and 100 ppm dose group.	NOEC **0.374 mg/L air (100 ppm)** No effects	NOEC **0.037 mg/L air (10 ppm)** based on retarded development and increased incidence of malformations at 0.12 mg/L	Supporting study (1986)

Table 16: Repeated-dose, studies overview of exposure to EGDME (according to the dissemination site)

Species	Route of exposure	Dose/ Concentration	Observations, effects	NO(A)EC	Reference
rat (Hoechst) 10animals/sex/groug OECD 412	Inhalation 6h/day 5days/week for 2 weeks Recovery period: 36 days	10 ppm (0.037 mg/L) 50 ppm (0.187 mg/L) 250 ppm (0.935 mg/L)	All animals survived and no clinical signs were noted at any dose level. No neurological or ophthalmological effects or changes in mucosa were noted. Body weight gain of all animals was not affected. There were no effects upon the mean daily food consumption observed at all dose levels. There were no haematological changes noted at any dose level. All determined clinical parameters were within the control range. Relative organ weights were within the control range. **250 ppm:** The reduction of cell layers of seminiferous epithelium in male rats was observed at dose group. This effect was reversible.	**NOEC** **50 ppm** (0.187 mg/L). Based on the observed slight changes in the seminiferous epithelium in male rats at the 250 ppm dose group.	Key study 1986
rat (Hoechst) male/pregnant female 5animals/group OECD 412	Inhalation 6h/day 5days/week For 2 weeks Recovery period: 3 days	0, 100, 500ppm	**100 ppm:** All animals survived and no clinical signs were noted. Body weight gain of the rats was unaffected. There were no effects upon the mean daily food consumption. There were no changes in haematology noted. The microsopic examination of the testes and epidymis showed oligospermia. A retardation of foetal development was observed. **500 ppm** : No deaths or clinical signs occurred in the rats. The body weight of the male rats of the 500 ppm dose group was unaffected; the body weight of three female rats was decreased. Food consumption of all females was decreased. the leucocyte count was decreased in all animals. No macroscopic changes occurred in all rats. Severe lesions of the seminiferous epithelium. An increase of resorptions occurred.	**NOAEC** < 100 ppm Based on the observed oligospermia in rats and the retardation of foetal development and resorption of embryos in rats.	Supporting study (1985)

Rabbit (SPF Wiga) Male/Female 6animals/group OECD 412	Inhalation 6h/day 5 days/ week For 2 weeks Recovery period: 36 days	0, 10, 50, 250ppm	All other animals survived and no clinical signs were noted at any dose level. No neurological or ophthalmological effects or changes in mucosa were noted. Body weight gain of all animals was not affected within the first 15 days of the study. With one exception there were no effects upon the mean daily food consumption observed at all dose levels. **250 ppm:** During the 36 days recovery period the body weight gain of the male animals was considerably decreased, the body weight gain of the females of this dose group was slightly decreased. The food consumption of the animals was decreased during the exposure period. No macroscopic/microscopic changes occurred at any dose level with the exception of changes of the seminiferous epithelium in male rabbits of the 250 ppm dose group which caused aspermia. This effect was irreversible within the recovery period of 36 days	**NOEC** 10 ppm Based on the decreased reticulocyte count in female rabbits exposed to 50 ppm and the observed changes in the seminiferous epithelium in male rabbits at 250 ppm	Supporting study (1985)