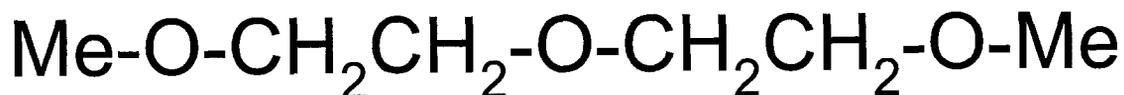


201-15023B

Diglyme

CAS Number 111-96-6



ROBUST SUMMARIES

Existing Chemical	: ID: 111-96-6
Memo	: Ferro
CAS No.	: 111-96-6
EINECS Name	: bis(2-methoxyethyl) ether
EC No.	: 203-924-4
TSCA Name	: Ethane, 1,1'-oxybis[2-methoxy-
Molecular Formula	: C6H14O3
Producer related part	
Company	: Ferro Incorporated, Grant Chem. Div.
Creation date	: 21.12.2003
Substance related part	
Company	: Ferro Incorporated, Grant Chem. Div.
Creation date	: 21.12.2003
Status	:
Memo	:
Printing date	: 29.12.2003
Revision date	:
Date of last update	: 28.12.2003
Number of pages	: 36
Chapter (profile)	: Chapter: 1.0.1, 1.2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.3.1, 3.3.2, 3.5, 4.1, 4.2, 4.3, 4.4, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.4, 5.5, 5.6, 5.7, 5.8.1, 5.8.2
Reliability (profile)	:
Flags (profile)	:

04 JAN 12 AM 10:33

RECEIVED
DPPT CBIC

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : lead organisation
Name : Toxicology and Regulatory Affairs
Contact person : Elmer Rauckman
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Street : 1201 Anise Court
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Homepage : ToxicSolutions.com

21.12.2003

1.2 SYNONYMS AND TRADENAMES

(2-METHOXYETHYL) ETHER

21.12.2003

2-(2-METHOXYETHOXY)-1-METHOXYETHANE

21.12.2003

BIS(2-METHOXYETHYL) ETHER

21.12.2003

DIETHYLENE GLYCOL DIMETHYL ETHER

21.12.2003

DIGLYCOL METHYL ETHER

21.12.2003

DIGLYME

21.12.2003

ETHANE, 1,1'-OXYBIS(2-METHOXY-

21.12.2003

ETHANOL, 2,2'-OXYBIS-, DIMETHYL ETHER

21.12.2003

ETHER, BIS(2-METHOXYETHYL)

1. General Information

Id 111-96-6
Date 29.12.2003

21.12.2003

POLY-SOLV

21.12.2003

2. Physico-Chemical Data

Id 111-96-6
Date 29.12.2003

2.1 MELTING POINT

Value : = -68 °C

Test substance : Diglyme, CASNO 111-96-6

Reliability : (2) valid with restrictions

Flag : Handbook values are assigned a score of 2
21.12.2003 : Critical study for SIDS endpoint (16)

2.2 BOILING POINT

Value : = 162 °C at 1010 hPa

Test substance : Diglyme, CASNO 111-96-6

Reliability : (2) valid with restrictions

Flag : Handbook values are assigned a score of 2
22.12.2003 : Critical study for SIDS endpoint (16)

2.3 DENSITY

Type :

Value : = .9451 g/cm³ at 20 °C

Test substance : Diglyme, CASNO 111-96-6

Reliability : (2) valid with restrictions

22.12.2003 : Handbook values are assigned a score of 2 (16)

2.4 VAPOUR PRESSURE

Value : = 3.49 hPa at 25 °C

Test substance : Diglyme, CASNO 111-96-6

Reliability : (2) valid with restrictions

Flag : Handbook values are assigned a score of 2
22.12.2003 : Critical study for SIDS endpoint (4)

2. Physico-Chemical Data

Id 111-96-6
Date 29.12.2003

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = -.36 at 25 °C
pH value :

Test substance :
Diglyme, CASNO 111-96-6

Reliability : (2) valid with restrictions

Flag : Handbook values are assigned a score of 2
22.12.2003 : Critical study for SIDS endpoint

(6)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : > 1000 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : not soluble
Stable :

Test substance :
Diglyme, CASNO 111-96-6

Reliability : (2) valid with restrictions

Flag : Handbook values are assigned a score of 2
22.12.2003 : Critical study for SIDS endpoint

(16)

3.1.1 PHOTODEGRADATION

Type : air
 Light source :
 Light spectrum : nm
 Relative intensity : based on intensity of sunlight
INDIRECT PHOTOLYSIS
 Sensitizer : OH
 Conc. of sensitizer : 1500000 molecule/cm³
 Rate constant : = .0000000000175 cm³/(molecule*sec)
 Degradation : = 50 % after 7.3 hour(s)
 Deg. product :
 Method : other (calculated)
 Year :
 GLP : no
 Test substance :

Method :
 The structure was initially examined to determine if there was a chromophore that could absorb light energy at wavelengths above 295 um. As there is not, it was assumed that direct photolysis would be unimportant to the fate of the test material.

The indirect photolysis rate was then calculated from an experimental rate constant for diglyme found in the literature of 17.5 10⁻¹² cm³/molecule-sec, assuming the equilibrium concentration of tropospheric hydroxyl radicals as 1,500,000 molecules of hydroxy radical per cm³.

The APOWIN program was also run to determine an estimated rate of reaction with hydroxyl radical. This was compared against the measured value as supporting data.

SMILES : COCCOCCOC
 CHEM : Diglyme
 MOL FOR: C6 H14 O3
 MOL WT : 134.18

----- SUMMARY (AOP v1.90): HYDROXYL RADICALS -----
 Hydrogen Abstraction = 29.6904 E-12 cm³/molecule-sec
 Reaction with N, S and -OH = 0.0000 E-12 cm³/molecule-sec
 Addition to Triple Bonds = 0.0000 E-12 cm³/molecule-sec
 Addition to Olefinic Bonds = 0.0000 E-12 cm³/molecule-sec
 Addition to Aromatic Rings = 0.0000 E-12 cm³/molecule-sec
 Addition to Fused Rings = 0.0000 E-12 cm³/molecule-sec

OVERALL OH Rate Constant = 29.6904 E-12 cm³/molecule-sec
 HALF-LIFE = 0.360 Days (12-hr day; 1.5E6 OH/cm³)
 HALF-LIFE = 4.323 Hrs

Experimental Database Structure Match:
 Chem Name : 2-Methoxyethyl ether
 CAS Number: 000111-96-6
 Exper OH rate constant : 17.5 E-12 cm³/molecule-sec
 Exper OH Reference: ATKINSON,R (1989)
 Exper Ozone rate constant: --- cm³/molecule-sec
 Exper NO3 rate constant : --- cm³/molecule-sec

3. Environmental Fate and Pathways

Id 111-96-6
Date 29.12.2003

Result :

Hydrogen Abstraction Calculation:
Kprim = 0.136 F(-O-)=0.136(6.100)= 0.830
Ksec = 0.934 F(-CH2-)F(-O-)=0.934(1.230)(6.100)= 7.008
Ksec = 0.934 F(-O-)F(-CH2-)=0.934(6.100)(1.230)= 7.008
Ksec = 0.934 F(-CH2-)F(-O-)=0.934(1.230)(6.100)= 7.008
Ksec = 0.934 F(-O-)F(-CH2-)=0.934(6.100)(1.230)= 7.008
Kprim = 0.136 F(-O-)=0.136(6.100)= 0.830
H Abstraction TOTAL = 29.690 E-12 cm³/molecule-sec

The calculated half-life is 7.33 hours based on 1,500,000 molecules of hydroxyl radical per cc. The APOWIN program estimates a faster reaction rate with a subsequent estimated half-life of 4.3 hours. As these values are similar the experimental value is accepted for use.

SMILES : COCCOCCOC
CHEM : Diglyme
MOL FOR: C6 H14 O3
MOL WT : 134.18

----- SUMMARY (AOP v1.90): HYDROXYL RADICALS -----
Hydrogen Abstraction = 29.6904 E-12 cm³/molecule-sec
Reaction with N, S and -OH = 0.0000 E-12 cm³/molecule-sec
Addition to Triple Bonds = 0.0000 E-12 cm³/molecule-sec
Addition to Olefinic Bonds = 0.0000 E-12 cm³/molecule-sec
Addition to Aromatic Rings = 0.0000 E-12 cm³/molecule-sec
Addition to Fused Rings = 0.0000 E-12 cm³/molecule-sec

OVERALL OH Rate Constant = 29.6904 E-12 cm³/molecule-sec
HALF-LIFE = 0.360 Days (12-hr day; 1.5E6 OH/cm³)
HALF-LIFE = 4.323 Hrs

----- SUMMARY (AOP v1.90): OZONE REACTION -----

***** NO OZONE REACTION ESTIMATION *****
(ONLY Olefins and Acetylenes are Estimated)

Experimental Database Structure Match:
Chem Name : 2-Methoxyethyl ether
CAS Number: 000111-96-6
Exper OH rate constant : 17.5 E-12 cm³/molecule-sec
Exper OH Reference: ATKINSON,R (1989)
Exper Ozone rate constant: --- cm³/molecule-sec
Exper NO₃ rate constant : --- cm³/molecule-sec

Test substance :

Diglyme, CASNO 111-96-6

Conclusion :

7.33 hours is accepted as the atmospheric half-life of diglyme in the troposphere due to indirect photolysis. No direct photolysis or reaction with atmospheric ozone is anticipated.

3. Environmental Fate and Pathways

Id 111-96-6
Date 29.12.2003

Reliability : (2) valid with restrictions
EPIWIN calculated values that are scientifically sound are assigned a reliability score of 2
Flag : Critical study for SIDS endpoint
22.12.2003 (1)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other: calculated and vehicle stability
Year :
GLP :
Test substance :

Method :
The water stability of this material may be reliably estimated from chemical principles. Aliphatic ethers linkages are one of the groups not considered susceptible to aqueous hydrolysis at environmental pH levels (Harris 1990).

Result :
Additional support for hydrolytic stability comes from an experimental approach that was used to demonstrate test material dosing vehicle stability by the NTP in aqueous solution.

The knowledge that ethers are not susceptible to hydrolysis allows prediction of a half-life > 1 year for diglyme.

Vehicle stability testing of diglyme prior to a developmental toxicity study indicated that diglyme was hydrolytically stable. Gas chromatography analysis of an aqueous solution at 47.2 g/L kept in the dark for 21 days, allowed the National Toxicology Program to conclude that diglyme is hydrolytically stable.

Test substance :
Diglyme, CASNO 111-96-6

Conclusion :
The hydrolysis half-life of diglyme at ambient temperatures and typical environmental pH levels is greater than one year.

Reliability : (2) valid with restrictions
A reliability code of 2 is assigned to values obtained from reliable estimation methods.

Flag : Critical study for SIDS endpoint
22.12.2003 (7) (18)

3. Environmental Fate and Pathways

Id 111-96-6
Date 29.12.2003

3.3.2 DISTRIBUTION

Media : other: air - water- soil -sediment
Method : Calculation according Mackay, Level III
Year :

Method :
Measured values for physical values of diglyme were input into EPIWIN as shown below. Biodegradation rates were estimated from limited experimental results. Model was allowed to assume equal distributions to air, water and soil. EQC Level III model (as found in EPIWIN 3.05) was utilized.

Result : Results of the Level III fugacity modeling are:
Level III Fugacity Model (Full-Output):
=====

Chem Name : Diglyme
Molecular Wt: 134.18
Henry's LC : 5.23e-007 atm-m³/mole (calc VP/wsol)
Vapor Press : 2.96 mm Hg (user-entered)
Log Kow : -0.36 (user-entered)
Soil Koc : 0.179 (calc by model)

	Concentration (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.505	7.33	1000
Water	60.4	2e+003	1000
Soil	38.9	2e+003	1000
Sediment	0.113	4e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction percent	Advection percent
Air	1.87e-011	970	103	32.3	3.42
Water	2.39e-011	425	1230	14.2	40.9
Soil	5.62e-010	274	0	9.13	0
Sed	2.22e-011	0.396	0.0458	0.0132	0.00153

Persistence Time: 677 hr
Reaction Time: 1.22e+003 hr
Advection Time: 1.53e+003 hr
Percent Reacted: 55.7
Percent Advected: 44.3

Half-Lives (hr), (based upon user-entry):
Air: 7.33
Water: 2000
Soil: 2000
Sediment: 4000

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Test substance : Diglyme, CASNO 111-96-6
Conclusion : Under conditions of equal initial distribution to water, soil and air, Biphenyl is expected to distribute preferentially in water > soil > air > sediment.
Reliability : (2) valid with restrictions
A reliability code of 2 is assigned to values obtained from reliable estimation methods.
Flag : Critical study for SIDS endpoint
23.12.2003

(2)

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge, non-adapted
Concentration	:	2 mg/l related to Test substance related to
Contact time	:	
Degradation	:	(±) % after
Result	:	under test conditions no biodegradation observed
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	
GLP	:	
Test substance	:	
Method	:	An OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test" was conducted on diglyme at a concentration of 2 mg/L using an activated sludge from an unspecified source. The degradation was reported as 0.1% after 5 days but no 28-day result was provided.
Remark	:	Result supported by the following studies indicating diglyme is difficult to biodegrade: Tessier, S et al. Degradation of Polyoxyethylenes: Biodegradation using an Enzyme from Psuedomonas P-400 and Chemical Degradation using Sodium Hypochlorite. J. Chem research 1983: 174-175 (1983) Roy, D. Anagnostu, G. Chaphalkar, P. Biodegradation of Dioxane and Diglyme in Industrial Waste. Journal of Environmental Science and Health Part A Environmental Science And Engineering; 29 (1). 1994. 129-147 Harada T and Y Nagishima, Utilization of Alkylether Compounds by Soil Bacteria. J. Fement. Tech. 53:218-222 (1975) Cowan RM, et al. Activated Sludge and Other Aerobic Suspended Culture Processes Water Environment Research; 67 (4). 1995. 433-450
Test substance	:	Diglyme, CASNO 111-96-6
Conclusion	:	Not readily biodegradable
Reliability	:	(2) valid with restrictions
Flag	:	Guideline study, but original report was not available for review. Study was also indicated as not GLP.
24.12.2003	:	Critical study for SIDS endpoint

(13)

3. Environmental Fate and Pathways

Id 111-96-6

Date 29.12.2003

Type : aerobic
Inoculum : activated sludge, industrial, non-adapted
Concentration : 375 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time : 28 day(s)
Degradation : = 31 - 42 (±) % after 28 day(s)
Result :
Deg. product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1989
GLP :
Test substance :

Method :
An OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test" was conducted on diglyme. The initial concentration of diglyme, based on dissolved organic carbon, was 375 mg/L. The bacterial culture was non-adapted industrial activated sludge.

Result :
Results are given as follows in the IUCLID-2000 document:

TIME	Degradation (%)
3 hours	0
1 day	10
7 days	10
15 days	15
20 days	36
28 days	31

Results are cited in the IPCS CICAD document:
"...adsorption of diglyme onto activated sludge was 17% after 3 h, and total removal was 42% after 28 days. The degree of elimination and the degradation curve are indicative of inherent primary degradation, according to OECD criteria (Hoechst, 1989a)."
Both results are attributed to Hoechst AG; however, it appears the CICAD may reference a secondary Hoechst document.

Test substance :
Diglyme, CASNO 111-96-6

Conclusion :
Not inherently biodegradable but the degree of elimination and the degradation curve are indicative of inherent primary degradation

Reliability : (2) valid with restrictions

Guideline study, but original report was not available for review. Study was also indicated as not GLP.

Flag : Critical study for SIDS endpoint
24.12.2003 (9) (13)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= 2000 measured/nominal
LC0	:	> 2000 measured/nominal
Method	:	other: DIN 38412, L15 guideline
Year	:	
GLP	:	no
Test substance	:	
Method	:	An acute fish toxicity test was performed according to the DIN 38412, L15 guideline.
Remark	:	It could not be determined how the concentration of the test substance was established in this study, or if only nominal concentrations were used. The use of measured concentrations is not considered to be of much importance for this water soluble, low volatility, and low adsorption potential test material. It can be assumed that all nominal concentrations of the test substance are expected to correspond closely to actual concentrations, even using open systems and longer exposure periods. This study is supported by the EPIWIN predicted 96-hour LC50 for freshwater fish of 16,650 mg/L
Result	:	No mortality was observed in the 96-hour study. No adverse effects were seen in the in-life phase of this study. Fish were sectioned at the end of the study and no visible changes were apparent.
Test substance	:	Diglyme, CASNO 111-96-6
Conclusion	:	The acute LC0 and LC50 for the golden orfe is > 2000 mg/L under these conditions
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint
28.12.2003		(12)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
NOEC	:	= 1000 measured/nominal
EC0	:	> 1000 measured/nominal
Limit Test	:	no
Method	:	OECD Guide-line 202
Year	:	
GLP	:	no data

5. Toxicity

Id 111-96-6
Date 29.12.2003

	:	
Method	:	An acute toxicity test with <i>D. magna</i> was performed according to the OECD 202 guideline.
Remark	:	<p>It could not be determined how the concentration of the test substance was established in this study, or if only nominal concentrations were used. The use of measured concentrations is not considered to be of much importance for this water soluble, low volatility, and low adsorption potential test material. It can be assumed that all nominal concentrations of the test substance are expected to correspond closely to actual concentrations, even using open systems and longer exposure periods.</p> <p>This study is supported by the EPIWIN predicted 48-hour EC50 for <i>Daphnia magna</i> of 14,971 mg/L</p>
Result	:	No adverse effects were observed at concentrations of 100 or 1000 mg/L.
Test substance	:	Diglyme, CASNO 111-96-6
Reliability	:	(2) valid with restrictions
		Guideline study, but original report was not available for review. GLP status could not be determined.
Flag 28.12.2003	:	Critical study for SIDS endpoint

(10)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	<i>Scenedesmus subspicatus</i> (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
EC10	:	> 1000 measured/nominal
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	
GLP	:	
Remark	:	<p>It could not be determined how the concentration of the test substance was established in this study, or if only nominal concentrations were used. The use of measured concentrations is not considered to be of much importance for this water soluble, low volatility, and low adsorption potential test material. It can be assumed that all nominal concentrations of the test substance are expected to correspond closely to actual concentrations, even using open systems and longer exposure periods.</p> <p>This study is supported by the EPIWIN predicted 96-hour EC50 for green algae of 8171 mg/L</p>
Test substance	:	Diglyme, CASNO 111-96-6
Reliability	:	(2) valid with restrictions
		Guideline study, but original report was not available for review. GLP status could not be determined.
Flag 28.12.2003	:	Critical study for SIDS endpoint

(11)

5.1.1 ACUTE ORAL TOXICITY

Type : other: Approximate Lethal Dose
Value : ca. 7500 mg/kg bw
Species : rat
Strain : CD-1
Sex : male
Number of animals : 8
Vehicle : water
Doses : 1500 to 23000 mg/kg
Method :
Year :
GLP : no data

Method :
 Young adult ChR-CD male rats were administered the test material by intragastric intubation as a water solution in single doses. Surviving animals were observed for 14 days and were sacrificed and necropsied.

Remark :
 This result is supported by a GLP study reported in IUCLID-2000 in which female Wistar rats were treated with doses of 1600, 2500, 4000, 4500, 5600 or 6300 mg/kg diglyme. Clinical signs were restlessness unrest, disturbed sense of balance, prone position and reduced respiration rate. At the higher dose levels there was also discharge of a reddish secretion from the eye sockets. These signs only persisted for 24 hours in animals that survived the 14-day observation period.

At > = 4500 mg/kg deaths occurred 24 to 96 hours afer dosing.
 At < = 4000 mg/kg there were no deaths.

Body weight development of survivors was normal after 14 days. The lungs of animals dying on test showed a gray-red colouring and were partly dark red spotted; some animals showed liver changes. No findings were reported from the 14-day necropsy of surviving animals.

The Oral LD50 was determined to be 4760 mg/kg

Hoechst (1979b) Akute orale Toxizität von Diethylenglykoldimethylether an weiblichen Ratten. Frankfurt am Main, Hoechst AG, 4 pp. (Report 376/79; unpublished). Study details as reported in IUCLID-2000 Document in German.

Result : Results are given in the table

Dose	% in water	Mortality	Time of Death
23,000	80	D	1 hour
17,000	80	D	3 hours
11,000	80	D	1 day
7,500	80	D	2 days
5,000	50	S	14 days
3,400	50	S	14 days
2,250	50	S	14 days
1,500	50	S	14 days

D= Died
 S= Survived to terminal sacrifice

CLINICAL EFFECTS:

@ Lethal Doses: Ataxia, loss of muscle tone, lethargy, prostration, labored respirations. and belly-to-cage posture at 7,500 mg/kg and above; pallor at 17,000 mg/kg and above; loss of righting reflex at 25,000 mg/kg.

@ Nonlethal Doses: Lethargy, belly-to-cage posture and ruffled fur at 1,500 mg/kg and above; prostration at 5,000 mg/kg on day of dosing. Ruffled fur at 5,000 mg/kg on day after dosing; weight loss 1-2 days at 2,250 mg/kg and above.

Test substance	:	Diglyme, CASNO 111-96-6
Conclusion	:	Diglyme is slightly toxic when administered orally to young adult ChR-CD male rats in single doses; its Approximate Lethal Dose (ALD) is 7,500 mg/kg of body weight.
Reliability	:	(2) valid with restrictions
Flag	:	Study was conducted by a scientifically defensible procedure and results are supported by other data.
28.12.2003	:	Critical study for SIDS endpoint

(5)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	> 11000 mg/m ³
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	7 hour(s)
Method	:	Wistar rats of each sex were exposed to diglyme vapors in an "inhalation risk test" using air "saturated" with diglyme and an exposure period of 7 hours. After exposure, animals were maintained for a 14-day observation period after which they were sacrificed and subjected to a gross necropsy.
Remark	:	The CICAD document for diglyme states that this was a nose-only exposure but the IUCLID-2000 document does not provide details about the method of exposure. In the IUCLID-2000 document details are given about the nominal exposure concentration in which 46.8 grams of test material were used in the 7 hour exposure with a flow rate of 600 L/hr. This calculates to 11.14 grams per cubic meter or about 2000 ppm. As the vapor pressure of diglyme is 2.96 mm Hg at 25 C, saturated air could contain up to 3900 ppm diglyme. Given the difficulty in saturating air with test material using a flow-through apparatus, the 2000 ppm nominal concentration is reasonable.

This result is supported by the results of repeated-dose studies reported by McGregor et al. (1983)*, who exposed CD rats for 7 hours a day for 5 days

at a measured diglyme concentration of 1000 ppm without mortality. It is also supported by the work of Valentine et al. (1999) who exposed groups of 20 male and 10 female rats to measured concentrations of up to 1100 ppm diglyme, six hours a day five days a week for 10 exposures without mortality.

*McGregor DB, Willins MJ, McDonald D, Holmstrom M, McDonald D, Niemeier RW (1983) Genetic effects of 2-methoxyethanol and bis(2-methoxyethyl)ether. Toxicology and Applied Pharmacology, 70:303-316.

Valentine R, O'Neill AJ, Lee KP, Kennedy GL Jr. (1999) Subchronic inhalation toxicity of diglyme. Food Chem Toxicol. 37:75-86.

Result

:

All animals survived exposure and a 14-day observation period. No macroscopic findings were observed at necropsy 14 days after the exposure. Clinical signs were restlessness, narrowing of palpebral fissures, and irregular breathing in rats. Based on the vapor pressure the concentration could have been as high as 3800 ppm (21 mg/L) but in the IUCLID 2000 summary is given as > 11 grams/m3. This is based on the nominal concentration calculated by the weight loss of test material and the flow rate of the apparatus. The actual nominal concentration calculates to 11.14 mg/L or about 2000 ppm

Test substance

:

Diglyme, CASNO 111-96-6

Reliability

:

(2) valid with restrictions

Study was conducted by a scientifically defensible procedure and results are supported by other data.

Flag

28.12.2003

:

Critical study for SIDS endpoint

(8) (14)

5.1.3 ACUTE DERMAL TOXICITY

5.4 REPEATED DOSE TOXICITY

Type : Sub-acute
Species : rat
Sex : male/female
Strain : other: Crl:CD1BR
Route of admin. : inhalation
Exposure period : 10 exposures in 2 weeks
Frequency of treatm. : 5 days per week
Post exposure period : Up to 84 days for males and 14 days for females
Doses : 110, 370 or 1100 ppm
Control group : other: concurrent negative (air) and positive 300 ppm (2-methoxyethanol)
LOAEL (males) : = 110 ppm
Method :
Year :
GLP : yes

Method

:

Crl:CD1BR rats (7 weeks old), received from Charles River Breeding Laboratories (Kingston, NY, USA), were maintained on a 12-hr/12-hr light/dark cycle at a targeted temperature of 21-25 deg C 28C and relative humidity of 40-60%. Except during exposure, Purina 5002 rat feed and water were available ad lib.

Five groups of 20 male and 10 female rats were used in this study. Three groups were exposed nose-only to target concentrations of 100, 300 or 1000 ppm diglyme. 2-Methoxyethanol at a target concentration of 300 ppp was used as a positive control on a group of the same size. The control group was exposed to air only. Rats were randomly assigned to treatment groups using a computer-based randomization and body weights. During exposure, rats were individually restrained in perforated, stainless-steel cylinders with conical nose pieces. Restrainers were inserted into face-plates on 150-litre exposure chambers such that the nose of each rat protruded into the chamber. Exposures were 6 hours a day and 5 days a week for 2 weeks. A recovery period lasting up to 84 days was utilized for some animals. Five rats of each sex were sacrificed after the 10th exposure and after 2 weeks recovery. Five male rats per group were also sacrificed after 6 and 12 weeks of recovery.

Test material or positive control substance vapors were generated by pumping the liquid test material through Teflon tubing using Harvard Model 975 compact infusion pumps into three-neck, glass, round-bottomed mixing flasks. For diglyme the flask was heated to 111-123 C and for 2-methoxyethanol the flask was heated to 79-87 C to facilitate evaporation.. Conditioned and filtered air was added to the mixing flask at approximately 35-46 liters/min to dilute and sweep the vapor through unheated glass connecting tubes into the inlets of the 150-liter exposure chambers. Exposure chamber concentrations were adjusted by varying the test material feed rate into the mixing flasks.

Chamber concentrations were determined at approximately 30-min intervals during each exposure. For diglyme analysis, known volumes of the chamber atmospheres were drawn from the rats' breathing zone through tandem glass impingers containing acetone as the trapping solvent. For 2-methoxyethanol analyses, replicate gas samples (approx. 0.5 ml) were collected from the breathing zone of the rats with a gas-tight syringe. Samples were analyzed by gas chromatography using a fame ionization detector. Exposure concentrations were calculated with standard curves prepared daily. Chamber temperature and relative humidity were measured regularly during each exposure.

Experimental observations.

All rats were weighed and observed for clinical signs daily and for the 14-day post-exposure recovery period. Male rats assigned to the extended recovery groups were also weighed and observed at least once a week for up to 12 weeks after the last exposure.

Urine samples were collected only from rats that were assigned to be sacrificed from those within 24 hours of urine collection. Urine specimens were collected overnight from five rats of each sex per exposure group after the 9th exposure and on the 13th day of recovery. Urine was also collected from the long-term male recovery rats on the 41st day of recovery and on the 83rd day of recovery. Samples were analyzed for volume,

osmolality, urobilinogen, pH, haemoglobin or occult blood, glucose, protein, bilirubin and ketone.

Blood samples (from rats lightly anaesthetized with carbon dioxide) were taken from the orbital sinus of five rats of each sex per group after the 10th exposure and on the 14th day of recovery, and from five male rats per group on the 42nd day of recovery, and on the 84th day of recovery. Blood samples were analyzed for erythrocyte count, haemoglobin concentration, haematocrit, platelet count, leucocyte count, and relative numbers of neutrophils, band neutrophils, lymphocytes, atypical lymphocytes, eosinophils, monocytes and basophils. Mean corpuscular volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration were calculated from the erythrocyte data. Serum activities/levels of the following were determined :

alkaline phosphatase (AP),
alanine aminotransferase (ALT),
aspartate aminotransferase (AST),
urea nitrogen,
creatinine,
total protein
cholesterol

Rats were sacrificed as assigned by sodium pentobarbital anesthesia and exsanguination for gross and histopathological examinations. The lungs, liver, kidneys, spleen and male reproductive organs (testes, epididymides, seminal vesicles and prostate) were weighed at necropsy. Bone, eyes testes and epididymides were fixed in Bouin's solution. All other organs and tissue were fixed in 10% formalin solution. Paraffin sections were prepared according to standard laboratory SOPs. All sections were stained with hematoxylin and eosin. In addition, all testes were stained with the PAS method.

Representative samples of the following tissues were prepared for microscopic examination: heart, lungs, mesenteric and mediastinal lymph nodes, nasal cavities, trachea, liver, pancreas, oesophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum, kidneys, urinary bladder, bone/bone marrow (sternal), spleen, thymus, thyroid gland, adrenal glands, brain, eyes, testes, epididymides, prostate, seminal vesicles, vagina, ovaries, uterus, and any other organs or tissues with gross lesions.

Statistical analyses: Mean body weights, body weight gains, absolute organ weights, and relative organ weights (organ to body weight ratios) of treated animals were compared with control rats during the exposure and recovery periods. Data were statistically analyzed by one-way analysis of variance. Exposure group values were compared with controls by the least significant difference or Dunnett's tests when the ratio of variance (F) indicated a significant among-to-within group variation. Differences were considered significant at the 0.05 probability level. Clinical pathology data were analyzed by a one-way analysis of variance and Bartlett's test. When the F-test was significant, Dunnett's test was used to compare means from the control group with each treatment.

Result

:

EXPOSURES

Analytical glyme concentrations were 110, 370 and 1100 ppm. The mean concentration of 2-methoxyethanol was 300 ppm.

In the diglyme exposure chambers temperatures ranged from 23 to 35 deg. C and relative humidity varied from 42 to 77%. In the 2-methoxyethanol chamber, temperature ranged from 22 to 32 deg C and relative humidity varied from 41 to 61%. In the air control chamber, temperature ranged from 22 to 28 deg C, relative humidity varied from 38 to 51%. The maximum observed temperature of 35 C was a transient excursion and occurred only once in the 300 ppm diglyme group. Restrainer temperatures were at ambient conditions.

CLINICAL OBSERVATIONS

At the high concentration, seven males had colored ocular discharge and 17 males and one female had diarrhea during the exposure phase. Diarrhea was observed in eight males from the 300 ppm 2-methoxyethanol group. Diarrhea and ocular discharge were transient clinical signs first noted during week 1 or 2 of exposure. No other chemical-related clinical observations were observed.

BODY WEIGHTS

Mean body weights of male rats from all test groups were lower than controls throughout the exposure period. Body weight gains were less with higher exposure levels. Weight losses in rats exposed to 2-methoxyethanol were greater than in the 370 ppm diglyme group but lower than the 1100 ppm diglyme group. Weight recovery began after the 10th exposure such that mean body weights were comparable to control values by recovery day 14 for the 110 ppm group rats, by recovery day 28 for the 370 ppm group, and by recovery day 42 for the 1100 ppm diglyme and 300 ppm 2-ME groups. No significant body weight differences were observed in female rats throughout the study.

BODY WEIGHTS, MALES

Ex Day	-----DIGLYME----				2-ME 300ppm
	0	110	370	1100	
1	246	244	245	244	239
3	259	246*	245*	232*	240*
5	271	257*	257*	233*	243*
8	297	285*	284*	246*	277*
12	312	280*	285*	250*	270*
rd-7	362	342*	338*	291*	330*
rd-14	398	385	377*	342*	371*
rd-28	491	463	476	438	461
rd-42	533	524	577	530	531
rd-84	582	570	632	573	571

* p < 0.05

BODY WEIGHTS, FEMALES

Ex Day	-----DIGLYME-----				2-ME 300ppm
	0	110	370	1100	
1	187	192	191	189	185
3	190	193	192	180*	189
5	195	200	198	187	194
8	200	208	212	202	211
12	203	213	214	202	208
rd-7	238	244	236	228	246
rd-14	247	252	238	239	253

* p < 0.05

CLINICAL PATHOLOGY:

Male and female rats exposed to 1100 ppm diglyme or 300 ppm 2-methoxyethanol were moderately anemic showing a reduction in red blood cell count, hemoglobin and hematocrit after the 10th exposure. After 14 days of recovery, clinical signs of anemia were not detected in any treatment group.

Platelet counts of male and female rats from several of the diglyme and 2-methoxyethanol groups were reduced after 14 days of recovery but not on day-10 after the last exposure. Platelet counts returned to control values by 42 days of recovery in male rats.

Compared with control values, mean leukocyte counts were reduced in male rats from all test groups and in female rats from the 1100 ppm diglyme and 300 ppm 2-methoxyethanol groups after the last exposure. Lymphopenia was concentration related, with the most severe effects seen in the 1100 ppm diglyme group. Lymphopaenia was also observed in the 1100 ppm diglyme and 300 ppm 2-methoxyethanol females.

Serum activities of ALT, AST and AP and total protein concentrations were reduced in male and female rats exposed to 1100 ppm diglyme compared with controls after the 10th exposure. Similar, but less severe, effects were noted in male and female rats exposed to 2-methoxyethanol. After 14 days of recovery, serum hepatic enzyme activities and serum protein concentrations were similar to control values in all test groups.

ORGAN WEIGHTS:

Absolute and relative weights of male reproductive organs were reduced in diglyme and 2-methoxyethanol exposed rats compared with controls (see table for absolute weights). The extent of the effects was generally concentration related, with the most severe effects observed in the 1100 ppm diglyme and the 300 ppm 2-methoxyethanol groups. A concentration-related reduction in prostate and seminal vesicle weights occurred in the 370 and 1100 ppm diglyme and 300 ppm 2-methoxyethanol groups.

Testes weights were lower in the 1100 ppm diglyme and 300 ppm 2-methoxyethanol groups. After 14 days recovery, mean absolute testes and epididymides weights in the 370 and 1100 ppm diglyme and 300 ppm 2-methoxyethanol groups and prostate weights in the 1100 ppm diglyme and 300 ppm 2-methoxyethanol groups remained lower than controls. After 42 and 84 days of recovery, mean testes weights in the 1100 ppm diglyme and 300 ppm 2-methoxyethanol groups were lower than control values;

mean absolute testes weights were also lower than controls in the 110 and 370 ppm diglyme groups after 42 days of recovery and mean relative epididymides weights were lower than controls in the 370 ppm diglyme group after 84 days of recovery.

In female rats, the only significant weight changes associated with diglyme exposure was increased mean absolute and relative liver weights in the 1100 ppm group and increased mean absolute liver weights in the 370 ppm group after the 10th exposure.

ORGAN	Test day	0	-----DIGLYME-----			2-ME (300)ppm
			110	370	1100	
Testes	10	2.88	2.75	2.64	1.45*	1.76*
	R14	3.10	2.89	2.66*	1.08*	1.43*
	R42	3.41	3.05	2.85*	1.33*	1.98*
	R84	3.49	3.29	3.40	2.69*	2.85*
Prostate	10	0.58	0.53	0.40*	0.33*	0.34*
	R14	0.79	0.82	0.87	0.64*	0.65*
	R42	1.17	1.28	1.23	1.09	1.02
	R84	1.49	1.36	1.61	1.40	1.56
Seminal vesicles	10	1.38	1.23	1.07*	0.92*	0.92*
	R14	1.83	1.96	1.40	1.52	1.65
	R42	2.75	2.00	2.53	2.61	2.74
	R84	3.28	2.76	2.86	2.76	2.91
Epididym.	10	0.77	0.86	0.80	0.70	0.68
	R14	1.06	1.06	0.93*	0.66*	0.79*
	R42	1.38	1.29	1.23	0.84*	1.04*
	R84	1.60	1.59	1.52	1.18*	1.36*

GROSS PATHOLOGY:

After 10 exposures, the thymus and reproductive organs (testes, prostate, seminal vesicles and epididymides) of male rats exposed to 1100 ppm diglyme or 300 ppm 2-methoxyethanol were smaller than controls. After 42 days of recovery, the prostate, seminal vesicles and thymus appeared normal at necropsy in both these groups; however, testes and epididymides in rats from these groups were observed to be small at all examination times. Overall, the gross lesions in male rats were consistent with the microscopic observations. These observations were noted in rats exposed to either 100 or 300 ppm diglyme.

No compound-related gross lesions were noted upon necropsy in female rats.

MICROSCOPIC EXAMINATION

DIGLYME

After 10 diglyme exposures at 110 ppm, slight testicular atrophy was observed microscopically in two of five male rats, while two of five controls had minimal testicular atrophy. In both groups, the epididymal tubules contained exfoliated degenerative germ cells. No control rats had testicular atrophy following 14, 42 or 84 days recovery. After 14 days recovery, two of five rats exposed to 110 ppm diglyme were observed to have slight testicular atrophy. After 42 days recovery, two of five rats in this group showed minimal testicular injury involving a small number of atrophic tubules; most seminiferous tubules had normal germinal epithelium. After 84 days recovery, the testicular germinal epithelium morphology was normal.

After 10 diglyme exposures at 370 ppm, slight testicular atrophy primarily affecting spermatocytes and immature spermatids were seen in all males. After 14 days of recovery, minimal to moderate testicular atrophy was present in all five rats. Immature spermatids and spermatocytes were found, but mature spermatozoa had not yet developed. Exfoliated degenerative germ cells and a slightly reduced number of spermatozoa were found in the epididymal tubules. After 42 days recovery, only the testes of two of five rats exhibited very slight testicular atrophy. After 84 days recovery, the morphology of the testicular germinal epithelium was since considered normal.

After 10 diglyme exposures at 1100 ppm all males showed severe testicular atrophy. The germinal epithelium showed extensive damage and all spermatogenic stages of germ cells were affected; numerous spermatid giant cells were also present. The epididymal tubules showed numerous exfoliated degenerative germinal cells and slight to moderate oligospermia. After 14 days recovery, the seminiferous tubules showed slight regeneration of spermatocytes and spermatids. Some seminiferous tubules were lined with only Sertoli cells and a few spermatogonia. Slight Leydig cell hyperplasia was present in all rats. The epididymal tubules contained numerous spermatid giant cells with only a few spermatozoa (moderate to severe oligospermia). After 42 days recovery, many tubules showed a regenerating germinal epithelium consisting of spermatocytes and immature spermatids although minimal to moderate Leydig cells hyperplasia persisted. The epididymal tubules contained numerous exfoliated germinal cells and few spermatozoa (moderate to severe oligospermia). After 84 days recovery, three of four rats had almost normal germinal epithelium, but the remaining rat showed moderate testicular atrophy with only partially regenerated germinal epithelium. In addition to the testicular effects, the seminal vesicles and prostate were atrophic after 2 wk of exposure but these effects had reversed by 14 and 42 days of recovery, respectively. Minimal to severe bone marrow hypoplasia and lymphoid tissue atrophy of the spleen and thymus were apparent in both male and female rats exposed to 1100 ppm diglyme. Atrophic changes in the hematopoietic tissues of rats from this group resolved after 14 days of recovery; however, extramedullary hematopoietic foci were evident in the liver of rats of each sex and in the spleens of males. Evidence of hematopoietic effects in males was essentially absent after 42 days of recovery.

2-METHOXYETHANOL

2-Methoxyethanol exposure also produced adverse effects in hematopoietic tissues of male and female rats and testicular injury in males. Ten exposures to 300 ppm 2-methoxyethanol for produced a transient, minimal to moderate atrophy of thymic lymphoid tissues in males and females and atrophy of splenic lymphoid tissues in males; these effects were not evident after 14 days recovery. Slight to severe testicular atrophy was a finding in all rats killed at the end of the exposure period. The germinal cells (spermatocytes) were the primary cell type damaged. The magnitude of the testicular injury produced by 300 ppm 2-methoxyethanol was more severe than that in the 370 ppm diglyme group but slightly less severe than that produced by 1100 ppm diglyme. After 14 days recovery, male rats had severe testicular atrophy, although slight regeneration of germinal epithelium, spermatocytes and immature

spermatids was noted in seminiferous tubules. In addition, minimal to mild Leydig cell hyperplasia was observed in all five rats. The epididymal tubules contained exfoliated degenerative germinal cells, spermatid giant cells, and a decreased number of spermatozoa (severe oligospermia). After 42 days recovery, many tubules had normal germinal epithelium, but slight atrophy persisted. Some tubules exhibited regenerating spermatocytes or immature spermatids, but were devoid of mature spermatids and spermatozoa. Severely damaged tubules were lined with Sertoli cells and a few spermatogonia or spermatocytes. Epididymal tubules were filled with numerous exfoliated germinal cells and a few spermatogonia (moderate to severe oligospermia). After 84 days of recovery, most of the testes had normal germinal epithelium morphology, but some testes still had a few seminiferous tubules showing incompletely regenerated germinal epithelium. The prostate and seminal vesicles exhibited a slightly atrophic structure after 10 exposures and 14 days of recovery, but had regained the normal structure by 42 days recovery.

Test substance : Diglyme, CASNO 111-96-6 >99% pure

Conclusion : Administration of diglyme by inhalation produced a variety of concentration-related effects to the reproductive system of male rats and the hematopoietic system of male and female rats. Adverse effects occurred at lower exposure concentrations in males than in females.

The reproductive and hematopoietic effects were generally reversible, although complete recovery from testicular injury was not observed in some rats exposed to the highest concentration of diglyme. The NOEL for repeated exposure to diglyme in female rats is 370 ppm, while a NOEL for male rats was not demonstrated (<110 ppm).

Reliability : Diglyme appeared to be approximately two- to threefold less potent than 2-methoxyethanol on a molar basis.
(1) valid without restriction

Flag : Modern guideline-like GLP study with full documentation available.
26.12.2003 : Critical study for SIDS endpoint (19)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Salmonella typhimurium reverse mutation assay

System of testing :

Test concentration :

Cycotoxic concentr. :

Metabolic activation : with and without

Result : negative

Method : other: NTP Protocol

Year :

GLP : yes

Test substance :

Method : As each strain of Salmonella typhimurium is genetically different, using several strains in a test increases the opportunity of detecting a mutagenic chemical. All strains of Salmonella typhimurium used for mutagenicity

testing carry a defective (mutant) gene that prevents them from synthesizing the essential amino acid histidine. Mutations leading to the ability to synthesize histidine are called "back" or "reverse" mutations and the process is referred to as "reversion."

Some test protocols utilize extracts of Aroclor rat or hamster liver enzymes (S9) to promote metabolic conversion of the test chemical. This is necessary since the Salmonella bacterium does not have the mammalian metabolic capabilities.

In the Salmonella assay, a test tube containing a suspension of one strain of Salmonella typhimurium plus S9 mix or plain buffer without S9, is incubated for 20 minutes at 37° C with the test chemical. Control cultures, with all the same ingredients except the test chemical, are also identically incubated. In addition, positive controls with a known potent mutagen, are prepared. After 20 minutes, agar is added to the cultures and the contents of the tubes are thoroughly mixed and poured onto the surface of petri dishes containing standard bacterial culture medium. The plates are incubated, and bacterial colonies that do not require an excess of supplemental histidine appear and grow. These colonies are comprised of Salmonella that have undergone reverse mutation to restore function of the histidine-manufacturing gene. The number of colonies is counted after 2 days.

Several doses (at least 5) of each test chemical and multiple strains of Salmonella typhimurium are used in each experiment. In addition, cultures are set up with and without added S9 liver enzymes at 10% concentration in these studies.

The pattern and the strength of the mutant response are taken into account in determining the mutagenicity of a chemical. All observed responses are verified in repeat tests. If no increase in mutant colonies is seen after testing several strains under several different culture conditions, the test chemical is considered to be nonmutagenic in the Salmonella test.

Reference

Mortelmans K, Zeiger E. The Ames Salmonella/microsome mutagenicity assay. *Mutat Res.* 2000 Nov 20;455(1-2):29-60.

Remark

:

This result is supported by negative results from three other Ames tests. McGregor reported two and the other is contained in two unpublished reports from Hoechst AG

References for supporting studies:

McGregor DB, Willins MJ, McDonald D, Holmstrom M, McDonald D, Niemeier RW (1983) Genetic effects of 2-methoxyethanol and bis(2-methoxyethyl)ether. *Toxicology and applied pharmacology*, 70:303-316 .

Hoechst (1979d) Test for mutagenicity in bacteria strains in the absence and presence of a liver preparation. Frankfurt am Main, Hoechst AG, 7 pp. (Report 53/79; unpublished). as cited in: Concise International Chemical Assessment Document 41, Diethylene Glycol Dimethyl Ether. International Program on Chemical Safety, World Health Organization Geneva, 2002

Hoechst (1979e) Mutagenicity evaluation of diethyleneglycoldimethylether in the Ames Salmonella/microsome plate test. Frankfurt am Main, Hoechst AG, 15 pp. (Report 743/79, unpublished). as cited in: Concise International Chemical Assessment Document 41, Diethylene Glycol Dimethyl Ether. International Program on Chemical Safety, World Health Organization Geneva, 2002

5. Toxicity

Id 111-96-6
Date 29.12.2003

Result

: Summary Information for Diglyme (111-96-6)
Study Vehicle: Water
Protocol: Preincubation
Result: Negative

Strain: TA100

Dose	No MA (equiv)		No MA (neg)		10% RLI (neg)		10% RLI (neg)		10% HLI (equiv)		10% HLI (neg)	
	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem
0	142	10	104	19.4	199	5	139	7.7	191	10.1	141	6.2
100	138	10.1	105	3.5	184	1.5	121	3.9	188	9.5	133	4.9
333	164	6.2	96	12.9	196	22.3	124	6.7	185	25.8	136	2.4
1000	189	11.5	103	17.9	237	18.2	151	14.2	228	8.1	148	13.5
3333	179	14.6	107	12.2	219	3.2	142	5.5	254	7.8	150	18.9
10000	180	9.9	85	1.7	222	24.3	159	12	251	18.9	160	12.4
Pos Co	390	42.2	287	6.8	498	10.3	326	12.2	650	90.7	547	20.3

Strain: TA1535

Dose	No MA (neg)		No MA (neg)		10% RLI (neg)		10% RLI (neg)		10% HLI (neg)		10% HLI (neg)	
	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem
0	10	1.2	9	1.2	15	0.7	11	2.6	11	1.5	8	0.6
100	8	1.2	7	1.2	8	2.7	7	2.3	11	2.1	8	1.5
333	10	1.5	9	1.5	8	1.7	6	1.2	8	1.2	5	1
1000	8	2.2	8	1.9	13	1.5	10	1.2	8	2.2	6	1.5
3333	9	1.5	8	1.5	9	2.1	7	1.5	10	0.9	6	1.5
10000	7	0.9	6	1	7	2.1	5	1.5	7	1.7	5	1.2
Pos Co	229	8	232	12.5	56	10.7	29	3.2	62	8.2	87	7.4

Strain: TA1537

Dose	No MA (neg)		No MA (neg)		10% RLI (neg)		10% RLI (neg)		10% HLI (neg)		10% HLI (neg)	
	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem
0	8	1.5	6	1.2	7	2.3	7	1.7	9	1.5	9	0.3
100	5	2.6	5	1.3	8	1.9	8	1.5	9	1.3	7	2.3
333	6	0	5	1.2	7	2	7	1.2	8	1.2	6	1.2
1000	7	1.2	6	0.6	8	2.3	9	0.3	7	0.9	7	0.3
3333	5	0.6	5	2.3	8	1.8	8	0.9	4	0.3	7	1.8
10000	6	1.2	6	0.7	12	0.6	8	2.1	7	2.2	8	0.7
Pos Co	496	32	218	19.9	88	14	31	3.5	134	6.4	79	8.4

Strain: TA98

Dose	No MA (neg)		No MA (neg)		10% RLI (neg)		10% RLI (neg)		10% HLI (neg)		10% HLI (neg)	
	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem	Mean	sem
0	13	0.9	14	0.7	24	3.8	20	1.2	28	3	19	1.5
100	14	2.1	15	1.5	21	1.5	19	1.2	27	1.8	21	2
333	14	1.5	15	1.7	21	1.9	16	1.8	27	0.7	21	1.2
1000	15	1	16	0.3	20	4	18	1.2	21	2.6	17	1.2
3333	16	2.6	17	0.3	30	2.9	21	3.1	21	2	17	1
10000	23	2.6	18	4.1	29	0.3	19	2.6	24	2.3	22	2.7
Pos Co	374	18.7	209	27	529	48.8	125	7.6	905	73.9	251	10.7

S = Slight Toxicity
MA = Metabolic Activation
RLI = Rat Liver, Induced
HLI = Hamster Liver, Induced

Test substance

: Diglyme, CASNO 111-96-6

Conclusion

: Material was non-mutagenic in the presence or absence of a standard liver metabolic activating system

Reliability

: (1) valid without restriction
NTP guideline study using optimized conditions

Flag

22.12.2003

: Critical study for SIDS endpoint

(3)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 7 hr/day for 1 or 5 days
Doses : 0, 250 or 1000 ppm
Result : negative
Method :
Year :
GLP :
Test substance :

Method

: CD rats (Sprague-Dawley derived) were used and were obtained from Charles River (UK)

Test atmospheres were generated by bubbling dry oxygen-free nitrogen through diglyme contained in a Dreschsel bottle that was maintained in a water bath at 50 deg C. The vapor stream was diluted with filtered conditioned air and passed into the inhalation chamber. The chamber was a 1.5 cubic meter in volume, constructed of stainless steel and glass and contained in which individually caged rats were confined to a single tier of cages occupying 0.5 cubic meters. Air exchange rate was 12 exchanges per hour.

Atmospheres were analyzed by infrared spectroscopy with a Foxboro Miran-1A Gas Analyzer using a continuous flow and automatic monitoring system. Calibration was done by injecting a known volume of liquid test material into the chamber with a precision syringe and running the chamber in a closed-loop mode until the reading stabilized.

Groups of 10 adult rats of each sex were exposed for 7 hours/day for 5 days to 0, 250 or 1000 ppm diglyme as a vapor. After their last exposure period, animals were injected ip with 3 mg colchicine/kg 2 hr prior to sacrifice. Three sampling times (6, 24, and 48 hr after the end of exposure) were used for the 1-day of exposure groups. The 5-day exposed groups were sacrificed 6 hours after completion of the final exposure.

After sacrifice, bone marrow was removed and fixed to a microscope slide prior to standard staining with Giemsa. Stained slides were labeled with numbers not directly correlated with the animal numbers; therefore, all assessments of metaphases were conducted "blind." Where possible, 50 metaphases per rat were scored.

Remark

:

That the exposure levels were high enough for an adequate test of clastogenicity can be ascertained from the following information:

- 1.) Rats were severely sedated while in the chambers.
- 2.) The identical conditions and chambers were used to dose rate for the dominant lethal test. In this other test using the same equipment at the same dose, testes of male rats were severely affected as evidenced by

severe lack of reproductive function (ability to effectively cause pregnancy in an appropriate female) in high-dose exposed animals during the 4 to 8 week period after exposure.

3.) Using the same exposure concentrations and time, four of ten mice died as a result of only four exposures

Supporting a lack of clastogenicity is a study described in the same published report of the ability of diglyme to cause Unscheduled DNA Synthesis. In this in vitro study, concentrations of diglyme up to 19 mg/ml incubated with human embryonic intestinal fibroblasts (Flow 11,000 cells at passages 12 to 35) in the presence and absence of a S-9 mix to supply metabolic activation, did not induce the uptake of tritiated-thymidine using a standard procedure.

Also adding support is the information that the glycol ethers, as a class, lack significant genotoxic activity (ECETOC The toxicology of glycol ethers and its relevance to man. Brussels, European Centre for Ecotoxicology and Toxicology of Chemicals, pp. 1-350 (Technical Report No . 64), 1995.

Result	:	In neither the 5-day nor the single exposure test was there any good evidence for the induction of chromosomal damage, other than in the positive control groups. The only significant increases in aberrant cell frequency occurred in the low-dose male group 6 hr following a single exposure to the test material. Slides from male rats exposed to 250 ppm diglyme demonstrated a small increase in the frequency of total aberrations (t = 2.216, p < 0.05). These elevations were restricted to a single sex in each case and were not reproduced at the higher dose levels. It was concluded, therefore, that diglyme is not clastogenic
Test substance	:	Diglyme, CASNO 111-96-6, obtained from Aldrich (batch 21150)
Conclusion	:	Diglyme is not clastogenic to rats of either sex after high-dose administration by inhalation over 5 days
Reliability	:	(2) valid with restrictions
Flag	:	Published study with scientifically defensible design using appropriate dose levels.
28.12.2003	:	Critical study for SIDS endpoint

(15)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type : other: Dominant Lethal
Species : rat
Sex :
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 7h/day, 5 continuous days
Frequency of treatm. : daily for 5 days
Premating exposure period
 Male : fixed time exposure with recovery
 Female :
Duration of test :
No. of generation studies :
Doses : 250 or 1000 ppm
Control group : yes, concurrent vehicle

Method

:
 CD rats (Sprague-Dawley derived) were used and were obtained from Charles River (UK)

Test atmospheres were generated by bubbling dry oxygen-free nitrogen through diglyme contained in a Dreschsel bottle that was maintained in a water bath at 50 deg C. The vapor stream was diluted with filtered conditioned air and passed into the inhalation chamber. The chamber was a 1.5 cubic meter in volume, constructed of stainless steel and glass and contained in which individually caged rats were confined to a single tier of cages occupying 0.5 cubic meters. Air exchange rate was 12 exchanges per hour.

Atmospheres were analyzed by infrared spectroscopy with a Foxboro Miran-1A Gas Analyzer using a continuous flow and automatic monitoring system. Calibration was done by injecting a known volume of liquid test material into the chamber with a precision syringe and running the chamber in a closed-loop mode until the reading stabilized.

Groups of 10 adult male rats were exposed for 7 hours/day for 5 days to 0, 250 or 1000 ppm diglyme. After the exposure period they were serially mated with untreated virgin females, 2 females per male. The females were sacrificed 17 days after first being caged with exposed males and examined for evidence of pregnancy by the method of Bateman (Handbook of Mutagenicity Test Procedures ed. by BJ Kilbey et al., Elsevier, Amsterdam)

Result

:
 Exposure to 1000 ppm diglyme 7 hr/day for 5 days was associated with a significant reduction in the pregnancy frequency (females with implantations) starting with mating that occurred 4 weeks after dosing (week 4) where only 50% of mated females showed evidence of implantations. The pregnancy frequency was further reduced in week 5, 6 and 7 matings to about 10% of the mated females showing implantations when sacrificed 17 days after mating with males exposed to 1000 ppm diglyme. Air controls and male rats exposed to 250 ppm diglyme showed no changes in pregnancy frequency.

The number of corpora lutea per pregnancy, the live implants and the number of implantation sites were enumerated and manipulated using the Freeman-Tukey Poisson transformation and the Freeman-Tukey binomial transformation searching for evidence of early death that would be indicative of a dominant lethal effect. The mathematical transformations indicated some evidence of early deaths that could be indicative of a dominant lethal induction in exposed males. The results are given in the tables below:

##PREGNANCY FREQUENCY AND PERCENT

WEEK	-----DIGLYME CONCENTRATION-----					
	0		250 ppm		1000 ppm	
1	18/20	90%	19/20	95%	15/20	75%
2	19/20	95%	18/20	90%	19/20	95%
3	18/20	90%	18/19	95%	16/20	80%
4	19/20	95%	19/20	95%	10/20	50%
5	19/20	95%	18/20	90%	2/19	11%
6	20/20	100%	20/20	100%	2/20	10%
7	19/20	95%	20/20	100%	2/20	10%
8	19/20	95%	20/20	100%	8/20	40%
9	19/20	95%	19/20	95%	10/20	50%
10	18/20	90%	19/20	95%	17/20	85%

##TOTAL NUMBER CORPORA LUTEA PER PREGNANCY

WEEK	-----DIGLYME CONCENTRATION-----		
	0	250 ppm	1000 ppm
1	12.7 ±0.54	12.5 ±0.53	12.6 ±0.59
2	13.3 ±0.50	13.2 ±0.52	13.3 ±0.50
3	14.8 ±0.79	13.8 ±0.79	12.4 ±0.84*
4	12.2 ±0.54	12.5 ±0.54	11.1 ±0.74
5	13.8 ±0.55	12.6 ±0.57	12.5 ±1.71
6	13.4 ±0.55	12.3 ±0.55	7.0 ±1.75**
7	12.2 ±0.34	11.8 ±0.33	2.5 ±1.04***
8	11.8 ±0.62	11.9 ±0.60	11.9 ±0.96
9	13.7 ±0.57	13.2 ±0.57	12.0 ±0.79
10	12.9 ±0.51	12.3 ±0.50	12.6 ±0.52

##TOTAL IMPLANTATIONS PER PREGNANCY

WEEK	-----DIGLYME CONCENTRATION-----		
	0	250 ppm	1000 ppm
1	13.0 ±0.63	12.0 ±0.61	13.4 ±0.61
2	13.6 ±0.54	12.4 ±0.55	13.7 ±0.54
3	13.8 ±0.78	12.5 ±0.78	12.4 ±0.82
4	12.4 ±0.60	12.3 ±0.60	9.9 ±0.82*
5	13.5 ±0.53	13.1 ±0.55	11.0 ±1.64
6	13.0 ±0.47	13.6 ±0.47	2.5 ±1.49***
7	12.0 ±0.31	11.7 ±0.31	2.0 ±0.97***
8	12.1 ±0.68	12.3 ±0.67	11.8 ±1.06
9	11.6 ±0.63	12.4 ±0.63	10.4 ±0.87
10	12.3 ±0.50	12.1 ±0.49	11.5 ±0.52

##SUM OF LIVE IMPLANTS AND LATE DEATHS

WEEK	-----DIGLYME CONCENTRATION-----		
	0	250 ppm	1000 ppm
1	12.5 ±0.69	11.6 ±0.67	12.4 ±0.75
2	13.2 ±0.56	12.1 ±0.57	13.1 ±0.56
3	13.3 ±0.78	11.6 ±0.78	11.6 ±0.82
4	11.9 ±0.64	11.8 ±0.64	9.5 ±0.88*
5	13.3 ±0.54	12.4 ±0.55	9.5 ±1.65*
6	12.3 ±0.46	13.3 ±0.46	1.5 ±1.47***
7	11.3 ±0.33	11.5 ±0.32	2.0 ±1.01***
8	11.5 ±0.72	11.6 ±0.70	11.0 ±1.11
9	11.1 ±0.62	12.0 ±0.62	10.0 ±0.85
10	12.3 ±0.48	12.2 ±0.47	11.6 ±0.50

##EARLY DEATH FREQUENCY Freeman-Tukey Poisson Transformation

WEEK	-----DIGLYME CONCENTRATION-----		
	0	250 ppm	1000 ppm
1	1.63 ±0.209	1.52 ±0.204	2.00 ±0.229
2	1.52 ±0.186	1.43 ±0.192	1.86 ±0.186
3	1.67 ±0.262	1.96 ±0.262	1.63 ±0.278
4	1.64 ±0.196	1.60 ±0.196	1.50 ±0.269
5	1.30 ±0.188	1.82 ±0.193	2.78 ±0.579*
6	1.85 ±0.187	1.50 ±0.187	2.07 ±0.591
7	1.79 ±0.169	1.28 ±0.164	1.00 ±0.519
8	1.67 ±0.207	1.78 ±0.201	1.89 ±0.318
9	1.55 ±0.191	1.63 ±0.191	1.50 ±0.264
10	1.36 ±0.219	1.96 ±0.213	1.71 ±0.225

- Test substance** : Diglyme, CASNO 111-96-6, obtained from Aldrich (batch 21150)
- Conclusion** : Although there was some evidence for post-implantation losses that are suggestive of a dominant lethal effect, the result was confounded by the very low number of total implantations in those weeks. As there is an independent association between a low number of implantations and post implantation loss and as the numbers of post-implantation losses were very small and only occurred in weeks where the number of total implantations was low, the results of the test are equivocal regarding a dominant lethal effect.
- The authors concluded that the effect of diglyme "on male fertility and embryonic development are of much greater importance than genetic effects when setting tolerable limits"
- Reliability** : (2) valid with restrictions
- Flag** : Published study with robust design at appropriate dose levels.
28.12.2003 : Critical study for SIDS endpoint

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : mouse
Sex : female
Strain : CD-1
Route of admin. : gavage
Exposure period : gestation day 6-15
Frequency of treatm. : daily
Duration of test : to gd 17
Doses : 0, 62.5, 125, 250 or 500 mg/kg-day
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 500 mg/kg bw
NOAEL teratogen. : = 125 mg/kg bw
NOAEL Fetotoxicity : = 62.5 mg/kg bw
Result : Specific Developmental Toxin
Method : other: NTP
Year :
GLP : yes
Test substance :

Method

Mice of the strain Crl:CD-1(ICR)Br were obtained from Charles River Laboratory (Kingston, NY) and maintained at 19.4 to 22.2 deg C and RH 40-76% on a 12 hour light/dark cycle with food and water ad libitum. Females were mated one to one with males of the same strain. Vaginal plug positive females (called gestational day zero when found) were randomly (stratified to keep mean body weights per group even) assigned to dose groups and group housed.

Diglyme () was administered to pregnant mice by oral gavage, using water as vehicle, on gestational days (gd) 6-15 in the morning between 8:30 and 10:30 AM at dose levels of 0, 62.5, 125, 250 or 500 mg/kg/day. These dose were selected on the basis of preliminary study on pregnant mice of the same strain. There were 20-24 confirmed pregnant mice per group, divided into two replicates at least 2 weeks apart. Mice were monitored daily during treatment for evidence of maternal toxicity.

OBSERVATIONS.

Mice were weighed alive on gd 0, 6 through 15, and immediately following sacrifice on gd 17. Dams were observed daily during treatment for clinical signs of toxicity. Maternal liver weights and gravid uterine weights were measured following sacrifice by cervical dislocation. Uterine contents were evaluated for the number of implantation sites, resorptions, late fetal deaths (i.e., fetuses with discernible digits and weighing greater than 0.3 g, but displaying no vital signs on gd 17) and live fetuses. When visible evidence of pregnancy was not observed, the uterus was stained with 10% ammonium sulfide to reveal possible early resorptions. Live fetuses were dissected from the uterus and anesthetized by using hypothermia. Each live fetus was weighed and examined for external morphological abnormalities. The viscera were then examined using a fresh tissue dissection technique. Half of the fetuses' heads were removed prior to dissection and the heads were fixed in Bouin's solution for free-hand sectioning and examination. All fetal carcasses were cleared and double stained with Alcian blue/Alizarin red S prior to examination for skeletal malformations.

STATISTICAL ANALYSES.

Analyses of data were carried out using the General Linear Model procedure in the SAS software library (SAS Institute, Inc., Cary NC). Prior to analysis, an arcsine-square root transformation was performed on all litter-derived percentage data. Dose-response relationships for selected measures were evaluated using a test for linear trend. Analysis of variance was employed to determine whether significant dose effects, replicate effects or dose X replicate interactions had occurred. When ANOVA revealed significant differences among groups, then Williams' multiple comparison test and Dunnett's test were used to compare diglyme-treated groups to the vehicle control group (using an alpha level = 0.05). Nominal scale measures were analyzed by a test for linear trend on proportions, and a XZ test for independence among treatment groups. When XZ revealed significant ($p < 0.05$) differences among groups, then a one-tailed Fisher exact probability test (alpha level = 0.05) was used for pairwise comparisons between each treated group and the vehicle control group.

Remark

:

This result is also supported by an inhalation study of pregnant rats indicating diglyme is a developmental toxin below maternally toxic doses (i, ii) and a gavage study in rabbits indicating developmental toxicity in the rabbit (iii, iv)

i.) Driscoll CD, Valentine R, Staples RE, Chromey NC, Kennedy GL Jr Developmental toxicity of diglyme by inhalation in the rat. Drug and chemical toxicology, 21(2):119-136 (1998).

ii.) DuPont Teratogenicity study of diglyme in the rat . Newark, NJ, E.I. Du Pont de Nemours & Co., 289 pp .1988

iii.) Schwetz BA, Price CJ, George JD, Kimmel CA, Morrissey RE, Marr MC The developmental toxicity of diethylene and triethylene glycol dimethyl ethers in rabbits. Fundamental and applied toxicology, 19(2):238-245 (1992)

iv.) NTP Teratologic evaluation of diethylene glycol dimethyl ether (CAS No. 111-96-6) administered to New Zealand White rabbits on gestation days 6 through 19. Research Triangle Park, NC, National Institute of Environmental Health Sciences, National Toxicology Program NTP-87-108; PB 87-209532, (1987)

Result

:

Diglyme-treated dams did not exhibit treatment-related clinical signs, death, or differences from control in corrected maternal body weight gain (i.e., gestational weight gain minus gravid uterine weight) or relative maternal liver weight. Maternal intact body weight (including gravid uterine weight) was reduced in groups dosed with 250 and 500 mg/kg-day on gd 15 and 17, as was maternal weight gain during treatment and gestation. Gravid uterine weight in diglyme-treated groups was significantly reduced at all doses in a dose-related manner. There were dose-related and significant increases at 250 and 500 mg/kg/day in the percentage of nonlive implants per litter (4.88%, 8.41%, 7.05%, 12.02% and 50.41% in the vehicle control through high-dose groups, respectively), as well as the percentage of adversely affected implants per litter (5.25%, 8.41%, 9.35%, 32.29% and

96.93% nonlive or malformed in the vehicle control through high-dose groups, respectively).

The mean live litter size was significantly less than control at 500 mg/kg/day and was marginally reduced at all lower dose levels. The mean fetal body weight per litter was reduced at and above 125 mg diglyme/kg-day. Anatomical malformations displayed a dose-dependent trend toward an increased percentage of malformed live fetuses per litter, and the difference from control was statistically significant in the 250 and 500 mg groups. The mean percent malformed live fetuses per litter was 0.37%, 0.00%, 2.47%, 23.86% and 95.82% in the vehicle through high-dose groups, respectively. The proportion of litters with gross, visceral or skeletal malformations was increased at the high dose, and the proportion of litters with gross or skeletal malformations was increased in the 250 mg/kg-day group. The types of malformations observed were diverse. Major malformations affected primarily development of the neural tube, limbs and digits, craniofacial structures, abdominal wall, cardiovascular system, urogenital organs, and both the axial and appendicular skeleton. The two most frequently observed malformations were fused ribs in 74% of high dose fetuses and exencephaly in 54% of high dose fetuses.

Exposure of pregnant CD-1 mice to diglyme throughout the period major organogenesis produced no notable evidence of maternal toxicity. The lowest dose level, 62.5 mg/kg/day, appeared to be a no observed effect level for indices of fetal development. At higher doses, diglyme produced adverse effects upon fetal growth (greater than or equal to 125 mg/kg/day), fetal viability (greater than or equal to 250 mg/kg/day), and fetal morphological development (greater than or equal to 250 mg/kg/day). At the highest dose, all 23 litters contained at least one malformed fetus compared to 1 of 21 control litters, and 94% of the high-dose fetuses were malformed compared to 0.35% of the fetuses in the control group. Thus, diglyme administration by gavage to the pregnant mouse represents a risk to the embryo or fetus at dose levels that did not cause observable toxicity to the maternal organism.

MATERNAL PARAMETERS

	0	-----Diglyme mg/kg-----			
	0	62.5	125	250	500
Treated dams	28	28	29	28	28
Preg at sac	21	20	24	23	23
Mat BW gd-0	30.67	31.03	30.75	30.5	30.46
Mat BW gd-17	56.3	53.41	54.5	52.17**	47.09**
Maternal wt gain					
- gestation	25.63	22.38	23.75	21.67**	16.64**
- treatment	15.32	13.3	14.06	12.98**	10.03**
- corrected	6.28	6	6.4	5.72	6.14
Uterus wt	19.35	16.38*	17.35*	15.96**	10.50**
Mat Liver wt	3.08	2.94	2.99	2.89	2.65**
Relative mat liver weight % of body	5.48	5.52	5.49	5.54	5.62

All weights in grams * = p < 0.05, ** = p < 0.01

- (1) Calculated from the experimental rate constant published by Dagaut P, Wallington IJ, Liu R, Kurylo MJ (1988) 22nd International Symposium on Combustion, Seattle, WA; as cited in Atkinson R (1989) Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. *Journal of Physical and Chemical Reference Data*, 1:143. as cited in Concise International Chemical Assessment Document 41, Diethylene Glycol Dimethyl Ether. International Program on Chemical Safety, World Health Organization Geneva, 2002
- (2) Calculation performed by Toxicology and Regulatory Affairs, December 2003
- (3) Data found on NTP public database at http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm
- (4) Daubert, T.E., R.P. Danner. *Physical and Thermodynamic Properties of Pure Chemicals Data Compilation*. Washington, D.C.: Taylor and Francis, 1989 as cited in National Library of Medicine Hazardous Substance Data Base, Record #72, Last Revision Date: 20030305
- (5) DuPont Chemical, Haskell Laboratories report 51-73. Initial Submission: Acute Oral Test of Ether,
- (6) Hansch, C., Leo, A., D. Hoekman. *Exploring QSAR - Hydrophobic, Electronic, and Steric Constants*. Washington, DC: American Chemical Society. 1995
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- (8) Hoechst (1979a) Inhalationstoxizität im Zeitsättigungstest von Diethylenglykol-dimethylether an männlichen und weiblichen SPF-Wistar-Ratten. Frankfurt am Main, Hoechst AG, 10 pp. (Report 488/79; unpublished) as cited in: Concise International Chemical Assessment Document 41, Diethylene Glycol Dimethyl Ether. International Program on Chemical Safety, World Health Organization Geneva, 2002
- (9) Hoechst (1989) Prüfberichte: ökologische Untersuchungen. Frankfurt am Main, Hoechst AG, 4 pp. (unpublished report). as cited in: Concise International Chemical Assessment Document 41, Diethylene Glycol Dimethyl Ether. International Program on Chemical Safety, World Health Organization Geneva, 2002
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- (11) Hoechst (1995) Prüfung der Schadwirkung gegenüber Algen (Algentoxizität) von Diethylenglykoldimethylether. Hoechst AG, Frankfurt am Main (unpublished report). as cited in: Concise International Chemical Assessment Document 41, Diethylene Glycol Dimethyl Ether. International Program on Chemical Safety, World Health Organization Geneva, 2002.
- (12) Hoechst Abwasserbiologische Untersuchung von Dialkylglykoläthern auf die Goldorfe (*Leuciscus idus*). Report Nr.79.0555 (1979) as cited in: Concise International Chemical Assessment Document 41, Diethylene Glycol Dimethyl Ether. International Program on Chemical Safety, World Health Organization Geneva, 2002 and using data found in the ECB IUCLID 2000 document for diglyme.

- (13) Hoechst AG (1989): Unveroeffentlichte Untersuchung (V-89-903-A) as cited in European Chemicals Bureau, IUCLID 2000 for CASNO 111-96-6
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- (16) O'Neil, MJ (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Thirteenth edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001
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