FOREWORD INTRODUCTION

2-BUTENEDIOIC ACID (E)-DIETHYL ESTER (DIETHYL FUMARATE)

CAS N°:623-91-6

SIDS Initial Assessment Report

SIAM 4 Tokyo, 20-22 May 1996

Chemical Name: 2-Butenedioic acid (*E*)-, diethyl ester
(Diethyl fumarate)

CAS No: 623-91-6

Sponsor Country: Japan

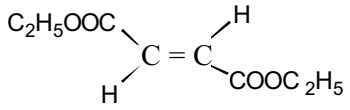
National SIDS Contact Point in Sponsor Country:

Mr. Yasuhisa Kawamura, Ministry of Foreign Affairs, Japan

History: As a high priority chemical for initial assessment, diethyl fumarate was selected in the framework of the OECD HPV Programme.
At SIAM-4, the conclusion was approved with comments.
Comments at SIAM-4: Rearrangement of the documents.

Deadline for circulation:
Date of Circulation:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	623-91-6
Chemical Name	2-Butenedioic acid (E)-, diethyl ester (Diethyl fumarate)
Structural Formula	

CONCLUSIONS AND RECOMMENDATIONS

A potential hazard to the environment due to moderate toxicity to fish and algae, and also a potential hazard to man due to a low no-effect-level in repeated dose animal studies are identified, but exposure is considered to be low.

Unless further information from other Member countries presents evidence to the contrary, it is currently considered of low potential risk and low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Exposure

Diethyl fumarate is not produced in Japan, and there are no imported volumes. However, this chemical is registered in TSCA and EINECS. This chemical is stable in acidic solution, but unstable in neutral (half-life: 10 days) or alkaline solutions, and is considered as "readily biodegradable".

Environment

For the environment, various NOEC and LC_{50} values were gained from test results; 72h LC_{50} = 2.4 mg/l (acute fish); 24h EC_{50} = 11 mg/l (acute daphnia); 72h EC_{50} = 1.1 mg/l (acute algae); 72h NOEC < 0.56 mg/l (acute algae); 21d NOEC = 1.8 mg/l (long-term daphnia reproduction). As the lowest toxicity data to algae, acute-NOEC of *Selenastrum capricornutum* (0.56 mg/l) was adopted. Using an assessment factor of 100, the PNEC of the chemical is 0.0056 mg/l.

Human Health

Although positive results were obtained from a chromosomal aberration test *in vitro*, negative results were obtained in a bacterial mutation assay. In an oral combined repeated dose and reproductive/developmental toxicity test at doses of 0, 11, 30 and 100 mg/kg/day [OECD TG 422], no effects were observed on clinical signs, body weight, food consumption, urinalysis, haematology or blood chemistry examinations. Histopathological examination of the forestomach revealed thickening of the mucosal layer in both sexes of all treated groups, hyperkeratosis in males of all treated groups and in females of the 30 and 100 mg/kg groups. These changes were dose-dependent. In addition, edema in the submucosal tissue as well as ulcer and focal edema in lamina propria mucosae were noted in males and females of the 30 mg/kg groups, and vesiculation in the superficial zone of the mucosal layer was apparent in males of the 30 and 100 mg/kg groups. Absolute or relative organ weights of the kidney and liver increased in both sexes of the 100 mg/kg groups, and atrophy of the thymus was noted in females of the 30 and 100 mg/kg groups. Therefore, NOEL was considered to be less than 11 mg/kg/day. As the reproductive/developmental endpoints, no effects were observed on the following items: reproductive ability, organ weights and histopathological appearance of the reproductive organs, parturition and maternal behavior, viability, clinical signs, body weight change and autopsy findings for offspring. Therefore, NOEL was more than 100 mg/kg/day for reproductive toxicity. For human health, NOEL is estimated as less than 11 mg/kg/day for repeated dose toxicity and 100 mg/kg/day for reproductive toxicity.
In conclusion, no further testing is needed at present considering its toxicity and exposure levels.

NATURE OF FURTHER WORK RECOMMENDED

FULL SIDS SUMMARY

CAS NO: 623-91-6		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			0.2 °C
2.2	Boiling Point			218 – 219 °C
2.3	Density			1.052 at 20 °C
2.4	Vapour Pressure		OECD TG 104	260 Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	2.12 at 25 °C
2.6 A.	Water Solubility		OECD TG 105	3.1 g/l at 25 °C
B.	pH			No data available.
	pKa			No data available
2.12	Oxidation: Reduction Potential			No data available.
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Calculated	Half-life: 7.72 years
3.1.2	Stability in Water		OECD TG 111	Stable (pH 4.0). Unstable at pH 7, 9. Half-life: 10.2 days at pH 7 Half-life: 3.52 days at pH 9
3.2	Monitoring Data			No data available
3.3	Transport and Distribution		Calculated (Fugacity Level III)	100% released to water, In Air 8.10 % In Water 90.9 4% In Soil 0.51 % In Sediment 0.44 %
3.5	Biodegradation		OECD TG 301C	Readily biodegradable: 92 - 95 % (BOD) in 28 days, 93 – 98% (TOC), 100% (GC) in 28 days
3.6	Bioaccumulation			No data available
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (24hr): 5.3 mg/L LC_{50} (72hr): 2.4 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (24hr): 11 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50} (72hr): 1.1 mg/l NOEC: < 0.56 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (21d, Immobility): 1.5 mg/l EC_{50} (21d, Reproduction): 2.0 mg/l NOEC(21d, Reproduction): 1.8 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			No data available.

CAS NO: 623-91-6		SPECIES	PROTOCOL	RESULTS
4.6.2	Toxicity to Terrestrial Plants			No data available.
(4.6.3)	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			No data available
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD_{50} : 1,367 mg/kg (female) LD_{50} : 1,500 – 2,000 mg/kg (male)
5.1.2	Acute Inhalation Toxicity			No data available.
5.1.3	Acute Dermal Toxicity			No data available
5.4	Repeated Dose Toxicity	Rat	OECD Combined Test	NOEL = < 11 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. .typhimurium* *E. coli*	OECD Guidelines No.471 and 472 and Japanese Guideline	Negative with and without metabolic activation
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	CHL cells	OECD Guideline No.473 and Japanese Guideline	Positive (Without metabolic activation) Negative (With metabolic activation)
5.6	Genetic Toxicity In Vivo			No data available
5.8	Toxicity to Reproduction	Rat	OECD Combined Test	NOEL Parental = 100 mg/kg/day NOEL F1 offspring = 100 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity			
5.11	Experience with Human Exposure			

SIDS Initial Assessment Report

1. Identity

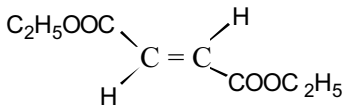
OECD Name: 2-Butenedioic acid (E)-, diethyl ester

Synonym Diethyl fumarate

CAS Number: 623-91-6

Empirical Formula: $C_8H_{12}O_4$

Structural Formula:



Degree of Purity: Unknown (Tests were performed using reagent grade : 95 %)

Major Impurities: Unknown

Essential Additives: Unknown

2. Exposure

2.1 General discussion

Diethyl fumarate is not produced in Japan, and there are no imported volumes. However, this chemical is registered in TSCA and EINECS. This chemical is stable in acidic solution, but unstable in neutral (half-life: 10 days) or alkaline solutions, and is considered as "readily biodegradable".

2.2 Environmental exposure

a) Biodegradability:

If released into water, this substance is readily biodegraded. In a MITI (I) test, corresponding to OECD TG 301C, 92 -95 % was degraded during 28 days based on BOD, 93 -98 % based on TOC and 100% on GC analysis).

b) Hydrolysis as a function to pH:

The chemical is stable in water at pH 4, but unstable at pH 7 (half-life: 10 days) and pH 9 (half-life: 3.52 days) at 25 °C (OECD TG 111).

c) Photodegradability (estimation)

The half-life time of 7.22 years is estimated for the direct photodegradation of diethyl fumarate in water by absorption of UV light (MITI, Japan).

d) Bioaccumulation:

No data are available.

e). Global exposure

The potential environmental distribution of diethyl fumarate obtained from a generic level III fugacity model is shown in Table 1. The results show that if diethyl fumarate is released mainly to air, water or soil, it is unlikely to be transported to other compartments.

Table 1. Environmental distribution diethyl fumarate using a generic level III fugacity model.

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	80.98%	8.10%	4.05%
Water	13.81%	90.94%	7.85%
Soil	5.14%	0.51%	88.07%
Sediment	0.07%	0.44%	0.04%

f) Local exposure

No information available

2.3 Consumer Exposure

No information available

2.4 Exposure via the environment

No information available

2.5 Occupational exposure

No information available

3. Toxicity

3.1 Ecotoxicity

Diethyl fumarate has been tested in a limited number of aquatic species (*Selenastrum capricornutum*, *Daphnia magna* and *Oryzias latipes*), under OECD test guidelines [OECD TG 201, 202, 203, 204 and 211]. Acute and chronic toxicity data to test organisms for diethyl fumarate are summarized in Table 2. No other ecotoxicological data are available.

Various NOEC and LC_{50} values were gained from above tests; 72h LC_{50} = 2.4 mg/l (acute fish); 24h LC_{50} = 11 mg/l (acute daphnia); 72h EC_{50} = 1.1 mg/l (acute algae); 72h NOEC < 0.56 mg/l (algae); 21d NOEC = 1.8 mg/l (long-term daphnia reproduction). Therefore, the chemical is considered to be moderately toxic to fish, daphnids and algae. Using the lowest toxicity data (NOEC of *Selenastrum capricornutum* <0.56 mg/l) and applying an assessment factor of 100, a PNEC of 0.0056 mg/l is derived.

Table 2. Acute and chronic toxicity data of diethyl fumarate to aquatic organisms.

Species	Endpoint[*1]	Conc. (mg/L)	Reference
Selenastrum capricornutum (algae)	Biomass: EC_{50} (72h) NOEC	 1.1 mg/L < 0.56 mg/L	MOE, Japan. (1994)
Daphnia magna (water flea)	Mor: LC_{50}(24h) Imm: EC_{50}(21d) Rep: EC_{50}(21d) NOEC(21d)	11 mg/L 1.5 mg/L 2.0 mg/L 1.8 mg/L	
Oryzias latipes (fish, Medaka)	Mor: LC_{50}(24h) Mor: LC_0(72h)	5.3 mg/L 2.4 mg/L	

Notes: [*1] Mor; mortality, Rep; reproduction, Imm; Immobility

3.2 Human Toxicity

a) Acute toxicity

LD_{50} values from acute oral toxicity studies in rats were reported as 1,500–2,000 mg/kg for males and 1,367 mg/kg for females. LD_{50} and LC_{50} values from acute inhalation and dermal toxicity study are not available.

b) Repeated toxicity

There is only one key study on repeated dose toxicity of diethyl fumarate. This chemical was studied for oral toxicity in rats according to the OECD combined repeated dose and reproductive/developmental toxicity test [OECD TG 422]. As the study was well controlled and conducted under GLP, this was appropriate to regard as a key study. Male and female SD rats were orally administered (gavage) at doses of 0, 11, 30 and 100 mg/kg/day. In male rats, the administration period was two weeks prior to mating, 2 weeks of mating and 2 weeks after the completion of mating period. In female, in addition to maximum four weeks pre-mating and mating period, they were given through pregnant period until day 3 of post

delivery. Histopathological examination of the forestomach revealed thickening of the mucosal layer in both sexes of all treated groups, hyperkeratosis in males of all treated groups and in females of the 30 and 100 mg/kg groups. These changes were dose-dependent. In addition, edema in the submucosal tissue as well as ulcer and focal edema in lamina propria mucosae were noted in males and females of the 30 mg/kg groups, and vesiculation in the superficial zone of the mucosal layer was apparent in males of the 30 and 100 mg/kg groups. Absolute or relative organ weights of the kidney and liver increased in both sexes of the 100 mg/kg groups, and atrophy of the thymus was noted in females of the 30 and 100 mg/kg groups. No effects were observed on clinical signs, body weight, food consumption, urinalysis. NOEL was considered to be less than 11 mg/kg/day.

c) Reproductive toxicity

Diethyl fumarate was studied for oral toxicity in rats according to the OECD combined repeated dose and reproductive/developmental toxicity test [OECD TG 422] at doses of 0, 11, 30 and 100 mg/kg/day. No effects were observed on the following items: reproductive ability, organ weights and histopathological appearance of the reproductive organs, parturition and maternal behavior, viability, clinical signs, body weight change and autopsy findings for offspring. The NOEL was more than 100 mg/kg/day for reproductive toxicity.

d) Genetic toxicity

Bacterial test
A reverse gene mutation assay was conducted in line with Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guidelines 471 and 472, using the pre-incubation method. This study was well controlled and regarded as a key study.
Diethyl fumarate showed negative results in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvr*A at concentrations up to 5 mg/plate with or without metabolic activation system (MHW, 1994).

Non-bacterial test *in vitro*
A chromosomal aberration test in line with Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD Test Guideline 473 was conducted using cultured Chinese Hamster lung (CHL/IU) cells. This study was well controlled and regarded as a key study. The maximum concentration of the chemical was used with no apparent cytotoxic effect in continuous treatment. In short term treatment, it was set to 0.083 mg/ml. Although chromosomal aberrations were not recognized up to a maximum concentration of 0.083 mg/ml under conditions of both continuous treatment and short-term treatment with an exogeneous metabolic activation system, a positive result was obtained without metabolic activation (MHW, 1994).

in vivo test
No data are available on *in vivo* genotoxic effects.

e) Other human health related information

None

4. Initial assessment

4.1 Ecotoxicity

For the environment, various NOEC and LC_{50} values were gained from test results; 72h LC_{50} = 2.4 - 5.3 mg/l (acute fish); 24h EC_{50} = 11 mg/l (acute daphnia); 72h EC_{50} = 1.1 mg/l (acute algae); NOEC < 0.56 mg/l (acute algae); 21d NOEC = 1.8 mg/l (long-term daphnia reproduction). Using the lowest toxicity data (NOEC of *Selenastrum capricornutum* < 0.56 mg/l) and applying an assessment factor of 100, a PNEC of 0.0056 mg/l is derived.

4.2 Toxicity

Although a positive result was obtained from chromosomal aberration test *in vitro*, a negative result was obtained in bacterial mutation assay. In an oral combined repeated dose and reproductive/developmental toxicity test with doses of 0, 11, 30 and 100 mg/kg/day [OECD TG 422], no effects were observed on clinical signs, body weight, food consumption, urinalysis, haematology or blood chemistry examinations. Histopathological examination of the forestomach revealed thickening of the mucosal layer in both sexes of all treated groups, hyperkeratosis in males of all treated groups and in females of the 30 and 100 mg/kg groups. These changes were dose-dependent. In addition, edema in the submucosal tissue as well as ulcer and focal edema in lamina propria mucosae were noted in males and females of the 30 mg/kg groups, and vesiculation in the superficial zone of the mucosal layer was apparent in males of the 30 and 100 mg/kg groups. Absolute or relative organ weights of the kidney and liver increased in both sexes of the 100 mg/kg groups, and atrophy of the thymus was noted in females of the 30 and 100 mg/kg groups. Therefore, the NOEL was considered to be less than 11 mg/kg/day. As the reproductive/developmental endpoints, no effects were observed on the following items: reproductive ability, organ weights and histopathological appearance of the reproductive organs, parturition and maternal behavior, viability, clinical signs, body weight change and autopsy findings for offspring. Therefore, NOEL was more than 100 mg/kg/day for reproductive toxicity.
For human health, NOEL is estimated as less than 11 mg/kg/day for repeated dose and 100 mg/kg/day for reproductive toxicity. Health risks from the general environment are presumed to be low based on its degradability.

5. Recommendation

A potential hazard to the environment due to moderate toxicity to fish and algae, and also a potential hazard to man due to a low no-effect-level in repeated dose animal studies are identified, but exposure is considered to be low.

Unless further information from other Member countries presents evidence to the contrary, it is currently considered of low potential risk and low priority for further work.

6. REFERENCES

American Industrial Hygiene Association Journal, 23, 95 (1962)

Dictionary of organic compounds (Edit., The society of synthetic organic chemistry, Japan, 1985)

EA, Japan (1994) "Investigation of the ecotoxicological effects of OECD high production volume chemicals", Office of health studies, Environmental health department, Environment agency, Japan (HPV/SIDS test conducted by EA, Japan)

EA & MITI, Japan (1994) Unpublished report on exposure estimation (HPV/SIDS test conducted by EA and MITI, Japan)

ECDIN database (1994)

Lyman, W.J, W. F. Reehl and D. H. Rosenblatt (1981) "Handbook of chemical property estimation method", McGraw Hill Book Co.

MHW, Japan (1994a) Unpublished report on acute toxicity test of diethyl fumarate. (HPV/SIDS test conducted by MHW, Japan)

MHW, Japan (1994b) Unpublished report on combined repeat dose and reproductive/developmental toxicity screening test of diethyl fumarate. (HPV/SIDS test conducted by MHW, Japan)

MHW, Japan (1994c) Unpublished report on mutagenicity test of diethyl fumarate. (HPV/SIDS test conducted by MHW, Japan)

MITI, Japan (1994a): Unpublished data

MITI, Japan (1994b) Unpublished report (HPV/SIDS test conducted by MITI, Japan. Test was performed in Chemicals Inspection and Testing Institute, Japan)

SIDS DOSSIER

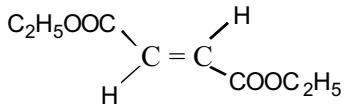
2-Butenedioic acid, (E)-, diethyl ester (Diethyl fumarate)

CAS No. 623-91-6

Sponsor country: Japan

DATE: April, 2002

S I D S P R O F I L E

1.01 A.	**CAS No.**	623-91-6
1.01 C.	**CHEMICAL NAME (OECD Name)**	2-Butenedioic acid (*E*)-, diethyl ester
1.01 D.	**CAS DESCRIPTOR**	Not applicable
1.01 G.	**STRUCTURAL FORMULA**	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	**QUANTITY**	No production in Japan
1.7	**USE PATTERN**	Intermediate for plasticizer, pesticides, flavoring agents and surface coatings in Europe
1.9	**SOURCES AND LEVELS OF EXPOSURE**	Unknown
ISSUES FOR DISCUSSION (IDENTIFY, IF ANY)		

Diethyl fumarate **S I D S S U M M A R Y**

CAS NO: 623-91-6		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.3	Density	Y	N	N	Y	N	Y	N
2.4	Vapour Pressure	N						Y
2.5	Partition Coefficient	N						Y
2.6	Water Solubility	N						Y
	pH and pKa values	N						N
OTHER P/C STUDIES RECEIVED								
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	N						Y
3.1.2	Stability in water	N						Y
3.2	Monitoring data	N						N
3.3	Transport and Distribution	N						N
3.5	Biodegradation	N						Y
3.6	Bioaccumulation	Y	Y	Y	N	N	Y	N
OTHER ENV FATE STUDIES RECEIVED								
ECOTOXICITY								
4.1	Acute toxicity to Fish	N						Y
4.2	Acute toxicity to Daphnia	N						Y
4.3	Toxicity to Algae	N						Y
4.5.2	Chronic toxicity to Daphnia	N						Y
4.6.1	Toxicity to Soil dwelling organisms	N						N
4.6.2	Toxicity to Terrestrial plants	N						N
4.6.3	Toxicity to Birds	N						N
OTHER ECOT OXICITY STUDIES RECEIVED								
TO XICITY								
5.1.1	Acute Oral	N						Y
5.1.2	Acute Inhalation	N						N
5.1.3	Acute Dermal	N						N
5.4	Repeated Dose	N						Y
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	N						Y
	. Chromosomal aberration	N						Y
5.6	Genetic Toxicity *in vivo*	N						N
5.8	Reproduction Toxicity	N						Y
5.9	Development / Teratogenicity	N						Y
5.11	Human experience	N						N
OTHER TOXICITY STUDIES RECEIVED								

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. CAS-Number 623-91-6

B. Name (IUPAC name) Diethyl fumarate

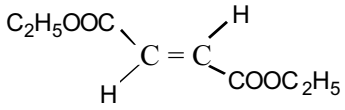
C. Name *(OECD name)* 2-Butenedioic acid (*E*)-, diethyl ester

D. CAS Descriptor Not applicable

E. EINECS-Number 210-819-7

F. Molecular Formula $C_8H_{12}O_4$

G. Structural Formula



H. Substance Group Not applicable

I. Substance Remark None

J. Molecular Weight 172.20

1.02 OECD INFORMATION

A. Sponsor Country: Japan

B. Lead Organization:

Name of Lead Organization:
Ministry of Health and Welfare (MHW)
Ministry of International Trade and Industry (MITI)
Environment Agency (EA)
Ministry of Labor (MOL)

Contact person: Mr. Yasuhisa Kawamura
Director
Second International Organization Bureau
Ministry of Foreign Affairs

Address: 2-2-1 Kasumigaseki, Chiyoda-ku
Tokyo 100, Japan
TEL 81-3-3581-0018
FAX 81-3-3503-3136

C. **Name of responder** Same as above contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. **Type of Substance**

element **[ ]**; inorganic **[ ]**; natural substance **[ ]**;
organic **[X]**; organometallic **[ ]**; petroleum product **[ ]**

B. **Physical State** gaseous **[ ]**; liquid **[X]**; solid **[ ]**

C. **Purity** Unknown

1.2 SYNONYMS Diethyl fumarate

1.3 IMPURITIES Unknown

1.4 ADDITIVES None

1.5 QUANTITY	Location	Production (tonnes)	Date
	Japan	0 /year	1994

Reference: MITI, Japan (1994a)

1.6 LABELLING AND CLASSIFICATION

None

1.7 USE PATTERN

A. **General**

Type of Use:	**Category:**
(1) None	
(2) Industrial use	Plasticizer Intermediate for plasticizer, pesticides, flavoring agents, surface coatings

Reference: (1) MITI, Japan (1994a)
(2) ECDIN database (1994)

B. **Uses in Consumer Products**

None

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

Unknown

1.9 SOURCES OF EXPOSURE

Source:	Media of release: Water from a production site Quantities per media: 0 tonnes/year
Reference:	MITI, Japan (1994a)

1.10 ADDITIONAL REMARKS

A. Options for disposal Unknown

B. Other remarks None

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

Value:	0.2 °C
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reference:	Dictionary of Organic Compounds (1985)

2.2 BOILING POINT

Value:	218 - 219 °C
Pressure:	1013 hPa
Decomposition:	Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reference:	Dictionary of Organic Compounds (1985)

2.3 DENSITY (Relative density)

Type:	Bulk density **[ ]**; Density **[ ]**; Relative Density **[X]**
Value:	1.052
Temperature:	20 °C
Method:	Unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reference	ECDIN Database (1994)

2.4 VAPOUR PRESSURE

Value:	260 Pa
Temperature:	25 °C
Method:	calculated **[ ]**; measured **[X]** OECD Test Guideline 104 Static method
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reference:	MITI, Japan (1994b)

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

Log Pow:	2.12
Temperature:	25 °C
Method:	calculated **[ ]**; measured **[X]** OECD Test Guideline 107
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reference:	MITI, Japan (1994b)

2.6 WATER SOLUBILITY

A. Solubility

Value:	3.1 g/l
Temperature:	25 °C
Description:	Miscible **[ ]**; Of very high solubility **[ ]**; Of high solubility **[ ]**; Soluble **[X]**; Slightly soluble **[ ]**; Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method:	OECD Test Guideline 105
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reference:	MITI, Japan (1994b)

B. pH Value, pKa Value

No data available

2.7 FLASH POINT

Value:	104 °C
Type of Test:	Closed cup **[ ]**; Open cup **[ ]**; Other **[ ]**
Method:	Unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reference:	ECDIN Database

2.8 AUTO FLAMMABILITY

No data available

2.9 FLAMMABILITY

No data available

2.10 EXPLOSIVE PROPERTIES

No data available

2.11 OXIDIZING PROPERTIES

No data available

2.12 OXIDATION: REDUCTION POTENTIAL

No data available

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

No data available

B. Other data

None

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Type:	Air **[ ]**; Water **[X]**; Soil; Other **[ ]**	
Light source:	Sunlight **[X];** Xenon lamp **[ ];** Other **[ ]**	
Spectrum of substance:	epsilon = 5.74 x 10 at 300 nm	
Estimated parameter for calculation:		
	Quantum yield	0.01
	Concentration	5×10^{-5} M
	Depth of water body	500 cm
	Conversion constant	6.023×10^{20}
Result:	Degradation rate	1.42×10^{-13} mol/l/s
	Half life	7.72 years
Reference:	W. J. Lyman, W. F. Reehl and D. H. Rosenblatt, "Handbook of Chemical Property Estimation Method", McGraw Hill Book Co., 1981.	

3.1.2 STABILITY IN WATER

Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment) **[ ]**
Result:	Stable at pH4 Half life:10.2 days at pH 7 3.52 days at pH 9 at 25 °C
Method:	OECD Test guideline 111
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Diethyl fumarate
Reference:	MITI, Japan (1994b)

3.1.3 STABILITY IN SOIL

No data available

3.2 MONITORING DATA (ENVIRONMENT)

No studies located

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT No data available

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

The potential environmental distribution of Diethyl fumarate obtained from a generic level III fugacity model is shown in Table. The results show that if Diethyl fumarate is released mainly to air, water or soil, it is unlikely to be transported to other compartments.

Environmental distribution Diethyl fumarate using a generic level III fugacity model.

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	80.98%	8.10%	4.05%
Water	13.81%	90.94%	7.85%
Soil	5.14%	0.51%	88.07%
Sediment	0.07%	0.44%	0.04%

Reference: EA & MITI (1994)

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No studies located.

3.5 BIODEGRADATION

Type:	aerobic **[X]**; anaerobic **[ ]**
Inoculum:	adapted **[ ]**; non-adapted **[X]**;
Concentration of the chemical:	100 mg/l related to Test Substance **[X]**
Medium:	water**[ ];**water-sediment**[ ];**soil **[ ];**sewage treatment **[ ]** other **[**Japanese standard activated sludge**]**
Degradation:	Degree of degradation after 28 days 93, 95 and 92 % from BOD 95, 93 and 98 % from TOC analysis 100, 100 and 100 % from GC analysis
Results:	Readily biodeg. **[X];** Inherently biodeg. **[ ]**; under test condition no biodegradation observed **[ ]**
Method:	OECD Test Guideline 301 C
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Diethyl fumarate
Reference:	MITI, Japan (1994b)

3.6 BOD_5,COD OR RATIO BOD_5/COD

Not applicable

3.7 BIOACCUMULATION

No data available

3.8 ADDITIONAL REMARKS

A. Sewage treatment None

B. Other information None

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other **[ ]** open-system **[X]**; closed-system **[ ]**
Species:	*Oryzias latipes*
Exposure period:	96 hr
Results:	LC_{50} (24h) = 5.3 mg/l (95% confidence limits: 4.4-6.4 mg/l) LC_{50} (48h) = 3.5 mg/l (95% confidence limits: 3.0-4.3 mg/l) LC_{50} (72h) = 2.4 mg/l (95% confidence limits: 1.9-3.0 mg/l) LC_{50} (96h) = 2.4 mg/l (95% confidence limits: 1.9-3.0 mg/l) NOEC = LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 203 (1981)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Diethyl fumarate, purity = 95 %
Remarks:	A group of 10 fish were exposed to each of 5 nominal concentrations (1.0-10 mg/l). Stock solution was prepared with DMSO:HCO-40=4:1 (1.0-10 mg/l). Controls with and without this vehicle were taken for test.
Reference:	EA, Japan (1994)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**; open-system **[X]**; closed-system **[ ]**
Species:	*Daphnia magna*
Exposure period:	24 hr
Results:	EC_{50} (24h) = 11 mg/l (95% confidence limits: 8.8-13 mg/l) EC_{50} (48h) = NOEC = LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 202 (1984)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Diethyl fumarate, purity = 95 %
Remarks:	20 daphnids (4 replicates; 5 organisms per replicate) were exposed to each of 5 nominal concentrations (5.6-56 mg/l). Stock solution was prepared with DMSO:HCO-40=9:1 (5.6-56 mg/l). Controls with and without this vehicle were taken for test.
Reference:	EA, Japan (1994)

B. Other aquatic organisms

No data available

4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

Species:	*Selenastrum capricornutum* ATCC 22662
End-point:	Biomass **[X]**; Growth rate **[ ]**; Other **[ ]**
Exposure period:	72 hours
Results: Biomass:	EC_{50} (24h) =
	EC_{50} (72h) = 1.1 mg/l
	NOEC < 0.56 mg/l ($p < 0.05$)
	LOEC =
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	open-system **[**X**]**; closed-system **[ ]**
	OECD Test Guideline 201 (1984)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Diethyl fumarate, purity = 95 %
Remarks:	The EC_{50} values for biomass were calculated based on 5 nominal concentrations (0.56-5.6 mg/l). Stock solution was prepared with DMSO:HCO-40=9:1(0.56-5.6 mg/l). Controls with and without This vehicle were taken for test.
Reference:	EA, Japan (1994)

4.4 TOXICITY TO BACTERIA

No data available

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1. CHRONIC TOXICITY TO FISH

No data available

4.5.2. CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type of test:	static **[ ]**; semi-static **[**X**]**; flow-through **[ ]**; other **[ ]**;
	open-system **[X]**; closed-system **[ ]**
Species:	*Daphnia magna*
End-point:	Mortality **[ ]**; Reproduction rate **[X]**; Other **[X]**
Exposure period:	21 day
Results:	
Immobility:	EC_{50} (48 h) = 5.6 mg/l
	EC_{50} (21 d) = 1.5 mg/l (95% confidence lim its: 1.3-1.7 mg/l)
	NOEC =
	LOEC =
Reproduction:	EC_{50} (21 d) = 2.0 mg/l (95% confidence limits: 1.9-2.1 mg/l)
	NOEC = 1.8 mg/l ($p < 0.05$)
	LOEC = 3.2 mg/l ($p < 0.05$)
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	OECD Test Guideline 202 (1984)
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	Diethyl fumarate purity = 95 %

Remarks: 40 daphnids (4 replicates; 10 organisms per replicate) were exposed to each of 5 nominal concentrations (0.56-5.6 mg/l) Stock solution was prepared with DMSO:HCO-40=9:1(0.56-5.6 mg/l). Controls with and without this vehicle were taken for test.

Reference: EA, Japan (1994)

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data available

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data available

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data available

4.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES

No data available

4.9 ADDITIONAL REMARKS

None

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type :	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat/Crj:CD(SD)
Value :	1,500 - 2000 mg/kg for male 1367 mg/kg for female
Method:	OECD Test Guideline 401
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	purity: 98 %
Remarks:	
Reference:	MHW, Japan (1994a)

(b)

Type :	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value :	1780 mg/kg
Method:	Unknown
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	Purity: unknown
Remarks:	None
Reference:	American Industrial Hygiene Association Journal, 23, 95 (1962)

5.1.2 ACUTE INHALATION TOXICITY

No data available

5.1.3 ACUTE DERMAL TOXICITY

No data available

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No data available

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

No data available

5.2.2 EYE IRRITATION/CORROSION

No data available

5.3 SKIN SENSITIZATION

No data available

5.4 REPEATED DOSE TOXICITY

Species/strain:	Rat (Crj:CD(SD))
Sex:	Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration:	oral gavage
Exposure period:	Males: 46 days including 14 days before mating Females: from 14 days before mating to day 3 of lactation
Frequency of treatment:	7 days/week
Post exposure observation period:	
Dose:	0, 11, 30 or 100 mg/kg (12 animals/group)
Control group:	Yes **[X]**; No **[ ]**; No data **[ ]**; Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOEL:	< 11 mg/kg/day
LOEL:	11 mg/kg/day
Results:	Histopathological examination of the forestomach revealed thickening of the mucosal layer in both sexes of all treated groups, hyperkeratosis in males of all treated groups and in females of the 30 and 100 mg/kg groups. These changes were dose-dependent. In addition, edema in the submucosal tissue as well as ulcer and focal edema in lamina propria mucosae were noted in males and females of the 30 mg/kg groups, and vesiculation in the superficial zone of the mucosal layer was apparent in males of the 30 and 100 mg/kg groups. Absolute or relative organ weights of the kidney and liver increased in both sexes of the 100 mg/kg groups, and atrophy of the thymus was noted in females of the 30 and 100 mg/kg groups. No effects were observed on clinical signs, body weight, food consumption, urinalysis, hematology or blood chemistry.
Method:	OECD Combined Repeat dose and reproductive/Developmental Toxicity Test (1992)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Diethyl fumarate, purity: 98 %
Reference:	MHW, Japan (1994b)

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type :	Bacterial reverse mutation assay
System of testing:	
Species/strain:	*S. typhimurium* TA 98, TA 100, TA 1535, TA1537, *E. coli* WP2 uvrA
Concentration:	Without metabolic activation 0, 9.375, 18.75, 37.5, 75. 150, 300 µg/plate (TA100) 0, 78.13, 156.3, 312.5, 625, 1250, 2500 µg/plate (TA1535, TA98, TA1537) 0, 156.3, 312.5, 625, 1250, 2500, 5000 µg/plate (WP2) With metabolic activation 0, 312.5, 625, 1250, 2500, 5000 µg/plate

Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**;No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: 5000 µg/plate
Without metabolic activation: 300 µg/plate
Genotoxic effects:

S. typhimurium TA 100, TA1535, TA98, TA 1537

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

E. coli WP2 uvrA

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Japanese Guideline for Screening Mutagenicity testing of chemicals
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Teat substance: Diethyl fumarate, purity: 93.3 %
Remarks: Procedure: Plate incorporation method
Plates/test: 3
Activation system: Liver S-9 fraction from phenobarbital and 5,6-benzoflavone pretreated male SD rats with NADPH-generating system
Media:Histidine selective
No. replicates: 2
Reference: MHW, Japan (1994c)

B. NON-BACTERIAL IN VITRO TEST

Type : Cytogenetics Assay
System of testing:
Species/strain: Chinese hamster lung (CHL/IU) cells
Concentration: -S9 (continuous treatment) 0, 0.003, 0.007, 0.013 mg/ml
-S9 (short-term treatment) 0, 0.008, 0.015, 0.030 mg/ml
+S9 (short-term treatment) 0, 0.021, 0.042, 0.083 mg/ml
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results:
Cytotoxicity conc: With metabolic activation: > 0.083 mg/ml
Without metabolic activation: 0.013 mg/ml
Precipitation conc:
Genotoxic effects:

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[X]**	**[ ]**	**[ ]**

Method: Japanese Guideline for Screening Mutagenicity testing of chemicals
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Diethyl fumarate, purity 93.3 %
Remarks: Plates/test:2
Activation system: S-9 fraction from the liver of Phenobarbital and 5,6-Benzoflavone induced male SD derived rats with NADPH-generating system
Media: RPMI 1640 medium *plus* 10% foetal calf serum *plus* phytohaemagglutinin

No. replicates: 1
Reference: MHW, Japan (1994c)

5.6 GENETIC TOXICITY IN vivo

No data available

5.7 CARCINOGENICITY

No data available

5.8 TOXICITY TO REPRODUCTION

Type: Fertility **[ ]**; One generation study **[ ]**; Two generation study **[ ]**; Other **[X]**
Species/strain: Rat Crj:CD(SD)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral, gavage
Exposure period: Males: 46 days including 14 days before mating
Females: from 14 days before mating to day 3 of lactation.
Frequency of treatment:7 days/week
Postexposure observation period:
Premating exposure period: male: 14 days, female: 14 days
Duration of the test;
Doses: 0, 11, 30, or 100 mg/kg (12 animals/sex/group)
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**;
Historical **[ ]**
NOEL Parental : 100 mg/kg/day
NOEL F1 Offspring: 100 mg/kg/day
NOEL F2 Offspring: N/A
Results: No effects were observed on the following items: reproductive ability, organ weights and histopathological appearance of the reproductive organs, parturition and maternal behavior, viability, clinical signs, body weight change and autopsy findings for offspring.
Method: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Test (1992)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Diethyl fumarate, purity 98 %
Remarks:
Reference: MHW, Japan (1994b)

5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

See 5.8

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

No studies located

B. Toxicodynamics, toxicokinetics

No data available

5.11 EXPERIENCE WITH HUMAN EXPOSURE

None

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