

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 110-17-8
CAS No.	110-17-8
EINECS Name	fumaric acid
EINECS No.	203-743-0
Molecular Formula	C4H4O4

Dataset created by: EUROPEAN COMMISSION - European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non-confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

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1.0.1 OECD and Company Information

Name: AB SCANLATEX
Town: VALLVIK
Country: Sweden

Name: AKZO NOBEL COATINGS SPA
Street: Via Emilia, 2
Town: 26861 Fombio
Country: Italy
Phone: +3903774101
Telefax: +39037732632

Name: ALUSUISSE Italia SpA - FTALITAL Factory
Town: Scanzorosciate BG
Country: Italy

Name: Atochem
Street: 4, Cours Michelet
Town: 92080 Paris la Defense
Country: France

Name: Bang & Bonsomer Oy
Street: Itälahdenkatu 18 A
Town: 00210 HELSINKI
Country: Finland
Phone: +358-0-681081
Telefax: +358-0-6924174
Telex: 121439 BABO FI

Name: BASF AG
Street: Karl-Bosch-Str
Town: 67056 Ludwigshafen
Country: Germany

Name: BRENNTAG (UK) LIMITED
Street: 45c HIGH STREET, HAMPTON WICK
Town: KT1 4DG KINGSTON ON THAMES
Country: United Kingdom
Phone: 0181 977 3200
Telefax: 0181 943 4350

Name: Helm AG
Street: Nordkanalstrasse 28
Town: 20097 Hamburg
Country: Germany
Phone: +49402375-0
Telefax: +49402375-90
Telex: 2170150

Name: Hickson Coatings Italia S.p.A
Street: Via del Fiffo, 12-CP. 18
Town: 40065 Pianoro
Country: Italy
Phone: +39 51 77 72 11
Telefax: +39 51 77 74 37

Name: Honeywill and Stein Ltd
Street: 1 Finsbury Circus
Town: EC2M 7BA London
Country: United Kingdom
Phone: +44(0)171 496 4000
Telefax: +44(0)171 496 4516

Name: Huels AG
Street: Postfach
Town: D-45764 Marl
Country: Germany

Name: Hydro Chemicals Norge
Street: Fyrstikkalleen 3B, P.O. Box 23 Haugenstua
Town: N-0604 OSLO
Country: Norway
Phone: 47 2243 2400
Telefax: 47 2243 2402
Telex: 71771 nchem n

Name: Krems Chemie Aktiengesellschaft
Street: Hafenstrasse 77
Town: A-3500 KREMS
Country: Austria
Phone: +43-2732-899/254
Telefax: +43-2732-899/302
Telex: 71121

Name: MARE S.p.A.
Street: Via Verdi, 3
Town: 20010 Ossona/Fraz. Asmonte (MI)
Country: Italy
Phone: 02 903261
Telefax: 02 90380474

Name: MB SVEDA AB
Street: Box 4072
Town: 203 11 Malmö
Country: Sweden
Phone: 0094640352800
Telefax: 0094640125172
Telex: 33188

Name: NEUBER GES.M.B.H.
Street: BRÜCKENGASSE 1
Town: 1060 WIEN
Country: Austria
Phone: 0222/599950
Telefax: 0222/5970200

Name: Petrasol B.V.
Street: P.O.Box 222
Town: 4200 AE Gorinchem
Country: Netherlands
Phone: +31 183 630555
Telefax: +31 183 632272
Telex: 23602 petr nl

Name: PRODECHIM
Street: 191 C AVENUE ST EXUPERY
Town: 69500 BRON
Country: France

Name: RHODIA AUSTRIA GmbH
Street: Werk Pischelsdorf
Town: 3435 Zwentendorf
Country: Austria
Phone: 0043 2277 2003
Telefax: 0043 2277 2003-70

Name: RHODIA CHIMIE
Street: 25 QUAI PAUL DOUMER
Town: 92408 COURBEVOIE CEDEX
Country: France
Telex: 01 47 68 12 34

Name: SINTOFARM SPA
Street: TOGLIATTI, 5
Town: 42016 GUASTALLA
Country: Italy
Phone: 0522831321
Telefax: 0522831422

Name: VOS B.V.
Street: Ondernemingsweg 1A
Town: 2404 HM Alphen aan den Rijn
Country: Netherlands
Phone: 31-172-431601
Telefax: 31-172-432494

Name: ÖMV - Chemie Linz GMBH
Street: St. Peterstrasse 25
Town: 4021 Linz
Country: Austria
Phone: *43/(0)732/5916-2386
Telefax: *43(0)732/5916-3738
Telex: 221324

1.0.2 Location of Production Site

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1.0.3 Identity of Recipients

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1.1 General Substance Information

Substance type: organic
Physical status: solid

1.1.1 Spectra

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1.2 Synonyms

1,2-ETHYLENEDICARBOXYLIC ACID

Source: MARE S.p.A. Ossona/Fraz. Asmonte (MI)

2-butenedioic (E) acid

Source: Honeywill and Stein Ltd London

2-Butenedioic acid (E)-

Source: Huels AG Marl

2-Butenedioic acid (E)- (9CI)

Source: BASF AG Ludwigshafen

2-Butenedioic acid(E)

Source: AB SCANLATEX VALLVIK

2-Butenedioic acid, (E)-

Source: BASF AG Ludwigshafen

Acido Allomaleico

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Acido Boletico

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Acido Fumarico

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Acido Lichenico

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Acido Trans 1,2-Etenedicarbossilico

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Acido Trans 1,2-Etilendicarbossilico

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Acido Trans Butendioico

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Allomaleic acid

Source: BASF AG Ludwigshafen

Boletic acid

Source: BASF AG Ludwigshafen

Fumaric acid

Source: ISIS/RISKLINE release VI, 1997, Haskoning
Petrasol B.V. Gorinchem

Fumaric acid (8CI)

Source: BASF AG Ludwigshafen

Fumaric acid; Butenedioic acid; trans-1,2-Ethylenedicarboxylic acid; Allomaleic acid; Boletic acid

Source: Atochem Paris la Defense

Fumarsaeure

Source: Huels AG Marl

Fumarsäure

Source: ÖMV - Chemie Linz GMBH Linz

Lichenic acid

Source: BASF AG Ludwigshafen

NA 9126 (DOT)

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

NSC-2752

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

trans-1,2-Ethylenedicarboxylic acid

Source: BASF AG Ludwigshafen

trans-2-Butendisaeure

Source: Huels AG Marl

trans-2-Butenedioic acid

Source: BASF AG Ludwigshafen

trans-2-Butenedioic acid, trans-1,2-Ethylenedicarboxylic acid.

Source: Hickson Coatings Italia S.p.A Pianoro

Trans-butendioic acid

Source: AKZO NOBEL COATINGS SPA Fombio

Trans-Butendisäure

Source: NEUBER GES.M.B.H. WIEN

TRANS-BUTENEDIOIC ACID

Source: MARE S.p.A. Ossona/Fraz. Asmonte (MI)

Trans-Butenedioic-acid

Source: RHODIA AUSTRIA GmbH Zwentendorf

Trans-Ethylendicarbonensäure

Source: RHODIA AUSTRIA GmbH Zwentendorf

U-1149

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

USAF EK-P-583

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG**1.3 Impurities**

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1.4 Additives

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1.5 Quantity

Quantity 50 000 - 100 000 tonnes

1.6.1 Labelling**Labelling:** as in Directive 67/548/EEC**Symbols:** Xi

D

Specific limits: no data**R-Phrases:** (36) Irritating to eyes**S-Phrases:** (2) Keep out of reach of children

(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice

1.6.2 Classification**Classification:** as in Directive 67/548/EEC**Class of danger:** irritating**R-Phrases:** (36) Irritating to eyes

1.7 Use Pattern

Type: type
Category: Non dispersive use

Type: type
Category: Use in closed system

Type: type
Category: Use resulting in inclusion into or onto matrix

Type: type
Category: Wide dispersive use

Type: industrial
Category: Agricultural industry

Type: industrial
Category: Basic industry: basic chemicals

Type: industrial
Category: Chemical industry: used in synthesis

Type: industrial
Category: Paints, lacquers and varnishes industry

Type: industrial
Category: Paper, pulp and board industry

Type: industrial
Category: Polymers industry

Type: industrial
Category: other: Raw material for synthetic resins

Type: industrial
Category: other

Type: use
Category: Fixing agents

Type: use
Category: Food/foodstuff additives

Type: use
Category: Intermediates

Type: use
Category: pH-regulating agents

Type: use
Category: Stabilizers

Type: use
Category: other

1.7.1 Technology Production/Use

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1.8 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Remark: Come polvere.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(1)

Type of limit: MAK (DE)
Limit value:
Country: Germany
Remark: MAK not established
Source: Huels AG Marl

(2)

Type of limit:
Limit value:
Remark: No data on Occupational Exposure Limit Values
Source: Atochem Paris la Defense

Type of limit:
Limit value:
Remark: No Exposure Limit Value assigned.
Source: Hickson Coatings Italia S.p.A Pianoro

Type of limit:
Limit value:
Remark: kein MAK-Wert festgelegt
Source: BASF AG Ludwigshafen

(3)

1.9 Source of Exposure

Remark: Isomerisation of maleic acid in aqueous solution in presence of thiourea.
One production site.
Source: Atochem Paris la Defense

Remark: Nel sito produttivo di Scanzorosciate è installato un unico impianto di produzione di Acido Fumarico costituito dalle seguenti sezioni:
- Produzione di acido fumarico da anidride maleica
- produzione di acido fumarico da acque maleiche
La soluzione ottenuta dalle due sezioni viene cristallizzata, filtrata ed il prodotto ottenuto essiccato prima di passare alla sezione insaccamento.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Remark: Nell' impianto sono stati individuati numero 4 punti di emissione e precisamente:
- Essiccamento acido fumarico portata 2600 Nmc/h di aria
- Essiccamento FA granulare portata 7000 Nmc/h di aria
- Trasporto FA granulare portata 50 Nmc/h di aria
- Insaccamento portata 7000 Nmc/h di aria
Tutte le emissioni sono di tipo continuo e riferite a polveri di FA del quale è prevista una concentrazione massima di 30 mg/Nmc nei punti di emissione siti a 5.5 - 20 metri dal suolo.
Gli abbattitori di polveri utilizzati sono filtri a maniche o a tasche.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Remark: Used as an intermediate in the manufacture of resins which are used in the production of surface coatings for furniture.

Source: Hickson Coatings Italia S.p.A Pianoro

1.10.1 Recommendations/Precautionary Measures

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1.10.2 Emergency Measures

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1.11 Packaging

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1.12 Possib. of Rendering Subst. Harmless

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1.13 Statements Concerning Waste

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1.14.1 Water Pollution

Classified by: other: Huels AG
Labelled by: other: Huels AG
Class of danger: 1 (weakly water polluting)
Country: Germany
Source: Huels AG Marl

(2)

Classified by: other: Selbsteinstufung
Labelled by:
Class of danger: 1 (weakly water polluting)
Source: BASF AG Ludwigshafen

(4)

1.14.2 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: yes
Country: Germany
Remark: siehe Anhang II, Nr. 4a (betr. explosionsfaehige Staeube)
Source: Huels AG Marl

(2)

Legislation:
Substance listed:
Remark: kein Stoff der StoerfallVO
Source: BASF AG Ludwigshafen

(5)

1.14.3 Air Pollution

Classified by: other: Huels AG
Labelled by: other: Huels AG
Number: 3.1.7 (organic substances)
Class of danger: II
Country: Germany
Source: Huels AG Marl

Classified by:
Labelled by:
Number:
Class of danger:
Remark: keine Angabe
Source: BASF AG Ludwigshafen

(4)

1.15 Additional Remarks

Remark: Smaltimento:
l' acido fumarico può essere miscelato o disciolto in un
solvente combustibile per l' incenerimento.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(6)

Remark: Trasporto:
L' acido fumarico (FA) viene insaccato in sacchi da 25 kg
cadauno o in sacconi da 500-1000 kg.
Il trasporto avviene mediante automezzi dotati di pianale su
cui vengono disposti i pallets con i sacchi/sacconi di FA.
Il prodotto non è soggetto alle regolamentazioni nazionali
ed internazionali relative al trasporto di merci pericolose
sia aereo che ferroviario e stradale.
Attualmente la frequenza di spedizione è di circa 25-90
autotreni al mese.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

Remark: Delivered in 25 kilo net bags.
Source: Hickson Coatings Italia S.p.A Pianoro

Remark: Not dangerous for transport.
Source: MARE S.p.A. Ossoona/Fraz. Asmonte (MI)

Remark: The Company Honeywill and Stein was part of BP Chemicals Ltd until sold on 31st July 1998 to Internatio-Muller of Rotterdam.
Source: Honeywill and Stein Ltd London

1.16 Last Literature Search

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1.17 Reviews

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1.18 Listings e.g. Chemical Inventories

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2.1 Melting Point

Value: = 200 degree C
Sublimation: yes
GLP: no data
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (7)

Value: 276 - 287 degree C
Sublimation: yes
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (8)

Value: 286 - 287 degree C
Decomposition: yes
Sublimation: yes
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9)

Value: = 286 degree C
Decomposition: no
Sublimation: ambiguous
GLP: no
Remark: Sublimation above ca. 200 degree C, yet boiling point > melting point.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Value: = 287 degree C
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

2.2 Boiling Point

Value: = 290 degree C at 1033 hPa
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

Value: = 290 degree C at 1013 hPa
Decomposition: no
GLP: no
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (12)

2.3 Density

Type: bulk density
Value: .6 - .9 g/cm³ at 20 degree C
GLP: no data
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (7)

Type: density
Value: ca. 1.51 - 1.635 g/cm³ at 20 degree C
GLP: no
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Type: density
Value: = 1.63 g/cm³ at 20 degree C
GLP: no
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Type: relative density
Value: = 1.635 at 20 degree C
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (8)

Type: bulk density
Value: ca. 800 kg/m³ at 20 degree C
GLP: no
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Type: density
Value: = 1.635 at 25 degree C
Remark: Solido.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11) (9)

2.3.1 Granulometry

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2.4 Vapour Pressure

Value: < .001 hPa at 20 degree C
GLP: yes
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (13)

2.5 Partition Coefficient

log Pow: .07 - .56
Method: other (calculated)
Year:
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (8)

log Pow: = .33 at 23 degree C
Method: other (measured): OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year: 1981
GLP: no
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (14)

2.6.1 Water Solubility

Value: = .428 other: g/100 g di acqua at 15.5 degree C
Remark: Costante di dissociazione in acqua:
K1: 9.57×10^{-4}
K2: 4.13×10^{-5}
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9)

Value: = 4.9 g/l at 20 degree C
Qualitative: slightly soluble
pH: = 2.1 at 5 g/l and 20 degree C
GLP: no
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Value: = .7 other: % peso at 25 degree C
Remark: Dissociation constant at 25°C:
K1: 9.57×10^{-4}
K2: 4.13×10^{-5}
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

Value: = 7 g/l at 25 degree C
Qualitative: slightly soluble
pKa: 3.02 at 25 degree C
GLP: no
Remark: Dissociation constants:
K1 = 9.51×10^{-4} ==> pK1 = 3.02
K2 = 3.5×10^{-5} ==> pK2 = 4.46
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10) (8)

Value: = 1.05 other: % peso at 40 degree C
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

Value: = 2.34 other: % peso at 60 degree C
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

Value: = 8.93 other: % peso at 100 degree C
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

Value: = 9.97 other: g/100 g di acqua at 100 degree C
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9)

Value: = 100 g/l at 100 degree C
GLP: no data
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (7)

Value: = 98000 mg/l at 100 degree C
Qualitative: of high solubility
GLP: no
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10) (8)

2.6.2 Surface Tension

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2.7 Flash Point

Value: = 273 degree C
Type: open cup
Method: other: DIN 51584
Year:
GLP: no
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

2.8 Auto Flammability

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2.9 Flammability

Result: other: Its fire hazard is slight.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

2.10 Explosive Properties

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2.11 Oxidizing Properties

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2.12 Additional Remarks

Remark: Calore di sublimazione (92°C) 136.1 KJ/mole
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9)

Remark: molar volume: 79
heat of formation, KJ/mol: -811.03
free energy of formation, KJ/mol: -655.63
heat of combustion, MJ/mol: -1.335
heat of hydrogenation, KJ/mol: -130.3
crystal structure: monoclinic,
prismatic,
needless or leaflets

solubility, g/100g soln:
acetone at 29.7°C 1.69
benzene at 25°C 0.003
95% ethanol at 29.7°C 5.44
chloroform at 25°C 0.02
carbon tetrachloride at 25°C 0.027
diethyl ether at 25°C 0.71
2-butenenitrile at 50°C 0.034

Source: Dipole moment in dioxane at 25°C, debye 2.449.
ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

Remark: Calore di combustione: -2760 cal/gr.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (15)

Remark: Punto di solidificazione a 1013 hPa: 290°C.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Remark: La polvere può produrre miscela esplosiva.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Remark: Solubility in ethanol at 30°C: 55 g/l.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (7)

Remark: Henry's Law constant estimated to be 8.5E-14 atm cm³/mole.
This value indicates that the substance will not volatilize from water.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (16)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: O3
Conc. of sens.: 700000000000 molecule/cm3
Rate constant: = .00000000000000000175 cm3/(molecule * sec)
Degradation: = 50 % after 6.5 day
Method: other (calculated)
Year: **GLP:**
Test substance:
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (17)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm3
Rate constant: = .00000000000000528 cm3/(molecule * sec)
Degradation: = 50 % after 7.3 hour(s)
Method: other (calculated)
Year: **GLP:**
Test substance:
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (18)

Type: water
INDIRECT PHOTOLYSIS
Sensitizer: OH
Method:
Year: **GLP:**
Test substance:
Result: At pH 4.5-10, the rate constant for the aqueous fumaric acid with photochemically produced OH radicals is 6.0E9 M sec (Ref. 1).
Assuming an hydroxy radical concentration of 3E-17 M in brightly sunlit natural water, the half-life time would be about 45 days (Ref. 2).
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (19) (20)

Type:
Method:
Year: **GLP:**
Test substance:
Remark: Fumaric acid does not absorb UV light above 290 nm in methanol, acidic methanol or basic methanol solution; therefore, direct photolysis in the environment is unlikely to occur.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (21)

3.1.2 Stability in Water

Type: abiotic
Method:
Year: **GLP:**
Test substance:
Remark: Hydrolysis of fumaric acid in the environment is not expected to be important since carboxylic acid and alkene functional groups are resistant to hydrolysis.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (22)

3.1.3 Stability in Soil

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3.2 Monitoring Data (Environment)

Type of measurement:
Medium: air
Remark: Air samples collected in west and downtown Los Angeles, CA, during june and october 1984 contained fumaric concentrations of 3.5-147.4 ng/cm³.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (23)

Type of measurement:
Medium: other: rain, snow.
Remark: Rain and snow water collected from rural areas near Hubbard Brook, NH and semi-rural areas near Ithaca, NY between june 1976 and may 1977 found to contain fumaric acid.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (24)

Type of measurement:
Medium: other: effluents.
Remark: A fumaric acid concentration of 0.94 µg/cm³ was detected in the motor exhaust from a 1982 Toyota Corolla.
A concentration of 3.2 µg/cm³ was detected in the exhaust from a diesel engine 1971 Mercedes Benz.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (23)

Type of measurement:**Medium:** sediment**Remark:** Bog sediments collected in the foothills of the Sierra Nevada mountains contained fumaric acid levels of 4.76 mg/kg.

Soil samples collected on the campus of UCLA in Los Angeles, CA contained fumaric acid levels of 0.2-0.6 mg/kg.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

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Type of measurement:**Medium:** other**Remark:** Dust collected from the outside window ledge and balcony of two buildings in Los Angeles contained fumaric acid levels ranging from 2.65 to 6.67 mg/kg.**Source:** ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

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Type of measurement:**Medium:** food**Remark:** Reported uses:

- non alcoholic beverage: 50 ppm
- Baked goods: 1300 ppm
- gelatins and puddings: 3600 ppm.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

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3.3.1 Transport between Environmental Compartments**Type:** adsorption**Media:** water - soil**Method:** other: estimation**Year:****Remark:** Based upon a water solubility of 7 g/l at 25°C, the Koc of fumaric acid can be estimated to be 33.5, value which indicates high soil mobility. However, with step 1 and step 2 pKa's of 3.02 and 4.44 at 18°C, fumaric acid will exist predominantly in the ionized state at environmental pHs. The ability of ionized fumaric acid to leach in soil cannot be predicted adequately without experimental data.**Source:** ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

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3.3.2 Distribution

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3.4 Mode of Degradation in Actual Use

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3.5 Biodegradation

Type: aerobic
Inoculum: predominantly domestic sewage
Concentration: 10 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 98 % after 21 day
Result: readily biodegradable
Method: OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year: 1981 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Type: aerobic
Inoculum: activated sludge
Concentration: 10 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 99.99 %
Method: OECD Guide-line 303 A "Simulation Test - Aerobic Sewage Treatment: Coupled Unit Test"
Year: 1981 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Mean retention time: 3 hours.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

3.6 BOD5, COD or BOD5/COD Ratio**B O D 5**

BOD5: = .18 mgO₂/l
Result: ThOD: 0.827
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (8) (27)

B O D 5

BOD5: = .57 mgO₂/l
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
Test condition: Warburg, sewage. (8)

B O D 5

BOD5: = .65 mgO₂/l
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
Test condition: Standard dilution at 4-8 mg/l. (8) (28)

B O D 5**BOD5:** = .7 mgO2/l**Source:** ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG**Test condition:** Warburg, sewage.

(8)

Result: BOD5: 34% of ThOD.

KMnO4 value: acid: 87% of ThOD; alkaline: 68% of ThOD.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(29) (8)

3.7 Bioaccumulation

-

3.8 Additional Remarks**Remark:** Waste water treatment (bench scale activated sludge, fill and draw operations):

after 6 hr: 1.0% of ThOD

12 hr: 0.1% of ThOD

24 hr: 1.7% of ThOD

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(8) (30)

AQUATIC ORGANISMS**4.1 Acute/Prolonged Toxicity to Fish**

Type: static
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC50: = 245
Method: other: DIN 38412 Part 15
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC50: = 73.6
Method: other: DIN 38412 Part 11.
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: 95 % confidence interval: 67.0 - 80.8 mg/l.
The toxicity depends on the pH.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (10)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC50: 204 - 220
Method:
Year: **GLP:**
Test substance:
Remark: Temperature: 22°C
Hardness: 154.5 (mean) mg/lt CaCO₃
Alkalinity: 137.7 (mean) mg/lt CaCO₃
pH: 7.7 (mean).
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (31)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 32
EC50: = 41
CE90 : = 49
Method: other: Algenwachstums-Hemmtest nach UBA (Verfahrensvorschlag
Stand Februar 1984)
Year: 1984 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
(32)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 6 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 23.2
Method: other: Test for inhibition of oxygen consumption by
Pseudomonas putida (Huels-Methode), 5-6 h.
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
Test condition: plus emulsifier.
(10)

4.5 Chronic Toxicity to Aquatic Organisms**4.5.1 Chronic Toxicity to Fish**

-

4.5.2 Chronic Toxicity to Aquatic Invertebrates

-

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

-

4.6.2 Toxicity to Terrestrial Plants

-

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

-

4.7 Biological Effects Monitoring

-

4.8 Biotransformation and Kinetics

-

4.9 Additional Remarks

-

5.1 Acute Toxicity**5.1.1 Acute Oral Toxicity**

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 10000 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 9300 mg/kg bw
Method: other: vedi riferimento.
Year: 1977 **GLP:** no
Test substance: no data
Remark: Female: 9300 mg/Kg range 6300 - 13800 mg/Kg
Male 10700 mg/Kg range 7200 - 15800 mg/Kg
no further details reported.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (33)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 10700 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: TOXIC EFFECTS NOT YET REVIEWED; TXAPA9 42,417,77 (Toxicol Appl Pharmacol).
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (34) (35)

Type: LDLo
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: = 5000 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: TOXIC EFFECTS NOT YET REVIEWED; IECHAD 15,628,23 [Ind Eng Chem]
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (34) (35)

5.1.2 Acute Inhalation Toxicity

-

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: > 20000 mg/kg bw
Method: other: vedi riferimento.
Year: 1977 **GLP:** no
Test substance: no data
Remark: 20 g fumaric acid/kg b.w. applied to the skin of three rabbits for 24 hours was not lethal (details not reported). TOXIC EFFECTS NOT YET REVIEWED; TXAPA9 42,417,77
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (34) (35) (33)

Type: other
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value:
Method:
Year: **GLP:**
Test substance:
Remark: 20 g/Kg applicati sulla cute non sono risultati letali.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9)

5.1.4 Acute Toxicity, other Routes

Type: LC50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: = 100 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: NO TOXIC EFFECT NOTED; NTIS** AD277-689 (Natl Tech Inf Serv)
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
(34) (35)

Type: LC50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: = 200 mg/kg bw
Method:
Year: **GLP:** no
Test substance: no data
Remark: Details not reported.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
(36)

Type: other: single administration
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value:
Method:
Year: **GLP:** no
Test substance: no data
Remark: Coden: JAPMA8 35,298,46
Fumaric Acid was given i.p. to 2 rats at a dose level of 587 mg/Kg and both animals died within 1 hour after injection. Autopsy showed hemorrhagic spots on the intestine near the spot of injection. The surface of the liver appeared to be "seared".
There was engorgement of the intestine and liver.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
(37) (34) (35)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: slightly irritating
EC classificat.:
Method:
Year: GLP:
Test substance:
Remark: 500 mg/24H; Mild; 28ZPAK -,51,72
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
(34) (35) (38)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result: not irritating
EC classificat.:
Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: 1981 GLP: no
Test substance: as prescribed by 1.1 - 1.4
Remark: Result: Erythema: x = 0.72
Oedema : x = 0.11
irritation index: 0,63/8
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
(39)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of
Animals:
Result: moderately irritating
EC classificat.:
Method:
Year: GLP:
Test substance:
Remark: 100 mg/24H; Moderate; 28ZPAK -,51,72
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(34) (35) (38)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: irritating
EC classificat.:
Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year: 1981 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Result: Cornea: x = 2.0
Iris : x = 0.28
Conjunctiva:
Erytema : x = 2.83
Chemosis : x = 1.72
irritation index : 42,8/110
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (40)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification:
Method: OECD Guide-line 406 "Skin Sensitization"
Year: 1981 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Results: NO SENSITISATION WAS OBSERVED IN ANY OF 19 ANIMALS.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (41)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male
Strain: other: Yale, unidentified albino strain
Route of admin.: oral feed
Exposure period: 2 years
Frequency of treatment: daily (free access to the diet).
Post. obs. period: none
Doses: 0.1 and 1.0 % in the diet
Control Group: other: si, 0.2 % acetic acid
Method: other: see reference
Year: 1946 **GLP:** no
Test substance: no data
Result: Rats (14 per group) were maintained on the diets for two years. At the end of the first six months one half of the rats (7 animals) were autopsied and examined grossly and histologically. The remaining rats (7 animals) were continued on the experiment for the remainder of the two-year period. However, due to respiratory infections, survival in all groups (incl. control) was reduced drastically during the second half of the study: 0/7 control, 1/7 0.1 % fumaric acid treated and 2/7 1% fumaric acid treated animals survived until the end of the study. This reduction was not addressed to the action of the test substance. No clinical or pathological effects (i.e. differences in body weight, hemoglobin content, leukocyte and erythrocyte count, bone ash, gross pathology) were seen in rats fed 0.1 or 1.0 % fumaric acid.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (42)

Species: rat **Sex:** male/female
Strain: Osborne-Mendel
Route of admin.: oral feed
Exposure period: 2 years
Frequency of treatment: daily (free acces to the diet)
Post. obs. period: none
Doses: 0.1, 0.5, 0.8, 1.0 and 1.2 % fumaric acid in the diet
Control Group: other: si, ground commercial rat biscuits with 1 % cod-liver oil
Method: other: see reference
Year: 1947 **GLP:** no
Test substance: no data
Result: Groups of 24 rats were fed diets of 0.1, 0.5, 0.8 or 1.2 % fumaric acid, and groups of 12 rats were fed 1.0 or 1.5 %. INCREASED MORTALITY (10/12 animals died; control 6/12) and testes ATROPHY (details not reported) was seen at 1.5 % fumaric acid in the diet (approx. 750 mg/Kg b.w./day). Two rats receiving diets with 1.0 % or 0.5 % fumaric acid showed PHLEGMONOUS GASTRITIS, a condition not seen in any other group. Tumor incidence was not different among the various animal groups.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(43)

Species: rabbit **Sex:** male
Strain: New Zealand white
Route of admin.: oral feed
Exposure period: 150 days
Frequency of treatment: daily (free access to the diet)
Post. obs. period: none
Doses: 5.0 %
Control Group: yes
Method: other: see reference
Year: 1963 **GLP:** no
Test substance: no data
Remark: 15 animals/group
control: ground Rock land Rabbit Diet
The sodium salt of fumaric acid was incorporated into the diet of the test animals in a concentration of 6.9 %, being equivalent to 5.0 % of the organic acid.
Gross pathologic examinations were performed on 2 animals from each group after 30 days of feeding and on 1 animal from each group after 60 days. Organs were weighed, and the testes were subjected to histologic study. After 100 days, similar studies were performed on one-half of the surviving rabbits, the liver and kidney being examined histologically in addition to the testes. After 150 days all surviving animals were sacrificed and gross and histological studies were carried out.

Result: No effects on body weight, blood chemistry and organ weights were observed. Gross and microscopically examination revealed no substance-related findings. No signs of testicular toxicity were observed.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(44)

Species: rabbit **Sex:** no data
Strain: no data
Route of admin.: i.p.
Exposure period: 150-200 days
Frequency of treatment: twice weekly
Post. obs. period: no details reported
Doses: 60 mg/kg sodium fumarate
Control Group: no data specified
Method:
Year: **GLP:** no data
Test substance: other TS: sodium fumarate
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(45) (46) (47)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration: 10 - 5000 µg/plate
Metabolic activation: with and without
Result: negative
Method: other: According to Ames, B.N. et al., Mutat. Res. 31, 347-364
Year: 1975 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (48)

Type: Ames test
System of testing: Salmonella typhimurium TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537
Concentration: up to 10 mg/plate
Metabolic activation: with and without
Result: negative
Method: other: according to Ames, B.N. et al., Mutat. Res. 31, 347-364
Year: 1975 **GLP:** no
Test substance: other TS
Remark: Fumaric acid (purity 99.7%) was not mutagenic up to a maximum dose of 10 mg/plate.
solvent: DMSO
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
Test substance: Purity 99.7 % (49)

Type: Ames test
System of testing: Salmonella typhimurium TA 97, TA 98, TA 100, TA 1535
Concentration: 33, 100, 333, 1000 and 2000 µg/plate
Metabolic activation: with and without
Result: negative
Method: other: see reference
Year: 1988 **GLP:** no data
Test substance: no data
Remark: Fumaric acid was not mutagenic at dosis of 0, 33, 100, 333, 1000 and 2000 µg/plate in the absence and presence of rat and Syrian hamster liver S9 mix.
Solvent: DMSO.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (49)

Type: Cytogenetic assay
System of testing: Chinese hamster lung fibroblasts (CHL)
Concentration: 0.125, 0.25 and 0.5 mg/ml
Metabolic activation: with and without
Result: negative
Method: other: see reference
Year: 1983 **GLP:** no data
Test substance: other TS
Remark: CHL cells were treated with 0.125, 0.25 and 0.5 mg/ml fumaric acid for 24 and 48 hours. The incidences for polyploidy and structural aberrations of treated cells were not different from the negative controls.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
Test substance: purity 99.7 %

(50)

Type: Cytogenetic assay
System of testing: Chinese hamster lung fibroblasts (CHL)
Concentration: <= 0.5 mg/ml
Metabolic activation: no data
Result: negative
Method:
Year: **GLP:**
Test substance:
Remark: Fumaric acid (purity 99.7%) was tasted at three different doses, the highest of which was 0.5 mg/ml. After a treatment time of 24 hours the incidences for polyploidy or structural aberrations of treated cells did not differ from the negative controls.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(49)

Type: Mouse lymphoma assay
System of testing: L5178Y (TK+/-)
Concentration: 2856-8000 µg/ml
Metabolic activation: with and without
Result: positive
Method:
Year: **GLP:** no data
Test substance: other TS
Remark: Fumaric acid (purity 99.7%) was tested at concentrations of 2856-8000 µg/ml in the medium. It was mutagenic in the absence and presence of Aroclor 1254 induced rat liver S9 mix.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG
Test substance: purity 99.7 %

(51)

5.6 Genetic Toxicity 'in Vivo'

Type:
Species: Sex:
Strain:
Route of admin.:
Exposure period:
Doses:
Result:
Method:
Year: GLP:
Test substance:
Result: Experimental investigations did not reveal any evidence of genotoxic activity.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9) (52)

5.7 Carcinogenicity

Species: mouse Sex: female
Strain: Swiss
Route of admin.: dermal
Exposure period: 76 settimane
Frequency of treatment: twice weekly
Post. obs. period:
Doses: Iniziazione: 1 per settimana con 7,12-dimethylbenz(a)anthracene (1.5% in olio minerale).
Promozione: 2 per settimana con acido fumarico (1% in acetone)
Result:
Control Group: other: no promoting agent (negative control), croton oil (pos. control)
Method: other: see reference
Year: 1953 GLP: no
Test substance: no data
Result: Fumaric acid was found to induce MODERATE FOCAL HYPERPLASIA of the epidermis BUT NOT TUMORS.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (53)

Species: rat **Sex:** male/female
Strain: Osborne-Mendel
Route of admin.: oral feed
Exposure period: 2 YEARS
Frequency of treatment: daily in the diet
Post. obs. period:
Doses: 0.1, 0.5, 0.8, 1.0, 1.2, 1.5 % fumaric acid (approx. 750 mg/Kg/day)
Result:
Control Group: other: si, ground commercial rat biscuits with 1 % cod-liver oil
Method:
Year: **GLP:**
Test substance:
Remark: Experimental investigations did not reveal any evidence of carcinogenic activity.
Result: In the highest dose group there was a low level of survival (2/12) at the end of the experiment, while in the lower dose groups mortality did not differ significantly from the controls (details not reported). The gross and microscopic findings showed no difference between control and treated animals. Tumors showed no difference in incidence among the various animals groups.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (54) (55) (9)

5.8 Toxicity to Reproduction

Type:
Species: guinea pig **Sex:** male/female
Strain:
Route of admin.: oral feed
Exposure Period: not reported
Frequency of treatment: diet
Duration of test:
Doses: 1% in the diet (approx. 400 mg/Kg b.w./day)
Control Group: no
Method: other: see reference
Year: 1946 **GLP:** no
Test substance: no data
Remark: Guinea pigs were bred in order to determine whether fumaric acid might have any effect on reproduction or lactation. Twelve young pigs were cast by the two females which received fumaric acid in the diet. The male animals were also fed the fumaric acid containing diet (details not reported). There were no detectable toxic effects on growth, reproduction or lactation of the fumaric acid treated guinea pigs. Essential details were not reported.
Result: Experimental investigations did not reveal any evidence of reproductive-toxicological activity.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (55) (9)

5.9 Developmental Toxicity/Teratogenicity

Species: Drosophila melanogaster **Sex:**
Strain:
Route of admin.:
Exposure period:
Frequency of treatment:
Duration of test: 24 hours
Doses: 1/100 of the LD50 for Drosophila melanogaster
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: An in vitro assay of teratogenesis was developed that utilizes Drosophila embryonic cell cultures. The endpoint selected in assensing the teratogenic potential of any substance involves detection of interference with normal muscle and/or neuron differentiation; Drosophila eggs were collected for 2 hours and dechorionated and sterilized at the early gastrula stage, before any overt morphological or ultrastructural differentiation took place. The eggs were homogenized and the embryonic cells were collected after centrifugation. Cells were plated and covered with medium containing 1 mM fumaric acid (equivalent to 1/100 of the LD50 of fumaric acid for Drosophila melanogaster). After 24 hours cell and tissue differentiation could be scored.
Result: As compared to negative controls, no differences in differentiation of fumaric acid treated cells could be detected, while there was a clear effect caused by e.g. thalidomide, tolbutamide or 6-mercaptopurine.
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (56)

5.10 Other Relevant Information

Type: Biochemical or cellular interactions
Remark: Fumaric acid did not reduce the antitumor activity of mitomycin C against either the solid or the ascitic form of the Ehrlich tumor. Fumaric acid reduced the letal and hematologic toxicities of mitomycin C, and studies on the nucleic acids of animal tissues indicated that mitomycin C inhibited selectively DNA synthesis of liver and kidney, whereas fumaric acid exerted an enhancing effect, antagonistic to mitomycin C, on DNA synthesis of these tissues.
The toxic symptoms in ICR mice given mitomycin C (either successive daily i.p. doses of 1 mg/kg or two large doses of 4 mg/kg) were reduced by the concurrent administration of fumaric acid (40 mg/kg).
Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (57)

- Type:** Biochemical or cellular interactions
- Remark:** The effect of fumaric acid (FA) on DNA synthesis in hepatocytes or hepatoma cells from rats treated with toxic agents was examined. Male DONRYU rats were injected with mitomycin C or aflatoxin B1, singly or in combination with FA. After a specified period, hepatocytes were isolated from the liver, placed in culture, and their activities for DNA synthesis were measured. The i.v. injection of rats with mitomycin C (0.5 mg/Kg) reduced the semiconservative DNA synthesis of the hepatocytes, but simultaneous dosing of fumaric acid (FA) (40 mg/kg) enhanced the recovery of the DNA synthesis. The DNA synthesis of hepatoma cells was also reduced by the i.v. injection of mitomycin C, but this little influenced by simultaneous dosing of FA. The i.p. injection of FA also reduced the toxicity of aflatoxin B1 (0.25 mg/kg, i.p.), preventing the reduction of DNA synthesis as well as the occurrence of nuclear degenerative changes in the aflatoxin B1-exposed hepatocytes.
- Source:** ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (58)
- Type:** Biochemical or cellular interactions
- Remark:** An enhanced DNA synthesis of hepatocytes was noted in the rats given FA, indicating that FA enhanced the proliferation of hepatocytes to counteract the carcinogenic effect of 3'-Me-DAB. An electron microscopic examination indicate that the distribution of subcellular organella was almost normal in the FA-treated hepatocytes. Fumaric acid (FA) suppressed the carcinogenesis in the liver of rats fed 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB), and a study was performed to examine the effect of FA on DNA synthesis an subcellular structures of hepatocytes under the anticarcinogenic regimen. Male DONRYU strain rats were given 3'-Me-DAB by being fed a diet containing 0.06% 3'-Me-DAB for 50 days, after which they were divided into 2 groups. Rats of group 1 were given basal diet and ordinary drinking water for 53 to 69 weeks. Rats of group 2 were given a diet containing 1% FA and drinking water containing 0,025% FA for 53 to 69 weeks. Hepatocytes were isolated from the liver, placed in culture and their activity for DNA synthesis was measured in terms of the incorporation of [3H]dT into DNA.
- Source:** ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (59)
- Type:** other: Inhibitory effect on carcinogenesis by potassium 1-methyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (trans,NFN)
- Remark:** The inhibitory effect of fumaric acid (FA) on carcinogenesis by potassium 1-methyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (trans,NFN) was examined histologically with male ICR/JCL mice. NFN was fed to mice at a dose level of 0.012% in the diet for 14 weeks. These mice were then divided into 2 groups. One group was given a basal diet, and the other group was given a diet

containing 1% FA in the subsequent 39 weeks. In the group of 30 mice fed NFN alone, squamous cell carcinomas were found in the stomachs of 7 mice, multiple papillomas in the stomachs of 13 mice, and multiple and large papillary adenocarcinomas in the lungs of 27 animals. The administration of FA suppressed the NFN-induced stomach and lung carcinogenesis. In the group of 32 mice fed NFN and FA, no stomach tumors developed except 1 early-stage of squamous cell carcinoma. In the lungs, only a small focus of mild atypical hyperplasia and a few early-stage adenocarcinomas were noted in 7 and 11 animals, respectively.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (60)

Type: other: Inhibitory effect on hepatocarcinogenesis
Remark: The inhibitory effect of fumaric acid (FA) on hepatocarcinogenesis was examined in mice fed thioacetamide (TAA). A group of male ICR mice was fed TAA at a level of 0.035% in the diet for 40 weeks and then fed a basal diet for 48 weeks. Hepatocellular carcinomas developed in 11 of 24 animals of this group. The effect of FA on the carcinogenesis was examined in a group of mice fed this compound at a level of 1% in a basal diet after ingestion of TAA. The inhibitory effect of FA on TAA carcinogenesis was so marked that no hepatic carcinomas were found in any of the 15 animals fed FA in combination with TAA.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (61)

Type: other: Inhibitory effect on hepatocarcinogenesis
Remark: The inhibitory effect of fumaric acid (FA) on hepatocarcinogenesis was examined in rats fed thioacetamide (TAA). A group of male DONRYU rats fed TAA at a level of 0.035% in the diet for 40 weeks and then fed a basal diet for 40 weeks. Hepatic carcinomas developed in 9/41 animals of this group fed TAA alone. The effect of FA on the carcinogenesis was examined in 2 groups fed both TAA and FA; one group of rats were fed FA at 1% in a basal diet after ingestion of TAA, and another group of rats were fed TAA plus a supplement of 1% FA in the diet. The inhibitory effect of FA on TAA carcinogenesis was so marked that no hepatic carcinomas were found in both groups fed FA in combination with TAA.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (62)

Type: other: anticarcinogenesis
Remark: Fumaric acid was found to reduce markedly the growth and viability of Ehrlich, MH134 and L1210 mouse tumor cells in culture at concentrations of 0.3-1.2 mg/ml. In contrast, fumaric acid at these concentrations in the culture medium had no deleterious effect on the monolayer development of mouse and chick embryo cells but exhibited activity to enhance the recovery of the cells from the toxic effects of mitomycin C, aflatoxin B1, N-methyl-N'-nitro-N-nitrosoguanidine and potassium

1-methyl-7-(2-(5-nitro-2-furyl)vinyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (63)

5.11 Experience with Human Exposure

Remark: In humans, no changes in the blood and urine parameters on in liver function were found after administration of 8 mg of fumaric acid per kilogram of body weight per day for one year.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9)

Remark: The toxicological evaluation of fumaric acid on contact with the skin, mucous membrane, and eyes. In this respect, fumaric acid is classified as slightly irritant to the skin and moderately irritant to eyes and mucous membranes.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (9)

Remark: Man: oral ingestion: 500 mg/day for a year is tolerated.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (8) (64)

Remark: Fumaric acid is practically non-toxic. It has been approved for human consumption as a food additive and is used as substitute for tartaric acid as an acidulant in beverages, pharmaceutical preparations, etc. (see Food additives; Carbonated beverages).

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (11)

Remark: 75 hospitalized patients (42 females, 33 males, age 20 to 91) were dosed with 500 mg fumaric acid/day for one year. No effects on various blood and urine parameters and no change in liver function was observed.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (55)

Remark: Electron spin resonance investigations of the effect of various dicarboxylic acid compounds on the physical state of membrane proteins in human erythrocytes were performed. The results indicate, that these aliphatic dicarboxylic acids, including fumaric acid, produce highly significant ALTERATION IN THE PHYSICAL STATE of membrane proteins.

Source: ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG (65)

Remark: The total activity of labelled carbon dioxide in the blood entering and leaving the brain was determined following a single injection of fumarate-2-14C in four normal human subjects. Blood samples were drawn simultaneously from the femoral artery and the superior bulb of the internal jugular vein. Also, cerebrospinal fluid specimens were

collected. Evidence from the experiments indicates that there was an immediate formation of $^{14}\text{CO}_2$ by the brain after injection of isotope. It suggest that fumarate penetrates the blood-brain barrier with little difficulty.

Source:

ALUSUISSE Italia SpA - FTALITAL Factory Scanzorosciate BG

(66)

- (1) AIDA - Huels AG
- (2) Huels AG: Sicherheitsdatenblatt "Fumarsaeure (FS)" (inaktiv), Version 06, 17 Feb. 1997
- (3) TRGS 900 von 4/1995
- (4) Merck Schuchardt, Sicherheitsdatenblatt Fumarsaeure (15.03.1994)
- (5) StoerfallVO vom 20.09.1991
- (6) Aldrich, Catalogo 1992-93 pag 664.
- (7) Safety Data Sheet ELF ATOCHEM JUNE 1989.
- (8) K. Verschueren, Handbook of Environmental Data on Organic Chemicals - Second Edition (1983) 685.
- (9) Ullmann's Encyclopedia of Industrial Chemistry - 5th Ed. Vol. A16.
- (10) Huels AG: AIDA - Grunddatensatz, date of last update 04.03.92.
- (11) KIRK-OTHMER, Encyclopedia of Chemical Technology - Third Edition - Vol. 14 pp. 770-787.
- (12) Sicherheitsdatenblatt Huels AG vom 04.10.93
- (13) AIDA - Sicherheitsdatenblatt Huels AG vom 04.10.93
- (14) AIDA - Huels AG Untersuchung (non publicato), 1989.
- (15) Weiss, G. "Hazardous Chemicals Data Book", Second Ed.
- (16) Lyman, W.J. et al., 1982. Handbook of chemical property estimation methods, NY: McGraw-Hill, 15-15 to 15-29.
- (17) Atkinson, R. and Carter, W.P.L., 1984. Chem. Rev., 84, 437-480.
- (18) Atkinson, R., 1987. J. Inter. Chem. Kinet., 19, 799-828.
- (19) Ref. 2.
Mill, T. and Mabey, W.: pp 207-211, in Environmental Exposure from Chemicals, Vol. 1, Boca Raton, FL: CRC Press, 1985.
- (20) Ref.1.
Buxton, G.C. et al., 1988. J. Phys. Chem. Ref. Data, 17, 722.

- (21) Sadtler Research Lab., UV, 165, 1966.
- (22) Lyman, W.J. et al., 1982. Handbook of chemical property estimation methods, NY: McGraw-Hill, 7-4.
- (23) Kawamura, K. and Kaplan, I.R., 1987. Environ. Sci. Technol., 21, 105-110.
- (24) Mazurek, M.A. and Simoneit, B.R., 1986. CRC Critical Reviews in environmental control, 16, 74.
- (25) Fenaroli's Handbook of flavor ingredients. Vol. 2.
- (26) In: HSDB Database, 1991.
- (27) Meink, F., Stoof, H. and Kohlschutter, H., "Les eaux résiduaires industrielles," 1970.
- (28) Lund, Herbert F., Industrial Pollution Control Handbook, pp. 14-20, 14-21, table 2: Waste characteristics of some dissolved organic chemicals, McGraw-Hill, 1971.
- (29) Dore, M., Brunet, N., Legube, B., participation de différents composés organiques à la valeur des critères globaux de pollution," La tribune du Cebedeau, 28 (374), 3-11, Jan. 1975.
- (30) Malaney, G. W. and Gerhold, R. M., "Structural determinants in the oxidation of aliphatic compounds by activated sludge." JWPCF 41 (2). part 2; R18-R33, 1969.
- (31) Randall, T.L. and Knopp, P.V., 1980. Detoxification of specific organic substances by wet oxidation. J. Water Pollut. Control Fed., 52(8), 2117-2130.
- (32) AIDA - Huels AG Rapporto Nr. AW 150, 1988 non pubblicato.
- (33) Vernot, E.H. et al. (1977); Toxicol. Appl. Pharmacol. 42, 417-423.
- (34) NIOSH - Registry of Toxic Effects of Chemical Substances 1985-86
- (35) Sax-Lewis, Dangerous Properties of Industrial Materials - Seventh Ed., Vol 3.
- (36) Smith, C.G. et al. (1963); Cancer Chemother. Rep. 30, 9-12
- (37) Levey, S. et al. (1946); J. Am. Pharm. Ass. 35, 298-304.
- (38) Sb Vysledku Toxikologickeho Vysetreni Latek A Prinpravku 1972

- (39) AIDA - Huels AG-Report Nr. 0213, 1984 (non publicato).
- (40) AIDA - Huels AG-Report Nr. 0214, 1984 non publicato.
- (41) AIDA - Huels AG-Report Nr. 1603 (1989) non publicato.
- (42) Levey, S. et al. (1946); J. Am. Pharm. Ass. 35, 298-304
- (43) Fitzhugh, O.G. and Nelson, A.A. (1947); J. Am. Pharm. Ass. Sci. Ed. 36, 217-219
- (44) Packman, E.W. et al. (1963); Toxicol. Appl. Pharm. Ass. Sci. Ed. 36, 217-219.
- (45) Arai, T. and Suehiro, S. (1953); Wakayama Med. Repts. 1, 35-42
- (46) Arai, T. et al. (1955); Wakayama Med. Repts. 2, 115-124
- (47) BIBRA Toxicity Profile (1991); The British Industrial Biological Research Association
- (48) AIDA - Huels AG-Bericht Nr. 88/189, 1988 non publicato.
- (49) Ishidate, M. et al. (1984); Fd. Chem. Toxic. 22(8), 623-636.
- (50) Ishidate, M et al. (1984); Fd. Chem. Toxic. 22(8), 623-636
Ishidate, M. (1988); Data book of chromosomal aberration test in vitro. Elsevier, Amsterdam, New York, Oxford
- (51) Short-term test program sponsored by the Division of Cancer Etiology, NCI, Dr. Thomas P. Cameron, Project Officer, p. Y82
- (52) W.H. Rapson et al., Bull. Environ. Contam. Toxicol. 24 (1980) 590.
- (53) Saffioti, U. and Shubik, P. (1963); NCI Monograph 10, 489-507.
- (54) M. Ishidate Jr. et al., Food Chem. Toxicol. 22 (1984) 623.
- (55) S. Levey et al., J. Am. Pharm. Assoc. 35 (1946) 298.
- (56) Bournias-Vardiabasis, N. et al. (1983); Teratology 28, 109-122.
- (57) Kuroda, K. and Akao, M. (1980); Biochem. Pharmacol. 29, 2839-2844
- (58) Kuroda, K. et al. (1986); Jpn. J. Cancer Res. (Gann) 77, 750-758

- (59) Kuroda, K. and Akao, M. (1989); Chem. Pharm. Bull. 37(5), 1345-1346
- (60) Kuroda, K. et al. (1982); JNCI 69, 1317-1320.
- (61) Akao, M. and Kuroda, K. (1990); Chem. Pharm. Bull. 38(7), 2012-2014.
- (62) Kuroda, K. et al. (1987); JNCI 79, 1047-1051
- (63) Kuroda, K. and Akao, M. (1981); Gann 72, 777-782
- (64) Patty, Frank A., "Industrial hygiene and toxicology," Vol. 2, Interscience Publishers, 1967.
- (65) Butterfield, D.A. et al. (1986); Biochem. Arch. 2, 245-252
- (66) Sacks, W. (1956); Appl. Physiol. 9, 43-48

7.1 Risk Assessment

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