(b) (4)

Ethyl linoleate

Toxicity monograph (with existing HCVs)

May 2018

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of ethyl linoleate (CAS RN[1] 544-35-4), focussing on the inhalation route of exposure, with inclusion of existing Health Criteria Values (HCVs) where available. Data on the inhalation of tobacco smoke containing the substance (if available) have not been included in this monograph.

EXPERTISE

(b) was founded[2] in 1961 to provide independent, high-quality research, information and advice on chemical toxicology to industry and governmental departments. Its risk assessors have been working together for many years (more than 40 years in some instances) and have a record of objectivity and scientific excellence. All senior and principal scientists in the current team are accredited and listed in the European (Eurotox) and UK Royal Society of Biology/British Toxicology Society Registers of Toxicologists and are thus bound by their specific codes of conduct.

TOXICITY DATA SEARCH CRITERIA[3]

(b) has access to a wide range of data sources, including the unique (b) (4) databank (see the Appendix for details), PubMed, the TOXNET system of databases and databanks (which includes Toxline (the toxicity subset of Medline), HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB), and eChemPortal.

In addition, the industry REACH registration dossier[4] disseminated on the ECHA website was consulted for critical ADME and/or toxicity data, and also derived no-effect levels (DNELs).

All searches were conducted in May 2018 using the CAS RN and (in PubMed only) name and synonyms identified below, as appropriate.

The data summarised in this report refers to the unheated form unless otherwise stated.

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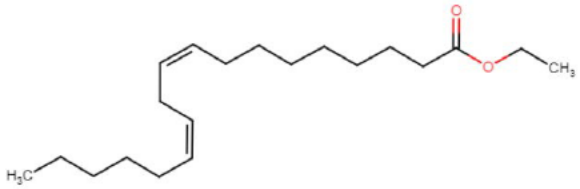
[1] Chemical Abstracts Service Registry Number.

[2] as the (b) (4)

[3] Disclaimer: searches are valid and complete as of the date of searching. (b) accepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

[4] Information on Registered Substances comes from registration dossiers which have been assigned a registration number. The assignment of a registration number does however not guarantee that the information in the dossier is correct or that the dossier is compliant with Regulation (EC) No 1907/2006 (the REACH Regulation). This information has not been reviewed or verified by the Agency or any other authority. The content is subject to change without prior notice.

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	Ethyl linoleate
Synonyms(s)	Linoleic acid ethyl ester 9,12-Octadecadienoic acid ethyl ester UNII-MJ2YTT4J8M
CAS RN	544-35-4
REACH registration number[5]	01-2120065784-47-xxxx
Molecular formula	$C_{20}H_{36}O_2$
Molecular weight	308.5
Structure	
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** Not available
	REACH joint registrants: Skin Irrit. 2. Causes skin irritation (H315)[6]

ADME[7]

No relevant data were identified on the ADME of inhaled ethyl linoleate[8].

Intravenous ^{14}C-labelled ethyl linoleate was very rapidly eliminated from the plasma of rats, a large part being "instantly" hydrolysed to linoleic acid and ethanol. About 9-11% of ethyl linoleate (or its breakdown products) was cleared from the plasma each minute. Most metabolites were found in the liver and lungs, and to a lesser extent in the heart, spleen and kidneys. Two hours after administration, only about 2.5-5.5% of radioactivity in the organs was associated with unmetabolised ethyl linoleate (Hungund *et al.*, 1995).

Rats were exposed to a diet containing 1.6% ethyl linoleate [supplying about 800 mg/kg bw/day] for five weeks. Following this, the test material was replaced by deuterium-labelled ethyl-9,10,12,13-d4-linoleate. When the rats were killed 3 days later, 54, 35 and 37.4% of

[5] REACH registration numbers are substance and company specific. Therefore, the substance-specific part of the registration number is included here, from data disseminated on the ECHA 'registered substance' website.
[6] Based on the studies described in the REACH dossier, classification as a skin sensitiser could also be justified.
[7] Absorption, Distribution, Metabolism and Excretion.
[8] ADME predictions could be estimated on the basis of the structure and physico-chemical properties, if required.

linoleate in the liver, heart and kidney phospholipids was deuterated (Luthria and Sprecher, 1994). Labelled arachidonate was also identified (mostly in the liver) of rats exposed for 4 or 5 weeks to diets containing ethyl linoleate, suggesting that linoleate is metabolised to this longer-chain fatty acid, particularly in the liver, and transported to the heart and kidney (Luthria and Sprecher, 1994, 1995).

A study in German, but without an abstract available, focuses on the behaviour of serum lipids in children after the intake of ethyl linoleate (Zollner, 1967)[9].

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

Skin irritation

Expert-group opinion

No substance-specific data were identified.

Human

No standard substance-specific data were identified.

The topical application of an agent containing [probably 75%] ethyl linoleate has evidently had beneficial effects on healing in burns patients (Jelenko and McKinley, 1976).

Non-human

No standard substance-specific data were identified.

Topical treatment with an agent containing 75% ethyl linoleate has been seen to have beneficial effects on the healing of burns in pigs (Jelenko *et al*., 1975a), rabbits (Jelenko *et al*., 1975a,b) and mice (Jelenko *et al*., 1975b).[10]

The industry REACH registration dossier submitter for ethyl linoleate describes a read-across study on methyl linoleate (CAS RN 112-63-0) which was said to have been conducted in accordance with OECD Test Guideline 404[11] and GLP[12]. Three rabbits were given semi-occlusive applications of 0.5 mL undiluted methyl linoleate to hairless skin for 4 hours. Slight-to-moderate erythema and oedema were observed during the first 72 hours after exposure, and eschar (scabbing) was seen in all animals from 72 hours to 1 week after exposure. Irritant effects were reversible within 22 days. Based on these findings, methyl linoleate was considered to be moderately irritating to the skin, and the dossier submitter concluded that

[9] The report could be obtained and translated in the future, if required.

[10] The following references (without freely available abstracts) also appear to be relevant to this:
Jelenko *et al*. (1972). Studies in burns. XI. Ethyl linoleate: the water-holding lipid of skin. B. Effects on *in vivo* burn eschar. Journal of Trauma 12(11), 974-8.
Jelenko *et al*. (1972). Studies in burns. X. Ethyl linoleate: the water-holding lipid of skin. A. The evidence. Journal of Trauma 12(11), 968-73.

[11] Acute dermal irritation/corrosion.

[12] Good laboratory practice.

ethyl linoleate "would exert similar characteristics in skin irritation", given its similar structure and metabolism (Anon., 1992a). [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time.]

Eye irritation

Expert-group opinion

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

The industry REACH registration dossier submitter for ethyl linoleate describes a study on the read-across substance, CAS RN 91051-53-5 [defined in ChemID*plus* as "fatty acids, safflower-oil, Et esters"], stating that "as the major component of the test item is ethyl linoleate, the data are considered valid for assessment of ethyl linoleate". The test was said to have been conducted in accordance with OECD Test Guideline 405[13] and GLP. 0.1 mL of the undiluted test substance was instilled into one eye of each of three rabbits. Slight conjunctival redness was observed within 1 hour, but signs of irritation had completely resolved by 24 hours in all animals. The test substance was, as a result, considered not irritating (Anon., 2010a). [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time.]

Other local effects

No substance-specific data were identified.

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

No substance-specific data were identified.

Skin sensitisation

Expert-group opinion

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

The industry REACH registration dossier submitter for ethyl linoleate describes a read-across study on methyl linoleate (CAS RN 112-63-0) which was said to have been conducted similarly

[13] Acute eye irritation/corrosion.

to OECD Test Guideline 406[14] and GLP. The test was a Buehler assay in which ten female guinea pigs[15] received a topical 6-hour application of 40% methyl linoleate (in olive oil) once weekly for 3 weeks. Challenge [presumably after a 2-week rest period] involved a 6-hour application of 20% methyl linoleate. Local reactions at challenge were seen in both the test (5/10 at 24 hours, 2/10 at 48 hours) and negative control groups (3/10 at 24 hours, 1/10 at 48 hours). A further negative control group confirmed the [presumably irritant] reactions in controls. The dossier submitters considered that "since no increased dermal alterations (incidence and severity) were observed in the animals of the treatment group compared with the animals of the control group after the challenge, the test substance is proved to be a "non-sensitizer" on the skin of guinea pigs", and that ethyl linoleate "would exert similar characteristics in pathophysiological mechanism of skin sensitization", given its similar structure and metabolism (Anon., 1992b).

The industry REACH registration dossier also summarises a local lymph node assay (LLNA) conducted on the read-across substance, CAS RN 91051-53-5 [defined in ChemID*plus* as "fatty acids, safflower-oil, Et esters"]; "as the major component of the test item is ethyl linoleate, the data are considered valid for assessment of ethyl linoleate". The assay was said to have been conducted in accordance with OECD Test Guideline 429[16] and GLP. Groups of five female CBA mice were topically treated with 25 µL of the test substance on each ear at concentrations of 0, 25, 50 or 100% in acetone/olive oil for three consecutive days. The SI values[17] were significant (≥3) for the 50 and 100% test concentrations, but the SI was 2.3 in the 25% group. The EC3 value[18] was calculated to be 29.1%. Based on this, the test compound (and by implication ethyl linoleate) was considered to be a skin sensitiser (Anon., 2010b).

[It is noted that the REACH registrant did not opt for the classification of ethyl linoleate as a skin sensitiser based on these read-across findings. However, it is questionable whether the findings in the Buehler assay would be sufficient to rule out classification for skin sensitisation based on the positive LLNA result[19].]

Oral allergy/intolerance

No substance-specific data were identified.

INHALATION TOXICITY STUDIES – SYSTEMIC EFFECTS

Single dose toxicity

No substance-specific data were identified.

Repeated dose toxicity

No substance-specific data were identified.

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[14] Skin sensitisation.
[15] Rather than the 20 guinea pigs in the treated group as recommended in the guideline.
[16] Skin sensitisation: local lymph node assay.
[17] OECD test guideline 429 defines stimulation index (SI) as "the ratio of the proliferation in treated groups to that in the concurrent vehicle control group". An SI of ≥3 is considered positive under this test method.
[18] i.e. the concentration giving rise to an SI of 3.
[19] These studies and the test materials can be further investigated in the future, and the studies compared to the EU CLP criteria to determine if classification as a skin sensitiser is warranted for ethyl linoleate.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

Expert-group opinion

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No standard substance-specific data were identified.

[Limited and non-standard tests investigating some of the particular effects of acute ethyl linoleate exposure are available (see Other toxicity considerations section). These are not considered to provide any information that would be critical or useful for risk assessment.]

The industry REACH registration dossier contains a summary of an acute oral toxicity test conducted on the read-across substance, CAS RN 91051-53-5 [defined in ChemID*plus* as "fatty acids, safflower-oil, Et esters"]; "as the major component of the test item is ethyl linoleate, the data are considered valid for assessment of ethyl linoleate". In this study, apparently conducted in accordance with OECD Test Guideline 423[20] and GLP, three female Wistar rats were administered the test substance (undiluted) at 2000 mg/kg bw by gavage. No deaths were seen within 14 days of treatment; the oral LD_{50} value[21] was >2000 mg/kg bw (Anon., 2010c).

A dermal test on the same read-across chemical (CAS RN 91051-53-5) was said to have been performed in accordance with OECD Test Guideline 402[22] and GLP. The undiluted test material was applied under occlusion to the skin of Wistar rats (five/sex) for 24 hours, supplying 2000 mg/kg bw. No deaths were seen within 14 days of treatment; the dermal LD_{50} value was >2000 mg/kg bw (Anon., 2010d).

Repeated dose toxicity

Expert-group opinion

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No standard substance-specific data were identified.

[Limited and non-standard tests investigating some of the particular effects of repeated dosing with ethyl linoleate are available (see Other toxicity considerations section). These are not considered to provide any information that would be critical or useful for risk assessment.]

[20] Acute oral toxicity - acute toxic class method.

[21] Lethal dose 50, i.e. the dose that is lethal to 50% of the exposed group.

[22] Acute dermal toxicity.

GENOTOXICITY

Expert-group opinions

No substance-specific data were identified.

Mammals (*in vivo*)

No substance-specific data were identified.

Mammalian cells (*in vitro*)

No substance-specific data were identified.

The industry REACH registration dossier submitter for ethyl linoleate, however, presents mutagenicity data on the read-across substance, CAS RN 91051-53-5 [defined in ChemID*plus* as "fatty acids, safflower-oil, Et esters"], stating that "as the major component of the test item is ethyl linoleate, the data are considered valid for assessment of ethyl linoleate". In this test, said to have been conducted in accordance with OECD Test Guideline 476[23] and GLP, no evidence of mutagenic activity was seen in duplicate cultures of mouse lymphoma (L5178Y) cells, tested for 3 hours with, or for 3 or 24 hours without, metabolic activation from S9 mix[24]. The test substance was applied in DMSO[25] at concentrations (limited by cytotoxicity) of up to 300 µg/mL with S9, or 90 (24 hours) or 150 µg/mL (3 hours) without S9 (Anon., 2010e).

Similarly, the industry REACH dossier submitter describes an *in vitro* chromosomal aberration study on the same read-across substance (CAS RN 91051-53-5). The was no evidence of clastogenicity in human peripheral lymphocytes exposed to the read-across substance (in DMSO) at up to 333 µg/mL (3-hour exposure without S9) or up to 1000 µg/mL (24- or 48-hour exposure without S9, 3-hour exposure with S9). The test was said to have been conducted in accordance with OECD Test Guideline 473[26] and GLP. Test concentrations were limited by precipitation (3-hour exposure) or cytotoxicity (24- and 48-hour exposures) (Anon., 2010f).

Micro-organisms

No substance-specific data were identified.

The industry REACH dossier submitter for ethyl linoleate describes a bacterial reverse mutation assay on the read-across substance, CAS RN 91051-53-5 [defined in ChemID*plus* as "fatty acids, safflower-oil, Et esters"], stating that "as the major component of the test item is ethyl linoleate, the data are considered valid for assessment of ethyl linoleate". In this test, said to have been conducted in accordance with OECD Test Guideline 471[27] and GLP, no evidence of mutagenic activity was seen in triplicate cultures of *Salmonella typhimurium* strains TA98, TA100, TA1535 or TA1537, or in *Escherichia coli* strain WP2, with or without S9, tested with up to precipitating concentrations of 1000 µg/plate (Anon., 2010g). [Two independent experiments were performed, the first examining TA98, TA1535 and TA1537 only, with and without 5% S9, the second looking at all five strains, with and without 10% S9.]

[23] *In vitro* mammalian cell gene mutation test.
[24] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.
[25] Dimethyl sulfoxide.
[26] *In vitro* mammalian chromosome aberration test.
[27] Bacterial reverse mutation assay.

Other
No substance-specific data were identified.

CARCINOGENICITY

Expert-group opinions
No substance-specific data were identified.

Human
No substance-specific data were identified.

Non-human
No standard substance-specific carcinogenicity data were identified, however limited tests are available which investigate the effects of ethyl linoleate on the activity of known carcinogens. These studies are not sufficient to conclude on a presence[28] or absence[29] of carcinogenic potential for ethyl linoleate itself, but have briefly been described below.

Some evidence of a tumour-promoting effect was seen in groups of 20 female Sprague-Dawley rats given a known carcinogen, then, 1 week later, a diet containing 17% coconut oil and 3% ethyl linoleate (another group was given 20% coconut oil in the diet, without ethyl linoleate). Rats were examined for mammary tumours 19 weeks after carcinogen exposure, and all those rats given the diet containing ethyl linoleate developed tumours, as compared to 70% of those given coconut oil alone (Hopkins *et al.*, 1981).

However, in another test, the presence or absence of 40 mg/day of ethyl linoleate in diets also including coconut oil, vitamin B_6 and a known carcinogen had no clear effect on liver tumour incidence in Sprague-Dawley rats (15/group), assessed at 4 or 6 months (Miller *et al.*, 1944).

The potential tumour-promoting effects of linoleic acid are discussed further in a review by Dupont *et al.* (1990).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Expert-group opinions
No substance-specific data were identified.

Human
No substance-specific data were identified.

Non-human
No standard substance-specific reproductive or developmental toxicity data were identified.

[28] The substance was given with known carcinogens.
[29] The relevant OECD Test Guideline (451: Carcinogenicity studies) recommends testing at least three doses in 50/sex/dose for at least 18 months (mice) or 2 years (rats).

Groups of six to eight pregnant Sprague-Dawley rats were given ethyl linoleate at 10, 20 or 50 mg/kg bw by gavage (in an ethanol/water mix) during the last two days of gestation (days 20-21), while ten controls were given the vehicle alone. Rats were observed for effects on gestation time, duration of parturition, and post-partal bleeding. For litters of less than six, dams were killed and examined for placental sites or dead foetuses. Pups were observed and weighed for at least 72 hours after delivery. In both the groups given 20 or 50 mg/kg bw, the length of gestation was increased slightly by about 8 hours. A "minimal" increase was seen in bleeding during parturition, but no other adverse effects were reported (Waltman *et al.*, 1977).

Exposure to ethyl linoleate (20 mg/day for 15 weeks) has been seen to have beneficial effects in male rats with arachis oil-induced degeneration of the spermatogenic tissues (Aaes-Jorgensen *et al.*, 1957).

CARDIOPULMONARY EFFECTS[30]

No substance-specific data were identified.

OTHER TOXICITY CONSIDERATIONS

A number of >20-year-old studies are available, focusing on the effects of ethyl linoleate on cholesterol and lipid metabolism in rats (Budijanto *et al.*, 1992; Huang *et al.*, 1988; Rivera, 1971); prostaglandin E2 excretion and activity in rats on a fat-free diet (Hansen and Jensen, 1985; Hansen *et al.*, 1983); prostaglandin I2 production in butter-fed rats (Steel *et al.*, 1990). Other earlier studies (>45-year-old) appear to focus on the beneficial effects of ethyl linoleate (Cheng *et al.*, 1954; Datey and Dalvi, 1966; Datey *et al.*, 1965, 1966, 1971; Fuld and Horwich, 1959; Hutsell and Quackenbush, 1967; Ito *et al.*, 1966; Novikova, 1968; Osumi *et al.*, 1966; Walker *et al.*, 1959).[31]

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific HCVs were identified.

REFERENCES

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Anon. (1992a). Skin irritation/corrosion. Key. https://echa.europa.eu/registration-dossier/-/registered-dossier/10362/7/4/2. [Cited in BASF Health and Care Products France S.A.S., 2017.]

[30] Potential effects on the heart, blood vessels and/or respiratory tract.

[31] These publications were generally not considered beyond their abstracts (or titles if no freely-available abstract was obtainable), as they are highly unlikely to provide information useful to the risk assessment of inhaled ethyl linoleate. The publications can be obtained and summarised in the future, if required.

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Anon. (2010b). Skin sensitisation. 002 Weight of evidence read-across (structural analogue/surrogate). https://echa.europa.eu/registration-dossier/-/registered-dossier/10362/7/5/2/?documentUUID=08aaf253-d2d2-4f61-835a-fcce8eb0b69e

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Cheng AL, Ryan M, Alfin-Slater R and Deuel HJ (1954). The effect of fat level of the diet on general nutrition. XI. The protective effect of varying levels of ethyl linoleate against multiple sublethal doses of x-irradiation in the rat. Journal of Nutrition 52, 637-643. [From title only.]

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Datey KK, Purandare NM and Dalvi CP (1966). Ethyl linoleate as an antiatherogenic agent. An experimental study in rabbits. Angiology 17, 732-737. [From abstract only.]

Datey KK, Dalvi CP, Mehta NJ and Purandare NM (1971). Ethyl linoleate, atherosclerosis and longevity. Indian Heart Journal 23, 141-144. [From title only.]

Dupont J, White PJ, Carpenter MP, Schaefer EJ, Meydani SN, Elson CE, Woods M and Gorbach SL (1990). Food uses and health effects of corn oil. Journal of the American College of Nutrition 9, 438-470.

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Hutsell TC and Quackenbush FW (1967). Reduction of atherogenicity of natural fats by small additions of ethyl linoleate in the diet of the rat. Lipids 2, 342-344. [From abstract only.]

Ito Y (1966). Effects of ethyl linoleate on chronic liver diseases with special reference to lipid metabolism. Nagoya Journal of Medical Science 29, 167-189. [From abstract only.]

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Zollner H (1967). [Studies of serum lipids in children. IX. The behavior of serum lipids after the intake of Linoleic acid ethyl ester concentrate]. Zeitschrift Fur Kinderheilkunde 99, 302-310. [Article in German, with no abstract available.]

APPENDIX: The (b) (4) database and databank

(b) (4)

(b) (4) includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, (b) (4) covers official publications and evaluations issued by authoritative groups including:

- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- IUCLID data sets
- EU Risk Assessment Reports
- EU expert committee opinions (including EU scientific committees, and EFSA scientific panels) and other reports from EU agencies and institutes etc (including ECHA, ECVAM, EMA and CPS&Q)
- ECETOC, HERA, Council of Europe and other pan-European programmes
- UK government agency (including Defra, EA, FSA, DoH, HSE, HPA, PSD and VMD) and advisory committee (e.g. COT, COM, COC, ACNFP, SACN, ACP, ACAF, VPC, VRC and ACRE) reports and evaluations
- Opinions from other UK organisations such as the Royal Society
- US agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS, CDC, OEHHA and ACGIH)
- Health Canada evaluations
- BUA, DFG, BG Chemie and BfR reports and monographs
- Gezondheidsraad opinions, including those from its various committees such as DECOS
- RIVM reports
- Danish EPA reviews
- Reports and other information provided by Swedish governmental organisations, including the National Food Administration and the Swedish Chemicals Agency
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
- Australian agency reviews including NICNAS Priority Existing Chemical Assessments, APMVA reports and (jointly with New Zealand) FSANZ assessments
- Japanese Chemical Industry Ecology-Toxicology & Information Center reports
- CIR, RIFM and other specialist industry groups
- (b)) Toxicity Profiles