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Ethyl stearate

Toxicity monograph (with existing HCVs)

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Ethyl stearate

Toxicity monograph (with existing HCVs)

INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of ethyl stearate (CAS RN[1] 111-61-5), 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) (4) 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.

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

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

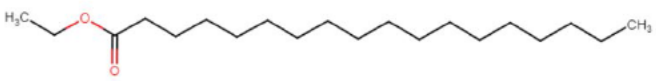
IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	Ethyl stearate
Synonyms(s)	Ethyl octadecanoate Stearic acid ethyl ester UNII-C64RTC734W

[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.

CAS RN	111-61-5
REACH registration number[4]	Not available
Molecular formula	$C_{20}H_{40}O_2$
Molecular weight	312.5
Structure	
Classification, according to EU CLP (EC 1272/2008)	Harmonised classification: Not available
	REACH joint registrants: Not available

ADME[5]

No relevant data were identified on the ADME of inhaled ethyl stearate[6].

In its evaluation of fifteen structurally-related ethyl esters (including ethyl stearate), the Joint FAO/WHO Expert Committee on Food Additives stated that the compounds are "considered to be completely hydrolysed in the human body to ethanol and their component carboxylic acids" … "which are endogenous intermediates in human metabolism. Therefore all the compounds were predicted to be metabolized to innocuous products" (JECFA, 1997).

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 skin irritation was seen in 26 subjects following a 48-hour covered application of ethyl stearate at a concentration of 12% in petrolatum (Epstein, 1976). [See also Skin sensitisation section.]

[4] 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.
[5] Absorption, Distribution, Metabolism and Excretion.
[6] ADME predictions could be estimated on the basis of the structure and physic-chemical properties, if required.

Non-human
Neat ethyl stearate applied to intact or abraded rabbit skin for 24 hours under occlusion was moderately irritating (Moreno, 1976).

Eye irritation
No substance-specific data were identified.

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
In a maximisation test[7], no skin sensitisation reactions were produced when 26 subjects were tested with ethyl stearate at 12% in petrolatum (Epstein, 1976). [See also Skin irritation section.]

Non-human
No substance-specific data were identified.

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.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES
Single dose toxicity
Expert-group opinion
No substance-specific data were identified.

[7] The test procedure typically involves an initial induction phase of five 48-hour covered patch tests, followed 10-14 days later by a 48-hour covered challenge patch.

Human
No substance-specific data were identified.

Non-human
The acute oral LD_{50} value[8] in rats and the acute dermal[9] LD_{50} in rabbits both exceeded 5000 mg/kg bw (Moreno, 1976).

Intravenous doses of 30 or 40 mg [about 1000 or 1333 mg/kg bw] killed 2/10 or 4/10 tested mice (Cooper and Stuart, 1962; Stuart and Cooper, 1962). [See also Other toxicity considerations section.]

Repeated dose toxicity
Expert-group opinion
No substance-specific data were identified.

Human
No substance-specific data were identified.

Non-human
A [presumably reliable] combined repeated dose toxicity/reproductive and developmental toxicity screening test has been conducted (to GLP) on ethyl stearate. The publicly-available study report (of >1000 pages) is predominantly in Japanese (Anon., 2016a), and has not been translated to English at this time[10]. [See also Reproductive and developmental toxicity section.]

No other standard good-quality repeated-dose studies on ethyl stearate were available. Some more limited oral studies are discussed below. Opdyke (1979) also provides details on further oral studies concerning the nutritional and metabolic (rather than toxic) effects of dietary ethyl stearate. These were considered of limited value to this report and therefore omitted.

In an early study focused on detecting lipogranulomas [nodules of granulomatous inflammation associated with lipid deposits in tissues], male and female Holtzman rats were fed diets containing 45% ethyl stearate [providing about 22,500 mg/kg bw/day] for 24 weeks. After the exposure period, rats were instead given a diet containing 20% corn oil for a further 24 weeks. The control group was fed a diet containing 4% corn oil and 10% triacetin[11] for 48 weeks. The incidences of lipogranulomas was recorded in groups of 5-6 rats that were killed every 8 weeks during the exposure period, and in groups of 3 killed every 8 weeks in the recovery (corn oil) period. Lipogranulomas were found in in the perigonadal fat of 4/7, 4/5

[8] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.
[9] Unspecified duration.
[10] A limited amount of English language text is included sporadically in the main body of the study report, and in tables and figures. From this it appears Sprague-Dawley rats (12/sex/group) were orally[10] exposed at 0, 100, 300 or 1000 mg/kg bw/day (and that 5/sex/group of the control and high dose animals were included in a 2-week recovery period). Unfortunately, it is not possible, at this time, to assess the study findings from the tabulated results presented. If required in the future, (b) (4) would be pleased to assist with organising a translation of this study report and to determine if any adverse effects were seen and at what doses these can be considered significant.
[11] Supplying acetyl equivalent to that in a diet containing 54% of distilled partially acetylated monoglycerides.

and 5/6 rats killed after 8, 16, or 24 weeks of exposure. The effect was "severe" in 0/6, 2/5 and 3/6 rats. After 8 weeks on the recovery diet, only one of the three rats killed had "slight" lipogranuloma, and none of the rats killed at 16 or 24 weeks displayed this effect (Herting and Harris, 1959).

Male Sprague-Dawley rats (7/group) received diets containing approximately 5% ethyl stearate[12] [providing about 2500 mg/kg bw/day] for 2 weeks. The treated animals were then assessed for endpoints including body weight, liver weight, and effects on lipid metabolism (plasma total cholesterol, free cholesterol, phospholipid, triglyceride, lipoprotein cholesterol and LCAT[13] activity). Results were compared to those from rats given diets containing other fatty acid ethyl esters, rather than an untreated control group, so are of limited usefulness. However, it was noted that ethyl stearate did not increase plasma cholesterol levels as much as did ethyl palmitate (Budijanto *et al*., 1992).

"Marked fatty changes" have been seen in the liver of male rats given ethyl stearate in the diet (with no choline) at a level of 35% [providing about 17,500 mg/kg bw/day] [no further study details are given in the citing source] (Stetten and Salcedo, 1945).

[See also Other toxicity considerations section.]

GENOTOXICITY

Expert-group opinions

No substance-specific data were identified.

Mammals (*in vivo*)

No substance-specific data were identified.

Mammalian cells (*in vitro*)

A Japanese report describing a chromosome aberration test in Chinese hamster (CHL/IU) fibroblasts is available on ethyl stearate. The study was evidently conducted to OECD Test Guideline 473 and to GLP. From the figures and tables (in English) it appears that exposure to ethyl stearate at concentrations of up to 2000 µg/mL (with or without metabolic activation by S9[14] mix) was not genotoxic to the cultured cells (Anon., 2016b).

Micro-organisms

A Japanese report describes a GLP bacterial reverse mutation assay on ethyl stearate. From the figures and tables (partially in English), it appears that the test material was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, or in *Escherichia coli* strain WP2 uvrA, when tested (with or without S9) at concentrations of up to 1250 µg/plate[15] (Anon., 2017).

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[12] The "fat" component was 94.1% ethyl stearate.
[13] Lecithin:cholesterol acyltransferase.
[14] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.
[15] It appears a preliminary assessment was conducted with concentrations of up to 5000 µg/plate. Presumably cytotoxicity was seen at the higher concentrations and, as such, the highest dose tested in the main study was 1250 µg/plate.

(b) there was no evidence of mutagenicity for ethyl stearate (in ethanol) at 3 µmol/plate in *S. typhimurium* strains TA100, TA1535 and TA1537, both with and without S9. Very few study details are given, but an "uncertain" result in TA98 appears to have led to retesting this strain with further concentrations of 0.03, 0.3, 3 and 30 µmol/plate. Cytotoxicity and precipitation were seen at 30 µmol/plate. The [unspecified] findings were not considered to indicate genotoxic potential, but "results obtained with these substances are difficult to evaluate" (Florin *et al.*, 1980).

Other

No substance-specific data were identified.

CARCINOGENICITY

No substance-specific data were identified.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Expert-group opinions

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

A [presumably reliable] combined repeated dose toxicity/reproductive and developmental toxicity screening test has been conducted (to GLP) on ethyl stearate. The publicly-available study report (of >1000 pages) is predominantly in Japanese (Anon., 2016a), and has not been translated to English at this time. [See also Repeated dose toxicity section for details.]

Groups of six pregnant Sprague-Dawley rats were given ethyl stearate at 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. A "minimal" increase was seen in bleeding during parturition, but no other adverse effects were reported (Waltman *et al.*, 1977).

CARDIOPULMONARY EFFECTS[16]

[The heart and lungs were assessed in a presumably reliable (GLP) combined repeated dose toxicity/reproductive and developmental toxicity screening test involving oral administration of ethyl stearate (Anon., 2016a). [See Repeated dose toxicity section for details.]

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

OTHER TOXICITY CONSIDERATIONS

A 1-ml oral dose of ethyl stearate reduced the phagocytic function of the reticulo-endothelial system (RES) of mice. This effect has also been seen following single intravenous injections of ethyl stearate (e.g. at doses of 128-1333 mg/kg bw). Intravenous ethyl stearate given at 20 mg/mouse every 48 hours [about 670 mg/kg bw per injection] maintained a depressed RES state "for a considerable period of time". Immune reactions (e.g. to endotoxin) have also been reduced in mice following injections of ethyl stearate (cited in Opdyke, 1979).

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific inhalation HCVs were identified.

JECFA has concluded that ethyl stearate is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive. At the time, these were 2.6 or 0.38 µg/person/day in the EU and US, respectively (JECFA, 1997).

REFERENCES

Anon. (2016a). Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (in Japanese). Available via http://dra4.nihs.go.jp/mhlw_data/jsp/FileListPageENG.jsp?parameter_csno=111-61-5

Anon. (2016b). *In vitro* mammalian chromosome aberration test (in Japanese). Available via http://dra4.nihs.go.jp/mhlw_data/jsp/FileListPageENG.jsp?parameter_csno=111-61-5

Anon. (2017). Bacterial reverse mutation test (in Japanese). Available via http://dra4.nihs.go.jp/mhlw_data/jsp/FileListPageENG.jsp?parameter_csno=111-61-5

Budijanto S, Ito M, Furukawa Y and Kimura S (1992). Effect of various dietary fatty acid ethyl esters on plasma cholesterol and lipoprotein metabolism in rats. Journal of Clinical Biochemistry and Nutrition 13, 13-22.

Cooper GN and Stuart AE (1962). Susceptibility of mice to pneumococcal infection after modification of the reticulo-endothelial system with simple lipids. Journal of Pathology and Bacteriology 83, 227-243 [cited in Opdyke, 1979].

Epstein WL (1976). Report to RIFM, 23 July [cited in Opdyke, 1979].

Florin I, Rutberg L, Curvall M and Enzell CR (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15, 219-232.

Herting DC and Harris PL (1959). Lipogranuloma from dietary saturated fats: production and reversal. Toxicology and Applied Pharmacology 1, 505-514.

JECFA (1997). Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and contaminants. Forty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 868. http://whqlibdoc.who.int/trs/WHO_TRS_868.pdf?ua=1

Moreno OM (1976). Report to RIFM, 31 July [cited in Opdyke, 1979].

Opdyke DLJ (1979). Monographs on Fragrance Raw Materials: Ethyl stearate. Food and Cosmetics Toxicology 17, 781-783.

Stetten D and Salcedo J (1945). The effect of chain length of the dietary fatty acid upon the fatty liver of choline deficiency. Journal of Nutrition 29, 167-170 [cited in Von Oettingen, 1960].

Stuart AE and Cooper GN (1962). Susceptibility of mice to bacterial endotoxin after modification of reticulo-endothelial function by simple lipids. Journal of Pathology and Bacteriology 83, 245-254 [cited in Opdyke, 1979].

Von Oettingen WF (1960). The aliphatic acids and their esters: toxicity and potential dangers. Archives of Industrial Health 21, 100-113.

Waltman R, Tricomi V, Shabanah EH and Arenas R (1977). Prolongation of gestation time in rats by unsaturated fatty acids. American Journal of Obstetrics and Gynecology 127, 626-738.

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