(b) (4)

Ethyl palmitate

Toxicity monograph (with existing HCVs)

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Prepared by:

(b) (4)

(b) (4)

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Ethyl palmitate

Toxicity monograph (with existing HCVs)

INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of ethyl palmitate (CAS RN[1] 628-97-7), 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

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TOXICITY DATA SEARCH CRITERIA[3]

(b) (4) has access to a wide range of data sources, including the (b) (4) (b (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[5] 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.

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[1] Chemical Abstracts Service Registry Number.

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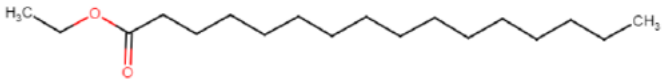
[3] Disclaimer: searches are valid and complete as of the date of searching. (b) (4) ccepts no responsibility for the accuracy, completeness or sufficiency of any databases or searching platforms employed.

[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.

[5] European Chemical Agency (ECHA).

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

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier	
Name	Ethyl palmitate
Synonyms(s)	Ethyl hexadecanoate Hexadecanoic acid, ethyl ester UNII-IRD3M534ZM
CAS RN	628-97-7
REACH registration number[6]	01-2120764435-50-xxxx
Molecular formula	$C_{18}H_{36}O_2$
Molecular weight	284.48
Structure	
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:** Not available
	REACH joint registrants: "Not classified"

ADME[7]

Emulsified ethyl palmitate, when incubated in mouse serum, was "rapidly" hydrolysed to free palmitic acid. Similarly, when it (at a concentration of 600 mM) was continuously infused (0.2 µL/min) into mice through the jugular vein for 2 or 14 hours, serum palmitate was significantly increased (Eguchi *et al.*, 2012).

In its evaluation of fifteen structurally-related ethyl esters (including ethyl palmitate), 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).

[6] 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.
[7] Absorption, Distribution, Metabolism and Excretion.

The European Food Safety Authority, in evaluating 86 straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters (including ethyl palmitate) as animal feed additives, considered that "the compounds considered to be safe for the target species are extensively metabolised by the target species and excreted as innocuous metabolites and carbon dioxide" (EFSA, 2013).

It was agreed by the industry submitter of the REACH registration dossier on ethyl palmitate that fatty acid esters such as ethyl palmitate are expected to be broken down in the gut to their free alcohols and fatty acids. "In contrast, substances that are absorbed through the pulmonary alveolar membrane or through the skin enter the systemic circulation directly before joining the liver where hydrolysis basically takes place" [however, hydrolysis will not be limited to the liver, and would also been seen in the blood etc.; it was also specifically stated that carboxylesterases in the skin could hydrolyse ethyl palmitate] (Anon., 2018).

In addition, the REACH registration dossier submitter predicted that "the fatty acid component [is] not expected to be excreted to a significant degree via urine or faeces but excreted via exhaled air as CO_2 or stored. The second route of excretion is expected to be by biliary excretion within the faeces. For the alcohol, the main route is renal excretion via the urine due to the low molecular weight and the high water solubility" (Anon., 2018).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

Expert-group opinion

EFSA, in evaluating 86 straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters (including ethyl palmitate) as animal feed additives, considered [in the absence of good data suggesting otherwise] it prudent to treat all compounds under assessment as respiratory tract irritants (EFSA, 2013).

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

Skin irritation

Expert-group opinion

EFSA, in evaluating 86 straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters (including ethyl palmitate) as animal feed additives, considered [in the absence of good data suggesting otherwise] it "prudent to treat all compounds under assessment as irritants to skin" (EFSA, 2013).

Human

No substance-specific data were identified.

Non-human
No substance-specific data were identified.

The REACH registration dossier submitter for ethyl palmitate stated that "no experimental study was available for the target substance the ethyl palmitate. However, several experimental *in vivo* studies [on related chemicals][8] were performed for skin irritation assessment. None of these studies showed irritation properties. The source substances and the target substance are structurally similar and showed common [physicochemical] properties. Based on these properties, it can be stated that the target substance followed the same health effect for skin irritation. Hence, the ethyl palmitate was considered as not irritant to skin." The skin irritation tests were apparently performed in accordance with OECD Test Guideline 404[9] (Anon., 2018). [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time.]

Eye irritation

Expert-group opinion
EFSA, in evaluating 86 straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters (including ethyl palmitate) as animal feed additives, considered [in the absence of good data suggesting otherwise] it prudent to treat all compounds under assessment as irritants to the eyes (EFSA, 2013).

Human
No substance-specific data were identified.

Non-human
No substance-specific data were identified.

The REACH registration dossier submitter for ethyl palmitate stated that "no experimental study was available for the target substance the ethyl palmitate. However, five key experimental *in vivo* studies were performed for eye irritation assessment. These studies were performed [on related chemicals][10] *in vivo* on rabbits or guinea pigs according to OECD 405[11] guideline method. None of these studies showed irritation properties. The source substances and the target substance are structurally similar and showed common [physicochemical] properties. Based on the properties, it can be stated that the target substance followed the same health effect for eye irritation. Hence, the ethyl palmitate was considered as not irritant to eye" (Anon., 2018). [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.

[8] Isopropyl myristate (CAS RN 110-27-0), isopropyl palmitate (CAS RN 142-91-6), ethyl linoleate (CAS RN 544-35-4), ethyl oleate (CAS RN 111-62-6) and isopropyl isostearate (CAS RN 68171-33-5).
[9] Acute Dermal Irritation/Corrosion.
[10] Isopropyl myristate (CAS RN 110-27-0), isopropyl palmitate (CAS RN 142-91-6), ethyl linoleate (CAS RN 544-35-4), ethyl oleate (CAS RN 111-62-6) and isopropyl isostearate (CAS RN 68171-33-5).
[11] Acute Eye Irritation/Corrosion.

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

No substance-specific data were identified.

Skin sensitisation

Expert-group opinion

EFSA, in evaluating 86 straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters (including ethyl palmitate) as animal feed additives, considered [in the absence of good data suggesting otherwise] it prudent to treat all compounds under assessment as skin sensitisers (EFSA, 2013).

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

The REACH registration dossier submitter for ethyl palmitate stated that "one study was performed on the isopropyl myristate [CAS RN 110-27-0]. It was conducted according to OECD 429[12] guideline method, using guinea pigs. This study did not [show] positive results or sensitisation after animal treatment" and that "it can be stated that the members of the category have the same toxicity due to the same metabolic pathways when absorbed in the organisms" (Anon., 2018). [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time.]

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.

Human

No substance-specific data were identified.

[12] Skin sensitisation.

Non-human

No standard substance-specific acute toxicity data were identified.

An LD_{50} value[13] of >470 mg/kg bw was reported for ethyl palmitate in deer mice (*Peromyscus maniculatus*) following dosing of 2-6 animals by an unspecified route[14]. Animals were observed over 7-14 days (Schafer and Bowles, 2004). [No further study details are available.]

The REACH registration dossier submitter for ethyl palmitate considered that the acute oral LD_{50} value for ethyl palmitate in rodents would exceed 2000 mg/kg bw. "Several studies [in rats and mice] were performed in members of the category[15] for acute oral toxicity. For acute oral toxicity studies, results showed an LD_{50} value greater than 2000 mg/kg bw". Similar conclusions were made for acute dermal toxicity, where rat data on ethyl linoleate (CAS RN 544-35-4) (in an OECD Test Guideline 402[16] study) were said to indicate an acute dermal LD_{50} value of >2000 mg/kg bw for ethyl palmitate (Anon., 2018). [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time.]

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 repeated-dose toxicity data were identified.

The REACH registration dossier submitter for ethyl palmitate considered that the oral no-observed-adverse-effect level (NOAEL) for ethyl palmitate in rodents would be about 1000 mg/kg bw. This was based on NOAELs of 1000 and 5500 mg/kg bw/day, said to be the highest tested doses for isopropyl myristate (CAS RN 110-27-0) and ethyl oleate (CAS RN 111-62-6) in OECD Test Guideline 407[17] compliant 28-day oral rodent studies involving [presumably gavage] treatment on 5 days/week (Anon., 2018).

Very limited repeated-dose studies[18] on ethyl palmitate have been identified, including those relating to its short-term toxicity to the non-standard species of deer mice[19] (Schafer and Bowles, 2004) and its propensity to increase plasma cholesterol levels in rats exposed in the diet for 2 weeks[20] (Budijanto *et al.*, 1992).

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

[14] Orally, dermally or by intraperitoneal or intraocular injection.

[15] Isopropyl myristate (CAS RN 110-27-0), isopropyl palmitate (CAS RN 142-91-6), ethyl linoleate (CAS RN 544-35-4), ethyl oleate (CAS RN 111-62-6), fatty acids C_{16-18} and C_{18}-unsatured isobutyl esters (CAS RN 84988-79-4) and isopropyl isostearate (CAS RN 68171-33-5).

[16] Acute dermal toxicity.

[17] Repeated Dose 28-day Oral Toxicity Study in Rodents.

[18] These studies were not considered to provide useful data for risk assessment.

[19] It was indicated that there was less than 50% mortality in deer mice given 1250 mg/kg bw/day in the diet for 3 days.

[20] 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.

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.

A lack of mutagenic activity was apparently seen for ethyl linoleate (CAS RN 544-35-4) in mouse lymphoma (L5178Y) cells, with and without metabolic activation [presumably by S9 mix[21]]. This study was used by the REACH registrant of ethyl palmitate to conclude that "the target substance was considered as not mutagenic in *in vitro* mutation test on mammalian cells" (Anon., 2018). [No further study details were provided.] [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time.]

Ethyl palmitate was not considered by the REACH registration dossier submitter to be clastogenic in mammalian cells, based on a lack of such effect seen for ethyl linoleate (CAS RN 544-35-4) in Chinese hamster ovary cells, with and without metabolic activation [presumably by S9 mix] (Anon., 2018). [No further study details were provided.] [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time.]

Micro-organisms

No substance-specific data were identified.

The REACH registrant of ethyl palmitate noted the existence of bacterial reverse mutation tests, said to be conducted according to OECD Test Guideline 471[22], on the chemicals ethyl linoleate (CAS RN 544-35-4) and isopropyl myristate (CAS RN 110-27-0). *Salmonella typhimurium* strains TA98, TA00, TA1535 and TA1537, and *Escherichia coli* strain WP2 uvr A, were tested "up to limit concentrations" with and without metabolic activation [presumably by S9 mix], and no evidence of mutagenicity was observed. [No further study details were provided.] On this basis, the submitter concluded that "ethyl palmitate was not considered as mutagenic for bacteria" (Anon., 2018). [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time.]

Other

No substance-specific data were identified.

CARCINOGENICITY

No substance-specific data were identified.

[21] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.
[22] Bacterial Reverse Mutation Test.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Expert-group opinions

No substance-specific data were identified.

Human

No substance-specific data were identified.

Non-human

No substance-specific data were identified.

The REACH registration dossier submitter concluded that "the [no-observed-adverse-effect level (NOAEL)] value for reprotoxicity as higher than 5500 mg/kg bw/day is validated for the category substances" [including ethyl palmitate]. The conclusion was based on a study on ethyl oleate (CAS RN 111-62-6) in which reproductive functions (oestrus cycles in females, sperm measurements in males) of rats exposed [presumably orally] for 91 days were evaluated. No adverse effects were observed at up to 5500 mg/kg bw/day (Anon., 2018). [The acceptability of the dossier submitter's read-across strategy has not been independently evaluated at this time, however the study itself is inadequate to conclude on an absence of reproductive/developmental toxicity as it does not adequately assess fertility or developmental effects in the offspring.]

CARDIOPULMONARY EFFECTS[23]

No substance-specific data were identified.

OTHER TOXICITY CONSIDERATIONS

The intravenous infusion of 600 mM ethyl palmitate solution [100 µL bolus injection, followed by infusion at 0.2 µL/minute] for 14 hours has been linked to pancreatic β-cell dysfunction in mice (Eguchi *et al.*, 2012). An older study also found pancreatic injury in rats infused with ethyl palmitate (Werner *et al.*, 1997)[24].

Further limited studies are available on ethyl palmitate, and a representative sample are briefly noted below.

Ethyl palmitate has also been seen to have anti-inflammatory activity in laboratory animals (*e.g.* see Saeed *et al.,* 2012). When given by gavage[25] on a single occasion, it did not induce ketogenic activity in rats (MacKay *et al.,* 1940).

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

[24] Only the abstract of this older (1997) study was consulted as a pragmatic step. It was considered highly unlikely to provide information useful to the risk assessment of inhaled ethyl palmitate. The administered dose was not specified in the study abstract. The study report can be purchased and summarised in future, if required.

[25] At 0.67 mM/sq.dm. body surface [not readily convertible to mg/kg bw].

Peer-reviewed journal publication abstracts[26] were identified relating to >30-year-old studies on the effects of injected ethyl palmitate on the liver and/or spleen of rats (Finch *et al*., 1972; Sebestik and Jelínek, 1980; Sebestik *et al*., 1976, 1978), mice (Stuart and Smith, 1975) and dogs (Areekul *et al*., 1973a), and on the blood of rats (Sebestik and Jelínek, 1982).

From the publication titles[27], several other ≥30-year-old studies appear to assess the beneficial effects of ethyl palmitate (Areekul *et al*., 1973b) or its toxicity to the spleen (Kuzela *et al*., 1985; Prosnitz *et al*., 1969; Sebestik *et al*., 1975), or the plasma membranes (Goldstein, 1987).

EXISTING HEALTH CRITERIA VALUES (HCVs)

No substance-specific HCVs were identified.

JECFA has concluded that ethyl palmitate is of "no safety concern" at ('current') estimated levels of dietary intake as a food additive. At the time, these were 88 or 1.3 µg/person/day in the EU and US, respectively (JECFA, 1997).

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Anon. (2018). REACH registration dossier on Ethyl palmitate. Last updated April 2018. https://echa.europa.eu/registration-dossier/-/registered-dossier/23690/1

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Areekul S, Chantachum Y, Suebsaeng L and Chaovanapricha K (1973b). Studies on the effect of ethyl palmitate on the inhibition of erythrophagocytosis in dogs. Southeast Asian Journal of Tropical Medicine and Public Health 4(2), 250-255. [From title only.]

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.

[26] As a pragmatic step, these were not considered further, as they are highly unlikely to provide information useful to the risk assessment of inhaled ethyl palmitate. The publications can be purchased and critical data assessed and summarised in future, if required.

[27] Abstracts are not available for these publications. However it was considered that if the investigations do in fact cover ethyl palmitate, they are highly unlikely to resemble OECD Test Guideline-compliant studies, or to be critical or useful for risk assessment. As a pragmatic step, these have not been discussed further in this report, however the study reports can be purchased and summarised in future, if required.

EFSA (2013). European Food Safety Authority. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). Scientific Opinion on the safety and efficacy of straight-chain primary aliphatic alcohols/aldehydes/acids, acetals and esters with esters containing saturated alcohols and acetals containing saturated aldehydes (chemical group 1) when used as flavourings for all animal species. EFSA Journal11(4), 3169. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3169

Eguchi K, Manabe I, Oishi-Tanaka Y, Ohsugi M, Kono N, Ogata F, Yagi N, Ohto U, Kimoto M, Miyake K, Tobe K, Arai H, Kadowaki T and Nagai R (2012). Saturated fatty acid and TLR signaling link β cell dysfunction and islet inflammation. Cell Metabolism 15, 518-533.

Finch SC, Clemett AR and Kawasaki S (1972). Radiological visualization of ethyl palmitate induced splenic atrophy. British Journal of Experimental Pathology 53, 621-624. [From abstract only.]

Goldstein DB (1987). Strong disordering of synaptosomal plasma membranes by compounds that contain long acyl chains. Neuroscience 22(Suppl.), S408 (meeting abstract). [From title only.]

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Kuzela L, Sebestík V, Růzicková J and Potměsilová I (1985). Proteins nucleic acids and lipids of rat liver and spleen after experimental chemical splenectomy induced by intravenous injection of an ethyl palmitate emulsion. Acta Universitatis Carolinae Medica 31(5-6), 369-378. [From title only.]

MacKay EM, Wick AE and Barnum CP (1940). Ketogenic action of short chain, even numbered carbon fatty acids in carbohydrate-fed animals. Journal of Biological Chemistry 135, 183-187.

Prosnitz L, Kawasaki S, Cohen GS, Dineen JL, Perille PE and Finch SC (1969). Ethyl palmitate-induced splenic destruction. Journal of the Reticuloendothelial Society 6(5), 487-497. [From title only.]

Saeed NM, El-Demerdash E, Abdel-Rahman HM, Algandaby MM, Al-Abbasi FA and Abdel-Naim AB (2012). Anti-inflammatory activity of methyl palmitate and ethyl palmitate in different experimental rat models. Toxicology and Applied Pharmacology 264, 84-93. [From abstract only.]

Schafer EW and Bowles WA (2004). Toxicity, repellency or phytotoxicity of 979 chemicals to birds, mammals and plants. US Department of Agriculture. Research Report No. 04-01. https://www.aphis.usda.gov/ws/nwrc/chem-effects-db/U_schafer041_2004.pdf

Sebestik V and Jelínek J (1980). Experimental elimination of splenic function by an intravenous injection of ethyl palmitate emulsion in Wistar rats. Blut 40, 429-436. [From abstract only.]

Sebestik V and Jelínek J (1982). Erythrocyte survival and haematocrit values in rats after i.v. application of ethyl palmitate and methyl palmitate emulsions. Folia Haematologica Internationales Magazin für Klinische und Morphologische Blutforschung 109, 608-611. [From abstract only.]

Sebestik V, Potměsilová I, Jirásek A and Jelínek J (1975). Ethyl palmitate-induced "experimental splenectomy" in Wistar rats. Physiologia Bohemoslovaca 24(6), 573-574. [From title only.]

Sebestik V, Kuzela L, Potmesilova I and Ruzickova J (1976). Effects of an i.v. injection of ethyl palmitate emulsion on nucleic acids and fat content of the liver. Research in Experimental Medicine 168, 101-104. [From abstract only.]

Sebestik V, Kselikova M, Freiova M and Potmesilova I (1978). Incorporation of [14C]-L-leucine in splenic and hepatic tissue of rats “chemically splenectomised” by ethyl palmitate. Acta Biologica et Medica Germanica 37, 127-130. [From abstract only.]

Stuart AE and Smith II (1975). Histological effects of lipids on the liver and spleen of mice. Journal of Pathology 115, 63-72. [From abstract only.]

Werner J, Laposata M, Fernandez-del Castillo C, Saghir M, Iozzo RV, Lewandrowski KB and Warshaw AL (1997). Pancreatic injury in rats induced by fatty acid ethyl ester, a nonoxidative metabolite of alcohol. Gastroenterology 113, 286-294. [From abstract only.]

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