SCIENTIFIC OPINION

Scientific Opinion on the evaluation of the substances currently on the list in the annex to Commission Directive 96/3/EC as acceptable previous cargoes for edible fats and oils – Part II of III [1]

EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Shipping of edible fats and oils into Europe is permitted in bulk tanks, in which substances, included in a positive list, had been previously transported. The European Commission requested EFSA to evaluate the list of substances in the Annex to Commission Directive 96/3/EC as acceptable previous cargoes for edible fats and oils, taking into account its review of the Scientific Committee on Food (SCF) criteria for acceptable previous cargoes and criteria proposed by the Codex Committee for Fats and Oils. This is the second of three scientific opinions by the Panel on Contaminants in the Food Chain (CONTAM Panel), in which thirty-five of these substances or groups of substances have been evaluated. The CONTAM Panel concluded that fatty acids, fatty alcohols, fatty alcohol blends, fatty acid methyl esters, fatty acid esters, and animal, marine and vegetable and hydrogenated oils and fats, all as specified, and acid oils and fatty acid distillates, acetic acid, sulphuric acid, formic acid, acetic anhydride, acetone, *n*-heptane, *n*-hexane, cyclohexane, pentane, iso-propanol, propyl alcohol, methyl isobutyl ketone, methyl ethyl ketone, *n*-propyl acetate, ammonium hydroxide, limonene, methyl tert-butyl ether, urea ammonia nitrate solution, calcium chloride solution, magnesium chloride solution, potable water, potassium hydroxide, sodium hydroxide, silicon dioxide, sorbitol, molasses and beeswax would not be of health concern as previous cargoes. However, because of its insolubility in water and high melting point, silicon dioxide is not suitable for transport in tankers for edible fats and oils. There was insufficient information available on the composition of wine lees for the CONTAM Panel to conclude that it would not be of health concern when used as a previous cargo. The CONTAM Panel made several recommendations regarding the way in which the substances are described in the Annex to Commission Directive 96/3/EC, to correct inaccuracies and to better reflect current transport practices.

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KEY WORDS

Acceptable previous cargo, edible fats and oils, sea transport, criteria for acceptability of previous cargoes

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SUMMARY

The worldwide trade of edible fats and oils in bulk requires their transport by road, railroad, inland waterways and sea. The carriage by sea of edible fats and oils into Europe is also permitted in bulk tanks that have previously been used to transport substances included in a positive list of acceptable previous cargoes. The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) recently reviewed the Scientific Committee on Food (SCF) criteria for acceptable previous cargoes and criteria proposed by the Codex Committee for Fats and Oils in 2009. In addition, the CONTAM Panel identified the importance of taking into account possible impurities of chemicals shipped as previous cargoes, as these might be more toxic than the chemical itself. In November 2009, the CONTAM Panel published an opinion on a limited number of substances that had been proposed at Codex level for addition to the list of Codex acceptable previous cargoes, which were evaluated against the criteria in the previously mentioned opinion of the CONTAM Panel.

Following a request from the European Commission (EC), the CONTAM Panel was asked to deliver a scientific opinion on the evaluation of the substances listed in the Annex to Commission Directive 96/3/EC as acceptable previous cargoes for edible fats and oils. This was to ensure that substances currently on the list of acceptable previous cargoes had been evaluated against the same criteria as recently agreed by EFSA.

This is the second of three scientific opinions by the CONTAM Panel on the evaluation of the substances listed in the Annex to Commission Directive 96/3/EC. The CONTAM Panel considered that fatty acids (individually specified), fatty alcohols (individually specified), fatty alcohol blends (lauryl myristyl alcohol (C12-C14) and cetyl stearyl alcohol (C16-C18)), fatty acid methyl esters (individually specified), fatty acid esters (produced by the combination of any of the individually specified fatty acids with any of the individually specified fatty alcohols), acid oils and fatty acid distillates (from vegetable oils and fats and/or mixtures thereof and animal and marine fats and oils), animal, marine and vegetable and hydrogenated oils and fats (as specified by the Marine Environment Protection Committee of the International Maritime Organization), acetic acid, sulphuric acid, formic acid, acetic anhydride, acetone, n-heptane, n-hexane (technical grades), cyclohexane, pentane, isopropanol, propyl alcohol, methyl isobutyl ketone, methyl ethyl ketone, n-propyl acetate, ammonium hydroxide, limonene, methyl tertiary butyl ether, urea ammonia nitrate solution, calcium chloride solution, magnesium chloride solution, potable water, potassium hydroxide, sodium hydroxide, silicon dioxide (microsilica), sorbitol, molasses and beeswax (white and yellow), when used as previous cargoes, would not raise any concerns regarding their acute or longer term toxicity, genotoxicity, carcinogenicity or reproductive toxicity. In addition, there were no concerns regarding possible allergenicity or adjuvant effects from such transport. The Panel noted that a number of the substances are, or contain, normal constituents of food (fatty acids, fatty alcohols, fatty alcohol blends, fatty acid methyl esters, fatty acid esters, acid oils and fatty acid distillates, animal, marine and vegetable and hydrogenated oils and fats, calcium chloride solution, magnesium chloride solution, potable water and molasses). For several of the substances, acceptable daily intakes (ADIs) of “not specified” or “not limited” have been established by the FAO/WHO Joint Expert Committee for Food Additives (JECFA), SCF or the European Food Safety Authority (EFSA), because of low toxicological concern. These are fatty acids, acetic acid, sulphuric acid, acetic anhydride, ammonium hydroxide, potassium hydroxide, sodium hydroxide, silicon dioxide and sorbitol. A number of the substances have had ADIs or tolerable upper intake levels established by the JECFA, SCF or EFSA that are greater than or equal to 0.1 mg/kg b.w. per day. These are formic acid, acetone (United States Environmental Protection Agency - US-EPA), isopropanol, methyl ethyl ketone (US-EPA), limonene, calcium chloride, and magnesium chloride. Most of the remaining substances, or their constituents, (heptane, hexane, cyclohexane, pentane, propyl alcohol, methyl isobutyl ketone, n-propyl acetate, methyl tertiary butyl ether, urea ammonia nitrate and beeswax) are of relatively low toxicity and the margin of exposure that would occur comparing the maximum assumed carryover from their transport as a previous cargo and the respective critical no-observed-adverse-effect level would indicate no concern for human health.

In general there were no possible reaction products with fats and oils of toxicological concern. The one potential exception is the formation of dioxolanes from acetone, methyl isobutyl ketone and methyl ethyl ketone. However, at the levels that would be present in subsequent cargoes of edible fats and oils there is no toxicological concern. All of these substances could easily be removed by cleaning of the tank, with the possible exception of silicon dioxide. Suitable analytical methods are available or are feasible for all of these substances. The remaining impurities of potential concern include dioxins and polychlorinated biphenyls (PCBs), which might be present in fat and oil-derived substances. For such substances, the levels of dioxins and PCBs should be such that the final concentration in edible fats and oils as subsequent cargoes complies with the European legislation. The only other impurity of potential concern is benzene, which might remain from the synthesis of acetone and cyclohexane. However, the levels that could be present in edible fats and oils as a subsequent cargo would be of no toxicological concern. No other impurities, either identified or anticipated, were considered of toxicological concern. The CONTAM Panel therefore concluded that these substances meet the criteria for acceptability as previous cargoes for edible fats and oils.

In the case of wine lees, there was insufficient information available for the CONTAM Panel to conclude that the risk from exposure to this substance when used as a previous cargo would not give rise to any toxicological concern. The product varies markedly in composition, is not well specified, there is no information on potential impurities, nor is there information on the presence of potential allergens. The CONTAM Panel therefore concluded that wine lees does not meet the criteria for acceptability as a previous cargo for edible fats and oils.

Although there are no health concerns should silicon dioxide be used as a previous cargo, because of its insolubility in water and high melting point, this substance is not suitable for transport in tankers for edible fats and oils. Hence, the CONTAM Panel recommends that silicon dioxide should be removed from the Annex to Commission Directive 96/3/EC.

In addition, the CONTAM Panel noted a number of inaccuracies in the chemical identification and inconsistencies in the restrictions or chemical specification of substances with respect to current transport practices, in the Annex to Commission Directive 96/3/EC. The CONTAM Panel therefore made a number of recommendations regarding the way in which the substances are described in this Annex, to correct such inaccuracies and inconsistencies.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

General hygiene requirements relating to transport of food applicable to all food business operators laid down in Regulation (EC) No 852/2004[4] (Annex II, Chapter IV) state, amongst others, that "receptacles in vehicles and/or containers are not to be used for transporting anything other than foodstuffs where this may result in contamination."

Information showed that the application of this principle to the bulk transport was not practical and imposed an unduly onerous burden on food business when applied to bulk transport in sea-going vessels of liquid oils and fats and of raw sugar. This led to the adoption of two derogations[5,6] providing equivalent protection to public health.

Equivalent protection to public health is guaranteed on technical (e.g. tank design) and procedural (e.g. intermediate cleaning) conditions, on record keeping (e.g. on effectiveness of cleaning and on the nature of the previous cargoes) and, in the case of bulk transport of liquid oils and fats in sea-going vessels, on a list of acceptable previous cargoes. The presence of substances on the list of acceptable previous cargoes for fats and oils in the Annex to Commission Directive 96/3/EC is based on three opinions of the former Scientific Committee on Food (SCF).[7,8,9]

On 26 May 2009, the Panel on Contaminants in the Food Chain (CONTAM Panel) issued a scientific opinion on the criteria for acceptable previous cargoes for edible fats and oils. In this opinion, the CONTAM Panel reviewed the 5 criteria for the assessment of acceptability as previous cargoes for edible fats and oils previously used by the SCF and evaluated the appropriateness of four criteria developed for the same purpose by the Codex Committee for Fats and Oils (CCFO).

The CONTAM Panel noted that by application of CCFO criterion 2 some substances will turn out to be unacceptable as previous cargoes. This could include substances with ADI (or TDI) < 0.1 mg/kg b.w. or substances with genotoxic activity. The Panel considers that the exclusion of such substances as previous cargoes is appropriate.

The criteria in this Scientific Opinion were subsequently applied in the CONTAM Scientific Opinion on the evaluation of substances as acceptable previous cargoes for edible fats and oils, adopted on 29 November 2009. In this opinion, a limited number of substances that had been proposed at Codex level for addition to the list of acceptable previous cargoes were evaluated against the criteria in the previously mentioned Scientific Opinion.

In order to assure that the substances currently on the list of acceptable previous cargoes are evaluated against the same criteria, an additional Scientific Opinion covering an evaluation of the substances currently on the list of acceptable previous cargoes against the criteria used in the Opinion on the

[4] Regulation (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foodstuffs (OJ L 139, 30.4.2004, p. 1).

[5] Commission Directive 96/3/EC of 26 January 1996 granting a derogation from certain provisions of Council Directive 93/43/EEC on the hygiene of foodstuffs as regards the transport of bulk liquid oils and fats by sea (OJ L 21, 27.01.1996, p. 42).

[6] Commission Directive 98/28/EC of 29 April 1998 granting a derogation from certain provisions of Directive 93/43/EEC on the hygiene of foodstuffs as regards the transport by sea of bulk raw sugar (OJ L 140, 12.05.1998, p. 10).

[7] SCF, 1996. Scientific Committee on Food. Opinion on the potential risk to human health arising from the transport in ships' tanks of oils and fats from substances proposed as acceptable previous cargoes, expressed on 20 September 1996 - Fortieth Series (1997) Catalogue No: GT 07 97652-EN-DE-FR). http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_40.pdf

[8] SCF, 2003. Updated opinion of the Scientific Committee on Food on the potential risk to human health arising from the transport in ships' tanks of oils and fats from substances proposed as acceptable previous cargoes, expressed on 4 April 2003. Health and Consumer Protection Directorate-General, European Commission, Brussels. http://ec.europa.eu/food/fs/sc/scf/out189_en.pdf

[9] SCF, 1997. Scientific Committee on Food. Amendment of its previous opinion of 20 September (SCF 1996). Opinion on Methyl esters of fatty acids in previous cargoes, expressed on 12-13 June 1997. Minutes of the 107th Meeting of the Scientific Committee for Food http://ec.europa.eu/food/fs/sc/oldcomm7/out13_en.html

evaluation of substances as acceptable previous cargoes for edible fats and oils carried out by EFSA would be needed.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Art 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for a scientific opinion on the evaluation of the substances currently on the list in the annex to Commission Directive 1996/3/EC as acceptable previous cargoes for edible fats and oils. The evaluation should be based on the SCF criteria and the criteria proposed by the CCFO as reviewed by the Panel on Contaminants in Food Chain in 2009[10] for acceptable previous cargoes for edible fats and oils.

[10] http://www.efsa.europa.eu/en/scdocs/scdoc/1110.htm

ASSESSMENT

1. Introduction

General hygiene requirements relating to transport of food applicable to all food business operators is laid down in Annex II, Chapter IV of Regulation (EC) No 852/2004[11] and state, amongst others, that '*receptacles in vehicles and/or containers are not to be used for transporting anything other than foodstuffs where this may result in contamination*'. However, the application of this principle to the bulk transport is not practical and imposes an unduly onerous burden on food business when applied to bulk transport in sea-going vessels of liquid oils and fats. Commission Directive 96/3/EC[5] permits sea transport of fats and oils in bulk tanks, which have previously been used to transport substances included in a positive list of acceptable previous cargoes.

The majority of the global trade in oils and fats is done under contracts of the Federation of Oils, Seeds and Fats Associations (FOSFA), a professional international contract-issuing and arbitral body concerned exclusively with the world trade in oilseeds, oils and fats, which provides a wide range of standards covering different methods of transportation and different terms of trade. FOSFA does not require dedicated containers and allows transport in tanks that have previously been used to transport substances from an approved positive list. A FOSFA list of banned previous cargoes also exists (FOSFA, 2008).

In 1996, the Scientific Committee on Food (SCF) assessed the risk to human health arising from potential contamination of oils and fats shipped in tanks, which may have been used to transport the substances as given in the Annex to Commission Directive 96/3/EC (SCF, 1997a). A number of substances were evaluated and a set of criteria for acceptable previous cargoes (SCF criteria) was proposed. In 2003, the SCF issued an update of its previous opinion in the light of new toxicological information, where available (SCF, 2003a).

Based on the evaluations carried out by the SCF in 1996 and 2003, the list of substances acceptable as previous cargoes set out in Annex to Commission Directive 96/3/EC was amended by Commission Decision 2004/4/EC.[12] However, the substances in the list were only considered to be acceptable as long as the legal provisions were applied, especially regarding the cleaning and condition of the tanks and the accurate documented evidence relating to the nature of the three previous cargoes, and to the efficacy of the cleaning process between cargoes, to be kept by the captain of the vessel.

The Codex Alimentarius Commission (CAC) also sets international food standards to protect the health of consumers and ensure fair practices in the food trade. Under the Codex system, the Codex Committee for Fats and Oils (CCFO) has been established to elaborate standards for fats and oils of animal, vegetable and marine origin, including margarine and olive oil. It has adopted the Recommended International Code of Practice for the Storage and Transport of Edible Fats and Oils in Bulk, which includes a Draft Codex List of Acceptable Previous Cargoes and a Proposed Draft List of Acceptable Previous Cargoes. In addition, a set of criteria (CCFO criteria) has been developed to determine the acceptability of substances as previous cargoes, based on the criteria proposed by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) (FAO/WHO) Joint Technical Meeting (FAO/WHO, 2007). Both the draft lists of acceptable previous cargoes and the criteria were adopted by the CAC (Geneva, 4-9 July 2011) (FAO/WHO, 2011).

[11] Regulation (EC) No 854/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific rules for the organisation of official controls on products of animal origin intended for human consumption. OJ L 139, 30.4.2004, p. 206-320.

[12] Commission Directive 2004/4/EC of 15 January 2004 amending Directive 96/3/EC granting a derogation from certain provisions of Council Directive 93/43/EEC on the hygiene of foodstuffs as regards the transport of bulk liquid oils and fats by sea. OJ L 15, 22.1.2004, p. 25-30.

In 2009, the European Commission (EC) requested the European Food Safety Authority (EFSA) to review the SCF criteria for acceptable previous cargoes for edible fats and oils, in the light of the CCFO criteria (CCFO, 2009). The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) issued an opinion in May 2009 and concluded that the criteria for evaluation of acceptable previous cargoes as proposed by the CCFO were not in conflict with any of the five criteria developed by SCF (EFSA, 2009a). Most of the SCF criteria were either explicitly or implicitly covered by the CCFO criteria. The last SCF criterion, dealing with the availability of analytical methods is not explicitly addressed in the CCFO criteria and the CONTAM Panel considered that this criterion is still important. The Panel also considered relevant the inclusion of criteria covering food allergens and compounds that may react with oils and fats.

The criteria in this Scientific Opinion were subsequently applied by the CONTAM Panel for the evaluation as acceptable previous cargoes of the substances included in the Codex Proposed Draft List of Acceptable Previous Cargoes (EFSA, 2009b).

The European Commission asked EFSA for a scientific opinion on the evaluation of the substances currently on the list in the Annex to Commission Directive 96/3/EC[5] as acceptable previous cargoes for edible fats and oils. The evaluation should be based on the review of the criteria performed by the CONTAM Panel in 2009, in order to ensure that the substances currently on the list are evaluated against the same criteria.

The outcome of the evaluation of the substances will be presented in three scientific opinions for practical purposes. A first opinion was published in December 2011 reporting the evaluation of 13 substances in the list (EFSA, 2011a). In this second opinion, the evaluation of 35 substances (or groups of substances) listed in Table 1 is described. The entries in Table 1 are as listed in the Annex to Commission Directive 96/3/EC.[5] In reviewing these substances, the CONTAM Panel concluded that modifications to some of these entries would improve accuracy and these are discussed in the Opinion (see Table 4). The evaluation of the remaining substances listed in the Annex to the Directive will be reported in a third and last scientific opinion by the CONTAM Panel.

This evaluation is applicable to substances with the specifications indicated, details for which were obtained, in part, from information obtained from FOSFA. The conclusions reached on the substances may not apply to substances with a different specification.

Table 1: Substances in the list to Annex to Commission Directive 96/3/EC[5] listed as acceptable previous cargoes for edible fats and oils and re-evaluated in the present opinion.

Substance (synonyms)	CAS Number
Wine lees (vinasses, vinaccia, argol, vini, argil, arcilla, weinstein, crude cream of tartare, crude potassium bitartrate)	868-14-4
Fatty acids:	
Butyric acid (n-butyric acid; butanoic acid; ethyl acetic acid; propyl formic acid)	107-92-6
Valeric acid (n-pentanoic acid; valerianic acid)	109-52-4
Caproic acid (n-hexanoic acid)	142-62-1
Heptoic acid (n-heptanoic acid)	111-14-8
Caprylic acid (n-octanoic acid)	124-07-2
Pelargonic acid (n-nonanoic acid)	112-05-0
Capric acid (n-decanoic acid)	334-48-5
Lauric acid (n-dodecanoic acid)	143-07-7

Table 1: Continued.

Substance (synonyms)	CAS Number
Fatty acids (cont.):	
Lauroleic acid (dodecenoic acid)	4998-71-4
Myristic acid (n-tetradecanoic acid)	544-63-8
Myristoleic acid (n-tetradecenoic acid)	544-64-9
Palmitic acid (n-hexadecanoic acid)	57-10-3
Palmitoleic acid (cis-9-hexadecenoic acid)	373-49-9
Stearic acid (n-octadecanoic acid)	57-11-4
Oleic acid (n-octadecenoic acid)	112-80-1
Ricinoleic acid	141-22-0
Linoleic acid (9,12-octadecadienoic acid)	60-33-3
Linolenic acid (9,12,15-octadecatrienoic acid)	463-40-1
Arachidic acid (eicosanoic acid)	506-30-9
Behenic acid (docosanoic acid)	112-85-6
Erucic acid (cis-13-docosenoic acid)	112-86-7
Fatty alcohols:	
Butyl alcohol (1-Butanol; butyric alcohol)	71-36-3
Caproyl alcohol (1-hexanol; hexyl alcohol)	111-27-3
Enanthyl alcohol (1-heptanol; heptyl alcohol)	111-70-6
Capryl alcohol (1-n-octanol; heptyl carbinol)	111-87-5
Nonyl alcohol (1-nonanol; pelargonic alcohol; octyl carbinol)	143-08-8
Decyl alcohol (1-decanol)	112-30-1
Lauryl alcohol (n-dodecanol; dodecyl alcohol)	112-53-8
Tridecyl alcohol (1-tridecanol)	27458-92-0 112-70-9
Myristyl alcohol (1-tetradecanol; tetradecanol)	112-72-1
Cetyl alcohol (alcohol C-16; 1-hexadecanol; cetylic alcohol; palmityl alcohol, n-primary hexadecyl alcohol)	36653-82-4
Stearyl alcohol (1-octadecanol)	112-92-5
Oleyl alcohol (octadecenol)	143-28-2
Fatty alcohol blends:	
Lauryl myristyl alcohol (C12-C14)	
Cetyl stearyl alcohol (C16-C18)	
Fatty acid methyl esters:	
Methyl laurate (methyl dodecanoate)	111-82-0
Methyl palmitate (methyl hexadecanoate)	112-39-0

Table 1: Continued.

Substance (synonyms)	CAS Number
Fatty acid methyl esters (cont.):	
Methyl stearate (methyl octadecanoate)	112-61-8
Methyl oleate (methyl octadecenoate)	112-62-9
Fatty acids esters — any ester produced by the combination of the above listed fatty acids with any of the above listed fatty alcohols. Examples of these are butyl myristrate, oleyl palmitate and cetyl stearate.	
Acid oils and fatty acid distillates — from vegetable oils and fats and/or mixtures thereof and animal and marine fats and oils	
Animal, marine and vegetable and hydrogenated oils and fats (other than cashew shell nut and crude tall oil)	
Acetic acid	64-19-7
Sulphuric acid	7664-93-9
Formic acid (methanoic acid; hydrogen carboxylic acid)	64-18-6
Acetic anhydride (ethanoic anhydride)	108-24-7
Acetone (dimethylketone; 2-propanone)	67-64-1
n-Heptane	142-82-5
n-Hexane (technical grades)	110-54-3 64742-49-0
Cyclohexane (hexamethylene; hexanaphthene; hexahydrobenzene)	110-82-7
Pentane	109-66-0
iso-Propanol (isopropyl alcohol; IPA)	67-63-0
Propyl alcohol (propane-1-ol; 1-propanol)	71-23-8
Methyl isobutyl ketone (4-methyl-2pentanone)	108-10-1
Methyl ethyl ketone (2-butanone)	78-93-3
n-Propyl acetate	109-60-4
Ammonium hydroxide (ammonium hydrate; ammonia solution; aqua ammonia)	1336-21-6
Limonene (dipentene)	138-86-3
Methyl tertiary butyl ether (MBTE)	1634-04-4
Urea ammonia nitrate solution (UAN)	
Calcium chloride solution - only where the immediate previous cargo to it is on the list and is not similarly restricted	10043-52-4
Magnesium chloride solution	7786-30-3
Potable water - only where the immediate previous cargo to it is on the list and is not similarly restricted	
Potassium hydroxide (caustic potash) - only where the immediate previous cargo to it is on the list and is not similarly restricted	1310-58-3

Table 1: Continued.

Substance (synonyms)	CAS Number
Sodium hydroxide (caustic soda) - only where the immediate previous cargo to it is on the list and is not similarly restricted	1310-73-2
Silicon dioxide (microsilica)	7631-86-9
Sorbitol (D-sorbitol; hexahydric alcohol; D-sorbite)	50-70-4
Molasses	57-50-1
Beeswax (white and yellow)	8006-40-4 8012-89-3

2. Previous risk assessments

2.1. Scientific Committee on Food (SCF)

In 1996, the SCF issued an opinion on the potential risk to human health arising from the transport of oils and fats in ships' tanks from substances proposed as acceptable previous cargoes (SCF, 1997a). The Committee was asked to examine the substances given in the Annex to Commission Directive 96/3/EC[5] and other substances that may be proposed for addition to the list. The SCF was asked to take into account the information provided by industry concerning (i) the likelihood and potential levels of contamination in the light of the information regarding cleaning procedures, dilution and limits of detection of analytical methods and (ii) the additional processing of oils and fats. The SCF focused its attention on the evaluation of the toxicological properties of the substances without considering other aspects such as the ecotoxicological characteristics, the microbial status or nutritional relevance. The Committee's view on the acceptability of the substances in the list of acceptable previous cargoes from Commission Directive 96/3/EC[5] was based on the criteria shown in Table 2.

Table 2: Criteria for the inclusion of substances in the list of acceptable previous cargoes according to the SCF (SCF, 1997a, 2003a).

	SCF Criteria[(a)]
1.	No toxicological concerns, particularly with regard to their genotoxic and carcinogenic potential, for which a threshold is difficult to establish.
2.	Efficacy of procedures used to clean ships' tanks between cargoes
3.	Dilution factor in relation to the potential amount of residue of the previous cargo and any impurity which the previous cargo might have contained and the quantity of oil or fat transported.
4.	Subsequent application of refining processes and solubility relevant to the occurrence of possible contaminating residues.
5.	Availability of analytical methods to verify the presence of trace amounts of residues or the absence of contamination of oils and fats.

(a): The SCF criteria have no numbering in the original reference. In the present opinion they have been included for an easier referral throughout the document.

The substances in the list were only considered to be acceptable as long as the provisions of the Hygiene of Foodstuffs Directive 93/43/EEC,[13] later replaced by Regulation (EC) 852/2004,[4] were applied, and especially regarding the cleaning and condition of the tanks, as well as the requirement included in Commission Directive 96/3/EC,[5] where accurately documented evidence relating to the

[13] Council Directive 93/43/EEC on the hygiene of foodstuffs of 14 June 1993. OJ L 175, 19.7.1993, p. 1-11.

three previous cargoes, and the efficacy of the cleaning process between cargoes, should be kept by the captain of the vessel.

Some of the substances evaluated were accepted as previous cargoes by the SCF because they are food or food components. A number of other substances were considered acceptable from a toxicological point of view.

For others, although the available toxicological information was insufficient to enable a full evaluation, the SCF was able to accept a number of compounds provisionally on the basis of their unlikely genotoxic potential, their easy removal by tank cleaning procedures, and the very low residues expected as a result of these factors and their likely dilution (e.g. iso-decanol, iso-nonanol, iso-octanol, montan and paraffin wax, white mineral oils and methyl tertiary butyl ether (MTBE)).

Ten substances were considered as not acceptable due to inadequate toxicological and/or technical data (e.g. 2,3-butanediol, 1,3-propylene glycol, methyl esters of fatty acids (laurate, palmitate, stearate, and oleate) and nonane or because their genotoxic and carcinogenic potential were a reason for concern (e.g. iso-butanol, cyclohexanol and cyclohexanone).

Later, the SCF was requested to update the list of substances from its previous opinion in the light of new toxicological information, if available (SCF, 2003a). Priority was given to those substances provisionally accepted as previous cargoes. As in its previous opinion, the SCF focused on the toxicological properties without considering other aspects. Neither the specifications of the transported oils and fats nor the purity of the previous cargo were taken into account. The criteria used for re-evaluation were the same as those described in its opinion from 1996 (Table 2). The re-evaluation led to the full acceptance of some substances previously considered as not acceptable (e.g. methyl esters of the following fatty acids: laureate, palmitate, stearate and oleate) or provisionally acceptable (e.g. MTBE) in view of the new toxicological information. Others were confirmed to be not acceptable as previous cargoes since the new information did not allow for a re-evaluation of their carcinogenicity or genotoxicity (e.g. 2,3-butanediol, isobutanol, cyclohexanol and cyclohexanone). Finally, some were considered to be still only provisionally acceptable, as there was insufficient new information on their toxicity to allow re-evaluation (iso-decanol, iso-nonanol, iso-octanol, montan and paraffin wax and white mineral oils).

Details of the SCF conclusions are given in the corresponding Section for each substance under evaluation.

2.2. European Food Safety Authority (EFSA)

At the request of the European Commission, the EFSA reviewed the criteria for acceptable previous cargoes for edible fats and oils set by the SCF (Table 2). In doing so, the CONTAM Panel assessed the appropriateness of the four CCFO criteria (Table 3), one by one, by comparing them with those set by SCF for acceptable previous cargoes for edible fats and oils in 1996.

Table 3: Criteria proposed for immediate previous cargoes by the CCFO during their 21st meeting (CCFO, 2009) and adopted by the CAC (Geneva, 4-9 July 2011).

	CCFO Criteria (adopted at Step 5)
1.	The substance is transported/stored in an appropriately designed system; with adequate cleaning routines, including the verification of the efficacy of cleaning between cargoes, followed by effective inspection and recording procedures.
2.	Residues of the substance in the subsequent cargo of fat or oil should not result in adverse human health effects. The ADI (or TDI) of the substance should be greater than or equal to 0.1 mg/kg b.w. per day. Substances for which there is no numerical ADI (or TDI) should be evaluated on a case by case basis.
3.	The substance should not be or contain a known food allergen, unless the identified food allergen can be adequately removed by subsequent processing of the fat or oil for its intended use.
4.	Most substances do not react with edible fats and oils under normal shipping and storage conditions. However, if the substance does react with edible fats and oils, any known reaction products must comply with criteria 2 and 3.

CCFO: Codex Committee on Fats and Oils; CAC: Codex Alimentarius Committee; ADI: acceptable daily intake; TDI: total daily intake; b.w.: body weight.

The CONTAM Panel concluded that the criteria for evaluation of acceptable previous cargoes for edible fats and oils as proposed by the CCFO are not in conflict with any of the five criteria developed by SCF. SCF criteria 1 to 4 are either explicitly or implicitly covered by the CCFO criteria. SCF criterion 5 dealing with the availability of analytical methods is not explicitly addressed in the CCFO criteria. The CONTAM Panel considers that SCF criterion 5 is still important. The CCFO criteria also cover food allergens and compounds that may react with oil and fats. The CONTAM Panel considers these additions relevant.

In addition, the CONTAM Panel made the following remarks:

- The CCFO criteria specifically apply to the immediate previous cargo. The CCFO criterion 1, which addresses among other issues, documentation procedures, does not specify for how many previous cargoes records should be kept. This might be particularly important in the event that earlier previous cargoes consist of substances for which an acceptable daily intake (ADI) (or tolerable daily intake (TDI)) has not been established. The CONTAM Panel was of the opinion that records of the three previous cargoes should be kept, in accordance with the Codex Recommended International Code of Practice for the Storage and Transport of Edible Fats and Oils in Bulk.

- With respect to CCFO criterion 2, the CONTAM Panel agreed with the proposed threshold of an ADI (or TDI) of ≥ 0.1 mg/kg body weight (b.w.). For substances for which there is no numerical ADI (or TDI) a case by case evaluation is needed. The Panel also considered the situation of second and third previous cargoes and concluded that for non-genotoxic substances their transport as second and third previous cargoes is not of concern, taking into account their very limited carry over. However, the CONTAM Panel noted that genotoxic substances would not be acceptable as previous cargoes. Also in relation to CCFO criterion 2, the CONTAM Panel noted that as consequence of the above some substances will turn out to be unacceptable as previous cargoes. This could include substances with ADI (or TDI) < 0.1 mg/kg b.w. or substances with genotoxic activity. The Panel was of the opinion that the exclusion of such substances as previous cargoes is appropriate.

- CCFO criterion 3 is sufficient to cover “known food allergens”. However, the CONTAM Panel considered that the scope of the CCFO criterion is too narrow, and should apply to all

known allergens, not just to known food allergens, given the fact that the same cargo may be sold for cosmetic use.

- The CONTAM Panel endorsed CCFO criterion 4 without any further remarks.

3. Evaluation of the substances currently on the list in the annex to Commission Directive 96/3/EC as acceptable previous cargoes for edible fats and oils

The CONTAM Panel has evaluated the acceptability of the substances listed in Table 1 (as amended, see Table 4) as previous cargoes for edible fats and oils. The evaluation is based on its review of the criteria for acceptable previous cargoes as described in Section 2.2. (EFSA, 2009a) and the experience gained in its subsequent evaluation of 13 substances as previous cargoes which highlighted the importance of addressing any impurities that might be present (EFSA, 2009b):

- The substance is transported/stored in an appropriately designed system; with adequate cleaning routines, including the verification of the efficacy of cleaning between cargoes, followed by effective inspection and recording procedures. The CONTAM Panel was of the opinion that records of the three previous cargoes should be kept, in accordance with the Codex Recommended International Code of Practice for the Storage and Transport of Edible Fats and Oils in Bulk.

- Residues of the substance in the subsequent cargo of fat or oil should not result in adverse human health effects. The ADI (or TDI) of the substance should be greater than or equal to 0.1 mg/kg b.w. per day. Substances for which there is no numerical ADI (or TDI) should be evaluated on a case by case basis. For non-genotoxic substances their transport as second and third previous cargoes is not of concern, taking into account their very limited carry over. However, genotoxic substances would not be acceptable as previous cargoes.

- The substance should not be or contain a known allergen, unless the identified allergen can be adequately removed by subsequent processing of the fat or oil for its intended use. This criterion covers all allergens, not only food allergens.

- If the substance reacts with edible fats and oils, any known reaction products must comply with criteria 2 and 3.

- Analytical methods of sufficient sensitivity to verify the presence of trace amounts of residues or the absence of contamination of oils and fats should be feasible. Generally, nowadays there are sensitive/suitable analytical methods available to determine the presence of relevant levels of the substances under evaluation (previous cargoes) in the subsequent fat and oil, or to verify the cleaning procedure. In those cases where, due to the nature or composition of the substance (or group of) to be evaluated as previous cargo, the feasibility of analytical methods is questioned, it will be indicated when discussing the substance (or group of) in the respective chapter.

- Potential impurities in the previous cargo should be taken into account since they may be toxicologically more relevant than the substance itself. As most products exist in different purities, a reasonable worst-case product within the specification is assumed, the concentration of the impurity estimated from available literature and evaluated in the same way as a listed substance. The source and synthesis of the substance is investigated to identify potential impurities, if no adequate measurements are available for impurities.

The current evaluation of the substances as acceptable previous cargoes is based on available studies/information from literature searches carried out up to the time of the evaluation on public databases, e.g. PubMed, International Uniform Chemical Information Database (IUCLID), European Chemicals Agency (ECHA), evaluations made by national and international bodies, e.g. WHO and

Organisation for Economic Co-Operation and Development (OECD) and on information requested from FOSFA.

The safety of the substances as identified chemically in the Annex (Table 1, with any clarifications necessary as indicated in Table 4) was evaluated first. If the substance was considered acceptable as a previous cargo from a toxicological point of view, it was further evaluated in accordance with the additional criteria defined above (EFSA, 2009a, b).

As part of the evaluation of safety for human health, responses of the immune system have been considered. This is necessary for allergens, but it is also relevant for substances which are not allergens themselves but can promote allergy, so-called adjuvants. Adjuvant activity has been shown e.g. for various natural lipids like pollen-associated oxylipins (Traidl-Hoffmann et al., 2009), for plant lectins (reviewed by Lavelle et al., 2001), for saponins from a variety of plants (Lacaille-Dubois, 2005; Sun et al., 2009), and for inulin and certain other carbohydrates (Petrovsky and Cooper, 2011). It has been determined on a case-to-case basis whether the documented adjuvant activity is sufficiently strong to be of relevance in the context of previous cargoes.

3.1. WINE LEES (vinasses, vinaccia, argol, vini, argil, arcilla, weinstein, crude cream of tartare, crude potassium bitartrate) (CAS No 868-14-4)

Wine lees, also often known as vinasses, is the slurry formed by residue of yeasts and other particulates after fermentation ends and wine is transferred to other containers. It also contains deposits of potassium bitartrate because of its limited solubility in a water/ethanol system. The composition of the wine lees depends on the wine production technology, and may therefore contain a broad variety of components.

The CONTAM Panel noted that the term used in the Annex to the Commission Directive 96/3/EC[5] is used for different wine making by-products, originating at different steps of the production chain, and because of this their composition is rather different: “Vinacce” (marcs) are vegetable parts (stems, fruit skins and seeds) separated at the very early step of fermentation, lees are the organic slurry separated at the end of fermentation and tartar/potassium bitartrate can be extracted from both of these materials (Ribérau-Gayon et al., 2005).

Other terms, less commonly used are argol, vini, argil, arcilla, weinstein, crude cream of tartare and crude potassium bitartrate. Although these terms have been used interchangeably, there may be some differences in the composition of the material involved, e.g. Commission Regulation 1006/2011[14] and the terms are not always used consistently.

The CAS number (868-14-4) in the definition of the material refers only to L(+)-potassium hydrogen tartrate, which may be a minor component in wine lees and is therefore inappropriate in referring to wine lees. Here the crude product best described by the term wine lees is meant.

Wine lees is used to recover alcohol and potassium bitartrate. It is used for animal feeds[15] and in compost production.

3.1.1. Previous evaluations

The SCF evaluated wine lees, with the synonym of crude potassium bitartrate, in 1996 and considered it as acceptable previous cargo on the basis of the previous group ADI established by JECFA (JECFA, 1978a) for tartrates, of 30 mg/kg b.w. per day (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes wine lees was not further evaluated as it was already considered acceptable (SCF, 2003a).

[14] Commission Regulation (EU) No 1006/2011 of 27 September 2011 amending Annex I to Council Regulation (EEC) No 2658/87 on the tariff and statistical nomenclature and on the Common Customs Tariff. OJ L 282, 28.10.2011, p. 1-912.

[15] Commission Regulation (EU) No 575/2011 of 16 June 2011 on the Catalogue of feed materials. OJ L 159, 17.6.2011, p. 25-65.

3.1.2. Current evaluation

The CONTAM Panel noted that pure tartrates (CAS No 868-14-4) are already included on the acceptable list as foodstuffs.

Some components of wine lees may be of toxicological concern, e.g. heavy metals, and there is no practical analytical approach to control the levels of all such substances in a given batch.

Wine lees will be expected to contain grape allergens. Grape allergy is well-documented but relatively rare. Grape (and products thereof) is not included in the European Union's (EU) list of allergens that are to be labelled without exemptions (EU's Annex IIIa). In contrast, for wine fining different substances including milk, egg and fish products are used, and these processing aids will to a large extent be found in the wine lees. Egg, milk and fish and 'products thereof' are included in Annex IIIa, and contamination by egg, milk and fish of materials to be used in food is not acceptable without proper labelling.

The CONTAM Panel did not have sufficient information to judge the effectiveness of cleaning a vessel following transport of wine lees.

3.1.3. Conclusions

The safety evaluation of wine lees as a previous cargo was previously based on the fact that tartrates have a group ADI of 30 mg/kg b.w. per day established by JECFA.

However, "wine lees" is a crude mixture, and while (potassium) tartrate is a constituent, there are many others. The mixture (wine lees) has not been evaluated in toxicological studies.

The CONTAM Panel considered that materials covered by the term wine lees (vinasses) could not be used as previous cargo because it cannot be excluded that substances of toxicological concern or significant food allergens are present. To ensure that this is not the case would take careful processing and may even require testing of all batches.

Therefore, the CONTAM Panel concludes that "wine lees" does not meet the criteria for acceptability as a previous cargo for edible fats and oils.

3.2. FATTY ACIDS (individually specified)

The individual fatty acids considered in the current evaluation are the following: butyric acid (*n*-butyric acid; butanoic acid; ethyl acetic acid; propyl formic acid) (CAS No 107-92-6), valeric acid (*n*-pentanoic acid; valerianic acid) (CAS No 109-52-4), caproic acid (*n*-hexanoic acid) (CAS No 142-62-1), heptoic acid (*n*-heptanoic acid) (CAS No 111-14-8), caprylic acid (*n*-octanoic acid) (CAS No 124-07-2), pelargonic acid (*n*-nonanoic acid) (CAS No 112-05-0), capric acid (*n*-decanoic acid) CAS No 334-48-5), lauric acid (*n*-dodecanoic acid) (CAS No 143-07-7), lauroleic acid (dodecenoic acid) (CAS No 4998-71-4), myristic acid (*n*-tetradecanoic acid) (CAS No 544-63-8), myristoleic acid (*n*-tetradecenoic acid) (CAS No 544-64-9), palmitic acid (*n*-hexadecanoic acid) (CAS No 57-10-3), palmitoleic acid (cis-9-hexadecenoic acid) (CAS No 373-49-9), stearic acid (*n*-octadecanoic acid) (CAS No 57-11-4), oleic acid (*n*-octadecenoic acid) (CAS No 112-80-1), ricinoleic acid (CAS No 141-22-0), linoleic acid (9,12-octadecadienoic acid) (CAS No 60-33-3), linolenic acid (9,12,15-octadecatrienoic acid) (CAS No 463-40-1), arachidic acid (eicosanoic acid) (CAS No 506-30-9), behenic acid (docosanoic acid) (CAS No 112-85-6), erucic acid (cis-13-docosenoic acid) (CAS No 112-86-7).

Fatty acids are monocarboxylic acids, usually with long linear alkyl chains, saturated or unsaturated. Saturated fatty acids of at least 10 carbon atoms are solids at room temperature. Some fatty acids are produced by hydrolysis of fats and oils. Free fatty acids are also obtained as by-products of refining oils and fats to increase their quality or to render them suitable for transesterification to methyl esters, e.g. in the production of biodiesel. "Fatty acids" may also be fully synthetic.

Fatty acids may be produced from fats and oils of a quality not acceptable for human consumption, for instance because of contamination. In this case it is important to consider whether the presence of contaminants may limit the suitability of the fatty acid as a previous cargo.

Some fatty acids, particularly those of short to medium chain length can be purified by distillation. However, isolation of pure long chain fatty acids from natural sources is difficult or impossible on a larger scale.

Saturated fatty acids are also produced by petrochemistry, e.g. by hydrocarboxylation of alkenes. However, there is no relevant commercial synthesis of unsaturated fatty acids.

In the past, alkali salts of fatty acids were primarily used as soaps, though without separation into individual fatty acids. Fatty acids are still important sources for detergents, but after chemical modifications, such as via reduction to fatty alcohols or formation of amides. Today a broad range of chemicals is produced from fatty acids by many types of modifications ("oleochemistry").

Butyric acid is produced by fermentation of sugars or by synthesis. It is used as starting material to prepare esters used in flavours and perfumes. Valeric acid is obtained by synthesis and mainly converted to esters used in perfumes. Heptanoic acid is also produced by synthesis. The triglyceride made from heptanoic acid, which does not occur in relevant amounts in nature, was used as a marker at up to 1.1 % for subsidized butter.[16]

Pelargonic (nonanoic) acid is a relatively high cost fatty acid, produced synthetically either by ozonolysis of unsaturated fatty acids or by hydrocarboxylation of octene. It is primarily used to form esters applied as plasticizers and lubricating oils. It is also used for alkyd resins. Finally it is a chemical intermediate for synthetic flavours, cosmetics, pharmaceuticals and corrosion inhibitors.

Butyric and valeric (pentanoic) acid have a strong, unpleasant smell and would be unlikely to be transported in open vessels. If they were, meticulous cleaning of the container, pipes and pumps would be a prerequisite to avoid an off-flavour in the edible oils transported later. This would, at the same time, ensure that the contamination is kept very low.

Some oils and fats are produced for industrial purposes and are not suitable for human consumption because of a particular fatty acid, such as high erucic acid rapeseed oil because of erucic acid or castor oil because of ricinoleic acid. Others are not edible because of by-products, such as tall oil.

The minor unsaturated fatty acids of 12 or more carbon atoms, such as lauroleic, myristoleic and palmitoleic acid, are commercially available only in milligram quantities and are unlikely to be transported in ship loads. As pure substances, also the major unsaturated fatty acids (oleic, linoleic and linolenic acid) are only available in small amounts, since their isolation from fatty acid mixtures is difficult. Larger amounts are crude products containing substantial amounts of other fatty acids.

3.2.1. Previous evaluations

The SCF evaluated these fatty acids as previous cargoes in 1996 and considered them as acceptable since they are normal constituents of food and many have been evaluated in relation to other food uses, e.g. flavours (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes the fatty acids were not further evaluated as they were already considered acceptable (SCF, 2003a).

In establishing their first list of food additives of miscellaneous technological functions, the SCF noted that no exhaustive systematic toxicological studies have been carried out with these fatty acids, but that they are all present in biological fat and are therefore present in food generally (SCF, 1991). They

[16] Commission Regulation (EEC) No 570/88 of 16 February 1988 on the sale of butter at reduced prices and the granting of aid for butter and concentrated butter for use in the manufacture of pastry products, ice-cream and other foodstuffs. OJ L 55, 1.3.1988, p. 31-50.

are also produced during the metabolism of fats. The SCF therefore established a group ADI not specified for the fatty acids (as miscellaneous food additives) (SCF, 1991).

The CONTAM Panel evaluated unfractionated fatty acid mixtures or mixtures of fatty acids from natural oils and fats in 2009 (EFSA, 2009b) and concluded that "*the anticipated toxicological profile of fatty acid mixtures derived from edible types of fats and oils would generally indicate a low level of concern for human health*".

3.2.2. Current evaluation

3.2.2.1. Expected impurities

For synthetic fatty acids the synthetic pathways render it unlikely that there will be impurities of toxicological concern.

In reality, the unsaturated fatty acids do not exist without isomers, particularly trans isomers. They would not be of concern in fatty acids transported as previous cargoes.

Owing to difficulties in separating clean fatty acids from edible fats and oils, most large scale products would contain elevated concentrations of other fatty acids. They are classified as impurities, but are not of concern since they are part of the mixed fatty acids accepted as previous cargoes in 2009 (EFSA, 2009b).

If fatty acids are obtained from oils and fats, these starting materials may be of a quality not suitable for human consumption, in particular because of contamination. In fact, edible fats and oils that cannot be sold for human consumption are often converted to industrial products. For instance, dioxins recently detected in animal feed were due to fatty acids originating from the deodoration of oils which were then converted to methyl esters used as biodiesel.[17] After fractionation, such fatty acid mixtures could be converted into the fatty acids in this list of previous cargoes. Such fractionation does not necessarily remove the contamination.

As the previous cargo is assumed to be present at a concentration of at most 100 mg/kg in a current cargo of fats or oils, such impurities are diluted 10 000 times and only extremely toxic or strongly accumulating compounds like dioxins or polychlorinated biphenyls (PCBs) are likely to be of concern. The levels of dioxins and PCBs should be such that the fats and oils comply with the European Legislation on dioxins and PCBs. Such contamination was considered sufficiently unlikely that fatty acids are generally acceptable as previous cargoes on the basis of this criterion.

3.2.2.2. Reactivity and reaction products

Fatty acids may interesterify with lipids and aliphatic alcohols, but this does not result in products of concern.

3.2.2.3. Toxicological profile

In considering the safety of individual fatty acids transported as previous cargoes, the carryover from the fatty acid is compared to the presence of fatty acids in commonly consumed edible fats and oils. As fatty acids are consumed in substantial amounts in the diet, carryover from previous cargoes would not make a significant additional contribution.

As a worst case of carryover from a previous cargo, a concentration of 100 mg/kg is assumed. The fatty acids in the list, perhaps with the exception of ricinoleic acid, may be present at concentrations above 100 mg/kg in edible types of fats and oils consumed in large quantities, i.e. butyric acid, valeric acid, caproic acid, heptanoic acid, caprylic acid, pelargonic acid (*n*-nonanoic acid), capric acid, lauric acid, lauroleic acid (3-dodecenoic acid), myristic acid, myristoleic acid (*n*-tetradecenoic acid), palmitic

[17] http://ec.europa.eu/food/food/chemicalsafety/contaminants/dioxin_germany_en.htm

acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid, behenic acid and erucic acid.

All these fatty acids are readily metabolised via the normal fatty acid and tricarboxylic acid pathways (JECFA, 1998). They are therefore unlikely to pose a toxicological concern at the levels that would occur in their use as previous cargoes and the available toxicological information is consistent with this (JECFA, 1998).

In its previous evaluation, the CONTAM Panel (EFSA, 2009b) expressed the view that also the minor fatty acids lauroleic acid and myristoleic acid were amongst the fatty acids for which there was a low level of concern for human health. Lauroleic acid (12:1n-3) has been described as a natural metabolite of lauric acid (12:0) in rat hepatocytes (Legrand et al., 2002).

Fats and oils may include fatty acids which render them unsuitable for human consumption, i.e. the fatty acids isolated from these may also be unsuitable (e.g. erucic acid in high erucic acid rapeseed oils intended for industrial use, ricinoleic acid in castor oil, gossypol in cottonseed oil, various substances in tall oil). Ricinoleic acid from castor oil has a TDI of 0.7 mg/kg b.w. per day, established by the SCF (SCF, 1997a). JECFA established an ADI for castor oil as a food additive of 0-0.7 mg/kg b.w. per day (JECFA, 1979). Hence, use of ricinoleic acid per se would not pose any toxicological concerns when used as a previous cargo.

US National Toxicology Program (NTP) have carried out genetic toxicity studies on castor oil, with negative results in *Salmonella typhimurium*, for induction of sister chromatid exchanges (SCEs) or chromosomal aberrations in Chinese hamster ovary (CHO) cells, and for induction of micronuclei in the peripheral blood erythrocytes of mice evaluated at the end of the 13-week studies (NTP, 1992).

Ricinoleic acid produced no neoplasms or hyperplasia in one long-term mouse study and was not a tumor promoter in another mouse study, but did produce epidermal hyperplasia (CIR Expert Panel, 2007).

Hence, if these fatty acids are present in an edible oil or fat at a level below 100 mg/kg from a previous cargo, which is the maximum assumed carryover, they are not considered to be of concern for human health.

3.2.2.4. Allergenicity

For the fatty acids listed, there is some evidence for an irritant capacity for caprylic (*n*-octanoic) acid (Robinson et al., 1999), pelargonic (*n*-nonanoic) acid (Wahlberg and Lindberg, 2003) and capric (*n*-decanoic) acid (Robinson et al., 1999). Stearic (*n*-octadecanoic) acid has been reported to be a contact allergen. Castor oil is reported not to be a significant sensitizer or photosensitizer in human clinical tests (CIR Expert Panel, 2007). However, contact allergy to ricinoleic acid (and castor oil) has been documented as an incidental finding in patch testing (Shaw, 2009). There are also a number of reports on contact dermatitis and contact cheilitis (e.g. Sai, 1983; Inoue et al., 1998). Clinical experience suggests that sensitization reactions to ricinoleic acid are seen only infrequently (CIR Expert Panel, 2007). Indeed, the irritant and allergenic potency appears to be relatively low for all the mentioned substances, and taking into account the dilution factor in the previous cargoes context, the CONTAM Panel considers that the fatty acids listed do not represent a significant problem in terms of irritancy, adjuvanticity, or allergenicity.

3.2.3. Conclusions

The fatty acids listed, butyric acid, valeric acid, caproic acid, heptanoic acid, caprylic acid, pelargonic acid (*n*-nonanoic acid), capric acid, lauric acid, lauroleic acid (3-dodecenoic acid), myristic acid, myristoleic acid (*n*-tetradecenoic acid), palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid, behenic acid, ricinoleic acid and erucic acid, are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible

allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs.

The CONTAM Panel therefore concludes that the fatty acids specified meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels in the fatty acids are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

3.3. FATTY ALCOHOLS (individually specified)

The individual fatty alcohols considered in the current evaluation are listed in the annex to Commission Directive 96/3/EC[5] as follows: butyl alcohol (1-butanol; butyric alcohol) (CAS No 71-36-3), caproyl alcohol (1-hexanol; hexyl alcohol) (CAS No 111-27-3), enanthyl alcohol (1-heptanol; heptyl alcohol) (CAS No 111-70-6), capryl alcohol (1-*n*-octanol; heptyl carbinol) (CAS No 111-87-5), nonyl alcohol (1-nonanol; pelargonic alcohol; octyl carbinol) (CAS No 143-08-8), decyl alcohol (1-decanol) (CAS No 112-30-1), lauryl alcohol (*n*-dodecanol; dodecyl alcohol) (CAS No 112-53-8), tridecyl alcohol (1-tridecanol) (CAS No 27458-92-0, 112-70-9), myristyl alcohol (1-tetradecanol; tetradecanol) (CAS No 112-72-1), cetyl alcohol (alcohol C-16; 1-hexadecanol; cetylic alcohol; palmityl alcohol, *n*-primary hexadecyl alcohol) (CAS No 36653-82-4), stearyl alcohol (1-octadecanol) (CAS No 112-92-5), oleyl alcohol (octadecenol) (CAS No 143-28-2).

The fatty alcohols evaluated in this opinion comprise nine individual fatty alcohols which occur naturally in substantial amounts (the saturated, linear alcohols C4, C6, C8, C10, C12, C14, C16 and C18, as well as oleyl alcohol). They should be distinguished from 1-heptyl-, 1-nonyl and 1-tridecyl alcohol (CAS 112-70-9), which are only available in relevant amounts through synthetic routes and are naturally present in plants at best in trace amounts.

The entry for tridecyl alcohol includes two CAS numbers which correspond to two structurally distinct substances. The CAS number 112-70-9 refers to 1-tridecanol, while the CAS number 27458-92-0 refers to 11-methyldodecane-1-ol. However, the product actually marketed, e.g. by BASF, with the CAS number 27458-92-0, is described as a mixture of iso-tridecanols without further specification of the structure.[18] It is primarily used for producing plasticizers for polyvinyl chloride. No information was available on the synthesis. On the basis of the information received from FOSFA, only 1-tridecyl alcohol (CAS number 112-70-9) should be considered as a previous cargo for edible fats and oils (see Documentation provided to EFSA). The inclusion of CAS number 27458-92-0 in the Annex appears to have been due to a transcription error.

The C12 alcohol (lauric alcohol) has a melting point of 24 °C. The higher saturated alcohols are solids at room temperature.

Many fatty alcohols can be obtained by reduction of the corresponding fatty acids obtained from oils and fats. Oleyl alcohol is obtained by reduction of oleic acid, which, however, is more like a mixture of fatty acids high in oleic acid than a pure substance (in industry, 90 % oleic acid is called “high purity”). The main production of saturated fatty alcohols is from petrochemical sources. In the Ziegler process, ethylene is oligomerised starting from triethyl aluminium, then oxidized and liberated by hydrolysis.

The major fatty alcohols are used primarily to produce detergents, surfactants (e.g. as sulphates or ethoxylates) and emulsifiers. They are also used as solvents (e.g. in printing inks). Their esters serve as waxes in cosmetics, plastics, printing inks, lubricants and many other applications.

1-Butanol is produced primarily by hydroformylation of propene followed by reduction of the resulting aldehyde. It can also be obtained from fermenting sugars. It is used as a solvent, e.g. for coatings, but also as a starting material for various polymers (e.g. phenolics) and other chemicals.

[18] http://www.weichmacher.basf.com/portal/streamer?fid=218607

1-Heptanol and 1-nonanol occur naturally in plants, though at low concentrations. They are produced synthetically in modest amounts by hydroformylation of hexene and octene, respectively, and are used for fragrances and perfumes.

n-Tridecan-1-ol (C13 alcohol, CAS No 112-70-9) can be obtained by hydroformylation of dodecene (made from ethylene) followed by reduction of the resulting aldehyde.

3.3.1. Previous evaluations

The SCF evaluated these fatty alcohols as previous cargoes in 1996 and considered them as acceptable (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes the fatty alcohols were not further evaluated as they were already considered acceptable (SCF, 2003a).

The primary linear and saturated fatty alcohols C4 to C24 as well as oleyl alcohol have been evaluated by the SCF as substances intended for use in materials in contact with food and are listed without a specific migration limit in Commission Regulation 10/2011.[19] Butyl, caproyl, capryl, nonyl, decyl, lauryl, tridecyl, myristyl, cetyl, stearyl and oleyl alcohols were all placed in List 3,[20] while the SCF noted that enanthyl alcohol should be regarded as a component of food (SCF, 1995).

A number of these fatty alcohols have also been evaluated as flavours. JECFA has evaluated butyl alcohol, caproyl alcohol, enanthyl alcohol, capryl alcohol, nonyl alcohol, decyl alcohol, lauryl alcohol and cetyl alcohol, and concluded for all eight that there was no safety concern at current levels of intake when used as flavouring agents (JECFA, 1999). JECFA at its 29th meeting did not establish ADIs to butyl alcohol or decyl alcohol because the data were considered to be inadequate (JECFA, 1986).

3.3.2. Current evaluation

3.3.2.1. Expected impurities

Synthetic fatty alcohols are not expected to contain impurities of concern.

Those from fatty acids obtained from contaminated oils and fats may be contaminated with highly toxic substances, in particular dioxins and PCBs (see Section 3.2.2.1.). Isolation and reduction to alcohols may reduce their concentration, but is unlikely to remove them. These alcohols are acceptable as previous cargoes provided the dioxin and PCB levels are such that the final concentration in the fats and oils of subsequent cargoes comply with the European legislation.

3.3.2.2. Reactivity and reaction products

Fatty alcohols acceptable as previous cargoes may form esters with fatty acids which fall under the class of wax esters and are not of concern.

3.3.2.3. Toxicological profile

The SCF (1997a) considered that the individual fatty acid alcohols in the list of the Commission Directive 96/3/EC[5] were acceptable, as many are normal constituents of food and some have been evaluated in relation to other food uses, e.g. as components of food contact materials and/or flavours.

In the EFSA opinion from 2009, “unfractionated fatty alcohol mixture or mixtures of fatty alcohols from natural oils and fats” were considered acceptable as previous cargoes on the basis that they are effectively converted to fatty acids in the body and are generally of low oral toxicity (EFSA, 2009b). The saturated linear alcohols C4, C6, C8, C10, C12, C14, C16 and C18, as well as oleyl alcohol are, or may be, predominant components of these mixtures.

[19] Commission Regulation (EU) 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1-89.
[20] Substances for which an ADI or TDI could not be established, but where the continued use could be accepted.

In view of the normal fate of fatty alcohols (EFSA, 2009b), the minor fatty alcohols 1-heptanol, 1-nonyl alcohol and 1-tridecanol would not give rise to toxicological concern.

3.3.2.4. Allergenicity

For butyl alcohol, caproyl alcohol, enanthyl alcohol, capryl alcohol, lauryl alcohol, nonyl (pelargonic) and tridecyl alcohol no evidence has been found for significant adjuvanticity, irritancy or allergenisity. Decyl alcohol has been reported to be an irritant (Robinson, 2002). Myristyl alcohol, cetyl alcohol, cetylic alcohol, stearyl alcohol and oleyl alcohol are reported to be contact allergens. Myristyl alcohol has been reported as a contact allergen both in medicaments and metal working fluid (Edman and Möller, 1986; Pecegueiro et al., 1987; Tosti et al., 1996; Geier et al., 2006). Cetyl alcohol is a well-recognized contact allergen (Blondeel et al., 1978; Tosti et al., 1996; Oiso et al., 2003; Aakhus and Warshaw, 2011). One study reports cetylic alcohol to be a contact allergen (Le Coz et al., 1998). Stearyl alcohol is reported to be a very weak contact allergen (Tosti et al., 1996; Yesudian and King, 2001; Thormann et al., 2009). Oleyl alcohol is reported to be a contact allergen, e.g. in cosmetic products (Andersen and Broesby-Olsen, 2006) and metal-working fluids (Tosti et al., 1996; Geier et al., 2006). The irritant and allergenic activity appears not to be very strong for any of the substances mentioned, and taking into account the high dilution factor in edible fats and oils as subsequent cargoes, the CONTAM Panel considers that none of the substances would represent a problem because of adjuvant, irritant or allergenic properties.

3.3.3. Conclusions

The CONTAM Panel recommends that the entry for tridecyl alcohol in the Annex to Commission Directive 96/3/EC[5] be amended to tridecyl alcohol (1-tridecanol) (CAS No 112-70-9) to reflect the chemical composition of the substance of transport (see Table 4 under Recommendations).

Caproyl alcohol (1-hexanol), myristyl alcohol (1-tetradecanol), stearyl alcohol (1-octadecanol), butyl alcohol (1-butanol), capryl alcohol (1-*n*-octanol), cetyl alcohol (1-hexadecanol), decyl alcohol (1-decanol), lauryl alcohol (*n*-dodecanol), tridecyl alcohol (1-tridecanol) (CAS No 112-70-9) and oleyl alcohol (octadecenol) are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicty. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs.

The CONTAM Panel therefore concludes that the fatty alcohols specified meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

3.4. FATTY ALCOHOLS BLENDS (Lauryl myristyl alcohol (C12-C14) and Cetyl stearyl alcohol (C16-C18))

The mixtures of lauryl and myristyl alcohol as well as of cetyl and stearyl alcohol are special cases of mixtures of fatty alcohols evaluated previously by EFSA (EFSA, 2009b). The alcohols do not necessarily originate from fats and oils (as those in the opinion from 2009b), but since no impurities of concern are expected in synthetic fatty alcohols, this does not affect their acceptability as previous cargoes.

The mixtures can also be considered combinations of the individual fatty alcohols evaluated above (see Section 3.3.).

As mentioned in Sections 3.2. (fatty acids) and 3.3. (fatty alcohols), there is a possibility that the alcohols are derived from edible oils which were heavily contaminated by dioxins or PCBs.

3.4.1. Conclusions

There are no toxicological concerns from the use of the fatty alcohol blends specified when used as previous cargoes for edible fats and oils. Nor is there any concern regarding their possible allergenictiy. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs.

The CONTAM Panel therefore concludes that mixtures of lauryl and myristyl alcohol as well as cetyl and stearyl alcohol meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

3.5. FATTY ACIDS METHYL ESTERS (individually specified)

The fatty acid methyl esters evaluated in the current opinion are: methyl laurate (methyl dodecanoate, CAS No 111-82-0), methyl palmitate (methyl hexadecanoate, CAS No 112-39-0), methyl stearate (methyl octadecanoate, CAS No 112-61-8) and methyl oleate (methyl octadecenoate, CAS No 112-62-9).

3.5.1. Previous evaluations

The SCF evaluated fatty acid methyl esters (laurate, palmitate, stearate, oleate) as previous cargos in 1996 and considered them not acceptable (SCF, 1997a) because the toxicological or technical data available were inadequate. No data were presented to the SCF neither concerning the ease of cleaning from tanks nor on the ease of removal during the refining process.

At its 107th Plenary meeting in June 1997 (SCF, 1997b), the SCF agreed an amendment to its opinion of 20 September 1996 (102nd Meeting) on acceptable previous cargoes (SCF, 1997a), that fatty acid methyl esters (laurate, palmitate, stearate, oleate) could be transferred to Annex I as acceptable previous cargoes. This was because additional information had been supplied, enabling the re-evaluation of the fatty acid methyl esters. Evidence was provided that all of the substances being evaluated occur in trace amounts in natural oils and fats. Their chemical composition is such that it is unlikely that their ingestion would cause any health problems, if present in trace amounts in edible fats and oils as a subsequent cargo. Information provided on cleaning and processing confirmed that the esters would be easily removed by tank cleaning and that processing of the edible fats and oils would reduce their presence to insignificant levels in the refined food products.

In its review of previous cargoes in 2009, the EFSA CONTAM Panel concluded that that "*Ester mixtures produced from fatty acids and alcohols derived from fats and oils, as well as methanol and ethanol, would not cause any health concern as previous cargoes, provided the sources are restricted such that the fatty acids and the fatty alcohols are from edible types of fats and oils not contaminated with compounds of toxicological concern (e.g. oils from waste collection sites, mineral oils, PCBs)*" (EFSA 2009b).

3.5.2. Current evaluation

3.5.2.1. Toxicological profile

It is anticipated that fatty acid methyl esters potentially present as residues in fats and oils from previous cargoes will be readily hydrolysed to fatty acids and methanol by esterases on entry into the body. Available information on the toxicological profiles of fatty acid methyl esters (APAG, 2009) indicates that these are broadly similar to those of their constituent fatty acids and methanol (see Sections 3.13. and 3.15.) and that they are likely to be metabolised to products that would be of no toxicological concern at the levels occurring in their use as previous cargoes. No further evaluation of these compounds is considered necessary.

3.5.2.2. Allergenicity

There are no reports of irritancy, adjuvanticity or allergenicity of the mentioned fatty acid methyl esters. They are therefore likely to have low or no activity with regard to the mentioned properties.

3.5.3. Conclusions

The fatty acid methyl esters methyl laurate (methyl dodecanoate), methyl palmitate (methyl hexadecanoate), methyl stearate (methyl octadecanoate) and methyl oleate (methyl octadecenoate), produced by the combination of the respective fatty acids with methanol, are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs.

The CONTAM Panel therefore concludes that the fatty acid methyl esters specified meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

3.6. FATTY ACIDS ESTERS - any ester produced by the combination of the above listed fatty acids with any of the above listed fatty alcohols. Examples of these are butyl myristate, oleyl palmitate and cetyl stearate.

Individual fatty acids and fatty alcohols evaluated above are esterified either by chemical or enzymatic means. They are used in a variety of cosmetics and other consumer products.

3.6.1. Previous evaluations

The SCF evaluated fatty acid esters as previous cargos in 1996 and considered them acceptable (SCF, 1997a). This was based on the conclusion that fatty acid esters would be unlikely to cause health problems if present in trace amounts, that processing would reduce possible contamination to low levels and they were easily removed by tank cleaning. In the 2003 SCF evaluation of acceptable previous cargoes, fatty acid esters were not further evaluated as they were already considered acceptable (SCF, 2003a).

In its evaluation of unfractionated fatty esters or mixtures of fatty esters from natural oils and fats in 2009, the CONTAM Panel noted that "*The fatty acid esters taken into consideration potentially present as residues in fats and oils from previous cargoes are anticipated to be readily hydrolysed to fatty acids and alcohols by esterases on entry into the body. The toxicological profile of fatty acid esters is broadly similar to that of the constituent acids and alcohols, namely they are of low oral toxicity, particularly those of higher molecular weight, both acute, sub-acute/sub-chronic and chronic, they are likely to be metabolised to innocuous products, and, where data are available, are negative in* in vitro *genotoxicity tests, and show no evidence of carcinogenic or reproductive toxicity potential*" (EFSA 2009b). In their conclusion, the CONTAM Panel stated that "*Ester mixtures produced from fatty acids and alcohols derived from fats and oils, as well as methanol and ethanol, would not cause any health concern as previous cargoes, provided the sources are restricted such that the fatty acids and the fatty alcohols are from edible types of fats and oils not contaminated with compounds of toxicological concern (e.g. oils from waste collection sites, mineral oils, PCBs)*."

3.6.2. Current evaluation

In considering individual fatty acid esters, the CONTAM Panel confirms the view reached in 2009, that they can be anticipated to be readily hydrolysed by esterases on entry into teh body to their constituent fatty acids and alcohols, which are of low toxicological concern (see Sections 3.15. and 3.16.). Available information on the toxicological profiles of fatty acid esters indicates that these are broadly similar to those of their constituent acids and alcohols and that they are likely to be metabolised to innocuous products. No further evaluation of these compounds is considered necessary.

3.6.3. Conclusions

Fatty acid esters produced by the combination of acceptable fatty acids with acceptable fatty alcohols are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs.

The CONTAM Panel therefore concludes that fatty acid esters produced by the combination of acceptable fatty acids with acceptable fatty alcohols meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

3.7. ACID OILS AND FATTY ACID DISTILLATES - from vegetable oils and fats and/or mixtures thereof and animal fats and oils

Acid oils and fatty acids distillates are by-products of the edible oil refining process. They are the main source of the free fatty acid mixtures and their derivatives evaluated previously.

Acid oils are a by-product obtained from the alkaline neutralization of edible fats and oils or oils for making technical products (e.g. special breeds of plant oils and contaminated edible oils not suitable for human consumption). They consist mainly of free fatty acids (over 50 %) and neutral oil, with 2-3 % moisture and other impurities. Acid oils are used for making soaps, for animal feed formulations and for distilled fatty acid production and as feedstock for the biofuel industry (see Documentation provided to EFSA).

Fatty acid distillates are a by-product (condensate) of the physical refining of edible oils or oils for making technical products. The crude oils are degummed using dilute phosphoric or citric acid, decoloured using bleaching earth and then subjected to a steam distillation process (deodoration) to remove the fatty acids (see Documentation provided to EFSA). The distillates are composed of free fatty acids (~70-90 %), glycerides, organic compounds, such as squalene, vitamins, sterols and other minor components found in crude oils.

Fatty acid distillates are used as an animal feed component as well as in laundry soap and the oleochemicals industry. Vitamin E, squalene and phytosterols may be extracted and sold separately.

Acid oils and distillates are produced during the refining of all vegetable, animal and fish oils, but the major internationally traded ones are from palm oil, palm kernel oil, coconut oil, maize/soyabean/sunflower oil and fish oil.

With physical refining, not only components of the oil, but also contaminants including dioxins, PCBs, polycyclic aromatic hydrocarbons (PAHs), pesticides and mineral oils are collected in the condensate. In essence, impurities in the oil are enriched in the condensate by roughly a factor of 100 (assuming a crude oil containing 1 % free fatty acids).

3.7.1. Previous evaluations

In the previous evaluation, the CONTAM Panel concluded that unfractionated fatty acids mixtures or mixtures of fatty acids from oils and fats would not cause a health concern as previous cargoes, provided their sources are edible types of fats or oils (EFSA, 2009b). Acid oils and fatty acids distillates are other terms for unfractionated fatty acids mixtures.

3.7.2. Current evaluation

As described in Section 3.2. on fatty acids, acid oils and fatty acid distillates may be from oils and fats not intended for human consumption. It was considered that fatty acids from oils and fats of varieties not suitable for human consumption would themselves not be a risk to human health when present in

edible fats and oils as a subsequent cargo. Highly toxic contaminants, however, may render them unacceptable.

When edible fats and oils are contaminated by acid oils or distillates transported as previous cargoes, the contaminants in the fatty acid oils or distillates are diluted by a factor of at least 10 000. However, some contaminants may be reconcentrated in the acid oils or distillates during their preparation, so that their final dilution in edible fats and oils transported as subsequent cargo may be less than this, compared to the concentration that was present in the oils and fats from which they were prepared. This is unlikely to be a concern other than for highly toxic substances such as dioxins and PCBs.

3.7.3. Conclusions

Acid oils and fatty acid distillates are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs.

The CONTAM Panel therefore concludes that acid oils and fatty acid distillates from vegetable oils and fats and/or mixtures thereof and animal fats and oils meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

3.8. ANIMAL, MARINE AND VEGETABLE AND HYDROGENATED OILS AND FATS (other than cashew shell nut and crude tall oil)

The fats and oils covered under this group are those animal, marine and vegetable oils and fats, including hydrogenated products, included in Annex 6 of the International Maritime Organisation (IMO, 2011, 2012) according to the Marine Environment Protection Committee (MEPC) of the IMO.

Some of the oils and fats on this list are not edible due to the presence of endogenous components (fatty acids or others), degraded quality (such as oxidation) or contamination (e.g. through waste collection) such that they are either unpalatable or could result in adverse effects in consumers.

Oils and fats are hydrogenated either to adjust their melting properties and improve their suitability for a given application (e.g. a fat or margarine) or to improve their thermal stability. For instance, fish oil is hydrogenated to eliminate its smell. Oils are also hydrogenated to enable admixture with animal feeds.

Hydrogenation involves a catalyst, most commonly nickel or palladium, and elemental hydrogen.

3.8.1. Previous evaluations

The SCF evaluated animal, marine and vegetable and hydrogenated oils and fats (other than cashew shell nut and crude tall oil) in 1996 as previous cargoes for edible fats and oils and considered this material as acceptable in view of the fact that it was a food (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes animal, marine and vegetable and hydrogenated oils and fats were not further evaluated as they were already considered acceptable (SCF, 2003a). No other evaluations could be identified, presumably as this material is a food, and therefore there is no requirement for consideration of safety in normal use.

3.8.2. Current evaluation

3.8.2.1. Expected impurities

As mentioned in Section 3.2. (fatty acids), all fats and oils, including those of varieties not suitable for human consumption, were considered acceptable as previous cargoes owing to the substantial dilution

in the edible fat or oil transported subsequently. The only exception concerns fats and oils heavily contaminated by highly toxic substances, like dioxins and PCBs.

Hydrogenation is unlikely to introduce toxic contaminants. As catalysts are sensitive to poisoning, contaminants in the oils to be hydrogenated may be a problem, which is why severely contaminated oils are unlikely to be hydrogenated.

3.8.2.2. Reactivity and reaction products

Oils and fats, including hydrogenated products, are not expected to react with other oils and fats to produce toxic products.

3.8.2.3. Toxicological profile

In considering the safety of animal, marine and vegetable oils and fats (including hydrogenated oils and fats) transported as previous cargoes, the dilution resulting from carryover by at least a factor of 10 000 is sufficient to reduce the presence of any potentially harmful fatty acids and other lipid components to a level of negligible toxicological concern (see also Section 3.2., fatty acids). In particular, the concentrations of erucic acid and ricinoleic acid are reduced to concentrations below those in edible fats and oils.

As many foods contain hydrogenated fats and oils, hydrogenation is not considered to be of concern. In particular, the levels of trans fatty acids from carryover is far below those commonly encountered in refined edible fats and oils or foods.

<u>Absorption, distribution, metabolism and elimination</u>

Dietary triglycerides are hydrolyzed to 2-monoglycerides and free fatty acids in the intestinal tract. They are then absorbed as part of the normal diet and subject to the same disposition as other dietary fatty acids and monoglycerides (ISEO, 2006).

<u>Genotoxicity</u>

The results of available genotoxicity studies on a number of vegetable oils (e.g. corn oil, rice bran oil and mango kernel oil) have shown that they are not genotoxic (e.g. Raj and Katz, 1984; Polasa and Rukmini, 1987). Given their chemical nature, it is not anticipated that even those substances not tested would be genotoxic.

3.8.2.4. Allergenicity

Most substances covered under this heading are not likely to be allergens or adjuvants, but depending on type, source and purity there may be some exceptions for some cargoes. Although no threshold for peanut in relation to triggering allergic reactions has been determined, the lowest dose triggering a reaction in a highly sensitized individual has been reported to be 100 µg peanut protein (Hourihane et al., 1997; Wensing et al., 2002). Crude peanut oil has been reported to contain up to 300 µg/mL of peanut protein (Crevel et al., 2000), which after dilution in a subsequent cargo, represents 0.03 µg/mL. Refined oils have lower protein contents. The dilution factor (1:10 000) makes it very unlikely that even the reportedly most potent allergenic oil, peanut oil, will trigger allergic reactions when transported as a previous cargo.

3.8.3. Conclusions

The CONTAM Panel recommends that the entry for the substances in the Annex to Commission Directive 96/3/EC[5] be amended to “Animal, marine and vegetable and hydrogenated oils and fats as specified by the MEPC of the IMO” (see Table 4 under Recommendations), as only those fats and oils have been evaluated by the CONTAM Panel. As the list specified by the MEPC does not include cashew shell nut or crude tall oil, these specific exclusions would no longer be necessary.

Animal, marine and vegetable and hydrogenated oils and fats as specified by the MEPC of the IMO (Annex 6) are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs.

The CONTAM Panel therefore concludes that animal, marine and vegetable and hydrogenated oils and fats according to the MEPC of the IMO (Annex 6) meet the criteria for acceptability as a previous cargo for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

3.9. ACETIC ACID (ethanoic acid, vinegar acid, methane carboxylic acid) (CAS No 64-19-7)

Apart from water, acetic acid is the main component of vinegar. It is present in many foods as a minor component from fermentation processes. Most acetic acid is, however, produced synthetically from methanol and carbon monoxide. Almost all acetic acid transported by vessels is likely to be of synthetic origin.

Acetic acid is also produced endogenously in animals and plants and is involved in intermediate metabolism through the Krebs cycle.

Acetic acid is used commercially in large amounts in chemical synthesis.

3.9.1. Previous evaluations

The SCF evaluated acetic acid in 1996 as a previous cargo for edible fats and oils and considered this substance as acceptable in view of the fact that it was an approved food additive (E260), with an ADI "not specified" (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes acetic acid was not further evaluated as it was already considered acceptable (SCF, 2003a).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated acetic acid at its 17th meeting. An ADI of "not limited" was established for acetic acid and its potassium and sodium salts, as it was considered that these substances would not present a safety concern at the estimated levels of intake, at that time (JECFA, 1973).

The SCF evaluated acetic acid in 1991. It was reported that "*human studies determining the maximum metabolic load of acetate are not available. In evaluating the acceptance of acetates, emphasis is placed on their established metabolic pathway and the consumption by man as normal constituents of the diet. The Committee established a group ADI 'not specified' for acetate including diacetate*" (SCF, 1991, as cited by EFSA, 2011b). It its recent Opinion on sodium diacetate, which included consideration of acetic acid (EFSA, 2011b), the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) concluded that "*Based on the current knowledge, the Panel does not see any reasons to deviate from this view*", i.e. ADI 'not specified'. Acetic acid can be used in food "quantum satis" (EC, 2010).

Acetic acid is "generally recognized as safe" (GRAS) by the US Food and Drug Administration (FDA, 2006).

Acetic acid has been evaluated for its acceptability for use as a herbicide in the European Union. It was considered unnecessary to establish an ADI or acute reference dose (ARfD) for the oral uptake of acetic acid for its intended use as a herbicide as it is a natural component in the metabolism of all plants and animals and is formed in many microbial processes (EC, 2008a).

Several organisations have evaluated the inhalational toxicity of acetic acid. In general, an 8-h time weighted average exposure of 10 ppm (25 mg/m^3) has been established [21] (NIOSH, 1994; OSHA, 2007; ACGIH, 2001).

3.9.2. Current evaluation

3.9.2.1. Expected impurities

Synthetically produced acetic acid is of high purity. Residual impurities from the synthesis are unlikely to be of toxicological concern.

3.9.2.2. Reactivity and reaction products

Acetic acid may react with many food components, but food-borne acetic acid also does so without any identified problems.

3.9.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Acetic acid can be found as a natural constituent of the diet and it occurs endogenously in the body. It is almost completely absorbed from the gastrointestinal (GI) tract and is also absorbed via the lungs following inhalation. It is a weak acid and hence at the pH of body fluids will be found in both the acid and acetate forms. Acetic acid is rapidly metabolised in plasma and most tissues, with a half-life of the order of a few minutes (3-5 min, depending on dose) (Freundt, 1973, as cited by ECHA, 2012). Acetate is readily converted to acetyl-CoA, which enters the citric acid cycle, being converted eventually to carbon dioxide. Only a small amount (~0.6 %) of acetic acid is excreted unchanged, in the urine as acetate (Smith et al., 2007).

Acute toxicity

Acetic acid is of low acute toxicity, with LD_{50} values in rodents of > 3 000 mg/kg b.w. (see US-EPA, 2001a; EFSA, 2008a). Acetic is not irritating to skin at concentrations of 2.5 % or less. Above this concentration, it becomes progressively more irritating, although in some studies no irritation was observed until the concentration exceeded 10 %. Acetic acid is irritating to the eyes at 5 % and above. Information is not available on lower concentrations, although at some point it will cease to be irritating (EFSA, 2008a).

Acetic acid is classified, with specific concentration limits, as follows: skin corrosive category 1A, H314: at concentrations ≥ 90 %; skin corrosive category 1B, H314: at concentrations ≥ 25 % and < 90 %; skin irrititant category 2, H315: at concentrations ≥ 10 % and < 25 %; irritating to eyes category 2, H319: at concentrations ≥ 10 % and < 25 % (Regulation (EC) No 1272/2008).[22]

Genotoxicity

Acetic acid was negative in tests for mutagenicity using the Ames Salmonella assay (CCRIS, 1995; EFSA, 2008a). Mixed results have been obtained in tests for clastogenicity in mammalian cells. However, Morita et al. (1990) have shown that acetic acid is not clastogenic when tested at physiological pH and that positive results obtained were a consequence of the low pH induced (pH < 5.7) in the culture medium by the high concentrations of the acid used.

[21] Commission Directive 91/322/EEC of 29 May 1991 on establishing indicative limit values by implementing Council Directive 80/1107/EEC on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work. OJ L 177, 5.7.1991, p. 22-24.

[22] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=85625&HarmOnly=no?fc=true&lang=en (accessed 08/04/2012).

Acetic acid has not been tested in an adequate study for genotoxicity *in vivo*.

EFSA (2008a) concluded in the draft assessment report (DAR) that "*Acetic acid, therefore, is considered to be not mutagenic for sufficiently buffered systems but such effects may become apparent when the capacity to maintain homeostasis is overwhelmed*".

Carcinogenicity

EFSA (2008a) concluded in the DAR for acetic acid that "*Long term toxicity/carcinogenicity studies in animals with oral exposure are not necessary, considering that humans are exposed to orally ingested acetic acid from various food sources and there is no evidence that such exposure is causally related to toxic effects and an increased cancer incidence*."

3.9.2.4. Allergenicity

Available data give no indication that acetic acid acts as an allergen or an adjuvant at the concentrations expected from previous cargoes.

3.9.3. Conclusions

On the basis of its low toxicity and its natural occurrence in food and in the body, the CONTAM Panel does not consider it necessary to establish an ADI for acetic acid. It causes adverse effects only when it is present at sufficient concentration to change the H^+ concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to acetic acid do not give rise to any toxicological concern. Exposure to small amounts of acetic acid locally may cause irritation to the skin or eyes. However, studies in experimental animals and humans have shown that the maximum potential levels of acetic acid arising in fats or oils following its transport as a previous cargo would be of no concern. Acetic acid is not genotoxic at physiological pH, and it is not allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated.

The CONTAM Panel therefore concludes that acetic acid meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.10. SULPHURIC ACID (CAS No 7664-93-9)

Sulphuric acid is produced in large amounts from sulphur, sulphur dioxide or salts and used for many large scale chemical processes, such as the production of phosphates. Its salts, sulphate or bisulphate, are ubiquitous.

Mineral waters may be labelled as sulphate-rich if they contain more than 200 mg/L sulphate.

3.10.1. Previous evaluations

The SCF evaluated sulphuric acid in 1996 as a previous cargo for edible fats and oils and considered this substance as acceptable as a previous cargo: Food additive (E513) ADI "not specified" (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, sulphuric acid was not further evaluated as it was already considered acceptable (SCF, 2003a).

Sulphuric acid was considered at the 20th JECFA (1976) when revised specifications were prepared. No toxicological information was assessed and no ADI was allocated.

OECD (2001a) concluded that the only further work necessary with regard to potential health effects was the collection of information about occupational exposure to sulphuric acid mist.

Sulphuric acid is not included in Annex I to Directive 91/414/EEC,[23] primarily because there was insufficient information to satisfy the requirements set out in Annex II and Annex III of the Directive. In its assessment for the use of sulphuric acid as a pesticide, the EC (2008b) concluded that sulphuric acid should not be included in Annex I to Directive 91/414/EEC due to specific concerns regarding ecotoxicity and the possible toxicological effects of heavy metal impurities. Several data gaps were also identified. However, it was noted that sulphuric acid is expected to dissociate into sulphate on contact with water and soil and become part of the natural sulphur cycle.

3.10.2. Current evaluation

3.10.2.1. Expected impurities

Sulphuric acid is usually of a high purity. No impurities of concern are expected when sulphuric acid is diluted to less than 100 mg/kg in edible fats and oils as subsequent cargoes, which is the maximum concentration anticipated to due to carryover.

3.10.2.2. Reactivity and reaction products

Sulphuric acid may render edible oils more acidic and promote reactions such as transesterification. However, at a level of at most 100 mg/kg, such effects are negligible, as the pH will not drop substantially. Even if it does react with lipids, it should be noted that sulphate is almost always present in mixed foods as a natural constituent.

3.10.2.3. Toxicological profile

The toxicological consequences of exposure to sulphuric acid are all attributable to the effects of the H^+ ion concentration. When the concentration of the acid is not sufficient to lower the pH, due to dilution and/or buffering, there are no adverse effects. However, relatively small amounts of sulphuric acid can produce a local increase in H^+ ion concentration. Hence, sulphuric acid, like other mineral acids, may cause toxicity at the site of contact.

Edible fats and oils are buffered to a sufficient extent such that after the addition of small amounts of sulphuric acid the pH remains above the pK_a2 of this acid (1.9), which means that sulphuric acid is deprotonated to sulphate.

Cleaning of the tank leaves behind a residue of diluted sulphuric acid. As a worst case scenario it is assumed that the carryover amounts to 100 mg/kg of a 10 % aqueous solution of sulphuric acid which is soluble in the oil or fat transported afterwards. Neutralized edible fats and oils still contain roughly 1 000 mg/kg fatty acids. As the pK_a of fatty acids is around 7, roughly half of this acid is deprotonated. The addition of 10 mg/kg sulphuric acid would protonate only a small fraction of these fatty acids

<u>Absorption, distribution, metabolism and elimination</u>

Sulphuric acid ingested orally will be rapidly diluted and buffered by the contents of the GI tract. Sulphuric acid per se is not absorbed from the GI tract. Following dissociation, sulphate anion will be absorbed and enter the body's normal electrolyte pool. It will not play any toxicological role at levels that would be ingested when sulphuric acid was a previous cargo (ATSDR, 1998; OECD, 2001a).

<u>Acute toxicity</u>

When concentrated, sulphuric acid is irritant and corrosive to skin. However, when diluted the acid is not irritant or corrosive. The threshold for irritation to the skin appears to be at least 2.5 %, and possibly up to 4 %, in rats, mice, guinea pigs and rabbits (Nixon et al., 1975; Vernot et al., 1977;

[23] Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market (91/414/EEC). OJ L 230, 19.8.1991, p. 1-32.

Sekizawa et al., 1994). In studies by Nixon et al. (1990) sulphuric acid at a concentration of 10 % was not irritating to the skin of rabbits, guinea pigs or humans.

Sulphuric acid is also irritant and corrosive to the eyes, in concentrated form. Direct administration of 0.01 mL of 10 % sulphuric acid to rabbit eyes was slightly irritating, whilst instillation of up to 0.1 mL of 10 % sulphuric acid into the corneal sac of rabbit eyes was not irritating (OECD, 2001a). Avol et al. (1988) reported that exposure of normal subjects to sulphuric acid as a respirable aerosol (MMD 0.9 µm) at a concentration of 1.578 mg/m^3 for 1 h had no effect on the eyes. Minor eye irritation was observed in asthmatics exposed to a concentration of 0.999 or 1.460 mg/m^3, but not at 0.396 mg/m^3, for 1 h.

Sulphuric acid is classified, with specific concentration limits, as follows: skin corrosive category 1A, H314: at concentrations ≥ 15 %; skin irritant category 2, H315: at concentrations ≥ 5 % and < 15 %; irritating to eyes category 2, H319: at concentrations ≥ 5 % ≤ and < 15 % (Regulation (EC) No 1272/2008[24]).[25]

The oral LD_{50} in the rat is 2 140 mg/kg b.w. per day (OECD, 2001a).

Subacute, subchronic and chronic toxicity studies

At high concentrations, sulphuric acid is locally irritating and/or corrosive to the upper GI tract, and hence the oral route of exposure is not appropriate for testing possible toxic effects (OECD, 2001a). At lower concentrations, as indicated above, sulphuric acid will be diluted and buffered by the content of the GI tract and hence will have no local effect. As the pK_a of the first proton is < 0 and of the second is 1.92 (IARC, 1992) it will rapidly dissociate and only the sulphate anion, a normal constituent of the diet and of the body, will be available for absorption. This will not cause any adverse effects following exposure to the levels that would from use of sulphuric acid as a previous cargo.

Genotoxicity

Sulphuric acid was negative in the Ames test using various strains of *S. typhimurium* (pH 4 to 9) and *E. coli*, with and without metabolic activation (Cipollaro et al, 1986; ATSDR, 1998). Sulphuric acid increased chromosomal aberrations in CFHO cells, but this was shown to be a consequence of low pH (OECD, 2001a; ATSDR, 1998).

3.10.2.4. Allergenicity

Available data give no indication that sulphuric acid is an allergen or an adjuvant at the concentrations expected from previous cargoes.

3.10.3. Conclusions

No ADI has been established for sulphuric acid. Sulphuric acid is toxic only when it is present at a sufficient concentration to change the H^+ concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to sulphuric acid do not give rise to any toxicological concern. Exposure to small amounts of sulphuric acid locally may cause irritation to the skin or eyes. However, studies in experimental animals and humans have shown that the maximum potential levels of sulphuric acid arising in fats or oils following its transport as a previous cargo would be of no concern. Sulphuric acid is not genotoxic

[24] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/458/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1-1355.

[25] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=9111&HarmOnly=no?fc=true&lang=en (accessed 08/04/2012).

at physiological pH, and it is not allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated.

The CONTAM Panel therefore concludes that sulphuric acid meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.11. FORMIC ACID (methanoic acid; hydrogen carboxylic acid) (CAS No 64-18-6)

Formic acid is one of the strongest carboxylic acids, with a pK_a of 3.75. It is produced industrially from carbon monoxide and sodium hydroxide or via addition of carbon monoxide to methanol to form methyl formate followed by hydrolysis. It is also a by-product of the production of acetic acid.

Formic acid is widely present in nature. For instance, honey contains 50-1 000 mg/kg of this acid.

Up to 1998, formic acid was authorized as a preservative for fish, fruit and vegetable products (E236). It is widely used for controlling fermentation of silage and for preservation of feeds (major use of this acid).

3.11.1. Previous evaluations

The SCF evaluated formic acid in 1996 as a previous cargo for edible fats and oils and considered this substance as acceptable as a previous cargo based on a group ADI of 0-3 mg/kg b.w. for formic acid and ethyl formate (JECFA, 1973; SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, formic acid was not further evaluated as it was already considered acceptable (SCF, 2003a).

The US FDA Select Committee on GRAS Substances considered formic acid as GRAS when used as ingredients of paper and paperboard food packaging materials (FDA, 1976).

JECFA (1999), at its 49th meeting in 1997, maintained the group ADI for formic acid and ethyl formate established in 1973. JECFA noted that formic acid is produced endogenously in humans and is a normal component of intermediate metabolism. According to the US EPA ACToR site, the oral reference dose (sub-chronic and chronic) for formic acid is 2 mg/kg b.w. per day.[26]

The OECD Screening Information Dataset (SIDS) review of formic acid concluded that "The chemicals of the formic acid and dissociative salts subcategory are currently of low priority for further work" (OECD, 2008a).

3.11.2. Current evaluation

3.11.2.1. Expected impurities

No impurities of concern are expected.

3.11.2.2. Reactivity and reaction products

Formic acid is a strong acid and a reducing agent, but at concentrations below 100 mg/kg no effects of concern are expected.

3.11.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

Formic acid ingested orally will be rapidly diluted and buffered by the contents of the GI tract. Formic acid per se is not absorbed from the GI tract. Following dissociation, formate anion will be absorbed and enter the body's normal electrolyte pool. It will not play any toxicological role at levels that would be ingested when formic acid was a previous cargo.

[26] http://actor.epa.gov/actor/GenericChemical?casrn=64-18-6 (accessed 17/03/2012).

Acute toxicity

Formic acid is classified, with specific concentration limits, as follows: skin corrosive category 1A; H314: at concentrations ≥ 90 %; skin corrosive category 1B; H314: at concentrations ≥ 10 % and < 90 %; skin irritant category 2; H315: at concentrations ≥ 2 % and < 10 %; irritating to eyes category 2; H319: at concentrations ≥ 2 % and <10 % (Regulation (EC) No 1272/2008).[27] Below 2 %, formic acid will not be an irritant.

Formic acid is of low acute toxicity by the oral route, with reported LD_{50} values of generally greater than 1 000 mg/kg b.w. in rats, mice and dogs.[28] In an OECD test guideline compliant study, the LD_{50} in rats was 730 mg/kg b.w.[29]

Genotoxicity

Formic acid was negative in tests for mutagenicity in bacteria and mammalian cells (cited in OECD, 2008a). At concentrations that reduced the pH to below 6.8, formic acid induced chromosomal aberrations in CHO cells, but not when buffered to physiological pH. Formic acid did not induce SCEs in Chinese hamster V79 cells or in human lymphocytes at concentrations lower than 10 mM. At higher concentrations, at which the pH would be reduced, SCEs were induced in human lymphocytes. Hence, formic acid is not genotoxic at physiological pH.

Carcinogenicity

Although formic acid itself has not been tested for carcinogenicity following oral administration, the closely related compound potassium hydrogen diformate was negative for carcinogenicity when administered to mice or rats at oral doses up to 2 000 mg/kg b.w. per day, in guideline studies (OECD, 2008a).

3.11.2.4. Allergenicity

Available data give no indication that formic acid is an allergen or an adjuvant at the concentrations expected from previous cargoes.

3.11.3. Conclusions

A group ADI for formic acid and ethyl formate of 0-3 mg/kg b.w. has been established, and on the basis of available evidence, the CONTAM Panel considers this appropriate. Formic acid is toxic only when it is present at sufficient concentration to change the H^+ concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to formic acid do not give rise to any toxicological concern. Exposure to small amounts of formic acid locally may cause irritation to the skin or eyes. However, the maximum potential levels of formic acid arising in fats or oils following its transport as a previous cargo would be of no concern. Formic acid is not genotoxic at physiological pH, and it is not allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated.

The CONTAM Panel therefore concludes that formic acid meets the criteria for acceptability as a previous cargo for edible fats and oils.

[27] ECHA http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=49202&HarmOnly=no?fc=true&lang=en (accessed 17/03/2012).
[28] NIOSH RTECS, http://www.cdc.gov/niosh-rtecs/LQ4AC4A0.html (accessed 17/03/2012).
[29] ECHA, http://www.echa.europa.eu/ (accessed 17/03/2012).

3.12. ACETIC ANHYDRIDE (ethanoic anhydride) (CAS No 108-24-7)

Acetic anhydride is a liquid boiling at 140 °C. It is highly reactive; in the presence of water it is hydrolyzed to acetic acid, in the presence of alcohols or amines to acetates.

Acetic anhydride is produced mostly from acetic acid, by elimination of water at high temperature, or by addition of carbon monoxide to methyl acetate.

It is used for acetylation, e.g. of cellulose, salicylic acid or morphine.

3.12.1. Previous evaluations

The SCF evaluated acetic anhydride in 1996 as a previous cargo for edible fats and oils and considered this substance as acceptable as a previous cargo because: "*During tank washing or on contact with water [it] would be converted to acetic acid*" (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, acetic anhydride was not further evaluated as it was already considered acceptable (SCF, 2003a).

For exposure via air at the workplace a limit of 5 ppm (21 mg/m³) acetic anhydride was set by the American Conference of Industrial Hygienists (ACGIH).

The OECD SIDS review of acetic anhydride concluded that "*Acetic anhydride is considered to be currently of low priority for further health-related work in the SIDS context*" (OECD, 1997a).

ECHA[30] has waived the need for the establishment of derived-no (or minimum)-effect levels (DN(M)EL) for systemic effects from acetic anhydride following oral exposure on the basis of anticipated low internal exposure.

Acetic anhydride is approved by the US FDA for esterification of food starch to an extent not to exceed 2.5 % (FDA, 2011a).

The US-EPA Office of Pesticide Programs has assigned acetic anhydride to List 4B, i.e. "*Other ingredients for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment*" (US-EPA, 2004).

No health based guidance values (e.g. ADI) have been established for oral exposure to acetic anhydride, because systemic effects would not be anticipated. Occupational exposure limits, in general 5 ppm (20 mg/m^3), have been established by a number of regulatory authorities.[31]

3.12.2. Current evaluation

3.12.2.1. Expected impurities

No impurities of concern are expected.

3.12.2.2. Reactivity and reaction products

When cleaning the tank of a cargo ship with water, acetic anhydride is immediately converted to acetic acid. Hence, acetic anhydride is evaluated in the same way as acetic acid (see Section 3.8.).

In the unforeseen case of incomplete or omitted cleaning, residual acetic anhydride would rapidly react with components in edible oil. Edible oil contains more humidity than needed to hydrolyse 100 mg/kg acetic anhydride. The anhydride could also react with mono- and diglycerides as well as other alcohols (e.g. fatty alcohols, sterols) to form acetates. These reaction products are not of concern.

[30] http://www.echa.europa.eu/ (accessed 17/03/2012).
[31] NIOSH RTECS, http://www.cdc.gov/niosh-rtecs/AK1D5F88.html (accessed 17/03/2012).

3.12.2.3. Toxicological profile

Acute toxicity

Acetic anhydride is chemically reactive and will cause toxicity at the site of contact. At high concentrations it is corrosive to skin and eyes. At lower concentrations it will cause local irritation.

Acetic anhydride is classified, with specific concentration limits, as follows: may cause respiratory irritation category STOT SE 3; H335: at a concentration ≥ 10 %; skin corrosive category 1B, H314: at concentrations ≥ 25 %; skin irritant category 2; H315: at concentrations ≥ 5 % and < 25 %; irreversible effects on the eye category 1, H318: at concentrations ≥ 5 % and < 25 %; irritating to eyes category 2, H319: at concentrations ≥ 1 % and < 5 % (Regulation (EC) No 1272/2008).[32]

The oral LD_{50} in rats has variously been reported as 630 mg/kg b.w. in olive oil[33] and 1 800 mg/kg b.w. (OECD, 1997a)

Genotoxicity

Acetic anhydride was negative in an Ames test for bacterial mutagenicity. Equivocal results in a mouse lymphoma assay are likely to be a consequence of the effects of low pH. Acetic anhydride was negative *in vivo* in a rat bone marrow micronucleus test, following inhalation (cited in OECD, 1997a). The weight of evidence indicates that acetic anhydride is not genotoxic at physiological pH.

3.12.2.4. Allergenicity

Acetic anhydride is a low molecular weight compound and would by itself only be able to act as a hapten, but it readily reacts with amino acids and may for this reason even at low doses induce occupational IgE-dependent hypersensitivity and asthma as well as IgG dependent late respiratory systemic syndromes (Yokota et al., 1999). However, the occupational allergic syndromes elicited by acetic anhydride are due to exposure via air which occurs after evaporation of acetic anhydride at high temperatures used during work procedures. Available data give no indication that acetic anhydride is an allergen or an adjuvant when present in liquid such as when used as a previous cargo, and such effects are not anticipated to occur.

3.12.3. Conclusions

No ADI has been established for acetic anhydride, as it is rapidly hydrolysed on contact with water to acetic acid, which is considered sufficiently innocuous that it is not necessary to establish an ADI. The CONTAM Panel considers this appropriate. Acetic anhydride is toxic at the site of contact through its chemical reactivity or when the acetic acid formed by hydrolysis is present at sufficient concentration to change the H^+ concentration. Hydrolysis of any intact acetic anhydride in the GI tract will be very rapid and the acetic acid formed will be diluted and buffered by the contents of the GI tract. Hence, the levels that would occur following oral ingestion of fats or oils transported subsequent to acetic anhydride do not give rise to any toxicological concern. Exposure to small amounts of acetic anhydride locally may cause irritation to the skin or eyes. However, the maximum potential levels of acetic anhydride and acetic acid arising in fats or oils following its transport as a previous cargo would be of no concern. Acetic anhydride is not genotoxic at physiological pH. It is not anticipated that unhydrolysed acetic anhydride survives and hence it does not pose a risk of allergenicity when it is transported as a previous cargo. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated.

[32] ECHA. http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=88932&HarmOnly=no?fc=true&lang=en (accessed 17/03/2012).
[33] ECHA: http://www.echa.europa.eu/ (accessed 17/3/2012).

The CONTAM Panel therefore concludes that acetic anhydride meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.13. ACETONE (dimethylketone; 2-propanone) (CAS No 67-64-1)

Acetone is a liquid miscible with water, boiling at 56 °C.

In the most important route of synthesis, propene is reacted with benzene to give isopropyl benzene (cumene) which is then oxidized to phenol and acetone. Alternatively propene is directly oxidized to acetone or hydrated to isopropanol which is then oxidized to acetone.

Acetone is used as a solvent, including storage of pressurized acetylene. It is also used, for example, to produce bisphenol A (polycarbonate) or methyl methacrylate.

Acetone is produced and eliminated by normal metabolism. The average concentration in the blood of unexposed individuals is 3.1 mg/L (Ashley et al., 1994). The reference range for unexposed subject is < 10 mg/L (Tietz, 1983).

3.13.1. Previous evaluations

The SCF evaluated acetone in 1996 as a previous cargo for edible fats and oils and considered this substance as acceptable as a previous cargo: It was "*Acceptable as extraction solvent for food*" (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, acetone was not further evaluated as it was already considered acceptable (SCF, 2003a).

The US-EPA in its Integrated Risk Information System (IRIS) assessment of acetone has established a reference dose for oral exposure of 0.9 mg/kg b.w. per day, which incorporates an additional 10-fold uncertainty factor to extrapolate from sub-chronic to chronic exposure (US-EPA, 2003a).

The OECD SIDS review of acetone concluded that "*Acetone has a low priority for further work. The health and environmental effects of acetone have both been well studied*." (OECD, 1999)

3.13.2. Current evaluation

3.13.2.1. Expected impurities

The most common impurities of acetone are diacetone alcohol (from aldol condensation) and isopropanol, which are not expected to be of concern as impurities in acetone used as a previous cargo.

From the synthesis it could be expected that crude acetone may contain benzene and isopropyl benzene. Acetone can easily be separated from benzene and isopropyl benzene by distillation, but it cannot be ruled out that crude products are shipped. The maximum concentration of benzene in acetone used as a previous cargo that could be considered to be of low concern can be derived from the WHO guideline value for drinking water, which is 0.01 µg/L (WHO, 2006). As the previous cargoes are assumed to be diluted at least 10 000 times in the oil or fat subsequently transported (maximum of 100 mg/kg in the transported fat or oil), 10 µg/L benzene would be achieved in the oil when the acetone contains 100 mg/kg benzene.

However, it should be noted that the WHO Guideline Value for drinking water was based on the assumption of lifetime exposure (70 years) to benzene in 2 litres of water per day. This was associated with an upper bound excess lifetime cancer risk of 10^{-5}, using a linear multistage extrapolation model. Similar estimates were obtained using data from experimental animals and from human epidemiology. Exposure to benzene from acetone as previous cargo will be for appreciably less than lifetime, and the amount of contaminated fat or oil consumed is assumed to be 25 g. Hence, the concentration of benzene in acetone considered to be of low concern could be at least 100 times greater than the guideline value for drinking water, whilst assuring no greater risk. Therefore acetone containing 1 % benzene is considered of low concern.

According to the information provided by FOSFA, the acetone transported as a previous cargo is unlikely to contain more than 0.1 % benzene (see Documentation provided to EFSA).

3.13.2.2. Reactivity and reaction products

In an acidic environment, acetone forms 1,3-dioxolane derivatives with vicinal diols (cyclic ketals), which is used in synthesis for protecting aldehyde and ketone functions. Possible reaction partners in edible oil are monoglycerides and dihydroxy fatty acids (e.g. from hydrolyzed epoxy fatty acids). Free fatty acids in the edible oil are probably adequate to support this reaction in view of the long time available.

Dioxolanes are labile in a weakly acidic environment and it is, therefore, unclear whether a significant amount will be present in edible oils. No information could be found in the literature.

3.13.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Acetone is readily absorbed from the GI tract. It enters the endogenous pool of acetone and is extensively and rapidly metabolised, primarily by enzymes of intermediary metabolism (IPCS/WHO, 1998a).

Specific information on the absorption and disposition of 1,3-dioxolane (CAS No. 646-06-0) is not available. However, given that its partition coefficient is approximately 0 (log P_{ow} = -0.37), i.e. it is almost equally soluble in water as in octanol and it has a low molecular weight (MW= 74.08),[34] it is likely that 1,3-dioxolane with be rapidly and extensively absorbed from the GI tract. It is also likely to be distributed widely throughout the body.

Acute toxicity

Acetone is of low acute toxicity, with LD_{50} values in rabbits, rats and mice of > 5 000 mg/kg b.w. (Tanii et al., 1986; IPCS/WHO, 1998a; OECD, 1999). Dilute aqueous solutions of acetone are only minimally irritating to the eyes (OECD, 1999).

Undiluted acetone is not irritating to the skin of rabbits but is irritating to the eyes (IPCS/WHO, 1998a; OECD, 1999). ECHA has classified acetone as irritating to eyes (category 2; H319).[35]

1,3-Dioxolane is not acutely toxic by the oral route, with LD_{50} values in the rat of > 2 000 mg/kg b.w. in several different studies (US-EPA, 2000, 2001b).

1,3-Dioxolane appears to causes some irritation to rabbit eyes but it has not been classified by ECHA as an eye irritant. It is slightly irritating to the skin of rabbits, but not such as to merit classification.[36]

2,2-Dimethyl-1,3-dioxolan-4-ylmethanol (CAS no. 100-79-8) is irritating to the skin and eyes. Under Regulation (EC) No. 1272/2008, most notifiers have proposed it be classified as a skin irritant category 2: H315 and irritating to eyes category 2; H319.[37]

[34] http://www.echa.europa.eu/ (accessed 09/04/2012).
[35] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=22981&HarmOnly=no?fc=true&lang=en (accessed 08/04/2012).
[36] http://www.echa.europa.eu/ (accessed 09/04/2012).
[37] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=22981&HarmOnly=no?fc=true&lang=en (accessed 08/04/2012).

Subacute, subchronic and chronic toxicity studies

Groups of 10 male and 10 female Crl:CD® (SD)BR Sprague-Dawley rats received 1,3-dioxolane by gavage in corn oil at doses of up to 2 000 mg/kg b.w. for 14 days. The no-observed-adverse-effect level (NOAEL) was 75 mg/kg b.w. per day. There was an increase in mortality at the highest dose. Effects seen at the lowest-observed-adverse-effect level (LOAEL) (250 mg/kg b.w. per day) were reduced body weight gain and reduced platelet and leukocyte counts (Argus Research Laboratories, 1991, as cited in US-EPA, 2012a).

Groups of 10 male and 10 female Charles River mice, Charles River rats and Syrian hamsters received 1,3-dioxolane in their drinking water at concentrations of up to 2 % for 4 weeks (Industrial BIO-Test Laboratories, Inc, 1977, as cited in US-EPA, 2012a). The no-observed-adverse-effect concentration (NOAEC) in mice and rats was 0.5 % (~500 mg/kg b.w. in rats) on the basis of reduced body weight gain at higher concentrations. The NOAEC in hamsters was 1 % on the basis of reduced body weight gain at 2 %.

1,3-Dioxolane was administered by gavage to groups of 8-10 rats (strain not stated) for 7 months as a 20 % aqueous solution to give doses of up to 580 mg/kg b.w. and also as the undiluted substance for 4 months, at a dose of 580 mg/kg b.w. (Czajkowska and Krysiak, 1987, as cited in US-EPA, 2000, 2001b). All animals survived. Animals in the high dose group (undiluted) showed reduced body weight gain and clinical signs of toxicity. This effect was not seen in the group receiving the diluted compound.

Genotoxicity

In most tests of genotoxicity *in vitro*, acetone was negative. It was also negative in mouse and Chinese hamster micronucleus tests *in vivo*. The occasional positive results *in vitro* were either not consistent, or were not exposed *in vivo*. The weight of evidence suggests that acetone does not pose a risk of genotoxicity to humans (IPCS/WHO, 1998a; OECD, 1999).

1,3-Dioxolane was tested for genotoxicity *in vitro* with and without metabolic activation (hepatic S9 fraction for Aroclor-1254 induced rats) using *S. typhimurium* strains TA 1535, TA1537, TA1538, TA98 and TA100, on a number of occasions. The results were consistently negative (US-EPA, 2000, 2001b). 1,3-Dioxolane was also tested with *S. typhimurium* strains TA1535, TA1537 and TA1538 and *S. cerevisiae* strain D4, using S9 fraction from a number of tissues from PCB-induced rat, mouse and monkey. 1,3-Dioxolane was negative in all of the tests (US-EPA, 2000, 2001b). 1,3-Dioxolane was also tested in several *in vitro* assay systems for genotoxic effects. These included a chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation using hepatic S9 from Aroclor 1254-induced rats, mutagenicity at the TK locus of cultured L5178Y mouse lymphoma cells, with and without metabolic activation using hepatic S9 from Aroclor-induced rats, DNA damaging potential in an SOS test using *S. typhimurium* TA1535/pSK102, using induced expression of β-galactosidase under the umuC promoter as a measure of induced DNA damage, in the presence and absence of a metabolic activation system, and transformation of cultured Balb/c-3T3 cells. In all of these tests, 1,3-dioxolane was negative. In a test for transformation using C3H/101 1/2 cells, there was some evidence that 1,3-dioxolane was positive, but there was a lack of concentration-effect relationship and the finding was poorly reproducible (US-EPA, 2000, 2001b).

1,3-Dioxolane has been tested for possible genotoxic effects *in vivo*: in a mouse micronucleus assay, and for dominant lethal mutations in male rat germ cells after both oral dosing and inhalation exposure to the compound. 1,3-Dioxolane produced positive results in two *in vivo* studies of genotoxicity, one a rat hepatic unscheduled DNA synthesis (UDS) test, and the other a mouse micronucleus test, which was relatively poorly reported. These results may have been due to the presence of an impurity in the test material. The weight of evidence suggests that 1,3-dioxolane is not genotoxic.

Carcinogenicity

No data are available on the carcinogenicity of 1,3-dioxolane. However, in view of its lack of genotoxicity, based on weight of evidence, and the absence of effects in the, albeit limited, repeat dose toxicity studies indicative of carcinogenic potential by a non-genotoxic mode of action, the CONTAM Panel concludes that any dioxolanes formed with acetone as a previous cargo would not pose a risk of carcinogenicity in consumers of edible fats and oils transported subsequently.

Developmental and reproductive toxicity

In the first phase of a 1-generation reproductive toxicity study, groups of 5 male Charles River rats were treated with 1,3-dioxolane in their drinking water at concentrations of 0.5 % and 1 % for 90 days prior to mating with untreated females (2/male). Treatment continued through the mating period. Effects were observed on both dams and pups at both concentrations of 1,3-dioxolane. In a second phase to the study, untreated males were mated with the females that produced the litters above. Dams were treated continuously from first mating through to the second mating. Animals were not treated after the second mating. Effects on the dams were observed at both treatment levels. There were no effects on the offspring (US-EPA, 2000, 2001b).

In a 1-generation reproductive toxicity study similar to phase 1 of that described above, groups of males were treated with 1,3-dioxolane on the drinking water at concentrations of 0.01, 0.03 and 0.1 %. Following mating, dams were treated through mating, gestation and lactation. No effects were observed on either dams or offspring up to the highest concentration tested, 0.1 % (US-EPA, 2000, 2001b).

Groups of 25 mated female Charles River rats were treated by gavage with 1,3-dioxolane on corn oil at doses of up to 1 000 mg/kg b.w. from days 6-15 of gestation. Animals were terminated on gestation day 20. Body weight and feed consumption were reduced in animals treated with 500 and 1 000 mg/kg b.w. per day on gestation days 6 and 7. Fetal body weights were reduced in the high dose group, and both the litter and fetal incidences of tail malformations, interrelated vertebral malformations and septel defects of the heart were increased in this dose group. Delayed ossification was also observed in this group and there was one incidence of cleft palate. The NOAEL for developmental effects was 500 mg/kg b.w. per day (US-EPA, 2000, 2001b). The NOAEL for maternal toxicity was 250 mg/kg b.w. per day.

The developmental toxicity of 1,3-dioxolane was investigated by Sitarek et al. (1992, cited by the US-EPA, 2000, 2001b). Groups of 17-19 female Imp:DAK rats were treated by gavage every other day with 1,3-dioxolane in a 20 % aqueous solution to give doses of 140, 580 and 1 150 mg/kg b.w. from days 8-20 of gestation. 1,3-Dioxolane had no effect on the incidences of intrauterine deaths or malformations. In the pre-natal phase, there were delays in fetal development in the mid- and high-dose groups, although the effects in the mid-dose group were marginal. The NOAEL for developmental toxicity was 140 mg/kg b.w., based on incomplete ossification (incomplete development of the skull bones) at the LOAEL. The maternal NOAEL was 580 mg/kg b.w., based on reduced body weight gain and increased relative adrenal weights at 1 150 mg/kg b.w.

3.13.2.4. Allergenicity

Available data give no indication that acetone is an allergen or an adjuvant at the concentrations expected from previous cargoes.

3.13.3. Conclusions

Acetone was considered acceptable as an extraction solvent for food but no ADI has been established. However, the US-EPA and IPCS have identified 900 mg/kg b.w. per day as the critical NOAEL, from a 90-day study in rats, in which acetone was administered in drinking water (Dietz et al., 1991). In the absence of data from chronic exposure, the CONTAM Panel considers this appropriate. This NOAEL

would be adequately protective of the toxicological effects of any acetone present in a subsequent cargo of edible fats or oils, using a conventional safety factor of 100 with an additional factor of 10 to allow for possible chronic exposure (i.e. 900 mg/kg b.w. per day divided by 1 000 would result in a health based guidance value of 0.9 mg/kg b.w. per day), albeit chronic exposure is unlikely from the use of acetone as a previous cargo. Acetone is not genotoxic *in vivo* and it is not allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. The toxicological profile of 1,3-dioxolane, and by analogy that of other dioxolanes, is such that there would be no toxicological concern from the use of acetone as a previous cargo to edible fats and oils from any such reaction products. The method for manufacture of acetone gives rise to benzene as a potential impurity. The CONTAM Panel concluded that levels of up to 1 % would not give rise to any toxicological concern from acetone as a previous cargo. The levels of benzene present in acetone are unlikely to exceed 0.1 %.

The CONTAM Panel therefore concludes that acetone meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.14. *n*-HEPTANE (CAS No 142-82-5)

n-Heptane is a liquid boiling at 98 °C, insoluble in water.

The CAS No (142-82-5) refers to *n*-heptane, but pure *n*-heptane is unlikely to be transported in large quantities. In reality, *n*-heptane, heptane, and heptane-fraction of petroleum hydrocarbons are often not clearly distinguished, i.e. the product may consist primarily of branched and cyclic hydrocarbons with 6-8 carbon atoms. The products likely to be transported as previous cargoes are technical grade heptane or petroleum hydrocarbons with boiling ranges around that of *n*-heptane.

Heptane is primarily used as a solvent.

3.14.1. Previous evaluations

The SCF evaluated *n*-heptane in 1996 as a previous cargo for edible fats and oils and considered this substance as acceptable as a previous cargo, as it was "*Acceptable as an extraction solvent for Food*" (JECFA, 1970a; SCF, 1997a). Althouth the SCF referred to *n*-heptane, the substance that had been evaluated previously was a petroleum hydrocarbon fraction. In the 2003 SCF evaluation of acceptable previous cargoes, *n*-heptane was not further evaluated as it was already considered acceptable (SCF, 2003a).

JECFA (1970a) was unable to establish an ADI for *n*-heptane (note that the substance evaluated was a petroleum hydrocarbon fraction), used as an extraction solvent, due to the lack of sufficient information. JECFA proposed to undertake a re-evaluation when new relevant data became available. However, to date, no such re-evaluation has been carried out. JEFCA (1970a) concluded that *n*-heptane could be used as an extraction solvent, but only in accordance with good manufacturing practices, which should result in minimal residues.

n-Heptane is approved under US FDA, Title 21 US CFR citations for indirect additives used in food contact substances (FDA, 2011b).

FDA (2012) has concluded that *n*-heptane should be considered as a Class 3 residual solvent in the manufacture of pharmaceuticals for human use. "*Solvents in Class 3 may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5,000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).*"

Occupation exposure limits, generally of 500 ppm, 2 085 mg/m^3, for *n*-heptane have been by established by various regulatory authorities.[38]

3.14.2. Current evaluation

3.14.2.1. Expected impurities

Commercial *n*-heptane may contain high levels of branched and cyclic saturated hydrocarbons with 6 to 8 carbon atoms. The most prevalent, other than *n*-heptane, are dimethylcyclopentanes, 3-ethylpentane, methylcyclohexane and 3-methylhexane.

3.14.2.2. Reactivity and reaction products

Heptane does not react with edible fats and oils.

3.14.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Heptane is lipophilic, with a log octanol:water partition coefficient of 4.75. It is readily absorbed from the GI tract, although specific details are not available (OECD, 2010). Once absorbed, heptane is rapidly and extensively metabolised, in part by sequential terminal C-oxidation.

Acute toxicity

Heptane is of low acute toxicity by the oral route, with an LD_{50} in the rat of 15 000 mg/kg b.w. (OECD, 2010; ECHA, 2012[39]).

Heptane is not irritating to the eyes (OECD, 2010). ECHA has classified *n*-heptane as a skin irritant category 2; H315 (Regulation (EC) No. 1272/2008[24]).[40]

Subacute, subchronic and chronic toxicity studies

No studies in which heptane was administered repeatedly by the oral route were identified. Following repeated inhalation exposure, C7-C9 aliphatic hydrocarbons were of low systemic toxicity. The NOAEC was often the highest concentration tested. In general, the only effect of significance observed was transient central nervous system depression (OECD, 2010).

Takeuchi et al. (1980) exposed groups of 7 male Wistar rats to atmospheric concentrations of 3 000 ppm *n*-pentane, *n*-hexane, *n*-heptane, (all > 99 % pure) or fresh air, 12 h per day 16 weeks. Peripheral nerve conduction velocity and distal latency were measured before exposure and at 4, 8, 12 and 16 weeks. Post mortem evaluation included light and electron microscopy of peripheral nerve, neuromuscular junction, and muscle fibre. Whilst exposure to *n*-hexane resulted in anticipated impairment of peripheral nerve function and damage to nerve and muscle, *n*-heptane (and *n*-pentane) had no such effects.

Genotoxicity

Heptane (purity not stated) was negative for tests of mutagenicity in bacteria (*S. typhimurium* and *E. coli*) with or without metabolic activation, and did not induce gene conversion in *S. cerevisiae*, with or without rat hepatic S9 preparation (Brooks et al., 1988). It had no effect on the frequency of chromosomal aberrations in the rat liver epithelial cell line RL4 (Brooks et al., 1988).

[38] NIOSH RTECS: http://www.cdc.gov/niosh-rtecs/MI757E20.html (accesed 17/03/2012).
[39] http://www.echa.europa.eu/ (accessed 17/03/2012).
[40] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=114760&HarmOnly=yes?fc=true&lang=e (accessed 17/03/2012).

Carcinogenicity

No specific information is available on the carcinogenicity of heptane. No data have been submitted to ECHA in support of read across.

Developmental and reproductive toxicity

No studies on the developmental or reproductive toxicity of heptane by any exposure route could be identified. Studies on hexane have been submitted to ECHA to support read across to heptane. These studies were by the inhalation route. Rats were exposed to concentrations of commercial hexane (approx. 52 %), at concentrations of up to 9 000 ppm, in a 2-generation study of reproductive toxicity. No adverse effects on reproduction were observed up to the highest concentration tested (9 000 ppm).[41]

Rats were exposed to concentrations of commercial hexane (approx. 52 %), at concentrations of up to 9 000 ppm, in a study of developmental toxicity. The NOAEC in dams was 900 ppm, based on changes in lung colour and the presence of dark brown foci in the lungs of some animals at the LOAEC of 3 000 ppm. In foetuses, at 9 000 ppm there were statistically significant increases in the number of litters showing bilateral bone island at the first lumbar arch, and of litters showing non-ossification of all intermediate phalanges of the hindlimb. The NOAEC for these effects was 3 000 ppm.

3.14.2.4. Allergenicity

Available data give no indication that heptane is an allergen or an adjuvant.

3.14.3. Conclusions

The CONTAM Panel recommends that the entry for the substance in the annex to Commission Directive 96/3/EC[5] be amended to "Heptane (commercial grades) (CAS No 142-82-5)", to reflect the substance of transport (see Table 4 under Recommendations).

Although the toxicological database for heptane is limited, available data suggest that the substance is of relatively low systemic toxicity. It is not genotoxic or allergenic. There are no reaction products or impurities of toxicological concern.

The CONTAM Panel therefore concludes that heptane meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.15. *n*-HEXANE (technical grades) (CAS No 110-54-3 / 64742-49-0)

n-Hexane is a straight chain aliphatic hydrocarbon with six carbon atoms. It is a colourless liquid, insoluble in water (0.076 g/L), but miscible with numerous organic solvents, like acetone, chloroform, diethyl ether and most alcohols. It is a volatile compound (boiling point 68.7 °C), flammable and its vapours can be explosive.

n-Hexane is often not clearly distinguished from hexane, hexane fraction or petroleum ether (listed with decreasing purity). In fact, *n*-hexane is expensive and for practically all large scale uses, technical grade hexane or petroleum hydrocarbons are used. CAS No 110-54-3 refers to *n*-hexane, whereas CAS No 64742-49-0 covers mixtures of petroleum hydrocarbons commonly called naphtha (petroleum), hydrotreated light. The petroleum hydrocarbons are hydrogenated, i.e. consist of saturated hydrocarbons. Commercial products are characterised by their boiling ranges. Products with CAS No 64742-49-0 cover boiling ranges from about 50 to 120 °C, which means that linear, branched and cyclic hydrocarbons from 5 to 9 carbon atoms may be present. "Hexane" refers to those petroleum hydrocarbons which are centred on *n*-hexane, i.e. with a boiling range around that of this compound.

[41] ECHA: http://www.echa.europa.eu/ (accessed 17/3/201).

The most commonly used technical hexanes consist of around 50 % *n*-hexane accompanied by cyclopentane, isohexane and isoheptane. Hexane is used for a variety of purposes, including the extraction of oils and fats from oil seeds and fruits, as a diluent and for cleaning.

Hexane and petroleum hydrocarbons are primarily produced by fractionated distillation of petroleum.

n-Hexane is a product of lipid peroxidation and is present in non-refined edible oils at around 1 mg/kg.

3.15.1. Previous evaluations

The SCF evaluated hexane as previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that hexane was considered acceptable as an extraction solvent for food (SCF, 1996). This was based on the evaluation of a 90-day toxicity study (TNO, 1992, as cited in SCF, 1996) performed on a technical hexane (*n*-hexane content 58 %) that had a no-observed-effect level (NOEL) of 40 mg/kg b.w. By assuming that the effects seen were due only to *n*-hexane, a NOEL of 23 mg/kg b.w. was calculated and on the basis of a series of assumptions regarding *n*-hexane occurrence and consumption in food a margin of exposure of around 200 was estimated. In the 2003 SCF evaluation of acceptable previous cargoes, *n*-hexane was not further evaluated as it was already considered acceptable (SCF, 2003a).

In 1999, the ATSDR reviewed the toxicological profile of *n*-hexane. It was reported that peripheral neuropathy is the major consequence of human exposure to *n*-hexane in the air but no data were available on the consequences of exposure to *n*-hexane by the dermal or oral route. There was no reliable information in animal studies on the potential carcinogenicity of *n*-hexane but there was no evidence that *n*-hexane increased the risk of cancer in exposed populations. It was concluded that the exposure of the general population to *n*-hexane is low and the risk of adverse health effects from *n*-hexane exposure appears to be negligible. Since vegetable oils are extracted with solvents containing *n*-hexane, it is possible that very small amounts are present in these products but these amounts were considered toxicologically insignificant.

In 2005, the US-EPA provided a toxicological review of data as scientific support to the IRIS assessment for *n*-hexane that proposed an inhalation reference dose (RfC) of 7×10^{-1} mg/m^3 (US-EPA, 2005). This value was established using data from an inhalation study in rats (Huang et al., 1989) where behavioral, neurophysiological, and neuropathological effects were analysed.

3.15.2. Current evaluation

3.15.2.1. Expected impurities

Hexane and petroleum hydrocarbons are usually mixtures of saturated hydrocarbons. They do not contain aromatic hydrocarbons or other products at concentrations which are expected to be of toxicological concern when hexane is are used as a previous cargo to edible fats and oils.

3.15.2.2. Reactivity and reaction products

Hexane and petroleum hydrocarbons are not expected to react with edible fats and oils.

3.15.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

No oral exposure studies evaluating absorption and distribution of *n*-hexane in humans or laboratory animals are available. However, absorption following oral exposure is very likely given its lipid solubility and has been suggested by the identification of *n*-hexane and its metabolites in expired air, serum, and urine. In addition, neurotoxicity observed following oral exposure of rats to *n*-hexane also suggests oral absorption of the chemical. Several inhalation studies in humans and animals show that *n*-hexane is absorbed into the circulation and transported to the liver, the major site of metabolism. In

the liver it is initially hydroxylated by the action of mixed function oxidases to form either 1- or 3-hexanol in a detoxification pathway or 2-hexanol in a bioactivation pathway. 2,5-Hexanedione is believed to be the major toxic metabolite produced in humans (Perbellini et al., 1981). *n*-Hexane metabolites are then distributed in the blood to various organs and tissues, including the liver, kidney, and brain. A single study in humans suggests elimination following oral exposure to *n*-hexane. No specific oral exposure studies in laboratory animals are available on the elimination of *n*-hexane. Transfer across the placenta has been demonstrated in rats for *n*-hexane and for the metabolites 2-hexanone and 2,5-hexanedione (Bus et al., 1979).

Acute toxicity

Few acute toxicity studies are available for *n*-hexane. HSDB (2005a) reports LD_{50} values of 28 710 mg/kg b.w., or 24 and 45 mL/kg (approximately 15 840 and 29 700 mg/kg b.w.) for juvenile and adult rats. For inhalation exposure, a 4-hour LC_{50} of 48 000 ppm has been reported for both rats and mice (HSDB, 2005a).

ECHA has classified *n*-hexane as a skin irritant category 2; H315 (Regulation (EC) No. 1272/2008[24]).[42]

Subacute, subchronic and chronic toxicity studies

The database for subchronic oral exposure to *n*-hexane is limited to two gavage studies in rats (Krasavage et al., 1980; Ono et al., 1981).

Krasavage et al. (1980) studied the neurotoxicity of *n*-hexane and practical grade hexane in rats receiving the chemicals by gavage, 5 days per week for 90 or 120 days. The onset of neuropathy was assessed by the initial appearance of hind-limb paralysis. This effect was observed only from exposure to the highest dose of *n*-hexane tested (3 980 mg/kg b.w. for 120 days). Practical grade hexane (4 000 mg/kg b.w.) and the lower doses of *n*-hexane tested (570 and 1 140 mg/kg b.w.) did not produce hind-limb paralysis during the 90 day testing period.

In the study by Ono et al. (1981) rats were administered *n*-hexane (99 % pure) by gavage in olive oil daily for 8 weeks and nerve conduction was assessed. The authors stated that they did not observe any definite clinical signs of neuropathy in any of the exposed groups (up to an estimated exposure of 2 022 mg/kg per day for 6-8 weeks). US-EPA (2005) considered these studies inadequate for the development of an oral health based guidance value for *n*-hexane.

No data are available regarding the potential toxicity of *n*-hexane in orally exposed humans. There are a considerable number of epidemiological studies on environmental /occupational exposure via other routes of exposure. The majority of these studies show an association between inhalation exposure to *n*-hexane and neurological symptoms in occupationally exposed individuals although the information on exposure is imprecise and data are inappropriate for dose-response modelling. Regarding the mode of action evidence has focused on the capacity of *n*-hexane to undergo metabolism to 2,5-hexanedione, which appears to have the ability to interact with specific proteins on the neurofilaments thus accounting for the induction of neurotoxicity.

Genotoxicity

Most studies indicate that *n*-hexane is nongenotoxic in short-term testing protocols in bacterial tester strains (NTP, 1991). *n*-Hexane induced a marginal effect on chromosome loss of *Saccharomyces cerevisiae* D61.M strain (Mayer and Goin, 1994). Treatment with *n*-hexane (99 % pure) at concentrations up to 5 000 µg/mL in the presence or absence of metabolic activation did not induce

[42] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=115449&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

chromosomal aberrations in CHO cells; SCEs were increased in the presence of S9 but the effect was not dose-related (NTP, 1991). Induction of polyploidy was reported in the absence of S9 in Chinese hamster lung fibroblasts (Ishidate et al., 1984), No induction of gene mutations was observed in Chinese hamster V79 cells (Lankas et al, 1978). *n*-Hexane (99 % pure) did not induce micronuclei in the peripheral blood of mice exposed via inhalation to up to 10 000 ppm *n*-hexane, 6 hours per day, 5 days per week for 13 weeks or in mice exposed to 1 000 ppm for 22 hours per day for 13 weeks (NTP, 1991). In an *in vivo* mouse bone marrow cytogenetics assay, doses of 500, 1 000 or 2 000 mg/kg *n*-hexane (99 % pure) administered by intraperitoneal (*i.p.*) injection did not increase the incidence of SCEs; chromosomal aberrations were slightly increased, but this increase was not significant (unpublished NTP studies, as cited in NTP, 1991). Overall these data suggest no concern for genotoxicity of *n*-hexane.

Carcinogenicity

There are no animal carcinogenicity studies available that examine exposure to *n*-hexane itself, and there is a single human study (Beall et al., 2001) where workers were chronically exposed to mixtures containing *n*-hexane along with other chemicals. In laboratory animals exposed for 2 years via inhalation to a commercial hexane mixture containing *n*-hexane (0, 900, 3 000 or 9 000 ppm), there was a statistically significant dose-related increase in hepatocellular combined adenomas and carcinomas in female B6C3F1 mice (Biodynamics, 1993, as cited in US-EPA, 2005; Daughtrey et al., 1999). There was also an increased incidence of pituitary hyperplasia, adenomas, and adenocarcinomas in exposed females. This increase was not observed in male mice or in either sex of F344 rats exposed to commercial hexane under the same conditions. The relevance of this study to the identification of the carcinogenic potential of *n*-hexane is unclear due to the unknown toxicity contribution of the other components of the mixture and uncertainty as to whether the apparent carcinogenic response in female mice was truly treatment related. US-EPA (2005) considered the data inadequate for an assessment of the human carcinogenic potential of *n*-hexane.

Developmental and reproductive toxicity

Marks et al. (1980, as cited in US-EPA, 2005) conducted a reproductive/developmental and teratological study in CD-1 mice in which dams were exposed to *n*-hexane (99 % pure) in cottonseed oil by gavage on gestational day (GD) 6 to GD15. Even at doses that caused maternal toxicity (highest dose tested 9 900 mg/kg per day in three injections) there were no reproductive, developmental, or teratological effects of *n*-hexane. Linder et al. (1992, as cited in US-EPA, 2005) included *n*-hexane in a survey of chemicals for spermatotoxic effects in male Sprague-Dawley rats. No effects were reported.

Upon exposure to hexane by inhalation, developmental toxicity was reported in rats (Mast, 1987, as cited in ATSDR, 1999). A NOAEL for developmental toxicity of 200 ppm in rats has been identified. Embryotoxicity was also reported (Mast et al., 1988, as cited in ATSDR, 1999) but only at the highest dose tested. Focal degeneration of spermatocytes and exfoliation of elongated spermatids was observed in rats treated with hexane but only at very high air concentrations (about 1 000 ppm) following exposure for 21-24 hours per day (De Martino et al., 1987, as cited in ATSDR, 1999). These signs were also reported in rats after large oral doses of ~ 4 g/kg b.w. per day administered by gavage 5 days per week for 120 days (Krasavage et al., 1980) and the administration of the *n*-hexane metabolite 2,5-hexanedione in drinking water (Gillies et al., 1981; Chapin et al., 1982). Short-term exposure to hexane vapour did not result in a male dominant lethal effect in CD-1 mice (Mast et al., 1989, as cited in ATSDR, 1999) and no effects were seen on reproductive tissues in male rats after intermediate-duration inhalation exposure up to 10 000 ppm *n*-hexane (Dunnick et al., 1989, as cited in ATSDR, 1999).

3.15.2.4. Allergenicity

Available data give no indication that hexane is an allergen or an adjuvant.

3.15.3. Conclusions

The CONTAM Panel recommends that the entry for the substance in the annex to Commission Directive 96/3/EC[5] be amended to "Hexane (technical grades) (CAS No 110-54-3 / 64742-49-0)", to reflect the substances of transport (see Table 4 under Recommendations).

Hexane (CAS No. 1110-54-3) and petroleum hydrocarbons, covered by CAS No. 64742-49-0, are of low systemic toxicity when admistered by the oral route. Subchronic oral studies, although inadequate for the establishement of a health based guidance value, did not show clinical signs of neuropathy except at very high doses. There are no adequate carcinogenicity data but the lack of mutagenic effects both *in vitro* and *in vivo* suggests that hexane is not a genotoxic carcinogen. Hexane is not allergenic. No impurities or reaction products with edible fats and oils of concern are known or expected when hexane is used as a previous cargo.

The CONTAM Panel therefore concludes that hexane meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.16. CYCLOHEXANE (hexamethylene; hexanaphthene; hexahydrobenzene) (CAS No 110-82-7)

Cyclohexane is a colourless liquid, insoluble in water, soluble or miscible with, e.g. ethanol, methanol, diethyl ether, acetone, benzene, carbon tetrachloride.

Cyclohexane is obtained industrially by hydrogenation of benzene or distillation of petroleum.

Cyclohexane is used as a solvent, e.g. for resins, varnish removers for the extraction of essential oils, and in industrial recrystallization of steroids. Cyclohexane is also used in the manufacture of adipic acid and caprolactam.

3.16.1. Previous evaluations

The SCF evaluated cyclohexane as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that cyclohexane was considered acceptable as an extraction solvent for flavourings following receipt of a negative mouse micronucleus study, and evidence that the commercial material meets an appropriate specification (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, cyclohexane was not further evaluated as it was already considered acceptable (SCF, 2003a).

In 2003, US-EPA provided a toxicological review of data as scientific support to an updated IRIS assessment that proposed an RfC of 6 mg/m^3 (US-EPA, 2003b). This value was established using data from a two-generation reproduction inhalation toxicity study in rats (DuPont, 1997a; Kreckmann et al., 2000, as cited in US-EPA, 2003b) where reduced pup weights in the F1 and F2 generations were observed and chosen as the critical effect.

In 2004, the European Commission Joint Research Centre published the European Union Risk Assessment Report (EU RAR) on cyclohexane (ECB, 2004). In this Assessment, the only effect of concern considered relevant for consumers was acute neurobehavioural toxicity. Exposure of 1 000 ppm was anticipated as a worst case, leading to a calculated margin of exposure of 0.25. This margin was not considered acceptable.

3.16.2. Current evaluation

3.16.2.1. Expected impurities

Cyclohexane obtained by hydrogenation may contain residues of benzene. Cyclohexane distilled from petroleum is likely to contain hydrocarbons of similar volatility, mainly C5-C7, possibly including benzene.

Benzene present as a contaminant in cyclohexane used as a previous cargo is not considered to be of any health concern to human health as long as its concentration in cyclohexane does not exceed 1 % (see Section 3.13.2.3.).

According to the information provided by FOSFA, the cyclohexane transported as a previous cargo is unlikely to contain more than 0.1 % benzene (see Documentation provided to EFSA).

3.16.2.2. Reactivity and reaction products

Cyclohexane is not expected to react with edible fats and oils.

3.16.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Cyclohexane is rapidly absorbed into the blood via the lungs, GI tract, and skin (Brugnone et al., 1980; Perbellini and Brugnone, 1980; Mutti et al, 1981; Yasugi et al., 1994, as cited in US-EPA, 2003b). Not surprisingly for a nonpolar organic compound, cyclohexane partitions preferentially to lipid-rich tissues such as fat, liver, and brain (Savolainen and Pfaffli, 1980, as cited in US-EPA, 2003b). Hydroxylation of cyclohexane to cyclohexanol, its primary metabolite, occurs in the liver. Cyclohexyl metabolites are conjugated to glucuronides for excretion, but at high doses sulfate conjugation may occur (Elliott et al., 1959, as cited in US-EPA, 2003b). Inhaled cyclohexane is excreted primarily via expiration from the lungs.

Acute toxicity

Reported LD_{50} and LC_{50} show that cyclohexane is of low toxicity via all routes of administration (US-EPA, 2003b). LD_{50} of 13 g/kg b.w. for rats (Kimura et al., 1971, as cited in US-EPA, 2003b) and of 0.8 and 1.3 g/kg b.w. for mice (as cited by US-EPA, 1994; Clayton and Clayton, 1993-4, as cited in HSBD, 2005b) have been reported for acute oral toxicity.

ECHA has classified cyclohexane as a skin irritant category 2; H315 (Regulation (EC) No. 1272/2008[24]).[43]

Subacute, subchronic and chronic toxicity studies

Inhalation studies performed in mice and rats showed slight liver effects (i.e. increases in mitotic index and in liver weight and centrolobular hypertrophy) after sub-acute or sub-chronic exposure at dose levels between 6 000 and 7 000 ppm (Malley et al., 2000, as cited in US-EPA, 2003b). The NOAEL for hepatic effects was 2 000 ppm (6 880 mg/m^3). In the EU RAR (ECB, 2004) it is noted that this value is very conservative since the effects observed in the liver from 6 000 ppm upwards may be of an adaptive nature.

No adequate observations in humans exposed orally or oral exposure studies in animals exist from which oral health based guidance values may be established. There are no adequate data for using route-to-route extrapolation from inhalation studies to establish oral health based guidance values.

Genotoxicity

Cyclohexane was not mutagenic with or without exogenous metabolic activation in Salmonella/microsomes tests (McCann et al., 1975; HLA, 1982a, as cited by US-EPA, 2003b; Mortelmans et al., 1986). There was only one positive study of mutation induction in cultured L5178Y mouse lymphoma cells in the presence of exogenous metabolic activation (HLA, 1982b, as cited by

[43] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=37570&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

US-EPA, 2003b) that was not confirmed in a second study (Litton Bionetics, 1982, as cited by US-EPA, 2003b). No increase in the number of SCEs either in the presence or the absence of exogenous metabolic activation was observed in cultured CHO cells (HLA, 1982c, as cited by US-EPA, 2003b). No significant increase in chromosome structural aberration frequency was observed in bone marrow cells of male or female rats exposed by inhalation for 5 consecutive days to levels of cyclohexane up to 1 000 ppm (Litton Bionetics, Inc., 1981, as cited by US-EPA, 2003b).

Overall these data indicate that cyclohexane is not genotoxic.

Carcinogenicity

Cyclohexane was assessed for its tumourigenic potential on mouse skin following multistage initiation-promotion protocols (Gupta and Mehrotra, 1990). The activity of ornithine decarboxylase, a marker of tumour promotion, was induced by the topical application of cyclohexane in a dose-related manner. In a chronic animal bioassay, topical application of cyclohexane to 7,12-dimethylbenz[α]anthracene initiated mouse skin showed a weak promotion effect. Given the low reliability and uncertainties of these results and of the method, the significance of this study is questionable. This view is supported by the conclusions in the EU RAR for cyclohexane (ECB, 2004).

Developmental and reproductive toxicity

No adequate studies of reproductive or developmental toxicity of oral exposure to cyclohexane were located. Unpublished reports on studies of two-generation reproductive toxicity in rats and prenatal developmental toxicity in rats and rabbits exposed to cyclohexane by inhalation were submitted by industry (DuPont, 1997a,b,c, as cited by US-EPA, 2003b) and later summarized in Kreckmann et al. (2000). In a two-generation study of rats (DuPont, 1997a, as cited by US-EPA, 2003b; Kreckmann et al., 2000), cyclohexane exposure of dams was associated with low pup weights in both the F1 and F2 litters at 7 000 ppm with slight maternal toxicity. A NOAEL of 2 000 ppm was identified for effects on pups and of 500 ppm for maternal toxicity.

3.16.2.4. Allergenicity

Available data give no indication that cyclohexane is an allergen or an adjuvant.

3.16.3. Conclusions

Cyclohexane is of low systemic toxicity via all routes of administration. No adequate observations in humans exposed orally or oral exposure studies in animals exist from which an oral health based guidance value may be established. There are no adequate carcinogenicity data but the lack of mutagenic effects both *in vitro* and *in vivo* suggests that cyclohexane is not a genotoxic carcinogen. Cyclohexane is not allergenic. There are no reactions of concern with edible fats and oils. However, cyclohexane obtained by hydrogenation may contain residues of benzene. The CONTAM Panel concluded that levels of up to 1 % would not give rise to any toxicological concern from cyclohexane as a previous cargo. The levels of benzene present in cyclohexane are unlikely to exceed 0.1 %.

The CONTAM Panel therefore concludes that cyclohexane meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.17. PENTANE (CAS No 109-66-0)

n-Pentane is a straight chain hydrocarbon with 5 carbon atoms. It is obtained by distillation from natural gasoline or naphtha.

The CAS No 109-66-0 refers to *n*-pentane, whereas “pentane” may include iso- and cyclopentane. However, even technical products contain a high proportion of *n*-pentane.

n-Pentane is widely used as solvent. It is a blowing agent to make foamed food packaging materials (e.g. for expanded polystyrene) and used in personal care products as well as car care products.

Pentane is a normal by-product of lipid peroxidation in all species including humans.

3.17.1. Previous evaluations

The SCF evaluated *n*-pentane as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). Note that the substance to which the SCF referred was entered as pentane in list 3 of the 33rd series of reports of the SCF (1995). In the 2003 SCF evaluation of acceptable previous cargoes, *n*-pentane was not further evaluated as it was already considered acceptable (SCF, 2003a).

In 2003 the European Commission Joint Research Centre published the EU RAR on *n*-pentane (ECB, 2003). The overall NOAEL of ≥ 20 000 mg/m^3 *n*-pentane from a 90-day repeated dose inhalation toxicity study was used in the risk assessment. A very large margin of exposure (greater than 600) was estimated for human exposure.

Pentane is approved in the list of substances for making food contact materials[19] without limit (other than the generic limit of 60 mg/kg food).

3.17.2. Current evaluation

3.17.2.1. Expected impurities

Technical grade pentane may contain branched and cyclic hydrocarbons of similar molecular mass, which are not expected to be of concern (see Section 3.15.).

3.17.2.2. Reactivity and reaction products

No reactions products of concern are expected with edible fats and oils.

3.17.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

Inhaled *n*-pentane is rapidly absorbed by the lungs and also rapidly eliminated by both exhalation and by biotransformation. The solubility of *n*-pentane in adipose, brain, liver, kidney, heart, and muscle tissues is higher than in blood, with adipose tissue having a very high affinity compared with blood and with all other tissues (Perbellini et al., 1985). However, the elimination of *n*-pentane is rapid and potential for accumulation in tissues is assumed to be very low. Only a minor part of the dose is excreted as metabolites in urine since the products formed initially by cytochrome P450-dependent oxidation (2- and 3-pentanol) (Frommer et al., 1970, as cited in ECB, 2003) are rapidly converted further to CO_2 (Van Rij and Wade, 1987).

<u>Acute toxicity</u>

Based on the available data, *n*-pentane has a low acute oral and respiratory toxicity, LD_{50} > 2 000 mg/kg (limit test) (McKee et al., 1998) and LC_{50} ≥ 300 000 mg/m^3 (100 000 ppm) (ChemID, online) in rats. In experimental animals, as typical of solvents, neurobehavioral and neurotoxic effects are major toxic effects seen following inhalation at high concentrations.

<u>Subacute, subchronic and chronic toxicity studies</u>

Most toxicity studies are by inhalation and there no adequate data for using route-to-route extrapolation from inhalation studies to establish oral health based guidance values.

The available data from a 13 week sub-chronic inhalation toxicity study (McKee et al., 1997, as cited by Galvin and Marashi, 1999) revealed an overall NOAEL of ≥ 20 000 mg/m^3 (6 660 ppm) that was used in the EU RAR for risk assessment (ECB, 2003). An additional inhalation study (Stadler et al., 2001), that was not considered in the EU RAR, showed a NOAEL of 1 000 ppm with reversible clinical pathology changes such as increases in serum calcium and phosphorus concentrations produced at 3 000 and 10 000 ppm.

Genotoxicity

In vitro, *n*-pentane was not mutagenic in different strains of *Salmonella typhimurium*, both in the absence and in the presence of a metabolic activation system (Kirwin et al., 1980 as cited by Galvin and Marashi, 1999). No significant increase in chromosomal aberrations was found in cultured mammalian cells (CHO cells) (McKee et al., 1998).

In vivo, *n*-pentane did not induce an increase in micronuclei or cytotoxicity in bone marrow cells of rats exposed to 5 000, 10 000 or 20 000 mg/m^3 for 90 days (6 h per day; 5 days per week) (McKee et al., 1997, as cited by Galvin and Marashi, 1999). It should be noted, however, that no clinical signs of toxicity were observed, which would have confirmed adequate systemic exposure. *n*-Pentane was not mutagenic in male mice in a dominant lethal study when it was injected into the peritoneum (Epstein et al., 1972, as cited by Galvin and Marashi, 1999).

Based on the available data *n*-pentane can be considered as non-genotoxic.

Carcinogenicity

No human or animal data are available on the carcinogenicity of *n*-pentane. Given the results from the mutagenicity and repeated dose toxicity studies, and the lack of a structural alert, the EU RAR conclusion was that there is no concern for carcinogenicity (ECB, 2003). The CONTAM Panel agrees with this conclusion

Developmental and reproductive toxicity

Developmental toxicity of *n*-pentane was not observed in studies performed in rats. A maternal and developmental NOAEL of > 1 000 mg/kg b.w. was identified (McKee et al., 1998).

No studies of reproductive toxicity of *n*-pentane could be identified. However, in a 13-week inhalation study in male and female rats, no signs of toxicity to reproductive organs were noted after exposure to *n*-pentane concentration up to 20 000 mg/m^3 (6 660 ppm) (McKee et al., 1997, as cited by Galvin and Marashi, 1999).

3.17.2.4. Allergenicity

Available data give no indication that *n*-pentane is an allergen, irritant or an adjuvant. A human study (n=15) concluded that *n*-pentane was clinically non-irritating, and a guinea pig study (maximization test) concluded that *n*-pentane was not sensitizing in guinea pigs (McKee et al., 1998).

3.17.3. Conclusions

n-Pentane is of low systemic toxicity via all routes of administration. No adequate observations in humans exposed orally or oral exposure studies in animals exist from which an oral health based guidance value may be established. No human or animal data are available on the carcinogenicity of *n*-pentane but given the lack of mutagenic effects and of relevant clinical signs in repeat-dose toxicity studies there would be no concern for carcinogenicity when *n*-pentane is used as a previous cargo. *n*-Pentane is not allergenic and there are no impurities or reactions products of toxicological concern.

The CONTAM Panel therefore concludes that pentane meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.18. ISO-PROPANOL (isopropyl alcohol; IPA) (CAS No 67-63-0)

Isopropanol (propan-2-ol, also called 2-propanol) is a clear and flammable liquid with an odour resembling that of a mixture of ethanol and acetone. It is miscible with, e.g. water, ethanol, acetone, chloroform and benzene. The melting point is -89 °C and the boiling point is 82 °C.

Isopropanol is mainly produced by hydration of propene catalyzed by sulphuric acid.

Isopropanol is used in the production of acetone (oxidation of isopropanol is now the major source of acetone) and other chemicals, such as isopropyl acetate, iso-propylamine, diiso-propyl ether, iso-propyl xanthate, fatty acid esters, herbicidal esters and aluminium isopropoxide. Other uses include the application as a coolant in beer manufacture, coupling agent, dehydrating agent, polymerization modifier in the production of polyvinyl fluoride, foam inhibitor, de-icing agent, preservative and heat-exchange medium. It is also used as a flavouring agent, as well as in household, personal care and pharmaceuticals products.

3.18.1. Previous evaluations

The SCF evaluated isopropanol as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that isopropanol was considered by the SCF acceptable as an extraction solvent for food (provided that residues are low) and the evidence that it is readily removed by tank cleaning and easily removed by the oil refining process. In assessing isopropanol for use as an extraction solvent, the SCF (1981) established a temporary ADI of 1.5 mg/kg b.w. per day, because of the lack of adequate information on reproductive toxicity. On subsequent evaluation (SCF, 1992a), the ADI remained temporary, because of the lack of information on carcinogencity and genotoxicity. The SCF noted that for applications other than as an extraction solvent, for example as a carrier solvent, which would result in significantly higher residues in food, it would be necessary to establish a full ADI before it could be considered acceptable (SCF, 1992a). In the 2003 SCF evaluation of acceptable previous cargoes, iso-propanol was not further evaluated as it was already considered acceptable (SCF, 2003a).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that isopropanol was acceptable as an extraction solvent if used according to good manufacturing practice (JECFA, 1970a) and as having no safety concerns when used as a flavouring agent (JECFA, 1999).

In 1997, OECD SIDS reviewed the toxicological data on isopropanol within the evaluation of high production volume chemicals. The conclusion of this review was that isopropanol was of low priority for further work (OECD, 1997b).

In 2005, a risk assessment of isopropanol by HERA (Human and Environmental Risk Assessment) was published. The lowest NOAEL of 400 mg/kg b.w. per day for chronic, reproductive and developmental toxicity in rats was used to estimate a margin of exposure of about 3 800 for the total aggregate consumer exposure.

In 2005, the former EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC Panel) established an ADI of 2.4 mg/kg b.w. per day for isopropanol, from the NOAEL of 240 mg/kg b.w. per day for maternal toxicity in rabbits. An uncertainty factor of 100 was used.

3.18.2. Current evaluation

3.18.2.1. Expected impurities

The production of isopropanol results in a crude mixture, from which it is extracted by distillation. The main by-products are 1-propanol, diiso-propyl ether and acetone. Assuming a high level of impurity, say 10 %, in crude isopropanol, carryover from a previous cargo may result in a concentration of 10 mg/kg in a subsequent cargo of edible fats or oils. At this level, these impurities are not expected to be of concern.

3.18.2.2. Reactivity and reaction products

Isopropanol may react with lipids by interesterification, but this does not result in products of concern.

3.18.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Isopropanol is readily absorbed in animals and man through the lungs, skin and GI tract. Isopropanol is rapidly distributed throughout the body and has been shown to cross the blood/brain barrier. Elimination from the blood follows first order kinetics. Approximately 80 % of an intravenous dose is oxidised to acetone in rats and mice (Slauter et al., 1994). Excretion occurs mainly through the expired air either as unchanged isopropanol or as acetone. Quantities of acetone and isopropanol are excreted in urine together with the glucuronide conjugate of isopropanol.

Acute toxicity

A substantial number of studies, supported by information *in vitro* demonstrate that isopropanol has a low order of acute toxicity. Effects of severe poisoning can be: comatose condition, pulmonary difficulty, nausea, vomiting, and headache accompanied by various degrees of central nervous system depression. In the absence of shock, recovery usually occurs. Following oral administration, LD_{50} values of 5 500 and 4 475 mg/kg b.w. have been observed in rats and mice, respectively (Guseinov, 1985, as cited by OECD, 1997b).

ECHA has classified isopropanol as irritating to eyes category 2; H319 (Regulation (EC) No. 1272/2008[24]).[44]

Subacute, subchronic and chronic toxicity studies

The systemic toxicity of repeated exposure to isopropanol has been evaluated in rats and mice by the oral and inhalation routes. In a 12-week oral drinking water study in rats, effects such as increased weights of kidneys, liver and adrenals as well as an increase in the formation of hyaline droplets in the proximal tubules of the kidney were observed at the lowest-observed-effect level (LOEL) of 1 280 mg/kg per day. The NOAEL was 870 mg/kg b.w. per day (Pilegaard and Ladefoged, 1993). Similar NOAELs were estimated from subchronic and chronic inhalation studies.

Genotoxicity

All reported *in vitro* and *in vivo* genotoxicity assays for isopropanol were negative. Isopropanol was not mutagenic in the *S. typhimurium*/Ames test either in the presence or absence of an S9 metabolic activation system (Florin et al., 1980; Shimizu et al., 1985, as cited in EFSA, 2005). Isopropanol was negative for aneuploidy in *Neurospora crassa* (Brockman et al., 1984, as cited in EFSA, 2005), for mutation induction in a CHO/HGPRT assay (Kapp et al., 1993, as cited in OECD, 1997b), for SCE

[44] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=22308&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

induction in Chinese hamster V79 cells (Von der Hude et al., 1987, as cited in OECD, 1997b) and for micronuclei induction *in vivo* in mice. Isopropanol did not induce transformation in Syrian hamster embryo cells (Kapp et al., 1993).

Overall these data indicate a lack of genotoxicity by isopropanol.

Carcinogenicity

There are no chronic toxicity and carcinogenicity studies of isopropanol by the oral route. Two chronic exposure, rodent inhalation studies were conducted to evaluate the carcinogenic potential of isopropanol. One study was performed exposing Fischer 344 rats to 500, 2 500 and 5 000 ppm of isopropanol for 6 hours per day, 5 days per week for 24 months (Burleigh-Flayer et al., 1997). A concentration-related increase in interstitial (Leydig) cell tumors in male rats was reported. Interstitial cell tumors of the testis are the most frequently observed spontaneous tumor in aged male Fischer 344 rats (Haseman and Arnold, 1990) and a very high mortality was observed in all groups, including controls, thus questioning the relevance of this observation.

A mouse inhalation study was performed exposing CD-1 mice to 500, 2 500 and 5 000 ppm of isopropanol for 6 hours per day, 5 days per week for 18 months. There was no increase in the frequency of neoplastic lesions in any of the treated groups (Burleigh-Flayer et al., 1997). On the basis of these data isopropanol was evaluated by IARC as “not classifiable as to its carcinogenicity to humans (Group 3)” (IARC, 1999a).

Developmental and reproductive toxicity

A developmental toxicity study was conducted with oral gavage by exposing pregnant rats to 0, 400, 800 or 1 200 mg /kg b.w. per day of isopropanol on gestational days 6 to 15 inclusive. The only treatment-related effects on the dams were reductions in maternal body weight and gravid uterine weight of about 10 % in the high-dose group. Fetal litter body weights were significantly reduced at the 800 and 1 200 mg/kg b.w. dose levels but no teratogenic effects were observed. A NOAEL of 400 mg/kg b.w. per day was identified for developmental toxicity and of 800 mg/kg b.w. for maternal toxicity (Tyl et al., 1994).

A developmental toxicity study was conducted in New Zealand White rabbits, by administration to pregnant females of isopropanol by gavage at 0, 120, 240 or 480 mg/kg b.w. per day on gestational days 6 to 18 inclusive. Maternal lethality was reported at the highest dose and the body weight of survivors was severely reduced (45.4 % of controls), associated with reduced food consumption. In a few animals of this group, profound clinical signs (peripheral vasodilatation, cyanosis, lethargy, laboured respiration) were observed. No evidence of reproductive or developmental toxicity including teratogenicity was seen in any dose group. The NOAEL for maternal toxicity was 240 mg/kg b.w. per day (Tyl et al., 1994).

A two-generation reproductive toxicity study with isopropanol was carried out in groups of Sprague-Dawley rats. Parental animals received doses to 0, 100, 500 or 1 000 mg/kg b.w. per day by gavage for at least 10 weeks prior to mating. Increased bodyweight during lactation as well as increased organ weights (e.g. liver and kidney) in both sexes were observed. Increased mortality was seen in the parental animals as well as in the offspring during the early postnatal period. The NOAEL for parental toxicity, based on lethality and kidney effects, was reported as < 100 mg/kg b.w. per day and 100 mg/kg b.w. per day in male and female rats, respectively. The NOAEL for developmental effects, based on decrease in pup weights and survival indices, was reported as 100 mg/kg b.w. per day. A statistically significant reduction in the male mating index was seen in the high-dose P2 males (Bevan et al., 1995, as cited in EFSA, 2005).

The data from these studies were the subject of several interpretations and modeling exercises. The US-EPA (1992, as cited by OECD, 1997b) interpreted the reductions in post-natal survival as related

to treatment and proposed a NOAEL of 100 mg/kg b.w. per day. A NOAEL for reproductive toxicity of 500 mg/kg b.w. per day was proposed by Bevan et al. (1995). A benchmark dose 95 % lower confidence limit for a benchmark response of 5 % ($BMDL_5$) of 420 mg/kg b.w. per day was calculated for the decrease in the male mating index (Allen et al., 1998).

A more recent review (Faber et al., 2008) conducted by British Industrial Biological Research Association of the reproductive and developmental toxicity studies in rats, including unpublished reproductive and developmental toxicity studies, where isopropanol was admistered in drinking water, concluded that the weight of evidence suggests that isopropanol, following oral gavage administration, does not affect male mating ability or fertility at doses up to 1 000 mg/kg b.w. per day and can cause decreases in postnatal pup survival at doses of 1 000-1 200 mg/kg b.w. per day to the dams. The NOAEL for this endpoint with oral gavage administration was 700 mg/kg b.w. per day. Indications of maternal toxicity were also noted at levels below 700 mg/kg b.w. per day and offspring may suffer indirectly from this toxicity. The LOAEL for decreased post-natal survival was 1 000 mg/kg b.w. per day and the NOAEL was 700 mg/kg b.w. per day. Decreased postnatal pup survival was noted when isopropanol was administered in the drinking water with a LOAEL of 2 278 mg/kg per day and a NOAEL of 1 947 mg/kg per day.

3.18.2.4. Allergenicity

Isopropanol has been considered to be an uncommon sensitizer, but several isolated cases have been reported (for references see Garcia-Gavín et al., 2011). However, in a recently published study of a series of 1 450 subjects with a history of exposure to isopropanol, performed according to international standards for patch testing, 44 individuals showed an allergic test response to the substance (García-Gavín et al., 2011). Pharmaceutical grade isopropanol was used ‘as is’ for testing. Taking into account the high degree of dilution in edible fats and oils that would occur when isopropanol is used as a previous cargo, the CONTAM Panel considers that isopropanol as a previous cargo is unlikely to represent a significant risk for allergic reactions.

3.18.3. Conclusions

The CONTAM Panel notes that the name iso-propanol is rarely used to refer to this substance. It is more normally referred to as isopropanol. The preferred IUPAC name is propan-2-ol. The CONTAM Panel therefore recommends that the entry for the substance in the annex to Commission Directive 96/3/EC[5] to be amended to “Isopropanol (propan-2-ol; isopropyl alcohol; IPA) (CAS No 67-63-0)”.

Isopropanol has a low order of acute toxicity. Isopropanol is not genotoxic and is unlikely to be carcinogenic. Maternal and developmental toxicity have been reported in rats and rabbits following oral administration of high doses. The former EFSA AFC Panel established an ADI of 2.4 mg/kg b.w. per day from the NOAEL of 240 mg/kg b.w. per day for maternal toxicity in rabbits. The CONTAM Panel considers this ADI appropriate. Isopropanol is not allergenic and there are no impurities or reactions products of toxicological concern.

Therefore, the CONTAM Panel concludes that isopropanol meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.19. PROPYL ALCOHOL (propane-1-ol; 1-propanol) (CAS No 71-23-8)

Propyl alcohol is a colorless liquid, miscible with, e.g. water, ethanol, diethyl ether, acetone and benzene. It forms binary azeotropes with most organic solvents and water.

The main production of propyl alcohol starts by hydroformulation of ethylene to propanal, which is hydrogenated to propyl alcohol. Propyl alcohol is also one of the products from Sasol's Fischer-Tropsch process. Coal is gasified to produce synthesis gas which is condensed by a powdered iron-based catalyst to a mixture of hydrocarbons and oxygenates. The alcohol stream is purified by distillation to yield propyl alcohol.

Propyl alcohol occurs in foods, e.g. in wine and alcohol distillates.

3.19.1. Previous evaluations

The SCF evaluated propyl alcohol as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that propyl alcohol was considered by the SCF acceptable as an extraction solvent for food. In the 2003 SCF evaluation of acceptable previous cargoes, propyl alcohol was not further evaluated as it was already considered acceptable (SCF, 2003a).

In 1990, the International Programme on Chemical Safety (IPCS) published an Environmental Health Criteria document on the assessment of propyl alcohol (IPCS/WHO, 1990). The conclusion of this Task Group was that it is unlikely that 1-propanol will pose a serious health risk for the general population under normal exposure conditions.

In the 49th report of JECFA (1998), propyl alcohol was considered as a substance of "*no safety concern*".

In 2008, the EU RAR on propyl alcohol was published within the program of the evaluation and control of the environment and health impact of "existing" substances. In the conclusions it was highlighted that there is a need for limiting the risks of propyl alcohol for several scenarios with short-term and repeated exposures especially for the inhalation exposure situation (ECB, 2008). The toxic effects leading to concern were respiratory depression due to stimulation of the trigeminus nerve, local effects in the airways after repeated exposure and reproductive toxicity concerning fertility as well as developmental toxicity.

3.19.2. Current evaluation

3.19.2.1. Expected impurities

Expected impurities in propyl alcohol are propanal and various oxygenates of similar volatility. At the concentrations resulting from carryover into edible fats and oils when used as subsequent cargoes, they are not expected to be of concern.

3.19.2.2. Reactivity and reaction products

Propyl alcohol may react with lipids by interesterification, but this does not result in products of concern.

3.19.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

Propyl alcohol, a compound highly soluble in water, is rapidly absorbed and distributed throughout the body following ingestion (Abshagen and Rietbrock, 1970; Rietbrock and Abshagen, 1971; IPCS/WHO, 1990). Propyl alcohol is metabolized by alcohol dehydrogenase (ADH) to propionic acid via the aldehyde and may enter the tricarboxylic acid cycle. This oxidation is a rate limiting step of propyl alcohol metabolism (Oerskov, 1950, as cited in IPCS/WHO, 1990). Propionic acid can form a coenzyme A (CoA) conjugate (Rietbrock and Abshagen, 1971). The formation of propionyl-CoA, its metabolism and effects on oxidative metabolism provide a possible explanation for the hepatic effects observed in rats after high oral exposure.

<u>Acute toxicity</u>

Propyl alcohol exhibits low acute toxicity for animals (based on lethality estimates), whether exposed via the dermal, oral, or respiratory route. Oral LD_{50} values for several animal species range between 1 870 and 6 800 mg/kg b.w. For very young rats significantly lower LD_{50} values of 560-660 mg/kg

b.w. were reported (Purchase, 1969, as cited in IPCS/WHO, 1990). The most likely acute effects of 1-propanol in man are alcoholic intoxication and narcosis (IPCS/WHO, 1990).

ECHA has classified propyl alcohol as causing irreversible effects on the eye (category 1; H318) (Regulation (EC) No. 1272/2008[24]).[24,45]

Subacute, subchronic and chronic toxicity studies

Several studies are available in the literature where rats or mice were exposed to repeated doses of propyl-alcohol in the drinking water. No significant adverse effects were reported at doses ranging from 3 000 to 16 000 mg/kg b.w. administered to rats for a maximum of 4 months (Hillbom et al., 1974; Wakabayashi et al., 1984). Oral administration of single doses of 3 000 or 6 000 mg/kg b.w. to rats produced a transient increase in hepatic triglycerides, which was related to the duration of elevated blood concentrations of propyl alcohol. This is likely due to the effect of this alcohol on palminate incorporation into triglycerides (Beauge et al., 1979).

Genotoxicity

Propyl alcohol was negative in mutagenicity assays in bacteria with and without metabolic activation (Hudolei, 1987; Stolzenberg and Hine, 1979). It did not increase the incidence of SCE or micronuclei in mammalian cells *in vitro* (Obe and Ristow, 1977; Lasne et al., 1984, as cited in IPCS/WHO, 1990; von der Hude et al., 1987). A dose-related increased in the inhibition of metabolic cooperation between hamster cells was reported, suggesting that propyl alcohol might behave as a tumor promoter (Chen et al., 1984).

Although the available database is limited, these findings suggest that propyl alcohol is not genotoxic.

Carcinogenicity

A group of 18 rats of both sexes received doses of 240 mg/kg b.w. by gavage twice a week for their lifetime (Gibel et al., 1975, as cited in IPCS/WHO, 1990). Another group of 31 rats received subcutaneous injections of 48 mg/kg b.w. twice a week for their lifetime. It was reported that “nearly all rats” treated with propyl alcohol showed liver damage including necrosis, fibrosis, metaplasia and hyperplasia of the hematopoietic bone marrow parenchyma but the incidence was not reported. This study is inadequate to evaluate the carcinogenicity of propyl alcohol because of the few animals used in each dose group, lack of histological characterization of the lesions and of statistical analysis.

The potential carcinogenicity of propyl alcohol cannot be evaluated on the currently available data.

Developmental and reproductive toxicity

Inhalation exposure to a concentration of 15 220 mg/m^3 caused impaired reproductive performance in male rats, but exposure to 8 610 mg/m^3 did not (Nelson et al., 1988, as cited in IPCS/WHO, 1990). In pregnant rats, 9 001 mg/m^3 (3 659 ppm) was a NOAEL and 14 893 mg/m^3 (6 054 ppm) was a LOAEL for both maternal and developmental toxicity. Behavioural effects were not detected in offsprings whose mothers were exposed during pregnancy to 15 220 mg/m^3, but oral dosing of neonatal rats produced biochemical changes in the brain that were detected 10 days after the last treatment.

One study was performed to address specifically the effects of propyl alcohol on brain development in the neonatal rat (Grant and Samson, 1984). Propyl alcohol was administered via an artificial milk formula through an intragastric catheter for 4 days at doses ranging between 3 000 to 7 800 mg/kg b.w. Biochemical analysis showed the alcohol exposed group had a decreased amount of DNA in all

[45] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=76373&HarmOnly=no?fc=true&lang=en; accessed 8/04/2012.

brain areas examined. Cholesterol levels were decreased in the forebrain and cerebellar samples of the alcohol group, while protein levels were decreased only in the forebrain samples. The results suggest that exposure to propyl alcohol of neonatal rats inhibits brain development.

3.19.2.4. Allergenicity

Available data give no indication that propyl alcohol is an allergen, irritant or an adjuvant. In a mouse sensitization test, propyl alcohol was not found to be a sensitizer (Gad et al., 1986).

3.19.3. Conclusions

The CONTAM Panel notes that the correct IUPAC name for propyl alcohol is propan-1-ol. The CONTAM Panel therefore recommends that the entry for the substance in the annex to Commission Directive 96/3/EC[5] to be amended to "Propyl alcohol (propan-1-ol; 1-propanol) (CAS No 71-23-8)".

Propyl alcohol exhibits low systemic toxicity in animal models. No valid carcinogenicity studies with propyl alcohol are available but the negative results of mutagenicity studies, although limited, do not indicate any concern for carcinogenicity when propyl alcohol is used as a previous cargo. Propyl alcohol is not an allergen. No impurities or reaction products of concern with edible fats and oils are known or expected.

Therefore, the CONTAM Panel concludes that propyl alcohol meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.20. METHYL ISOBUTYL KETONE (4-methyl-2pentanone) (CAS No 108-10-1)

Methyl isobutyl ketone (MIBK) boils at 117 °C. It is moderately soluble in water (1.9 %) and miscible with, e.g. alcohol, benzene and ether.

MIBK is produced from acetone, via aldol condensation to give diacetone alcohol, which dehydrates to mesityl oxide, which is then hydrogenated to give MIBK. The process can be carried out in a single step.

MIBK is primarily used as solvent, e.g. for synthetic resins (including cellulosic, vinyl co-polymers, acrylics, polyesters and epoxies), for inks, coatings and adhesives. MIBK is also applied for dewaxing and deoiling petroleum products, as well as in germicides and fungicides. MIBK is also used for denaturation of ethanol.

3.20.1. Previous evaluations

The SCF evaluated MIBK as a previous cargo in 1996 and considered it acceptable as an extraction solvent for food (SCF, 1997a). As a food contact material, a restriction of 5 mg/kg food was established. In the 2003 SCF evaluation of acceptable previous cargoes, MIBK was not further evaluated as it was already considered acceptable (SCF, 2003a).

In 2003, US-EPA provided a toxicological review of data as scientific support to the IRIS assessment that proposed an RfC of 3 mg/m^3 (approx. 0.85 mg/kg per day) that was developed by dividing the NOAEL for reduced fetal body weight and fetal skeletal variations of 1 026 mg/m^3 (Tyl et al., 1987) by an uncertainty factor of 300 (US-EPA, 2003c). This study is described below.

3.20.2. Current evaluation

3.20.2.1. Expected impurities

No impurities of concern are expected.

3.20.2.2. Reactivity and reaction products

MIBK may form dioxolanes in contact with fats and oils (see Section 3.13.2.). No other reaction products are expected.

3.20.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Available toxicokinetic data indicate that MIBK is readily absorbed into the blood after oral, dermal or inhalation exposure (Hjelm et al., 1990, 1991; Duguay and Plaa, 1995, as cited in US-EPA, 2003c). MIBK is rapidly metabolized in various tissues, including the brain (Granvil et al., 1994; Duguay and Plaa, 1995, as cited in US-EPA, 2003c). The major metabolite is 4-hydroxy-4-methyl-2-pentanone, formed by oxidation, while a minor metabolite is 4-methyl-2-pentanol, formed by reduction. MIBK toxicokinetics, together with mechanism of action data indicating MIBK-induced disruption of nerve membrane integrity (Huang et al., 1993), potentially explain the observation of neurological signs in humans and animals (see below).

Acute toxicity

The oral LD_{50} in rat and mouse was 1 900 and 4 600 mg/kg b.w. of MIBK, respectively (OECD, 1996).

Several occupational studies reported sensory irritation and transient neurological symptoms that were exposure-related but no alteration of performance in neurobehavioral tests (US-EPA, 2003c).

ECHA has classified MIBK as follows: may cause respiratory irritation (category STOT SE 3; H335); irritating to eyes category 2; H315 (Regulation (EC) No. 1272/2008[24]).[46]

Subacute, subchronic and chronic toxicity studies

In subchronic oral exposure studies in animals, MIBK induced effects associated with the liver, kidney, blood, and nervous system (US-EPA, 2003c).

Alteration of a variety of clinical blood and urine markers and changes in organ weight (mostly liver and kidney) were reported at doses of 250 up to 1 040 mg/kg b.w. per day, however there was no clear dose-response relationship and their severity (and therefore their relevance to effects in humans) was uncertain. No LOAEL was identified in either the subchronic gavage or subchronic drinking water study (Carnegie-Mellon Institute 1977a, b, as cited by US-EPA, 2003c; MAI, 1986). Similarly, a substantial subchronic inhalation database identifies MIBK-induced effects associated with the following tissues: liver, kidney, blood and nervous system.

Genotoxicity

A range of genotoxicity assays summarized in O'Donoghue et al. (1988, as cited in US-EPA, 2003c) yielded mostly negative responses. In particular MIBK was negative in *S. typhimurium* either in the presence or absence of Aroclor 1254-induced rat liver microsomal enzymatic activation (MAI, 1984a, as cited by US-EPA, 2003c). MIBK was also negative in the L5178Y TK+/- mouse lymphoma mutagenesis assay in the presence of S-9 but the results were equivocal in the absence of S-9 (increase in mutation frequency at some doses but lack of a dose-response relationship) (MAI, 1984b, as cited by US-EPA, 2003c). MIBK was negative in the UDS assay in rat primary hepatocytes (MAI, 1984c, as cited by US-EPA, 2003c) and in the micronucleus cytogenetic assay in mice administered MIBK *i.p.* at 0.73 mL/kg (MAI, 1984d, as cited by US-EPA, 2003c). MIBK induced a stastically significant

[46] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=71683&HarmOnly=no?fc=true&lang=en (accessed 08/04/2012).

increased in the frequency of morphological transformations in BALB/3T3 mouse embryo cells at the highest exposure level and only in the absence of exogenous metabolic activation (MAI, 1984e, as cited by US-EPA, 2003c) but was negative in a second cell transformation assay in both the presence and absence of S-9 (MAI, 1984e, as cited by US-EPA, 2003c). Overall the CONTAM Panel concludes that MIBK is not of concern for genotoxicity.

Carcinogenicity

No studies in animals of chronic oral toxicity or of carcinogenicity following oral exposure could be identified

Recent studies on inhalation carcinogenicity in rats and mice provide some evidence of the carcinogenic activity of MIBK (NTP, 2007, Stout et al., 2008). Under the conditions of these 2-year studies, the occurrence of malignant and benign proliferative lesions in the kidney of male F344/N rats and increased incidences of chronic nephropathy in all exposure groups of male and female rats exposed to MIBK (450, 900 or 1 800 ppm by inhalation, 6 hours per day, 5 days per week) indicated that the kidney is the target organ. Although chronic nephropathy is one of the most commonly recognized spontaneous lesions in the rat (Seely et al., 2002), this condition was clearly exacerbated by exposure to MIBK. In the NTP report (NTP, 2007) it was concluded that there is some evidence of carcinogenic activity of MIBK in male F344/N rats based on increased incidences of renal tubule neoplasms (adenomas and carcinomas) at 1 800 ppm whereas the evidence in female rats is equivocal (marginal increase in the 1 800 ppm group). Increased incidences of mononuclear cell leukemia in male rats were also reported after exposure to 1 800 ppm MIBK. There was some evidence of carcinogenic activity of MIBK in male and female B6C3F1 mice based on increased incidences of liver neoplasms (adenomas and carcinomas) at 1 800 ppm. Exposure to MIBK resulted also in non-neoplastic lesions of the kidney characteristic of α2u-globulin accumulation in male rats and nephropathy in female rats.

MIBK has been recently classified by IARC (2012, in preparation) as possibly carcinogenic to humans (2B).

In conclusion, there is some evidence of carcinogenic activity of MIBK in two animal species with a significant increase in the combined incidence of benign and malignant tumors at the highest dose tested. The lack of mutagenic/clastogenic effects in a variety of *in vitro* and *in vivo* genotoxicity assays suggests that MIBK is a non-genotoxic carcinogen.

Developmental and reproductive toxicity

No oral multi-generation reproductive, or oral developmental toxicity studies in animals are available.

In inhalation studies with mice, maternal toxicity (body and organ weigh changes) and fetotoxicity (body weight decrease and delayed ossification) were observed at 3 000 ppm inhalation on GD6 through GD15. A NOAEL of 1 000 ppm for both maternal and offspring toxicity was identified (Tyl et al., 1987). In another inhalation two-generation reproductive toxicity study with rats the NOAEL for parental systemic effects was 1 000 ppm, based on transiently decreased body weight and food consumption; for reproductive effects, 2 000 ppm, the highest concentration tested; and for neonatal toxicity, 1 000 ppm (based on acute central nervous system (CNS) depressive effects) (Nemec et al., 2004).

3.20.2.4. Allergenicity

Available data give no indication that methyl isobutyl ketone is an allergen, irritant or an adjuvant.

3.20.3. Conclusions

In subchronic oral exposure studies in animals, MIBK induced effects associated with the liver, kidney, blood, and nervous system, however there was no clear dose-response relationship and their severity and relevance to effects in humans was uncertain. Recent studies on inhalation carcinogenicity in rats and mice provided some evidence of the carcinogenic activity of MIBK in kidney and liver, respectively, at the highest dose tested. However, MIBK was not genotoxic in a variety of *in vitro* and *in vivo* assays suggesting that it is not carcinogenic in animals by a genotoxic mechanism. MIBK is not an allergen. No impurities of concern are expected. MIBK may react with fats and oils and form dioxolanes. The toxicological profile of 1,3-dioxolane, and by analogy that of other dioxolanes, is such that there would be no toxicological concern from the use of MIBK as a previous cargo to edible fats and oils from any such reaction products. On the basis of the available data there are no toxicological concerns regarding the use of MIBK as a previous cargo.

The CONTAM Panel therefore concluded that methyl isobutyl ketone meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.21. METHYL ETHYL KETONE (2-butanone) (CAS No 78-93-3)

Methyl ethyl ketone (MEK) is a clear, colourless, volatile, highly flammable liquid with an acetone-like odour. It is stable under normal conditions, but can form peroxides which may be explosive. It is soluble in water (27.5 %), miscible with alcohol, ether and benzene, and forms azeotropes with water and many organic solvents.

MEK is produced mainly by dehydrogenation of *sec*-butyl alcohol. In the USA, it is produced by oxidation of *sec*-butyl alcohol vapour at 400 to 550 °C with a zinc oxide catalyst (Liepins et al., 1977, as cited by IPCS/WHO, 1993). In Europe, *sec*-butyl alcohol is dehydrogenated over Rainey nickel or copper chromite catalyst at 150 °C (Papa and Sherman, 1978, as cited by IPCS/WHO, 1993). MEK is also produced by the oxidation of *n*-butane, either as the main product or as a by-product in the manufacture of acetic acid (Liepins et al., 1977; Papa and Sherman, 1978, as cited by IPCS/WHO, 1993).

MEK is an important component for organic synthesis, and used as a solvent, e.g. in the surface coating industry and for synthetic resins.

3.21.1. Previous evaluations

The SCF evaluated MEK as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that MEK was considered by SCF acceptable as an extraction solvent for food. In the 2003 SCF evaluation of acceptable previous cargoes, MEK was not further evaluated as it was already considered acceptable (SCF, 2003a).

In 1992, the Agency for Toxic Substances and Disease Registry (ATSDR) published a review of the human health effects that may result from exposure to MEK. MEK was selected because it was found in a large number of sites identified by US-EPA on its National Priorities List. No minimum risk levels were established due to the lack of sufficient information.

In 1993, IPCS published the environmental health criteria for the assessment of MEK (IPCS/WHO, 1993). It was concluded that "*MEK on its own appears a relatively safe organic solvent*".

In 2003, US-EPA provided a toxicological review of data as scientific support to the IRIS assessment. In the previous IRIS assessment from 1992, an RfC of 1 mg/m^3 was established based on a NOAEL of 2 978 mg/m^3 for decreased fetal weight in MEK-exposed mice (Schwetz et al., 1991). In the 2003 assessment (US-EPA, 2003d), benchmark dose models were employed to derive the point of departure for the RfC, yielding an RfC of 5 mg/m^3. Moreover, a reference dose (RfD) of 0.6 mg/kg b.w. per day was established from a study on 2-butanol in drinking water (Cox et al., 1975) because this was the only available oral study. This study is described below.

3.21.2. Current evaluation

3.21.2.1. Expected impurities

No impurities of concern are expected.

3.21.2.2. Reactivity and reaction products

MEK may form dioxolanes in contact with fats and oils (see Section 3.13.2.). No other reaction products are expected.

3.21.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Absorption of MEK is rapid via inhalation and ingestion. After absorption MEK is expected to distribute quite uniformly to the various soft tissue compartments but it is not expected to accumulate (Perbellini et al., 1984; Lowry, 1987, as cited in ATSDR, 1992). MEK can cross the placenta (Dowty et al., 1976, as cited in IPCS/WHO, 1993). MEK occurs naturally in the human body as a metabolite of α-methylacetoacetic acid (Browning, 1965, as cited in ATSDR, 1992), as a product of isoleucine catabolism (Tsao and Pfeiffer, 1957, as cited in IPCS/WHO, 1993; Przyrembel et al., 1979) and as a metabolite of natural gases (Tsukamoto et al., 1985, as cited in IPCS/WHO, 1993). MEK can follow two main metabolic pathways, a reductive and an oxidative pathway (Brady et al., 1989, as cited in US-EPA, 2003d; Traiger et al., 1989, as cited in ATSDR, 1992). All MEK metabolites can be further metabolized to CO_2 and H_2O_2 (Liira et al., 1988) or converted to O-glucuronides and O-sulfates before elimination (DiVincenzo et al., 1976, as cited in US-EPA, 2003d).

Acute toxicity

Accidental ingestion of an unknown dose of MEK by a woman produced unconsciousness, hyperventilation, severe metabolic acidosis, decrease in blood pressure and increase in pulse rate (Kopelman and Kalfayan, 1983, as cited in IPCS/WHO, 1993). Other effects reported from acute inhalation exposure in humans include irritation to the eyes, nose, and throat, central nervous system depression, headache, and nausea (as cited in IPCS/WHO, 1993; ATSDR, 1992). Dermatitis has been reported in humans following dermal exposure to MEK.

Tests involving acute oral exposure of rats and mice have shown LD_{50}s ranging between 2 600-5 400 mg/kg b.w. for rats and 3 140-4 044 mg/kg b.w. for mice (ATSDR 1992; IPCS/WHO, 1993).

ECHA has classified MEK as irritating to eyes category 2; H319 (Regulation (EC) No. 1272/2008[24]).[47]

Subacute, subchronic and chronic toxicity studies

Most studies of toxicity have been by inhalation and there no adequate data for using route-to-route extrapolation from inhalation studies to establish oral health based guidance values.

In general, the available human data do not produce a definitive picture of the possible adverse effects of long-term exposure to MEK. No increased risk of neurologic effects or irritation was reported after short-term inhalation exposure (4 hours) to MEK at or near 200 ppm (590 mg/m^3) (Dick et al., 1984, 1988, 1989, 1992, as cited in US-EPA, 2003d). The lack of a persistent neurotoxic effect of MEK exposure is also supported by animal studies that have focused on the possible neurotoxicity of MEK, including the development of peripheral and central nerve fiber degeneration (Saida et al., 1976;

[47] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=79649&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

Cavender et al., 1983; Takeuchi et al., 1983, as cited in US-EPA, 2003d). In experimental animals, the longest exposure study available for characterizing the health effects of repeated exposure to MEK is the 90-day inhalation study by Cavender et al. (1983), wherein no toxicity was observed with MEK at concentrations as high as 2 518 ppm (7 430 mg/m³).

Genotoxicity

MEK was not mutagenic by conventional short-term mutation assays in bacteria and mammalian cells with or without metabolic activation, or in the BALB/3T3 cell transformation assay (cited in ATSDR 1992; US-EPA, 2003d). MEK did not induce UDS in rat primary hepatocytes (O'Donoghue et al., 1988). No induction of micronuclei was found in the erythrocytes of mice (O'Donoghue et al., 1988) or hamsters (IPCS/WHO, 1993) after *i.p.* injection with MEK. The only evidence of mutagenicity was mitotic chromosome loss at a high concentration in a study on aneuploidy in yeast (Zimmermann et al., 1985).

Carcinogenicity

No studies were available on the carcinogenicity of MEK by the oral or inhalation routes. In a dermal carcinogenicity study, skin tumours were not reported from methyl ethyl ketone exposure (Horton et al., 1965, as cited in US-EPA, 2003d). US-EPA has classified MEK as Group D, not classifiable as to human carcinogenicity, based on a lack of data concerning carcinogenicity in humans and animals.

Overall according to US-EPA "*data are inadequate for an assessment of human carcinogenic potential*" of MEK because studies of cancer in humans chronically exposed to MEK are inconclusive, MEK has not been tested for carcinogenicity in animals by the oral or inhalation routes, and the majority of short-term genotoxicity testing of MEK has demonstrated no activity.

Developmental and reproductive toxicity

There are no studies available in the literature on the reproductive or developmental toxicity of MEK by the oral route. A two-generation reproductive and developmental toxicity study in Wistar rats exposed to 2-butanol, a metabolic precursor of MEK, in drinking water, reported no clear reproductive effects, but found body weight deficits in offspring and kidney histopathologic lesions in adult male rats at estimated dose levels of approximately 3 000 mg/kg per day (Cox et al., 1975, as cited by US-EPA, 2003d). The offspring body weight reduction was used by US-EPA to establish a RfD of 0.6 mg/kg b.w. per day for MEK (US-EPA, 2003d) by using benchmark dose modelling. The use of this metabolite to establish an RfD for MEK is justified by pharmacokinetics and toxicological data. In addition, several developmental toxicity studies in rodents (exposed by inhalation 6-7 hours per day during gestation) reported reduced fetal weight and increased skeletal variations at exposure levels of approximately 1 000 ppm (3 000 mg/m³) MEK (Schwetz et al., 1974, 1991; Deacon et al., 1981, as cited in US-EPA, 2003d). Available data consistently identify developmental effects in animals exposed to relatively high levels of MEK.

3.21.2.4. Allergenicity

Available data give no indication that methyl ethyl ketone is an allergen or an adjuvant.

3.21.3. Conclusions

No animal long term oral toxicity studies are available for MEK. MEK has not been tested for carcinogenicity by the oral or inhalation routes, but the majority of *in vitro* and *in vivo* genotoxicity tests have demonstrated no activity. MEK is not an allergen. Although the toxicological database is limited, based on the available data, there are no toxicological concerns regarding the use of MEK as a previous cargo. No impurities of concern are expected. MEK may react with fats and oils and form dioxolanes. The toxicological profile of 1,3-dioxolane, and by analogy that of other dioxolanes, is such

that there would be no toxicological concern from the use of MEK as a previous cargo to edible fats and oils from any such reaction products.

Therefore the CONTAM Panel concludes that methyl ethyl ketone meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.22. *n*-PROPYL ACETATE (CAS No 109-60-4)

n-Propyl acetate is a liquid, boiling at 102 °C, with limited solubility in water (about 2 %).

n-Propyl acetate is produced by esterification of acetic acid with *n*-propyl alcohol in the presence of sulphuric acid.

n-Propyl acetate is primarily used as a solvent for coatings, adhesives and inks.

3.22.1. Previous evaluations

The SCF evaluated *n*-propyl acetate as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that *n*-propyl acetate is generally used as a flavouring in food and is on the FEMA (Flavor and Extract Manufacturers Association of the US) and GRAS lists. In the 2003 SCF evaluation of acceptable previous cargoes, *n*-propyl acetate was not further evaluated as it was already considered acceptable (SCF, 2003a).

JECFA has evaluated *n*-propyl acetate as a flavouring substance and concluded that the substance posed no safety concern when used at the estimated levels of intake (JECFA, 1999) in its evaluation of esters of aliphatic acyclic primary alcohols. *n*-Propyl acetate is included in the EU register of flavouring substances used in or on foodstuffs (Commission Decision 1999/217/EC[48]) and has been evaluated by EFSA as a supporting substance in its evaluation of branched- and straight-chain aliphatic saturated primary alcohols and related esters of primary alcohols and straight-chain carboxylic acids and one straight-chain aldehyde from chemical groups 1 and 2 in FGE.02Rev 1 (EFSA, 2008b).

n-Propyl acetate has been evaluated under the OECD SIDS programme on High Production Volume (HPV) chemicals (OECD, 2008b). Overall, it was concluded that *n*-propyl acetate may present a hazard for human health (skin and eye irritation and potential reproductive/developmental toxicity at high doses).

3.22.2. Current evaluation

3.22.2.1. Expected impurities

n-Propyl acetate is produced from innocuous substances and expected to be without impurities of concern.

3.22.2.2. Reactivity and reaction products

n-Propyl acetate is not expected to react with edible fats and oils to products which could be of concern.

3.22.2.3. Toxicological profile

The following profile is limited to toxicological findings following oral administration of *n*-propyl acetate only, studies involving other routes of administration were judged to have less relevance to the

[48] Commission Decision of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96 of the European Parliament and of the council of 28 October 1996. OJ L 84, 27.3.1999, p. 1-74.

assessment of *n*-propyl acetate as a contaminant of fats and oils following transport as a previous cargo.

Absorption, distribution, metabolism and elimination

Specific data on the toxicokinetics of propyl acetate following oral administration are lacking. However, based on information on structurally similar compounds such as ethyl acetate and butyl acetate and on its physicochemical properties, it can be assumed that it will be absorbed rapidly from the GI tract, either as the intact molecule or as its hydrolysis products propyl alcohol and acetic acid (acetate) following the action of GI esterases. Any non-hydrolysed propyl acetate entering the systemic circulation following absorption will be hydrolysed similarly by plasma and hepatic esterases. The hydrolysis product propyl alcohol will be metabolised by ADH to propionic acid, which will enter the endogenous pool of such compounds and be broken down further via the carboxylic acid cycle (see also Section 3.18.). Acetate resulting from the hydrolysis of propyl acetate will undergo a similar fate.

Acute toxicity

n-Propyl acetate is of low acute toxicity, with reported LD_{50} values of 8 700 and 9 370 mg/kg b.w. in rats (OECD, 2008b), 8 300 mg/kg b.w. in mice[49] and 6 640 mg/kg b.w. in rabbits (Clayton and Clayton, 1993-94). At doses approaching the LD_{50}, propyl acetate produces narcosis and generalised CNS depression. Propyl acetate is mildly irritating to the skin, and causes mild, reversible corneal injury in the eye (OECD, 2008b).

ECHA has classified *n*-propyl acetate as irritating to eyes category 2; H319 (Regulation (EC) No. 1272/2008[24]).[50]

Subacute, subchronic and chronic toxicity studies

No subacute, subchronic and chronic toxicity studies are available on *n*-propyl acetate. Data on the structural analogue ethyl acetate and the metabolite *n*-propyl alcohol may however be used in a read-across approach to assess the likely toxicity of *n*-propyl acetate following repeated ingestion.

In a 90-day oral gavage study with ethyl acetate using doses of up to 3 600 mg/kg b.w. per day, a NOAEL of 900 mg/kg b.w. per day was identified, higher dose levels causing a decrease in body and organ weights in male rats (US-EPA, 1988). Ethyl acetate administered to rats in drinking water at a dose level corresponding to 4 mg/kg b.w. per day for 56 weeks produced no adverse effects at this dose (JECFA, 1997). Ethyl and butyl acetates have been evaluated for neurotoxicity in rats following repeat dose exposure (up to 90 days) by the inhalation route. No neurotoxic effects were observed, transient neurological signs were seen only at levels that were narcotic (OECD, 2008b). Rats exposed to high levels of *n*-propyl alcohol (> 10 g/L) in drinking water for up to 4 months showed no treatment-related effects on food consumption, body weight gain, and liver histopathology (a more detailed description of the subacute, subchronic and chronic toxicity of *n*-propyl alcohol is provided in Section 3.18.).

Genotoxicity

n-Propyl acetate was negative in a bacterial mutagenicity (Ames) test, with and without metabolic activation (San and Schadly, 1989). Induction of aneuploidy has been reported to occur in *Saccharomyces cervisiae* at cytotoxic levels of propyl acetate (Zimmermann et al., 1985) but it can be concluded that this result is not indicative of a genotoxic interaction with DNA. The genotoxicity of *n*-

[49] RTECS Registry of Toxic Substances on line: http://www.cdc.gov/niosh/rtecs/default.html

[50] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=113301&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

propyl acetate can be further assessed by reference to negative results with the structural analogues ethyl acetate and *n*-butyl acetate and the metabolite *n*-propyl alcohol, which have been tested in chromosomal aberration assays, *in vitro* mammalian cell gene mutation tests and other genotoxicity assays, as reported by OECD (2008b), and also, for ethyl acetate, by EFSA (2011a) and in Section 3.18. for *n*-propyl alcohol. It can be concluded that there is no concern regarding the genotoxicity of *n*-propyl acetate.

Carcinogenicity

No data were identified on the carcinogenicity of *n*-propyl acetate. There are also no valid data on the carcinogenicity of *n*-propyl alcohol or the structural analogues ethyl or butyl acetate.

Developmental and reproductive toxicity

No data were identified on the developmental or reproductive toxicity of *n*-propyl acetate. Based on data for the structural analogue butyl acetate and the metabolite *n*-propyl alcohol, OECD concluded that *n*-propyl acetate may have the potential for reproductive and developmental toxicity at high doses (OECD, 2008b). The developmental and reproductive toxicity of *n*-propyl alcohol is described in more detail in Section 3.18. of this opinion. No data were identified for ethyl acetate (OECD, 2002a). The CONTAM Panel concluded that there is no concern regarding the developmental or reproductive toxicity of *n*-propyl acetate at the anticipated levels in food resulting from transport of the substance as a previous cargo to edible fats and oils.

3.22.2.4. Allergenicity

Available data give no indication that *n*-propyl acetate is an allergen or an adjuvant.

3.22.3. Conclusions

No ADI or other toxicological reference value has been established for *n*-propyl acetate. The toxicological database has several data gaps (subacute, subchronic and chronic toxicity, carcinogenicity, reproductive toxicity). It can be concluded from data on the structural analogue ethyl acetate and the hydrolysis products *n*-propyl alcohol and acetic acid, that *n*-propyl acetate is of low concern for these endpoints, with the exception of carcinogenicity, where there are also no data on the structurally similar compounds. The limited data available did not demonstrate any evidence of genotoxicity and there is no concern regarding allergenicity. The CONTAM Panel considers that the available information was sufficient to conclude that the risk from short-term exposure to *n*-propyl acetate when used as a previous cargo would not give raise to any toxicological concern. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that *n*-propyl acetate meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.23. AMMONIUM HYDROXIDE (ammonium hydrate; ammonia solution; aqua ammonia) (CAS No 1336-21-6)

Ammonium hydroxide is a solution of ammonia in water. Commercial “concentrated” ammonium hydroxide solutions contain 25 % ammonia.

Ammonia is produced from nitrogen and hydrogen under high pressure and temperature (Haber-Bosch). It is primarily used for the production of fertilizer (such as ammonium nitrate), but also for many other chemicals.

3.23.1. Previous evaluations

The SCF evaluated ammonium hydroxide as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that ammonium hydroxide is an authorised food additive (E527) with an ADI "not specified" (SCF, 1991). In the 2003 SCF evaluation of acceptable previous cargoes, ammonium hydroxide was not further evaluated as it was already considered acceptable (SCF, 2003a).

The SCF evaluated ammonium, sodium, potassium, calcium and magnesium cations in combination with a series of anions including hydroxide (SCF, 1991). They concluded that these cations and anions constitute the major electrolytes present in all biological materials and occur naturally in foodstuffs. The SCF therefore considered that "*no safety problems are likely to arise from their use in food, provided the contributions from food intake do not disturb the homeostatic mechanisms controlling the electrolyte balance of the body.*" and based their ADI "not specified" for ammonium hydroxide on these considerations (SCF, 1991).

JECFA has also evaluated ammonia solution (ammonium hydroxide) as a food additive (acidity regulator) and established an ADI "not limited" (JECFA, 1966).

Ammonium hydroxide (ammonia solution) has been evaluated under the OECD SIDS programme on High Production Volume (HPV) chemicals as part of the ammonia category (OECD, 2007). The other substances in the category were ammonia, ammonium thiosulfate and ammonium phosphate sulphate, Overall, OECD concluded that ammonia solution and other members of the ammonia category are currently of low priority for further work.

Ammonia is included in the EU register of flavouring substances used in or on foodstuffs (Commission Decision 1999/217/EC[51]).

Ammonium hydroxide (substance number 413) and ammonia (substance number 510) are both in the list of substances authorised for use in food contact materials[19] without a limit (other than the generic limit of 60 mg/kg food).

3.23.2. Current evaluation

3.23.2.1. Expected impurities

Ammonium hydroxide is not expected to contain impurities of concern.

3.23.2.2. Reactivity and reaction products

Ammonium hydroxide or ammonia reacts with many functional groups and could also react with components in edible fats and oils. They are far less reactive, however, when protonated to ammonium salts. As the small amounts of ammonia transferred into edible fats and oils from previous cargoes are converted virtually completely to ammonium salts, no formation of derivatives of concern is expected.

3.23.2.3. Toxicological profile

When added in small amounts (up to 100 mg/kg) to edible fats and oils, ammonium hydroxide is neutralized by free fatty acids to ammonium salts: even fully refined edible fats or oils of low acidity contain around 1 000 mg/kg free fatty acids, i.e. protonate up to 25 mg/kg ammonia from a previous cargo even if the vessel was not cleaned at all. In an edible oil at approximately neutral pH, more than 99.9 % of ammonia is converted to ammonium salts.

[51] Commission Decision of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council of 28 October 1996 (1999/217/EC). OJ L 84, 27.3.1999, p. 1-137.

Absorption, distribution, metabolism and elimination

Following oral administration, ammonium hydroxide will dissociate in the acid milieu of the stomach into ammonium and hydroxide ions, which are directly absorbed. Ammonium ion is then converted to urea in the liver followed by excretion of urea in urine. Blood ammonium levels are generally less than 50 µmol/L and an increase to 100-200 µmol/L can result in loss of consciousness and convulsions. However this is very unlikely at the anticipated levels in food resulting from transport of the substance as a previous cargo.

Acute toxicity

An LD_{50} of 350 mg/kg has been reported for ammonia solution (ammonium hydroxide) in the rat (Smyth et al., 1941, as cited in OECD, 2007). Other ammonium salts are reported to have acute oral LD_{50}'s in the range of 1 950 to > 2 000 mg/kg b.w. in rats (OECD, 2007). Ammonia solution (ammonium hydroxide) is a strong irritant/corrosive to rabbit skin and rabbit eye and also in humans due to the high pH of the solution (OECD, 2007).

Ammonium hydroxide is classified as skin corrosive category 1B; H314 (Regulation (EC) No. 1272/2008[24]) at concentrations above 5 %. At concentrations between 1 % and 5 % it is classified as a skin irritant (category 2; H315). It is classified for irreversible effects on the eye (category 1; H318) at concentrations above 3 %, and as irritating to eyes (category 2; H319) at concentrations > 1 % but < 5 %. It is also classified as may cause respiratory irritation category STOT SE 3; H335, at concentrations ≥ 5 %.[52]

Subacute, subchronic and chronic toxicity studies

No data were identified on the subacute, subchronic or chronic toxicity of ammonium hydroxide. OECD (2007) reported that ammonium sulfate administered to rats at dietary levels of up to 1 975 mg/kg b.w. per day for 13 weeks did not have any effect on body weight, food consumption or hematological and clinical parameters, although increased kidney weights (in males and females) and increased liver weights (females) were observed at 1 975 mg/kg b.w. per day without associated histopathological changes. Males at this dose level also had diarrhoea. OECD concluded that the NOAEL of ammonium sulphate was 1 975 mg/kg b.w. per day for females and 886 mg/kg b.w. per day for males (OECD, 2007).

Genotoxicity

No specific data were identified on the genotoxicity of ammonium hydroxide. OECD report that ammonia, ammonium thiosulfate, ammonium sulfate and diammonium phosphate showed no evidence of genotoxicity in bacterial gene mutation assays and did not induce chromosomal aberrations in *in vitro* tests (OECD, 2007). Ammonium chloride was negative in an *in vivo* mouse micronucleus study, when administered to mice at single doses of 0, 62.5, 125, 250 or 500 mg/kg *i.p.* or four injections of 31.3, 62.5, 125 or 250 mg/kg *i.p.* within 24 hours (OECD, 2007). The CONTAM Panel concludes that ammonium hydroxide is unlikely to be genotoxic.

Carcinogenicity

Forty male and forty female Swiss mice administered ammonium hydroxide as a 0.1 % solution in drinking water over their entire life span did not show any evidence of a carcinogenic effect (Toth, 1972). The CONTAM Panel noted the limited validity of this study.

[52] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=128870&HarmOnly=no?fc=true&lang=en (accessed 08/0/2012).

Developmental and reproductive toxicity

No data on the developmental and reproductive toxicity of ammonium hydroxide were identified. OECD (2007) report the results of a combined repeated dose/reproductive/developmental screening study in rats given 0, 250, 750 or 1 500 mg/kg b.w. diammonium phosphate by oral gavage for 35 days (OECD, 2007). Increased alkaline phosphatase and decreased total protein in blood were reported at 750 and 1 500 mg/kg b.w. per day. Mating performance and fertility were unaffected by treatment, and parental treatment had no apparent effect on the offspring to day 4 of age. A NOAEL of 250 mg/kg b.w. per day was identified for systemic toxicity based on the clinical chemistry changes, with a NOAEL of 1 500 mg/kg b.w. per day for reproductive endpoints.

3.23.2.4. Allergenicity

Available data give no indication that ammonium hydroxide is an allergen or an adjuvant at levels expected from previous cargoes.

3.23.3. Conclusions

JECFA has established an ADI "not limited" and the SCF has established an ADI "not specified" for ammonium hydroxide, which the CONTAM Panel considers appropriate. Ammonium hydroxide is not genotoxic or allergenic. Ammonium hydroxide is only toxic when it is present at sufficient concentration that it changes the local OH^- concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to ammonium hydroxide as a previous cargo do not give rise to any toxicological concern. Exposure to small amounts of ammonium hydroxide locally may cause irritation to the skin or eyes. However, the maximum potential levels of ammonium hydroxide arising in fats or oils following its transport as a previous cargo would be of no concern. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that ammonium hydroxide meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.24. LIMONENE (dipentene) (CAS No 138-86-3)

Limonene or diterpene is a liquid boiling at about 177 °C. It is a cyclic hydrocarbon of 10 carbon atoms with two double bonds. It is virtually insoluble in water.

Limonene is chiral and exists as two enantiomers: (*R*)-(+)-limonene (*d*-limonene: CAS No 5989-27-5) and (*S*)-(–)-limonene (*l*-limonene: CAS No 5989-54-8). The (*R*)-(+)-limonene is the enantiomer predominantly occurring in nature, being, e.g. the principal component of orange oil. The CAS No of the entry, 138-86-3, refers to the molecules of unspecified chirality, including the racemate, and is also called diterpene.

Commercial limonene is obtained in large amounts from the skins of citrus fruits in the production of juices by means of centrifugal separation or steam distillation.

Limonene is used as a component of flavours and perfumes, but also to produce other flavour compounds. It is also used in cleaning products and coatings.

3.24.1. Previous evaluations

The SCF evaluated limonene as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that limonene is generally used as a flavouring for food, with ADI "not specified" (JECFA, 1993). In the 2003 SCF evaluation of acceptable previous cargoes, limonene was not further evaluated as it was already considered acceptable (SCF, 2003a).

JECFA evaluated *d*-limonene, the isomer used as a flavouring, at its 39th meeting and established an ADI of 0-1.5 mg/kg b.w. (JECFA, 1992). JECFA re-evaluated this ADI at its 41st meeting and replaced it with an ADI "not specified" (JECFA, 1993). JECFA reconsidered *d*-limonene at its 63rd meeting, as part of its evaluation of 20 aliphatic and alicyclic hydrocarbons, and concluded that *d*-limonene would not pose a safety concern at the estimated current intakes of 660 mg/kg b.w. per day in Europe and 210 mg/kg b.w. per day in the USA (JECFA, 2005).

The EFSA has evaluated limonene and *l*-limonene as flavouring substances, together with *d*-limonene as a supporting substance and concluded that they would present no safety concern at their estimated levels of intake based on the Maximised Survey-derived Daily Intake (MSDI) approach (EFSA, 2011c).

The International Agency for Research on Cancer (IARC) has evaluated the carcinogenicity of *d*-limonene and concluded that it was not classifiable as to its carcinogenicity to humans (IARC, 1999b).

d-Limonene has also been evaluated by the WHO, with the conclusion that *d*-limonene was of "*fairly low toxicity*", with the exception of its irritant and sensitising properties (WHO, 1998). IPCS established a tolerable intake of 0.1 mg/kg b.w. per day for *d*-limonene based on a NOEL for hepatic effects of 10 mg/kg b.w. per day in a 13-week oral gavage study in rats (WHO, 1998).

3.24.2. Current evaluation

3.24.2.1. Expected impurities

Limonene is a natural product obtained by physical processes. As there may be no purification, it may contain elevated proportions of other natural components, but these are not expected to be of concern.

Limonene may also contain pesticides, but the dilution involved in the carryover from previous cargoes will bring the concentrations to low levels: limonene may reconcentrate pesticides present on the skin of, e.g. oranges to above 10 mg/kg, but the dilution by at least a factor of 10 000 that would occur in a subsequent cargo of in edible fats or oils will reduce the concentration below the level of 0.01 mg/kg applied for unauthorized uses of pesticides.

3.24.2.2. Reactivity and reaction products

Limonene, an unsaturated hydrocarbon, is not expected to react with components of edible fats oils. It is, however, an unstable substance: it may isomerize or be oxidized, resulting in compounds many of which are natural flavour substances. These products are also not expected to be of concern.

3.24.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

As reported by WHO (1998), following oral administration *d*-limonene is rapidly and almost completely absorbed from the GI tract, both in animals and in humans (Igimi et al., 1974; Kodama et al., 1976). Highest levels were found in serum 2 hours after oral administration, with high levels also detected in liver and kidney (Igimi et al., 1974). Following absorption, *d*-limonene is distributed widely throughout body tissues and is rapidly metabolised in the liver, with almost complete clearance 48 hours after administration, mainly in urine. A major route of metabolism of *d* -limonene in both the rat and in humans is via allylic oxidation to form *d*-limonene-8,9-epoxide and subsequent hydrolysis to *d*-limonene-8,9-diol (Kodama et al., 1976). Kodama and co-workers reported that about 25-30 % of an oral dose of *d*-limonene in humans was excreted in urine as *d*-limonene-8,9-diol and its glucuronide, while about 7-11 % was excreted as perillic acid (4-(1-methylethenyl)-1-cyclohexene-1-carboxylic acid), perillic acid 8,9-diol and other metabolites (Kodama et al., 1976).

In another study, perillic acid was reported to be the principal metabolite in plasma in both rats and humans (Crowell et al., 1992). Minor metabolites include *d*-limonene-1,2-diol and metabolites formed by ring hydroxylation and oxidation of the methyl group of the molecule (Kodama et al., 1976). *D*-Limonene and/or one or more of its metabolites bind to α2u-globulin in the male rat kidney, causing accumulation of the protein in the kidney and ultimately nephrotoxicity (Lehman-McKeeman et al., 1989; Lehman-McKeeman and Caudill, 1992.)

Acute toxicity

d-Limonene is of low toxicity following oral administration, with LD_{50}'s of approximately 5 000 mg/kg b.w. in the rat and 6 000 mg/kg b.w. in the mouse (WHO, 1998). In animal studies it was found to be irritant to both skin and eyes (WHO, 1998)

ECHA has classified *d*-limonene as a skin irritant category 2; H315. It has also been classified as a skin sensitiser category 1 (H317; may cause an allergic skin reaction) (Regulation (EC) No. 1272/2008[24]).[53]

Subacute, subchronic and chronic toxicity studies

As reported by both JECFA (2005) and WHO (1998), short term (16-day) oral administration of *d*-limonene at dose levels of up to 6 600 mg/kg b.w. per day resulted in mortality in both rats and mice at doses of approximately 2 000 mg/kg b.w. per day and higher (NTP, 1990).

Other authors have reported increases in liver and kidney weight in rats administered *d*-limonene orally at doses of up to 300 mg/kg b.w. per day (Kanerva et al., 1987) and up to 2 770 mg/kg b.w. per day (Tsuji et al., 1975), for periods of up to 13 weeks, together with the development of nephropathy in male rats only.

In a 13-week study designed to investigate the renal effects of *d*-limonene, the substance was administered by gavage as dose levels of 0, 2, 5, 10, 30 and 75 mg/kg b.w. per day) to groups of 10 male rats, 5 days per week for 13 weeks (Webb et al., 1989). Treatment-related effects were seen in the liver and kidney, with organ weight relative to body weight being increased in a dose-dependent manner at 30 and 75 mg/kg b.w. per day, with statistical significance reached only at the highest dose. Increases in kidney weight were associated with the development of nephropathy, assessed histologically, in male rats only, with a NOEL of 5 mg/kg b.w. per day. The NOEL for liver hypertrophy was 10 mg/kg b.w. per day, and no histopathological changes were reported in the liver. The CONTAM Panel considered the effects in the liver to be an adaptive effect, and that the NOAEL in this study could be considered to be 75 mg/kg b.w. per day or higher. The CONTAM Panel considered that the renal effects in male rats could be attributed to binding of *d*-limonene and/or its metabolites to α2u-globulin in the male rat kidney, an effect not considered relevant to humans, who lack sufficient of an equivalent protein for such a reaction to occur.

Genotoxicity

As reported by JECFA (2005), WHO (1998) and EFSA (2011c) *d*-limonene has given negative results in a number of *in vitro* genotoxicity assays with and without metabolic activation, including bacterial mutagenicity studies, a mammalian gene mutation assay, gene mutation in *Saccharomyces cerevisiae,* chromosomal aberrations in CHO cells, SCE cytogenetic studies and in a cell transformation assay in Syrian hamster embryo (SHE) cells. Two *in vivo* Comet assays with *d*-limonene and a study with *d*-limonene in BigBlue™ rats also gave negative results (EFSA, 2011c)

[53] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=79785&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

Carcinogenicity

d-Limonene has been tested for carcinogenicity by oral gavage in mice and rats (NTP, 1990). *D*-Limonene was administered 5 days per week for 2 years at dose levels of 0, 75 or 150 mg/kg b.w. per day in male rats, and 0, 300 or 600 mg/kg b.w. per day in female rats. Male mice received 0, 250 or 500 mg/kg b.w. per day, while females received 0, 500 or 1 000 mg/kg b.w. per day. No treatment-related clinical signs were reported, although lower body weights were observed for rats in the high-dose groups and female mice in the high-dose group. Survival of high-dose female rats was reduced after 39 weeks. *d*-Limonene significantly increased the incidence of renal tubular tumours (adenomas and carcinomas) and induced atypical renal tubular hyperplasia in male rats. However, there was no evidence of carcinogenicity in female rats or in male and female mice. The mechanism of the carcinogenic response in the kidney of male rats is linked to binding of *d*-limonene and/or its metabolites to α2u-globulin in the male rat kidney, a mechanism which is considered to be species and sex- specific and of no relevance for human exposure (JECFA, 1993, 2005; IARC, 1999b).

Developmental and reproductive toxicity

As reported by WHO (1998) and by JECFA (2005), *d*-limonene does not appear to show developmental toxicity in the absence of maternal toxicity. *d*-Limonene administered orally to rats at a dose level of 2 869 mg/kg b.w. per day on days 9-15 of gestation caused mortality and decreased body weight and deaths in the dams, with delayed ossification and decreased total body and organ weights (thymus, spleen, and ovary) in the offspring. Oral administration of 2 869 mg/kg b.w. per day *d*-limonene to mice on days 7-12 of gestation caused decreased body weight in the dams and a statistically significant increased in the incidence of skeletal anomalies and delayed ossification in the offspring. Oral administration of *d*-limonene to rabbits at dose levels of 250, 500 or 1 000 mg/kg b.w. per day on days 6-18 of gestation had no dose-related effects on the offspring. Deaths and reduced body weight gain occurred in the dams at the highest dose, and reduced body weight gain was also apparent at 500 mg/kg b.w. per day. There are no specific studies on the reproductive toxicity of *d*-limonene.

3.24.2.4. Allergenicity

Limonene is used in many consumer products but is also known as an allergen (Matura et al., 2006), in particular in its oxidized form (Karlberg et al., 1991, 1992, as cited in WHO, 1998). Limonene has also been recognized as an indoor pollutant associated with immune modulations with suppression of both IL-4 and IFN-γ production suggesting immunosuppression without clear pro- or antiallergic effect (Lehmann et al., 2001). Another study has even reported reduction of IL-13 production following application of limonene and has suggested using it therapeutically (Cariddi et al., 2011). Overall it is clear that limonene in higher doses can affect the allergic branch of immunity, but its extensive use in consumer products makes it unlikely that it will act as an allergen or adjuvant at the concentrations expected from its transport as a previous cargo.

3.24.3. Conclusions

The WHO established a tolerable intake of 0.1 mg/kg b.w. per day for *d*-limonene based on a NOEL for hepatic effects in a 13-week study in rats, of 10 mg/kg b.w. per day. The CONTAM Panel noted that the effects for which this NOEL was identified were adaptive changes in the liver, without evidence of histopathological change, and that the NOAEL in this study was 75 mg/kg b.w. per day (the highest dose tested). This dose level was also a NOAEL in female rats in a 2 year carcinogenicity study, while 500 mg/kg b.w. per day was a NOAEL in a 2-year study in mice. The renal tumours seen in male rats in the 2-year carcinogenicity study and the nephropathy seen in shorter-term studies in male rats can be attributed to binding of *d*-limonene and/or its metabolites to α2u-globulin, a phenomenon which is considered not to be relevant for human risk assessment. The CONTAM Panel therefore considered the tolerable intake of 0.1 mg/kg b.w. per day established by WHO for *d*-limonene to be conservative, and that the toxicological profile of limonene does not raise any toxicological concern when it is used as a previous cargo. The substance is not genotoxic and there is

no concern regarding allergenicity. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that limonene meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.25. METHYL TERTIARY BUTYL ETHER (MBTE) (CAS No 1634-04-4)

Methyl tertiary butyl ether (MTBE) is a colourless liquid boiling at 55 °C, with limited solubility in water (about 5 %).

MTBE is an ether manufactured from isobutylene and methanol catalysed by a strong acid.

MTBE is used primarily as a component in gasoline, as it efficiently increases the octane number (replacing the previously used alkylated lead). It is also used as a solvent because of its low tendency to form peroxides.

3.25.1. Previous evaluations

The SCF evaluated MTBE as a previous cargo in 1996 and considered it provisionally acceptable, pending evaluation by the SCF of a long term NTP study, and studies concerning its use as an extraction solvent for food (SCF, 1997a). In 2003, the SCF re-evaluated MBTE as a previous cargo. The data available to the SCF at that time indicated that the tumours induced by MTBE in mice and rats probably arose by a non-genotoxic mode of action and hence thresholds could be established for the toxic events triggering carcinogenesis. The SCF also noted the solubility of MTBE in water (48 g/L) would allow effective cleaning of the cargoes by water washings at ambient temperature. In view of these data and provided that residues were low after tank cleaning, the SCF considered that MTBE could be accepted as a previous cargo (SCF, 2003a).

MTBE has been evaluated as an industrial chemical by a number of international and national risk assessment bodies including the European Union Programme on Risk Assessment of Existing Substances (ECB, 2002), the US ATSDR (ATSDR, 1996), the IPCS (IPCS/WHO, 1998b) and OECD (OECD, 2001b). The CONTAM Panel noted that these evaluations focussed on exposure to MTBE by the inhalation and dermal routes, the most relevant routes for human exposure to MTBE, although oral exposure indirectly by the environment (e.g. drinking water) was also addressed.

The EU risk assessment concluded, in relation to risks to human health, that for consumers and others exposed indirectly via the environment there was at present no need for further information or testing or risk reduction measures beyond those which are being applied already (ECB, 2002). However for occupational scenarios there is a need for limiting the risks due to the long-term local effects on skin. Concerns for aquatic ecosystems and ground water and drinking water aesthetic quality were also recorded (ECB, 2002).

MTBE has been evaluated under the OECD SIDS programme on HPV chemicals (OECD, 2001b). Overall, it was concluded that MTBE may present a hazard for human health (workers) because of concerns for repeated dose local skin effects. Concerns for aquatic ecosystems and ground water and drinking water aesthetic quality were also recorded.

The US ATSDR has prepared a toxicological profile on MTBE (ATSDR, 1996). ASTDR concluded on Minimal Risk Levels (MRLs) of 0.4 and 0.3 mg/kg per day for oral acute-duration and intermediate-duration exposure to MTBE, but did not identify a chronic-duration oral MRL due to lack of data. ASTDR noted that an oral RfD was undergoing review by a US-EPA Workgroup (IRIS), but US-EPA IRIS currently indicates that there are no data [to support an oral RfD] (US-EPA, 2012b).

The IPCS has produced an Environmental Health Criteria Document on MTBE, which concluded that MTBE should be considered a rodent carcinogen but noted that the carcinogenic response was only evident at high levels of exposure that also induce other adverse effects (IPCS/WHO, 1998b).

The IARC has evaluated the carcinogenicity of MTBE (IARC, 1999b). The Agency concluded that there is inadequate evidence in humans for the carcinogenicity of methyl tert-butyl ether and there is limited evidence in experimental animals for the carcinogenicity of methyl tert-butyl ether. Methyl tert-butyl ether is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1999b).

3.25.2. Current evaluation

3.25.2.1. Expected impurities

MTBE is usually of high purity. Impurities are related ethers and are not expected to be of concern.

3.25.2.2. Reactivity and reaction products

MTBE, as most ethers, is chemically rather inert and is not expected to react with edible fats and oils. Owing to the low formation of peroxides, it is also unlikely to promote oxidation of edible fats and oils.

3.25.2.3. Toxicological profile

In compiling a toxicological profile for MTBE, the CONTAM Panel has used the SCF opinion of 2003 (SCF, 2003a), the EU risk assessment (ECB, 2002) and the ATSDR, IPCS/WHO and OECD evaluations (ATSDR, 1996; IPCS/WHO, 1998b; OECD, 2001b) as primary sources of information. The profile has been compiled using toxicological data on MTBE following oral administration only, since this was considered by the Panel to be the most relevant route to assess the toxicity of MTBE as a previous cargo, and a comprehensive database of studies using the oral route of exposure is available. There is also an extensive toxicological database on MTBE involving the inhalation and dermal routes of exposure, as reviewed by ATSDR (1996), IPCS/WHO (1998b), OECD (2001b) and ECB (2002). Studies involving these routes of exposure are not included in the following toxicological profile, unless considered to be particularly relevant (e.g. for the endpoint carcinogenicity).

<u>Absorption, distribution, metabolism and elimination</u>

MTBE is well absorbed after oral administration, with peak plasma concentrations occurring within 15 minutes of administration (Miller, 1997, as cited by ECB, 2002, and other reviews). It is rapidly eliminated from blood, and given its lipophilic nature and low molecular weight is extensively distributed throughout the body (Miller, 1997). Some accumulation occurs in the male rat kidney, due to specific binding to α2u-globulin (Borghoff et al., 1995, as cited by IPCS/WHO, 1998b, and other reviews). MTBE is rapidly metabolised in the liver to tert-butanol and formaldehyde, and further metabolised to 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid (from tert-butanol), methanol and formic acid (from formaldehyde) (Miller, 1997, as cited by ECB, 2002, and other reviews). Elimination following oral administration is primarily in the urine, although some MTBE may be excreted via exhalation; the main urinary metabolite is α-hydroxyisobutyric acid, followed by 2-methyl-1,2-propanediol and conjugates of tert-butanol (Miller, 1997, as cited by ECB, 2002, and other reviews).

<u>Acute toxicity</u>

MTBE is of low acute toxicity, oral LD_{50}s of 4 000 mg/kg and 5 960 mg/kg in the mouse have been reported (ASTDR, 1996; IPCS/WHO, 1998b; SCF, 2003a). As reported in the EU risk assessment, MTBE was moderately irritating to rabbit skin, but only slightly irritating to eyes; slight respiratory irritancy has also been reported in humans and in animals (ECB, 2002).

ECHA has classified MBTE as a skin irritant category 2; H315 (Regulation (EC) No. 1272/2008).[54]

Subacute, subchronic and chronic toxicity studies

The main target organs following oral administration of MTBE are the liver and the kidney, with a sex and species difference in susceptibility, these changes being seen primarily in male rats. Similar effects are seen after inhalation exposure. MTBE causes increases in liver weight associated with hepatocyte hypertrophy and induction of hepatic (CYP) metabolising enzymes (ECB, 2002). The renal changes in male rats are considered to be due to binding of MTBE or its metabolite tert-butanol to proximal tubular α2u-globulin (Williams et al., 2000a, b, as reported by ECB, 2002).

As reported in the EU risk assessment (ECB, 2002), Williams et al. (2000a) administered MTBE orally to male Sprague-Dawley rats at dose levels of up to 1 500 mg/kg b.w. per day and reported dose-related increases in liver and kidney weight, with the latter being statistically significant at 250 mg/kg b.w. per day. Protein droplet nephropathy was evident at all dose levels. As reported by the SCF (2003a) and in other evaluations, Sprague-Dawley rats were administered MTBE by oral gavage at doses of 0, 90, 440 and 1 750 mg/kg b.w. per day for five days per week over a 28-day period (IITRI, 1992, as cited in SCF, 2003a). Pathology findings included hyaline droplet formation in proximal convoluted tubules of male rats in the mid- and high-dose groups; hyaline droplets were attributed to α2u-globulin accumulation. The NOAEL was 90 mg/kg b.w.

As reported by the SCF (2003a) and in other evaluations, rats were administered MTBE by oral gavage at dose levels of 0, 100, 300, 900 or 1 200 mg/kg b.w. per day for 90 days, preceded by a 14-day day study (Robinson et al., 1990). The EU risk assessment identified a NOAEL of 300 mg/kg b.w. from this study based on a dose-related increased liver weight in males, together with inconsistent increases in aspartate aminotransferase (AST) and cholesterol (ECB, 2002).

Genotoxicity

The genotoxicity of MTBE has been extensively investigated *in vitro* and *in vivo*. The expert evaluations carried out on MTBE have all concluded that overall MTBE can be considered as non-genotoxic (ATSDR, 1996; IPCS/WHO, 1998b; OECD, 2001b; ECB, 2002; SCF, 2003a). The 2003 SCF evaluation of MTBE as a previous cargo reports that the substance was generally negative in bacterial mutagenicity assays in *Salmonella typhimurium* although a positive result was reported in one study using TA102 in the presence of metabolic activation (as reported by ECB, 2002, and SCF, 2003a). Positive results were obtained in a mouse lymphoma (L5178Y TK +/-) gene mutation assay in the presence of a metabolic activation system; the mutagenic effect could be abolished by inclusion of formaldehyde dehydrogenase, suggesting involvement of formaldehyde (as reported by ECB, 2002, and SCF, 2003a). In contrast MTBE did not induce gene mutations in Chinese hamster V79 cells or UDS in two studies in rat hepatocytes *in vitro*, however a positive result for UDS was reported in a third study at the highest dose tested (as reported by ECB, 2002, and SCF, 2003a). MTBE did not induce chromosomal aberrations in Chinese hamster ovary cells or micronuclei in NIH/3T3 cells, while one equivocal and one negative result was obtained for SCE in Chinese hamster ovary cells *in vitro* (as reported by ECB, 2002, and SCF, 2003a).

In vivo, MTBE did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*, nor UDS in CD-1 mouse hepatocytes following exposure of the mice to MTBE by inhalation (400, 3 000 or 8 000 ppm 2 days, 6 hours per day). It did not induce gene mutations at the HPRT locus of spleen lymphocytes in CD-1 mice treated with MTBE by gavage (1, 10, 100 and 1 000 mg/kg b.w., 5 days per week for 3 days) and was negative in two mouse micronucleus studies using the inhalation route (400, 3 000 or 8 000 ppm 2 days, 6 hours per day) or by single *i.p.* injection of 250, 500, 1 000,

[54] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=65671&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

1 500, 1 750 mg/kg (as reported by ECB, 2002, and SCF, 2003a). An *in vivo* chromosomal aberration study in bone marrow of male Sprague-Dawley rats administered MBTBE by the *i.p.* route (0.04, 0.13 or 0.4 mg/kg, single dose or 3 doses per 5 days) was also negative, however MTBE gave a positive result (at the highest dose only) in a Comet assay in lymphocytes of rats treated by gavage at single doses of 40, 400 or 800 mg/kg (as reported by ECB, 2002, and SCF, 2003a). The CONTAM Panel concluded that the weight of evidence suggests that MTBE is not genotoxic.

Carcinogenicity

As reported in the ECB (2002) risk assessment and in other expert evaluations (ATSDR, 1996; IPCS/WHO, 1998b; OECD, 2001b), MTBE has been tested for carcinogenicity in mice and rats by the inhalation and oral routes.

An inhalation study in mice (Burleigh-Flayer et al., 1992; Bird et al. 1997), at levels of 0, 400, 3 000 or 8 000 ppm showed induction of hepatocellular hypertrophy in males at the top two dose levels and in females at the top dose only. A slight increase in hepatocellular adenomas and carcinomas was seen in high dose females, but the incidence was within the historical control range. In rats exposed to the same levels of MTBE as mice, again by inhalation (Bird et al., 1997), high dose animals showed a decreased body weight gain. A dose-related chronic progressive nephropathy was seen in both males and females, however renal tubular cell tumours were increased only in male rats in the two top dose groups. Testicular tumours were also statistically significantly increased in these dose groups. In a two year oral study in rats given 0, 250 or 1 000 mg/kg b.w. of MTBE by gavage in olive oil (Belpoggi et al., 1995, 1998), females in both dose groups had a significantly increased incidence of lymphoimmunoblastic lymphomas and lymphoblastic leukaemia compared with the historical control range, and also dysplastic proliferation of lymphoreticular tissues. Male rats in both dose groups showed an increase in incidence of testicular interstitial cell adenoma.

In line with the IARC conclusion that there is inadequate evidence in humans for the carcinogenicity of methyl tert-butyl ether, with limited evidence for carcinogenicity in experimental animals (IARC, 1999b), the expert evaluations used to compile this toxicological profile consider, taking into account the overall absence of genotoxicity, that MTBE is of low concern with regard to human carcinogenicity (ATSDR, 1996; IPCS/WHO, 1998b; OECD, 2001b; ECB, 2002; SCF, 2003a). It is generally accepted that MTBE should be considered a non-genotoxic, thresholded, rodent carcinogen but that the carcinogenic response was only evident at high levels of exposure that also induce other adverse effects (e.g. IPCS/WHO, 1998b; SCF, 2003a). The CONTAM Panel agrees with this conclusion.

Developmental and reproductive toxicity

As reported by the SCF (2003a) no effects of MTBE on reproductive function were seen in a single generation reproduction study in Sprague-Dawley rats exposed to concentrations of 250, 1000 and 2500 ppm for 12 weeks, 5 days per week for 6 hours (Biles et al., 1987) nor in a two-generation study at concentrations of 0, 400, 3000 and 8000 ppm that affected maternal food consumption (Bevan et al., 1997a). In a developmental toxicity study in CD-1 mice treated by inhalation at 0, 1 000, 4 000 and 8 000 ppm, increased incidences of post-implantation loss and cleft palate were seen at doses that also induced hypoactivity, ataxia and reduced food consumption in the dams (Bevan et al., 1997b). However, another study in CD-1 mice conducted by inhalation at lower doses (up to 2 500 ppm) that were less toxic to dams, did not show any developmental toxicity (Conaway et al., 1985) and NZW rabbits treated by inhalation at 1 000, 4 000 and 8 000 ppm did not show signs of developmental toxicity even at the highest dose (Bevan et al., 1997b). The NOAELs for maternal and developmental toxicity were both 1 000 ppm in mice and 1 000 ppm and 8 000 ppm, respectively in rats.

As also reported by the SCF (2003a) and in the EC risk assessment (ECB, 2002), at high dose levels by inhalation MTBE produces a number of endocrine-mediated effects in female mice, including increased metabolism of oestrogen in the liver, without affecting the level of the free hormone.

Reduced uterine weights and morphologic changes were seen in the uterus. Oestrous cycle length and stages were also altered (Moser et al., 1998). Increased interstitial testosterone level was found in rats after a 28-day exposure (Williams et al, 2000a). This study also reported decreased serum testosterone and luteinizing hormone (LH). Corticosterone and aldosterone levels were elevated after continued exposure to high doses of MTBE.

In a more recent study examining the effect of MTBE on a number of reproductive endpoints in rats, MTBE was administered by gavage at dose levels of 0, 400, 800 and 1 600 mg/kg per day. Adverse effects included a significant increase in abnormal sperm, histopathological changes in seminiferous epithelium, alterations in serum testosterone, luteinizing hormone and follicle stimulating hormone, and decreases in androgen binding protein (Li et al., 2008). In another recent study, mice exposed to 0.08-8 mg/mL MTBE in drinking water for 28 days (adult mice) or for 51 days (juvenile mice) no significant changes in the reproductive tract (of males) were evident and there were no signs of hepatic oxidative stress (de Peyster et al., 2008).

3.25.2.4. Allergenicity

Methyl tertiary butyl ether is not expected to be an allergen or an adjuvant.

3.25.3. Conclusions

MTBE is not genotoxic or allergenic. The CONTAM Panel concluded that there is no concern regarding the carcinogenicity, developmental or reproductive toxicity of MTBE at the anticipated levels in food resulting from transport of the substance as a previous cargo. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. The CONTAM Panel also agrees with the previous conclusion of the SCF in 2003, that the solubility of MTBE in water (48 g/L) would allow effective cleaning of the cargoes by water washings at ambient temperature.

Therefore, the CONTAM Panel concludes that methyl tertiary butyl ether meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.26. UREA AMMONIA NITRATE SOLUTION (UAN)

Urea ammonia nitrate solution (UAN), more correctly “urea ammonium nitrate solution”, is a liquid consisting of a mixture of urea (CAS No 57-13-6) and ammonium nitrate (CAS no. 6484-52-2) in water. The most commonly used grade is UAN 32.0.0 (32 % N) and contains 45 % ammonium nitrate, 35 % urea and 20 % water.

UAN is used as a fertilizer.

Urea is the diamide of carbonic acid, $CO(NH_2)_2$. It is a colourless solid.

The classic production of urea first involved formation of ammonium carbonate and then conversion of this, thermally, to urea. A more recent procedure starts with methane instead of hydrogen: natural gas, air and water are converted to urea via liberation of hydrogen and carbon dioxide.

Urea is widely used as a fertilizer, as a source of nitrogen. It is also used for the reduction of NO_x in the exhaust of power stations and diesel engines by the SCR- (selective catalyzed reduction) or SNCR- (selective non-catalyzed reduction) process. Urea is also an important raw material for the chemical industry.

Urea has an important role in the metabolism of nitrogen-containing compounds, particularly in the excretion of nitrogen. Urea is added to feeds for dairy cattle as a source of nitrogen for proteins. It is also used as source of nitrogen in fermented foods (E927b).

3.26.1. Previous evaluations

The SCF evaluated UAN as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that very low residual levels are expected in the subsequent cargo. In the 2003 SCF evaluation of acceptable previous cargoes, UAN was not further evaluated as it was already considered acceptable (SCF, 2003a).

Urea ammonia nitrate has not specifically been evaluated by any regulatory body, but the individual constituents urea, ammonium and nitrate have been the subject of several evaluations.

EFSA has previously evaluated calcium ammonium nitrate solution and calcium nitrate (CN-9) solution and concluded that they meet the criteria as a previous cargo (EFSA, 2009b).

JECFA evaluated urea as a food additive (texturiser in chewing gum) at its 41st meeting and concluded that since urea is a natural end-product of amino acid metabolism in humans, and that approximately 20 g per day is excreted in the urine in adults (proportionately less in children), that the use of urea at levels of up to 3 % in chewing-gum was of no toxicological concern (JECFA, 1993).

Urea has been evaluated under the OECD SIDS programme on HPV chemicals (OECD, 1994). OECD concluded that urea was currently of low priority for further work.

The SCF evaluated ammonium, sodium, potassium, calcium and magnesium cations in combination with a series of anions including hydroxide (SCF, 1991). They concluded that these cations and anions constitute the major electrolytes present in all biological materials and occur naturally in foodstuffs.

Ammonium hydroxide (ammonia solution) has been evaluated under the OECD SIDS programme on HPV chemicals as part of the ammonia category (OECD, 2007). The other substances in the category were ammonia, ammonium thiosulfate and ammonium phosphate sulphate, Overall, OECD concluded that ammonia solution and other members of the ammonia category are currently of low priority for further work.

Nitrate is an authorised food additive in the EU, and has been evaluated by JECFA and the SCF on a number of occasions. The SCF established an ADI of 0-3.7 mg/kg b.w. for nitrate in 1990 (SCF, 1992b) and reconfirmed this ADI in 1995 (SCF, 1997c). The most recent review by JECFA in 2002 reconfirmed its earlier ADI of 0-3.7 mg/kg b.w. for nitrate (JECFA, 2003).

In 2009, the CONTAM Panel recommended that solutions of calcium nitrate, ammonium nitrate and the double salt, 'nitric acid, ammonium calcium salt', be considered as acceptable previous cargoes (EFSA, 2009b).

3.26.2. Current evaluation

3.26.2.1. Expected impurities

No specific information was available on potential impurities. However, its use as a fertiliser is by itself an assurance that UAN does not contain significant amounts of highly toxic impurities.

UAN is corrosive and may, therefore, contain corrosion inhibitors. No information was available about the compounds and concentrations used for this purpose. However, no highly toxic compounds are used and the dilution involved in the carryover from transport as a previous cargo reduces the levels such that these inhibitors are not expected to be of any concern.

3.26.2.2. Reactivity and reaction products

Ammonium, nitrate and urea are of low reactivity. Further, they are normal constituents of many foods. They are not considered to be of concern.

3.26.2.3. Toxicological profile

Urea is an endogenous product of protein catabolism in mammals and is found in blood at concentrations in the range of 0.7-2.1 mg/mL. As noted by JECFA, approximately 20 g of urea is excreted daily in the urine of adults (JECFA, 1993). The toxicological database on urea is relatively limited, but the available information shows that it is of low acute and subacute/subchronic/chronic toxicity in most mammalian species with the exception of ruminants. Mice and rats administered diets containing 4 500, 9 000 or 45 000 mg/kg feed (highest dose level equivalent to approximately 6 750 mg/kg b.w. per day for mice and approximately 2 250 mg/kg b.w. per day for rats) did not show any treatment-related effects (JECFA, 1993; OECD, 1994).

No data are available on the reproductive or developmental toxicity of urea. Urea has given negative results in bacterial mutagenicity tests, but was positive in a gene mutation assay in mammalian cells and also induced chromosomal aberrations and single strand breaks in DNA *in vitro* (JECFA, 1993; OECD, 1994). An *in vivo* chromosomal aberration study in bone marrow at a dose level of 25 000 mg/kg was also positive. JECFA noted that this dose level substantially exceeded the lethal dose for urea (JECFA, 1993). As indicated by OECD (1994), the genotoxicity of urea in *in vitro* tests is likely to be due to the high osmolality of urea in the assay systems.

The SCF considered that "*no safety problems are likely to arise from* [the use of ammonium ion] *in food, provided the contributions from food intake do not disturb the homeostatic mechanisms controlling the electrolyte balance of the body*." and based their ADI "not specified" for ammonium hydroxide on these considerations (SCF, 1991). The toxicological profile of ammonium ion has been summarised in Section 3.22.

The SCF concluded that nitrate ion is of relatively low toxicity, based on the results of acute and subacute/subchronic/chronic studies in animals (SCF, 1992b). LD_{50} values of approximately 2 500-6 250 mg/kg b.w. per day have been reported in mice and 3 300-9 000 mg/kg b.w. per day in rats. In a 2-year carcinogenicity study on sodium nitrate in rats a no-effect level of 2 500 mg/kg b.w. per day was identified (Maekawa et al., 1982). There is no evidence that nitrate has carcinogenic effects in experimental studies (Maekawa et al., 1982; SCF, 1992b, 1997c) and nitrate ion is not genotoxic in *in vitro* systems, provided that no reduction to nitrite can occur (SCF, 1992b; JECFA, 2003). The adverse health effects of nitrate are related to its reduction to nitrite either before ingestion or *in vivo*, with two consequential effects (a) formation of methaemoglobin due to the coupling of nitrite with oxyhaemoglobin, (b) nitrosation of N-nitrosatable precursors such as secondary amines by nitrite to yield potentially carcinogenic N-nitroso compounds (SCF, 1992b, 1997c; JECFA, 2003). Reduction of nitrate to nitrite in humans occurs mainly in the saliva. JECFA concluded at its 44th meeting that the range of nitrate conversion is 5-7 % for normal individuals and 20 % for individuals with a high rate of conversion (JECFA, 1995). The ADI of 0-3.7 mg/kg b.w. for nitrate ion established by both JECFA and SCF takes into account the potential for conversion to nitrite and avoidance of methaemoglobin induction and formation of N-nitroso compounds (SCF, 1997c).

3.26.2.4. Allergenicity

Available data give no indication that urea ammonia nitrate solution is an allergen or an adjuvant.

3.26.3. Conclusions

The CONTAM Panel has previously evaluated calcium ammonium nitrate solution and calcium nitrate (CN-9) solution and concluded that they meet the criteria for acceptability as previous cargoes. Based on the evaluations for urea, ammonium hydroxide and nitrate described above, the CONTAM Panel considers that there are no toxicological concerns regarding urea ammonium nitrate when it is used as a previous cargo. The CONTAM Panel concluded that urea ammonium nitrate is not genotoxic or allergenic. The CONTAM Panel noted that urea ammonium nitrate solution is corrosive, but that it will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to the solution do not give rise to any

toxicological concern. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that urea ammonia nitrate solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.27. CALCIUM CHLORIDE SOLUTION - only where the immediate previous cargo to it is on the list and is not similarly restricted (CAS No 10043-52-4)

Calcium chloride is a strongly hygroscopic salt.

Calcium chloride is produced from calcium carbonate and hydrochloric acid or by the Solvay process from sodium chloride and calcium carbonate. It is used for desiccation as well as for de-icing roads, as an additive to concrete, and many other applications.

Calcium chloride is an accepted food additive as a firming agent and sequestrant, e.g. to prevent oxidation of fats (E509).

3.27.1. Previous evaluations

The SCF evaluated calcium chloride solution as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that calcium chloride is an authorised food additive (E509) with ADI "not specified". In the 2003 SCF evaluation of acceptable previous cargoes, calcium chloride solution was not further evaluated as it was already considered acceptable (SCF, 2003a).

The SCF evaluated calcium cation together with ammonium, sodium, potassium and magnesium cations in combination with a series of anions including chloride (SCF, 1991). They concluded that these cations and anions constitute the major electrolytes present in all biological materials and occur naturally in foodstuffs. The SCF therefore considered that "*no safety problems are likely to arise from their use in food, provided the contributions from food intake do not disturb the homeostatic mechanisms controlling the electrolyte balance of the body*." and based their ADI "not specified" for calcium salts including the chloride on these considerations (SCF, 1991).

JECFA has evaluated calcium chloride together with calcium acetate, calcium gluconate and calcium sulphate food additives, most recently in 1973, and established an ADI "not limited" for these substances (JECFA, 1973).

Calcium chloride has been evaluated under the OECD SIDS programme on HPV (OECD, 2002b). Overall, OECD concluded that calcium chloride was currently of low priority for further work.

The SCF allocated a Tolerable Upper Intake Level (UL) for calcium of 2 500 mg/person per day as a nutrient, and also established a Population Reference Intake (PRI) of 700 mg calcium per day (range 400-1 200 mg per day depending on age and physiological status) (SCF, 2003b).

Calcium chloride (substance number 585) is in the list of substances authorised for use in food contact materials[19] without a limit (other than the generic limit of 60 mg/kg food).

3.27.2. Current evaluation

The CONTAM Panel noted that the restriction "only where the immediate previous cargo to it is on the list and is not similarly restricted" was retained from when the positive list of previous cargoes was first prepared in 1996. It reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels. Current shipping practices permitted by the IMO and others, as well as the construction of the vessels in current use make this restriction unnecessary (see Documentation provided to EFSA).

3.27.2.1. Expected impurities

The bulk of the calcium chloride produced and transported is of technical quality. The main impurities will be other salts which are not expected to be of concern when calcium chloride is used as a previous cargo.

3.27.2.2. Reactivity and reaction products

Calcium chloride is not expected to produce reaction products of concern with edible fats and oils.

3.27.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Following oral administration, calcium chloride will dissociate in the acid milieu of the stomach into calcium and chloride ions, which are directly absorbed and enter into the electrolyte pool of the body. Plasma levels are maintained by control of absorption via an active uptake process, and homeostatic control including excretion is regulated separately for the two ions.

Acute toxicity

LD_{50}'s of 1 940-2 045 mg/kg b.w. have been reported in mice, 3 798-4 179 mg/kg b.w. in rats and 500-1 000 mg/kg b.w. in rabbits for calcium chloride (OECD, 2002b). High levels of calcium chloride given orally to experimental animals can cause severe gastrointestinal irritation, and the substance is highly irritant to the rabbit eye, but only slightly irritant to skin on single or short-term exposure (OECD, 2002b).

ECHA has classified calcium chloride as irritating to eyes category 2; H319 (Regulation (EC) No. 1272/2008[24]).[55]

Genotoxicity

Calcium chloride has been tested in several bacterial mutation tests and in a mammalian chromosome aberration test, with negative results (OECD, 2002b).

3.27.2.4. Allergenicity

Available data give no indication that calcium chloride solution is an allergen or an adjuvant.

3.27.3. Conclusions

The CONTAM Panel recommends that the restriction "only where the immediate previous cargo to it is on the list and is not similarly restricted" be removed, and that the entry for the substance in the annex to Commission Directive 96/3/EC be amended to "Calcium chloride solution (CAS No 10043-52-4)". This is because the restriction reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels at the time it was put in place. Changes in shipping practices and the current construction of vessels for the transport of edible fats and oils now make this restriction unnecessary.

JECFA has established an ADI not limited and the SCF has established an ADI "not specified" for calcium chloride, which the CONTAM Panel considers appropriate. The SCF allocated a UL for calcium of 2 500 mg/person per day as a nutrient, and also established a PRI of 700 mg calcium per day. The contribution of calcium from previous cargoes is not of safety concern, since the threshold in the criteria of an ADI (or TDI) above 0.1 mg/kg b.w. per day for previous cargoes is far below the

[55] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=61013&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

tolerable upper intake level of calcium. Calcium chloride is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that calcium chloride solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.28. MAGNESIUM CHLORIDE SOLUTION (CAS No 7786-30-3)

Magnesium chloride, $MgCl_2$, and its various hydrates, $MgCl_2(H_2O)_x$, are solids and highly soluble in water. Magnesium chloride is hygroscopic.

Hydrated magnesium chloride is primarily produced as a side product of potassium chloride, i.e. by fractionated precipitation from brine or sea water.

Magnesium chloride serves as a fertilizer, precursor to other magnesium compounds and as a component for certain cements. It is also used as a de-icer for roads, as it is less toxic to plant life and less corrosive to concrete and steel than other de-icers. Anhydrous magnesium chloride is the principal precursor for magnesium metal.

Magnesium chloride is a coagulant for the preparation of tofu from soy milk (E511). It is also an ingredient in baby formula.

3.28.1. Previous evaluations

The SCF evaluated magnesium chloride as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). It has been approved as a food additive by the European Union (E525) (Annex 1 of Directive 95/2.EU). An ADI “not specified” was established by the (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, magnesium chloride was not further evaluated (SCF, 2003a).

An ADI “not limited” was established at the 23rd JECFA (1980).

In 2001, the opinion of the SCF on a UL of Magnesium was published (SCF, 2001). The SCF established an UL of 250 mg Mg per day for readily dissociable magnesium salts including Mg chloride in nutritional supplements, water, or added to food and beverages. This UL does not include Mg normally present in foods and beverages. The NOAEL was identified in studies in which a pharmaceutical type of dosage formulation was taken in addition to Mg present in normal foods and beverages. This study is described below.

3.28.2. Current evaluation

3.28.2.1. Expected impurities

A large part of magnesium chloride is likely to be in the form of crude products, and contain substantial proportions of other salts, such as chlorides of other alkali and alkaline earth metals. These are not expected to be of concern once diluted in a subsequent cargo of edible fats or oils.

3.28.2.2. Reactivity and reaction products

Magnesium chloride is not reactive with edible fats and oils.

3.28.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

In aqueous solutions, magnesium chloride will be dissociated into magnesium and chloride ions. Magnesium is required as a cofactor for many enzyme systems and plays a multifunctional role in cell

metabolism. Magnesium is ubiquitous in foods. Magnesium is absorbed along the entire intestinal tract, but the sites of maximal absorption appear to be the distal jejunum and ileum (Brannan et al., 1976; Phillips et al., 1991). Magnesium is excreted primarily in the urine.

Acute toxicity

No adverse effects have been associated with the ingestion of magnesium as a naturally occurring substance in foods. The primary manifestation of excessive ingestion of magnesium from non-food sources is osmotic diarrhoea, which is reversible.

An oral toxicity study in rats administered magnesium chloride hexahydrate at a dose of 2 000 mg/kg b.w. by gavage showed lack of toxicity through the 14-day observation period. The LD_{50} was > 5 000 mg/kg b.w.[56]

Under Regulation (EC) No. 1272/2008,[24] a number of notifiers have proposed that magnesium chloride be classified as a skin irritant category 2: H315 and irritating to eyes category 2; H319 (ECHA).[57]

Subacute, subchronic and chronic toxicity studies

Mild diarrhoea is the most sensitive non-desirable effect of orally administered easily dissociable magnesium salts. In 2001, the SCF reviewed the human data from the literature where the presence or absence of "mild diarrhoea" was stated. It was concluded that mild diarrhoea occurs in a small percentage of adult subjects at oral doses of about 360/365 mg Mg per day, which therefore represents the LOAEL. No laxative effects were observed in adult men and women - including during pregnancy and lactation - at doses up to 250 mg Mg per day. Therefore, this dose is considered as the no-observed-adverse-effect level (NOAEL).

Genotoxicity

In vitro genotoxicity tests were negative for magnesium chloride as well as for magnesium sulphate.

Carcinogenicity

Mice given magnesium chloride in the diet for 96 weeks (up to 2 % in diet, equivalent to approximately 3 000 mg/kg b.w. per day) exhibited no evidence of substance-related carcinogenicity (Kurata et al., 1989).

3.28.2.4. Allergenicity

Available data give no indication that magnesium chloride solution is an allergen or an adjuvant.

3.28.3. Conclusions

JECFA has established an ADI not limited and the SCF has established an ADI "not specified" for magnesium chloride, which the CONTAM Panel considers appropriate. The SCF allocated a UL for magnesium of 250 mg per day in nutritional supplements, water, or added to food and beverages. Magnesium chloride is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that magnesium chloride solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

[56] Anonymous, 2009; OECD guidelines, as cited by ECHA online.
[57] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=93509&HarmOnly=no?fc=true&lang=en (accessed 8/04/2012).

3.29. POTABLE WATER - only where the immediate previous cargo to it is on the list and is not similarly restricted

The characteristics of potable water have been established by EU Directive 98/83.[58] The CAS no. of water is 7732-18-5.

The SCF evaluated potable water as a previous cargo in 1996 and considered it acceptable, but only where the immediate previous cargo to it was on the list and was not similarly restricted (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, potable water was not further evaluated as it was already considered acceptable (SCF, 2003a).

3.29.1. Current evaluation

The CONTAM Panel noted that the restriction "only where the immediate previous cargo to it is on the list and is not similarly restricted" was retained from when the positive list of previous cargoes was first prepared in 1996. It reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels. Current shipping practices permitted by the IMO and others, as well as the construction of the vessels in current use make this restriction unnecessary unnecessary (see Documentation provided to EFSA).

Potable water is a food and, therefore, is not of concern with regard to impurities and reaction products.

3.29.2. Conclusions

The CONTAM Panel recommends that the restriction "only where the immediate previous cargo to it is on the list and is not similarly restricted" be removed, and that the entry for the substance in the annex to Commission Directive 96/3/EC[5] be amended to "Potable water (CAS No 7732-18-5)". This is because the restriction reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels at the time it was put in place. Changes in shipping practices and the current construction of vessels for the transport of edible fats and oils now make this restriction unnecessary.

Water must meet specific requirements to be considered potable. Hence, there are no concerns from possible toxicity or allergenicity from the use of potable water as a previous cargo for edible fats and oils. There are no reaction products or impurities of concern.

The CONTAM Panel therefore concludes that potable water meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.30. POTASSIUM HYDROXIDE (caustic potash) - only where the immediate previous cargo to it is on the list and is not similarly restricted (CAS No 1310-58-3)

Potassium hydroxide, commonly called caustic potash with formula KOH, is strong alkaline and readily soluble in water. Potassium hydroxide is commercialised as a solid (flakes, beads, granules) or as solutions with varying concentrations. The most important industrial concentration is 50 % (Ullmann's Encyclopedia, 1998).

Potassium hydroxide is produced via electrolysis of aqueous potassium chloride.

Potassium hydroxide is used in agriculture, e.g. to correct the pH of acidic soils. It is a major industrial chemical used in a wide variety of chemical processes. Some uses of potassium hydroxide include acrylate ester copolymer coating, in defoaming agents in the manufacture of paper, saponification of fats and oils for liquid soap, formulation aid for food, pH control agent, in polyethylene resins, textile processing and as a catalyst in reactions like the production of biodiesel.

[58] Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. OJ L 330, 5.12.1998, 9.32-54.

3.30.1. Previous evaluations

The SCF evaluated potassium hydroxide as a previous cargo in 1996 and considered it acceptable only where the immediate previous cargo to it is on this list of the acceptable previous cargoes and is not similarly restricted (SCF, 1997a). It has been approved as a food additive by the European Union (E525) (Annex 1 of Directive 95/2/EC[59]). An ADI "not specified" was established by the SCF (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, potassium hydroxide was not further evaluated (SCF, 2003a).

An ADI "not limited" was established by JECFA at the 9th meeting (JECFA, 1966).

In 2001, an initial health and environmental risk assessment of potassium hydroxide was performed under the framework of the OECD HPV Chemicals Programme (OECD, 2001c). No further work was recommended if sufficient control measures are in place to avoid significant human and environmental impact, including prevention of accidental exposure.

3.30.2. Current evaluation

The CONTAM Panel noted that the restriction "only where the immediate previous cargo to it is on the list and is not similarly restricted" was retained from when the positive list of previous cargoes was first prepared in 1996. It reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels. Current shipping practices permitted by the IMO and others, as well as the construction of the vessels in current use make this restriction unnecessary (see Documentation provided to EFSA).

Potassium hydroxide is a solid at normal temperature and pressure, with a melting point above 400 °C. Hence, in this form it is not a suitable cargo for the type of tanker used to transport edible fats and oils by sea. When used as a previous cargo to edible fats and oils it has to be transported as a solution, to enable effective transfer and tank cleaning (see Documentation provided to EFSA).

3.30.2.1. Expected impurities

No impurities of concern are expected in potassium hydroxide.

3.30.2.2. Reactivity and reaction products

Potassium hydroxide interacts immediately with acids in edible fats and oils, being neutralised in the process. The resulting potassium salts of organic acids are not reactive. Potassium hydroxide could also catalyse the hydrolysis of triglycerides, a process known as saponification, although at the levels present from its use as a previous cargo, this will not occur. There are no reaction products of toxicological concern.

3.30.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

In body fluids potassium hydroxide dissociates into potassium and hydroxyl ions. Both K^+ and OH^- ions are normal constituents of body fluids. K^+ plays an essential role in the human physiology but starts to be toxic at levels exceeding 200-250 mg/L. Its concentration in the blood is regulated principally by renal excretion/reabsorption and controlled by an efficient feedback auto-regulation system. The systemic toxicity of hydroxyl ions (i.e. hyperactivity of the central nervous system) due to an excessive pH of the blood is prevented by the bicarbonate buffer system, respiration and renal compensation mechanisms.

[59] European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners. OJ L 61, 18.3.1995, p. 1-40.

Acute toxicity

Potassium hydroxide has moderate acute oral toxicity, which is essentially due to its corrosivity. Solutions with concentrations greater than 2 % are corrosive, while concentrations of about 0.5 to about 2.0 % are irritating. The observed systemic effects could be regarded as secondary effects to changes in pH.

Potassium hydroxide, with specific concentration limits, is classified as follows: skin corrosive category 1A; H314 at concentrations ≥ 5 %; skin corrosive category 1B; H314 at concentrations ≥ 2 % and < 5 %; skin irritant category 2; H315 at concentrations ≥ 0.5 % and < 2 %; eye irritant category 2; H319: at concentrations ≥ 0.5 % and < 2 % (Regulation (EC) No. 1272/2008[24]).[60]

Subacute, subchronic and chronic toxicity studies

No repeat-dose toxicity studies of potassium hydroxide could be identified. Based on results with potassium chloride, it can be concluded that chronic oral exposure to potassium hydroxide at non-irritating concentrations/conditions would result in a low level of toxicity, due to the K+ ion, similar to that of potassium chloride, which is well documented.

Genotoxicity

There is no evidence for mutagenic activity of potassium hydroxide (and corresponding potassium salts). K^+ and OH^- are not expected to be systemically available in the body over the normal limits, under non-irritating conditions. A genotoxic effect is also not very likely because both the K^+ and OH^- ions are naturally present in the human body.

Carcinogenicity

Valid carcinogenicity studies in animals are not available for potassium hydroxide. There is no evidence that potassium hydroxide is carcinogenic in exposure situations that are relevant for humans.

Developmental and reproductive toxicity

No studies are available on toxicity to reproduction and development but the substance will neither reach the foetus nor reach male and female reproductive organs in effective toxic concentrations. Therefore, no risk for reproduction or development is expected from the use of potassium hydroxide as a previous cargo.

3.30.2.4. Allergenicity

Available data give no indication that potassium hydroxide acts as an allergen or an adjuvant at the concentrations expected from its use as a previous cargo.

3.30.3. Conclusions

The CONTAM Panel recommends that the restriction "only where the immediate previous cargo to it is on the list and is not similarly restricted" be removed. This is because the restriction reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels at the time it was put in place. Changes in shipping practices and the current construction of vessels for the transport of edible fats and oils now make this restriction unnecessary. Current shipping practices also mean that when potassium hydroxide is transported prior to edible fats and oils, the design of the tanker will be such that potassium hydroxide has to be transported as a solution. Hence, the CONTAM Panel recommends that the entry for the substance in

[60] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=128217&HarmOnly=no?fc=true&lang=en (accessed 08/04/2012).

the annex to Commission Directive 96/3/EC[5] be amended to "Potassium hydroxide (caustic potash) solution (CAS No 1310-58-3)".

JECFA has established an ADI "not limited" and the SCF has established an ADI "not specified" for potassium hydroxide, which the CONTAM Panel considers appropriate. Potassium hydroxide is not genotoxic or allergenic. Potassium hydroxide is toxic only when it is present at sufficient concentration that it changes the local OH^- concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to potassium hydroxide as a previous cargo do not give rise to any toxicological concern. Exposure to small amounts of potassium hydroxide locally may cause irritation to the skin or eyes. However, the maximum potential levels of potassium hydroxide arising in fats or oils following its transport as a previous cargo would be of no concern. There are no reactions of health concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that potassium hydroxide solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.31. SODIUM HYDROXIDE (caustic soda) - only where the immediate previous cargo to it is on the list and is not similarly restricted (CAS No 1310-73-2)

Sodium hydroxide, commonly known as caustic soda, lye, or sodium hydrate, is a caustic compound, commercially available in solid forms and as solutions of various concentrations in water. It is soluble in water, alcohol and glycerol.

The principal method for the manufacture of sodium hydroxide is by electrolysis of brine, resulting in a solution of about 50 % sodium hydroxide. Sodium hydroxide can also be prepared by the reaction of sodium carbonate (soda) in concentrated solution with calcium hydroxide (slaked lime).

Sodium hydroxide is widely used in chemistry, mostly as a strong base to adjust pH, dissolve materials or as a reaction component (e.g. saponification). It is also an important component in cleaning agents, e.g. for dishwashers.

3.31.1. Previous evaluations

The SCF evaluated sodium hydroxide as a previous cargo in 1996 and considered it acceptable only where the immediate previous cargo to it is on this list of the acceptable previous cargoes and is not similarly restricted (SCF, 1997a). It has been approved as a food additive by the European Union (E524) (Annex 1 of Directive 95/2/EC[59]). An ADI "not specified" was established by the SCF (SCF, 1997a). In the 2003 SCF evaluation of acceptable previous cargoes, sodium hydroxide was not further evaluated (SCF, 2003a).

An ADI "not limited" was established by JECFA at the 9th meeting (JECFA, 1966).

In 2002 an initial health and environmental risk assessment of sodium hydroxide was performed under the framework of the OECD HPV Chemicals Programme (OECD, 2002c). No further work was recommended if sufficient control measures are in place to avoid significant human and environmental impact, including prevention of accidental exposure.

In 2006 an EU 'targeted risk assessments' (TRA) was published on sodium hydroxide because it is included in the EU 4th Priority-list of substances. This assessment was evaluated by the Scientific Committee on Health and Environmental Risks (SCHER, 2006). The risk assessment was restricted to respiratory, dermal and ocular irritation, which SCHER agreed are the major health risks from exposure to sodium hydroxide. These were a consequence of the high pH of aqueous solutions. Systemic toxicity was not anticipated due to the buffering capacity of the blood. SCHER agreed with

the conclusions of the TRA that sodium hydroxide is unlikely to cause cancer by a genotoxic mechanism.

3.31.2. Current evaluation

The CONTAM Panel noted that the restriction "only where the immediate previous cargo to it is on the list and is not similarly restricted" was retained from when the positive list of previous cargoes was first prepared in 1996. It reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels. Current shipping practices permitted by the IMO and others, as well as the construction of the vessels in current use make this restriction unnecessary (see Documentation provided to EFSA).

Sodium hydroxide is a solid at normal temperature and pressure, with a melting point above 320 °C. Hence, in this form it is not a suitable cargo for the type of tanker used to transport edible fats and oils by sea. When used as a previous cargo to edible fats and oils it has to be transported as a solution, to enable effective transfer and tank cleaning (see Documentation provided to EFSA).

3.31.2.1. Expected impurities

No impurities of concern are expected in sodium hydroxide.

3.31.2.2. Reactivity and reaction products

Sodium hydroxide interacts immediately with acids in edible fats and oils, being neutralised in the process. The resulting sodium salts of organic acids are not reactive. Sodium hydroxide could also catalyse the hydrolysis of triglycerides, a process known as saponification, although at the levels present from its use as a previous cargo, this will not occur. There are no reaction products of toxicological concern.

3.31.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

Sodium hydroxide in body fluids is dissociated into sodium and hydroxyl ions. Both Na+ and OH- ions are normal constituents of body fluids. Excess sodium is excreted in the urine and the potential alteration of the pH of blood is regulated to maintain homeostasis via urinary excretion of bicarbonate and via exhalation of carbon dioxide (OECD, 2002c).

<u>Acute toxicity</u>

Solid sodium hydroxide is corrosive. Depending on the concentration, solutions of sodium hydroxide are non-irritating, irritating or corrosive and they cause direct local effects on the skin, eyes and GI tract. Based on human data concentrations of 0.5-4.0 % were irritating to the skin, while a concentration of 8.0 % was corrosive to the skin of animals. Lethality has been reported for animals at oral doses of 240 and 400 mg/kg b.w. Fatal ingestion and fatal dermal exposure has been reported for humans.

Sodium hydroxide, with specific concentration limits, is classified as follows: skin corrosive category 1A; H314 at concentrations ≥ 5 %; skin corrosive category 1B; H314 at concentrations ≥ 2 % and < 5 %; skin irritant category 2; H315 at concentrations ≥ 0.5 % and < 2 %; eye irritant category 2; H319: at concentrations ≥ 0.5 % and < 2 % (Regulation (EC) No. 1272/2008[24]).[61]

[61] ECHA: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=134413&HarmOnly=no?fc=true&lang=en (accessed 08/04/2012).

Subacute, subchronic and chronic toxicity studies

No valid animal data are available on repeat dose toxicity studies by oral, dermal, inhalation or by other routes for sodium hydroxide. However, under normal handling and use conditions (non-irritating) neither the concentration of sodium in the blood nor the pH of the blood will be increased and therefore sodium hydroxide is not expected to be systemically available in the body.

Genotoxicity

Both *in vitro* (De Flora et al., 1984; Morita et al., 1989) and *in vivo* (Brook et al., 1985, as cited in OECD, 2002c; Aaron et al., 1989) genetic toxicity tests indicated no evidence for mutagenic activity of sodium hydroxide.

Carcinogenicity

Valid carcinogenicity studies in animals are not available for sodium hydroxide. There is no evidence sodium hydroxide to be carcinogenic in exposure situations that are relevant for humans.

Developmental and reproductive toxicity

No studies are available on toxicity to reproduction and development but the substance will neither reach the foetus nor reach male and female reproductive organs in effective toxic concentrations. Therefore, no risk for reproduction or development is expected from the use of sodium hydroxide as a previous cargo.

3.31.2.4. Allergenicity

Available data give no indication that sodium hydroxide acts as an allergen or an adjuvant at the concentrations expected from its use as a previous cargo.

3.31.3. Conclusions

The CONTAM Panel recommends that the restriction "only where the immediate previous cargo to it is on the list and is not similarly restricted" be removed. This is because the restriction reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels at the time it was put in place. Changes in shipping practices and the current construction of vessels for the transport of edible fats and oils now make this restriction unnecessary. Current shipping practices also mean that when potassium hydroxide is transported prior to edible fats and oils, the design of the tanker will be such that sodium hydroxide has to be transported as a solution. Hence, the CONTAM Panel recommends that the entry for the substance in the annex to Commission Directive 96/3/EC[5] be amended to "Sodium hydroxide solution (caustic soda) (CAS No 1310-73-2)"

JECFA has established an ADI "not limited" and the SCF has established an ADI "not specified" for sodium hydroxide, which the CONTAM Panel considers appropriate. Sodium hydroxide is not genotoxic or allergenic. Sodium hydroxide is toxic only when it is present at sufficient concentration that it changes the local OH^- concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to sodium hydroxide as a previous cargo do not give rise to any toxicological concern. Exposure to small amounts of sodium hydroxide locally may cause irritation to the skin or eyes. However, the maximum potential levels of sodium hydroxide arising in fats or oils following its transport as a previous cargo would be of no concern. There are no reactions of health concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that sodium hydroxide solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.32. SILICON DIOXIDE (microsilica) (CAS No 7631-86-9)

Silicon dioxide, also called silica, can occur either in crystalline or amorphous form. It is poorly soluble in water (15-68 mg/L in water at 20 °C and pH 5.5-6.6).

Raw silica occurs in nature as quartz or quartz sand, but also in sands from various organisms (diatomaceous earths). Purified silicon dioxide is usually precipitated from water glass (silica gels). Water glass is obtained after heating quartz sand and sodium carbonate to high temperatures, which removes carbon dioxide and yields sodium silicate.

Silicon dioxide is primarily used to form glass, optical fibers (fused silica), silicon wafers for electronics and sun collector panels, but also for ceramics, as an ingredient in Portland cement and tooth paste. Many of these products contain substantial proportions of nano size particles.

3.32.1. Previous evaluations

The SCF evaluated silicon dioxide as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that silicon dioxide was permitted as a food additive (E551, under Directives 95/2/EC[59] and 96/77/EC[62]). It was not necessary to establish an ADI ("ADI not specified"), as the SCF (1991) considered that following oral exposure to amorphous silicon dioxide, the substance was biologically inert and any material absorbed would be excreted by the kidneys without toxic accumulation. In the 2003 SCF evaluation of acceptable previous cargoes, silicon dioxide was not further evaluated as it was already considered acceptable (SCF, 2003a).

JECFA (1970b) evaluated the use of amorphous silica as an anti-caking agent, at its meeting in 1969. It was concluded that use was "Not limited except for good manufacturing practice".

In their draft screening assessment of quartz and cristobalite, Environment Canada concluded "*However, considering the substances are insoluble, have negligible vapour pressure and that they are particulates, it is unlikely that they would be bioavailable to cause generalised systemic effects or specific effects at the reproductive and developmental level*" (Environment Canada, 2011).

Synthetic amorphous silicas are used in a variety of cosmetics and are approved for use in human pharmaceuticals (OECD, 2004).

The US FDA (1979, 2010) has classified silica as GRAS and has approved its use as dietary food additives at levels up to 2 % by weight in food.

3.32.2. Current evaluation

Silicon dioxide is a solid at normal temperature and pressure, with a melting point above 1 400 °C. It is almost insoluble in water (< 70 mg/L). Hence, current shipping practices are such that it is not a suitable cargo for the type of tanker used to transport edible fats and oils by sea (see Documentation provided to EFSA).

3.32.2.1. Expected impurities

Silicon dioxide is not expected to contain impurities of concern.

3.32.2.2. Reactivity and reaction products

No reaction products of concern are known or expected when present in edible fats and oils as carryover.

[62] Commission Directive 96/77/EC of 2 December 1996 laying down specific purity criteria on food additives other than colours and sweeteners. OJ L 339, 30.12.1996, p. 1-69.

3.32.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Consistent with its physico-chemical properties, there is negligible absorption of silica from the GI tract following oral administration to rats for up to one month (Degussa, 1968; Klosterkoetter, 1969, as cited in OECD, 2004). In 12 human volunteers receiving 2 500 mg synthetic amorphous silica, there was a slight, not statistically significant increase in the urinary excretion of silicon dioxide (Degussa, 1966, as cited in OECD, 2004). OECD (2004) concluded that "*Intestinal resorption appears to be insignificant in animals and humans*". They also noted that "*the small apparent increases in the urine output (of silica) of human volunteers were remarkably low as compared with the high dose of 2,500 mg SiO_2 applied*". The CONTAM Panel agrees with the conclusion that there is negligible systemic exposure to silica, following exposure by the oral route.

Acute toxicity

Silica is of low acute toxicity following oral exposure. No deaths were observed following administration of single doses up to >10 000 mg/kg b.w. (cited in OECD, 2004).

Silica is not irritating to the skin of rabbits (OECD, 2004). Prolonged exposure in humans may lead to dryness or degenerative eczema of the skin (Wacker-Chemie, 2000, as cited in OECD, 2004).

Silica has no or only weak and transient irritating effects on the eyes (OECD, 2004). Silica does not require classification for irritation to the eyes.

Subacute, subchronic and chronic toxicity studies

Wistar rats were administered doses of up to 4 000-4 500 mg/kg b.w. per day amorphous silica in their diet for 13 weeks. CD-1 mice were fed up to 8 000 mg/kg b.w. per day amorphous silica in their diet for 6 months. No treatment related findings were observed in either study (OECD, 2004).

Genotoxicity

Tests for chromosome aberration in Chinese hamster ovary cells and human embryonic lung cells (WI-38), mammaliam gene mutation in Chinese hamster ovary cells, bacterial cell mutation with and without metabolic activation in *S. typhimurium* strains, and UDS in cultures rat hepatocytes were all negative.[63] Tests for mutations of the HPRT gene in alveolar type-II cells isolated from the lungs of Fischer rats exposed to amorphous silica by inhalation, chromosome aberrations in bone-marrow cells isolated from Sprague-Dawley rats exposed to silica by gavage, dominant lethal effects in Sprague-Dawley rats exposed to silica by gavage, host-mediated mitotic recombination in *Saccharomyces cerevisiae* D-3 in ICR mice exposed to silica by gavage and host-mediated gene mutation in *S. typhimurium* in ICR mice exposed to silica by gavage were also negative.[63] Sub-chronic inhalation of crystalline silica has been reported to increase the frequency of mutations of the HPRT gene in alveolar type-II cells isolated from the lungs of Fischer rats (Johnston et al., 2000). The CONTAM Panel concluded that silicon dioxide was not genotoxic.

Carcinogenicity

Groups of B6C3F1 mice were fed food grade micronised silica for 93 weeks to give total cumulative doses of up to 160 g/mouse (corresponding to 7 500 mg silica/kg b.w. per day). Groups of Fischer rats were also fed with this preparation of silica, for 102 weeks to give total cumulative doses of up to 435-580 g/rat (corresponding to 2 500 mg silica/kg b.w. per day). There were no treatment related increases in the incidences of any tumour type, not were there any significant effects on survival or morbidity (Takizawa et al., 1988, as cited in OECD, 2004).

[63] http://www.echa.europa.eu/ (accessed 25/03/2012).

Developmental and reproductive toxicity

In studies in pregnant animals, amorphous silica was administered to rats at doses up to 1 350 mg/kg b.w. for 10 days, to mice at doses up to 1 340 mg/kg b.w. for 10 days, to rabbits at doses up to 1 600 mg/kg b.w. for 13 days, and to hamsters at doses up to 1 600 mg/kg b.w. for 5 days. No effects on development were observed in any of the species tested. In their review of silica, OECD (2004) concluded that "*based on the weight of evidence, prolonged exposure to synthetic amorphous silica, applied before and during pregnancy at high doses, is not expected to produce harmful effects on the reproductive performance or embryonic/foetal development in experimental animals*." The CONTAM Panel agrees with this conclusion.

3.32.2.4. Allergenicity

Silica is not known to be an allergen. It may possess some irritant and adjuvant properties, depending on the particle size and specific properties of the preparation (Granum et al., 2001; Hirai et al., 2012; Vallhov et al., 2012). Considering the dilution factor for carryover into a subsequent cargo of edible fats or oils, the CONTAM Panel considers that this would not constitute a problem when silica is used as a previous cargo.

Nanosized silica particles are being investigated for medical applications, but pro-inflammatory activites of some types of nanosized silica particles have been reported as well (Napierska et al., 2010). Considering the dilution factor, the amount of nanosized silica particles resulting from carryover from a previous cargo would not constitute a concern.

3.32.3. Conclusions

Because silicon dioxide is a solid and essentially insoluble in water, current shipping practices mean that it is not possible to transport this substance by sea in a tanker suitable for the transport of edible fats and oils. This is because of difficulties in transfer and cleaning of the tanker.

JECFA has established an ADI "not limited except for good manufacturing practice" and the SCF has established an ADI "not specified" for silicon dioxide, on the basis that there will be negligible absorption from the GI tract. The CONTAM Panel considers this to be appropriate. Consistent with this, silicon dioxide has negligible systemic toxicity. It is not genotoxic and there is no allergenic potential of concern. There are no reaction products or impurities of toxicological concern.

The CONTAM Panel concludes that although silicon dioxide meets the toxicological criteria for acceptability as a previous cargo for edible fats and oils, it is not a suitable cargo on the basis of current shipping practices, due to difficulties in transfer and cleaning of the tanker. The CONTAM Panel therefore recommends that silicon dioxide be deleted from the annex to Commission Directive 96/3/EC.[5]

3.33. SORBITOL (D-sorbitol; hexahydric alcohol; D-sorbite) (CAS No 50-70-4)

Sorbitol is a natural food component, occuring in a number of berries and fruits, including apples, pears and plums. It has a low octanol/water partition coefficient, with log P_{ow} = -2.2. Sorbitol is very soluble in water (220 g/100 mL at 20 °C).

D-Sorbitol is produced mainly by the catalytic hydrogenation of naturally occurring hexoses, primarily D-glucose.

Sorbitol is used in foods because of its unique combination of functional properties as a humectant, sweetener, bulking agent, stabilizer, softener and emulsifier, and its surface-active properties. Use in personal care products (mainly toothpaste), food and confections, as well as in the manufacture of vitamin C accounted for 80 % of world consumption in 2010.

3.33.1. Previous evaluations

The SCF evaluated sorbitol as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that sorbitol was approved as a food additive (E420), with an ADI "not specified". In the 2003 SCF evaluation of acceptable previous cargoes, sorbitol was not further evaluated as it was already considered acceptable (SCF, 2003a).

Sorbitol is approved for use as a food additive (bulk sweetener: E420) by the European Commission (SCF, 1985). Rather than establish an ADI, the SCF designated sorbitol as "Acceptable", with a note that laxation may occur at high intakes, but in general undesirable laxative symptoms are unlikely at consumption of up to 20 g/person per day. In a subsequent clarification it was noted that this limit was not specific for sorbitol, but would be sufficient to cover all polyol sweeteners (SCF, 1989). The minimum laxative dose of sorbitol was likely to be greater than this (JECFA, 1973).

Sorbitol is approved for use as a food contact additive in plastics by the European Commission under Directive 2002/72/EC, with no restrictions other than the generic overall migration limit of 60 mg/kg food.

JECFA (1982), at its 26th meeting confirmed its earlier conclusion that it was not necessary to establish an ADI for sorbitol, i.e. ADI "not specified".

Sorbitol is classified as GRAS by the US FDA. It is considered a food substance and can be used as an ingredient in certain foods without limitation, other than that determined by good manufacturing practices. This can result in up to 99 % sorbitol in the resultant food. The FDA requires labelling of food containing sorbitol where reasonably foreseeable consumption may result in a daily ingestion of 50 grams, with the statement: "*Excess consumption may have a laxative effect.*" (FDA, 2011c).

The OECD SIDS review of sorbitol concluded that "This chemical is considered of low priority for further work at the OECD, due to its intrinsic properties indicating a low hazard" (OECD, 2009).

Sorbitol is not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.[24] It is not classified as dangerous according to Directive 67/548/EEC.[64]

3.33.2. Current evaluation

Sorbitol is a solid at normal temperature and pressure, with a melting point of ~100 °C. Hence, in this form it is not a suitable cargo for the type of tanker used to transport edible fats and oils by sea. When used as a previous cargo to edible fats and oils it has to be transported as a solution, to enable effective transfer and tank cleaning (see Documentation provided to EFSA).

3.33.2.1. Expected impurities

During the preparation of D-sorbitol from D-glucose by catalytic hydrogenation, D-mannitol is formed. However, no impurities are expected that would be of toxicological concern when sorbitol is used as a previous cargo for edible fats and oils.

3.33.2.2. Reactivity and reaction products

No reaction products of concern are known or expected with edible fats or oils.

[64] Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. OJ L 196, 16.8.1967, p. 1-98.

3.33.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Sorbitol is actively absorbed in the small intestine, though more slowly than glucose or fructose (JECFA, 1973; Rumessen, 1992). Once absorbed, sorbitol is subject to intermediary metabolism, either by oxidation after conversion to glucose or by direct oxidation of the primarily formed fructose, catalysed by sorbitol dehydrogenase. Like other carbohydrates, it is eventually transformed mainly to CO_2 (JECFA, 1973).

Acute toxicity

Sorbitol is of low acute toxicity by the oral route, with LD_{50} values in rats and mice > 15 000 mg/kg b.w. (JECFA, 1973). Sorbitol is not classifiable as irritating to the skin or eyes.[65] Based on its structure and characteristics, it is not anticipated that sorbitol would cause any irritation to the skin or eyes at the levels that would be encountered when used as a previous cargo.

Genotoxicity

Sorbitol was negative in an Ames test using strains TA92, TA1535, TA100, TA1537, TA94 and TA98 (Ishidate et al., 1984). Sorbitol had no effect on the frequency of chromosomal aberrations in Chinese hamster ovary cells (Yoshida et al., 1978) or in Chinese hamster lung fibroblasts (no activation), *in vitro* (Ishidate et al., 1978). Sorbitol was negative for mutagenicity in host mediated assays of mutagenicity in mice using *Salmonella* strains G46 and TA1530, and *S. cerevisiae* strain D3 as indicator strains (Stanford Research Institute, 1972). An assay *in vivo* in mouse bone marrow for chromosomal aberrations was also negative (Stanford Research Institute, 1972). High concentrations of sorbitol can cause non-specific effects on chromosomes in some *in vitro* assays, such as with WI-38 human embryonic lung cells (Galloway et al., 1987). The CONTAM Panel concluded that sorbitol is not genotoxic.

Carcinogenicity

Male and female CD rats were fed diets containing 0 or 20 % sorbitol for 2 years. There was no effect of treatment on the incidence of any tumour type. A number of non-neoplastic changes were observed, due to metabolic disturbance in the animals (cited in JECFA, 1978b).

Developmental and reproductive toxicity

In studies of reproduction in rats and of development in rats and rabbits, sorbitol produced no effects of concern. There was no increase in developmental abnormalities. Effects observed in the reproductive toxicity study appeared to be secondary to a marked reduction in food intake and the consequent suppression of body weight gain caused by the high concentration of sorbitol (20 %) in the diet (cited in JECFA, 1978b).

3.33.2.4. Allergenicity

Available data give no indication that sorbitol acts as an allergen or an adjuvant at the concentrations expected from its use as a previous cargo.

3.33.3. Conclusions

Current shipping practices mean that when sorbitol is transported prior to edible fats and oils, the design of the tanker will be such that sorbitol has to be transported as a solution. Hence, the CONTAM Panel recommends that the entry for the substance in the annex to Commission Directive 96/3/EC[5] be amended to “Sorbitol solution (D-sorbitol; hexahydric alcohol; D-sorbite) (CAS No 50-70-4)”.

[65] http://www.inchem.org/documents/icsc/icsc/eics0892.htm

An ADI for sorbitol was considered unnecessary by the SCF and JECFA, due to its natural occurrence in the diet and low toxicity. The CONTAM Panel considers this appropriate. Sorbitol is not genotoxic or allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated.

The CONTAM Panel therefore concludes that sorbitol solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.34. MOLASSES (CAS No 57-50-1)

Classically, molasses is the residue from processing sugar cane, sugar beets or, less frequently, sorghum or citrus, to sugar: sucrose is crystallized from the juice obtained after crushing and extraction with water, possibly in several steps and by reconcentration through boiling off water. The reconcentrated residue, a dark, viscous (honey-like) liquid called molasses, still contains a large proportion of sugars, but also other water-soluble components.

Raw molasses contain various sugars (the major one being sucrose), cellulose, calcium, potassium, iron, chloride, phosphate sulphate and a number of vitamins such as inositol, choline and niacin. Most molasses is used in animal feeds, either as a source of nutrients or to bind pellets. It is also used in foods or to produce alcohol (e.g. rum). Finally it is as a source of nutrients for fermentation in biotechnology.

The Codex Alimentarius recognises under *Processed Foods of Plant Origin/Derived Products of Plant Origin/Miscellaneous Derived Edible Products of Plant Origin* the following types of molasses: citrus, sorghum, sugar beet, and sugar cane (Codex Alimentarius, 2010). However, in general, any liquid food or feed ingredient obtained from plants that contains in excess of 43 % sugars is termed molasses. Hence, molasses can also be obtained as a by-product of the manufacture of pressed wood (Curtin, 1983).

Today an increasing amount of the sugar is converted to alcohol for fuel purposes, and technologies have been developed not only to utilize the sugars, but also polysaccharides from the stem and leaves of the sugar cane and other plants. This involves cleavage reactions and possibly other chemical reactions by means and chemicals unknown to the CONTAM Panel. It is unclear whether all the resulting residues are considered molasses and could fall under this item as previous cargoes. Therefore, the CONTAM Panel has restricted its consideration of molasses in this Opinion on acceptable previous cargoes for edible fats and oils to the product obtained from the conventional sugar processing industry using sugar cane, sugar beet, citrus or sorghum.

During the preparation of molasses from young sugar cane, sulphur dioxide is added as a preservative, leading to sulphite residues in the final product.

The CAS no. 57-50-1 refers to D(+)-sucrose, i.e. to a possibly minor component of the whole material.

3.34.1. Previous evaluations

The SCF evaluated molasses as a previous cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that molasses is an acceptable residue from sugar processing. In the 2003 SCF evaluation of acceptable previous cargoes, molasses was not further evaluated as it was already considered acceptable (SCF, 2003a).

In its opinion on products from glyphosate-tolerant genetically modified sugar beet H7-1, for food and feed uses, EFSA's Scientific Panel on Genetically Modified Organisms considered the safety of molasses (EFSA, 2007a). It was concluded that products from sugar beet H7-1, including molasses, are safe as food.

Molasses is exempt from certification by the US FDA (FDA, 2011d) when used as a colour additive for food.

JECFA considers a standard portion size of molasses to be 30 g (JECFA, 2007), i.e. 500 mg/kg b.w. in an adult.

3.34.2. Current evaluation

3.34.2.1. Expected impurities

The addition of sulphite (SO_2) as a preservative to young sugar cane during the extraction of sugar results in levels of sulphite in the molasses of up to 100 mg/kg. According to Codex Alimentarius, the maximum permissible level of SO_2 in molasses for human consumption is 70 mg/kg (Codex Alimentarius, 2012). This is also the maximum level permitted by Council Directive 95/2/EC[59] (EC, 1995). In its opinion on allergenic foods, the EFSA Panel on Dietetic Products, Nutrition and Allergies of EFSA (2004) considered molasses to be in the high sulphite (>100 mg/kg) group of foods. JECFA (2000) confirmed the ADI for sulphites in food as 0-0.7 mg/kg b.w., which was originally established in 1974. This ADI was based on effects in long-term studies in rats, including a 3-generation study, in which local irritation in the stomach was observed, with a NOAEL of 70 mg/kg b.w. per day.

Molasses may also contain pesticides, but the dilution involved in the carryover from it use as a previous cargo will bring the concentrations to below the level of 0.01 mg/kg applied for unauthorized uses of pesticides in food. The limited available information supports the conclusion that levels of pesticide residues and of organic contaminants would not be sufficient to cause concern when molasses is used as a previous cargo (Carnegie and Wood, 1972; Yang et al., 1976; Šovljanski et al., 2006; Erdoğrul, 2008).

3.34.2.2. Reactivity and reaction products

No reaction products of concern are anticipated with edible fats and oils.

3.34.2.3. Toxicological profile

<u>Absorption, distribution, metabolism and elimination</u>

Sucrose is a common component of the diet and is readily absorbed from the GI tract. It enters intermediary metabolism and is eventually converted to CO_2.

<u>Acute toxicity</u>

Molasses is not notably irritating to the skin or eyes (Chemwatch, 2010).

<u>Genotoxicity</u>

No specific information is available on the genotoxicity of molasses. However, in view of its composition it is not expected to be genotoxic.

3.34.2.4. Allergenicity

No reports have been found regarding allergenicity of molasses from sugar beet and sugar cane, or on allergenicity of sugar beet and sugar cane apart from rare reports on allergenicity of pollen from the two plants (Agata et al., 1994; Luoto et al., 2008). The CONTAM Panel considers that as a previous cargo, sugar beet and sugar cane molasses do not pose any concern in terms of irritancy, adjuvanticity, or allergenicity. No indications have been found in the literature that sorghum molasses from sorghum cane has significant allergenicity. Citrus molasses will contain citrus allergens (Ebo et al., 2007; Guarneri et al., 2008) which are relatively weak food and contact allergens. Taking into account the

dilution factor from carryover of molasses as a previous cargo, the CONTAM Panel considers that these allergens pose no concern in relation to citrus molasses as a previous cargo.

Molasses may contain high levels of sulphites (>100 mg/kg). Sulphites may cause hypersensitivity reactions in sensitive individuals (EFSA, 2004), and are listed in Annex IIIa of the EU Labelling Directive as an allergenic food with special labelling requirements at concentrations of more than 10 mg/kg or 10 mg/L (expressed as SO_2). Taking into account the high dilution factor (1:10 000) from carryover of molasses as a previous cargo, the CONTAM Panel considers that the sulphite content of molasses will not represent any problem when molassess is used as a previous cargo.

3.34.3. Conclusions

The CONTAM Panel recommends that the entry for the substance in the annex to Commission Directive 96/3/EC[5] to be amended to "Molasses", omitting the CAS No 57-50-1. This is because the CAS No refers to D(+)-sucrose, which may be only a minor component in molasses.

Given its long history of use as a food, and the available information on its components, there are no toxicological concerns regarding the use of molasses obtained from sugar cane, sugar beet, citrus or sorghum, as a previous cargo for edible fats and oils. There is no allergenic potential of concern for molasses from these sources. The amount of sulphite present in some molasses would not be of concern following dilution in edible fats and oils as subsequent cargo. No other impurities or reaction products of concern are known or anticipated.

The CONTAM Panel therefore concludes that molasses, which has been produced from the conventional sugar processing industry using sugar cane, sugar beet, citrus or sorghum, meets the criteria for acceptability as a previous cargoe for edible fats and oils.

3.35. BEESWAX (WHITE AND YELLOW) (CAS No 8006-40-4 and 8012-89-3)

The CAS No. 8006-40-4 refers to white beeswax, and the CAS No. 8012-89-3 refers to yellow beeswax.

Beeswax is used by bees to build up combs. The chemical composition of beeswax is rather complex: more than 300 compounds have been identified, mainly esters of higher fatty acids and alcohols, with small amounts of hydrocarbons, acids and other substances. Volatile compounds are also present, and about 50 chemicals have been identified. The main constituents are free fatty acids (mostly saturated, C24-C32); free primary fatty alcohols (C28-C35); linear wax monoesters and hydroxymonoesters (C40–C48), from palmitic acid, 15-hydroxypalmitic acid and oleic acid; complex wax esters (1527 %) containing 15-hydroxypalmitic acid or diols, which, through their hydroxyl group, are linked to another fatty acid molecule; odd-numbered, straight-chain hydrocarbons (12-16 %) with a predominant chain length of C27-C33.

The ratio of the acids to the esters is used by various pharmacopoeias to describe the quality of beeswaxes, but it can be influenced by technology used in beeswax production/purification. Usually, the ester/acid ratio is lower (3.3-4.3) for European beeswax than for Asian beeswax (8-9).

Beeswax is obtained from combs by hot water immersion, extraction with boiling water and press, steam extraction or centrifugation.

White beeswax can be produced from yellow beeswax by bleaching, e.g. with hydrogen peroxide or sunlight (JECFA, 2006).

3.35.1. Previous evaluations

The SCF evaluated beeswax (white and yellow) as previous a cargo in 1996 and considered it acceptable (SCF, 1997a). This conclusion was based on the fact that beeswax (white and yellow) is approved as a food additive with the number E901, for use as a glazing agent for food (SCF, 1992c).

In the 2003 SCF evaluation of acceptable previous cargoes, beeswax (white and yellow) was not further evaluated as it was already considered acceptable (SCF, 2003a).

Beeswax was evaluated as a glazing agent and as a carrier for flavours by the former AFC Panel (EFSA, 2007b). It was concluded that there were insufficient data on beeswax itself to enable an ADI to be established. However, the safety of beeswax could be assessed on the basis of information on its main constituents and on those of plant waxes with a similar structure. The former AFC Panel concluded that the use of beeswax as an additive for existing food uses and a proposed new food use as a carrier of flavours was not of safety concern. The former AFC Panel noted that the NOAELs for the main constituents of beeswax and of structurally similar plant waxes were 10-50 times higher than the very conservative exposure estimate of 22 mg/kg b.w. per day when used as a food additive, and that the NOAELs were generally the highest doses tested.

Beeswax (8012-89-3) is approved for use as a food contact additive in plastics by the European Commission under Directive 2002/72/EC,[66,] with no restrictions other than the generic overall migration limit of 60 mg/kg food.[19] It is also authorised for use as an additive in the coating of regenerated cellulose film, under Directive 2007/42/EC,[67] with no restrictions.

Beeswax is classified as GRAS by the US FDA. It is can be used as an ingredient in certain foods without limitation, other than that determined by good manufacturing practices (FDA, 2011e).

JECFA (1992) first evaluated beeswax at its 39th meeting when it was concluded that "*although an evaluation in the traditional manner could not be carried out, the long history of use of natural yellow beeswax without apparent adverse effects provided a degree of assurance that its present functional uses (release and glazing agent in bakery products, glazing agent on fresh and frozen fruit, glazing agent on candy, carrier for flavours and component of chewing-gum bases) did not raise any toxicological concerns*." This conclusion was also considered applicable to white beeswax. JECFA (2006) revaluated beeswax at its 65th meeting, as a carrier of flavourings in certain water-based drinks. No ADI was established. However, JECFA concluded that "*the proposed uses would not result in dietary exposure that raised concern about safety, especially in view of the long history of use of beeswax and the absence of toxicity of the main components*". JECFA (2006) estimated that exposure to beeswax could be as much as 650 mg per person per day, i.e. there would be no concern at dietary exposures of 0 - ~10 mg/kg b.w. per day in adults.

Beeswax (CAS No. 8012-89-3) has been designated by US-EPA as an inert ingredient eligible for use in pesticide products, List 4A. Such products may be used in whatever amounts are believed necessary to result in an effective product when combined with an approved active ingredient (US-EPA, 2010).

3.35.2. Current evaluation

3.35.2.1. Expected impurities

Beeswax may be contaminated by fat-soluble pollutants, such as acaricides applied in beekeeping and other pesticides at levels between < LOD (0.01-0.05 mg/kg) and 10 mg/kg (Wallner, 1999; Schroeder and Wallner, 2003). Also *p*-dichlorobenzene used against wax moths may contaminate beeswax (Wallner, 1992; Bogdanov et al., 2004). Another potential problem may be *Penibacillus* larvae spores, which can only be destroyed by heating at 140 °C for 30 minutes (Machova, 1993).

Furthermore, beeswaxes can be chemically treated to restore their colour and other characteristics by means of sulphuric acid, hydrogen peroxide, or potassium permanganate.

[66] Commission Directive 2002/72/EC of 6 August 2002 relating to plastic materials and articles intended to come into contact with foodstuffs. OJ L 220, 15.8.2002, p. 18-58.

[67] Commission Directive 2007/42/EC of 29 June 2007 relating to materials and articles made of regenerated cellulose film intended to come into contact with foodstuffs. OJ L 172, 30.6.2007, p. 71-82.

After dilution resulting from carryover into edible fats and oils, the substances resulting from the above sources are not expected to be of concern.

3.35.2.2. Reactivity and reaction products

No reaction products of concern are anticipated with edible fats and oils.

3.35.2.3. Toxicological profile

There are very few data on the toxicity of beeswax *per se*, but there are a number of studies on the major constituent groups of substances in beeswax.

Absorption, distribution, metabolism and elimination

Beeswax has a high melting point (relative to body temperature), is insoluble in water and is hydrophobic in nature. These properties suggest that absorption from the GI tract would be very poor and that it is unlikely to be susceptible to metabolism by digestive enzymes or the intestinal microbiota (JECFA, 2006). However, no experimental data are available on the absorption of beeswax. There is some evidence that beeswax can be digested by some microorganisms, for example present in the intestine of certain insects, such as larvae of the wax moth, *Galleria mellonalla* (Opdyke, 1976).

There is some evidence that the main constituents of beeswax, such as the fatty acid monoesters, are poorly absorbed (Place, 1992). It has been suggested that limited intestinal hydrolysis of esters to the corresponding alcohols and acids may occur, which would then be absorbed and enter normal cellular metabolic pathways (JECFA, 2006; EFSA, 2007b), although the rate of any such hydrolysis appears to be low (Place, 1992). Similarly, the long chain *n*-alkanes present in beeswax are poorly absorbed, and that which is absorbed will be metabolised to long chain alcohols and fatty acids, which will enter normal cellular metabolic pathways (JECFA, 2006; EFSA, 2007b).

Acute toxicity

The oral LD_{50} for beeswax (type not specified) in rats was > 5 g/kg b.w. (JECFA, 1992). A mixture of high molecular weight aliphatic alcohols extracted from hydrolysed beeswax, known as D-002, had an oral LD_{50} in rats of > 5 g/kg b.w. No signs of toxicity or histopathological changes were observed over the 14 days of observation (Rodeiro et al., 1995, as cited in EFSA 2007b). An alcoholic extract of yellow beeswax, known as beeswax absolute, was not irritating to the skin of mice or rabbits, either intact or abraded (Opdyke, 1976). Beeswax was not irritating to the skin of human volunteers in patch tests (Opdyke, 1976).

Subacute, subchronic and chronic toxicity studies

Studies of the main components of beeswax, and of the extract of high molecular weight aliphatic alcohols from hydrolysed beeswax known as D-002 for up to 13 weeks in rats and studies of D-002 in rats and dogs for 52 weeks, showed them to be of low toxicity. NOAELs were generally the highest doses tested, the lowest in the 52-weeks studies being 250 mg/kg b.w. per day in dogs (JECFA, 2006; EFSA, 2007b).

Beeswax has a long history of safe use as a foodstuff in humans. It is also used as a food supplement. Studies on the main component groups of substances in beeswax in humans have not shown any adverse effects, other than possible accumulation of long chain *n*-alkanes in rare, high consumers, possibly due to some inborn error of *n*-alkane absorption or disposition (JECFA, 2006; EFSA, 2007b).

Genotoxicity

Yellow beeswax was not mutagenic in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 or TA100, or in *E. coli* Wp2, with and without metabolic activation with hepatic S9 (Prival et al., 1991).

White beeswax was negative for tests of genotoxicity in *S. typhimurium* strains TA1535, TA1537, and TA1538, and in *Saccharomyces cerevisiae*, with and without metabolic activation (Opdyke, 1976; JECFA, 2006). The beeswax extract D-002 was not mutagenic *in vivo* in a bone marrow micronucleus test in mice and in a dominant lethal test in mice (Rodeiro et al., 1998, as cited in JECFA, 2006).

Carcinogenicity

In the absence of any evidence of genotoxicity of beeswax or its major components, and on the basis of the results of carcinogenicity studies with the major components of beeswax (JECFA, 2006; EFSA, 2007b) the CONTAM Panel concluded that there is no concern for potential carcinogenicity when beeswax is used as a previous cargo to edible fats and oils.

Developmental and reproductive toxicity

There are no specific studies on the developmental or reproductive toxicity of beeswax. Studies of the main component groups of beeswax have shown they have a very low potential for developmental or reproductive toxicity. In general, the NOAEL was the highest dose tested, and the lowest NOAEL was 500 mg/kg b.w. per day (the highest dose tested) (JECFA, 2006; EFSA, 2007b).

3.35.2.4. Allergenicity

Beeswax will be contaminated with propolis and other substances, including pollen, in the bee hive (Rajpara et al., 2009; Walgrave et al., 2005). It will therefore contain both IgE-eliciting allergens like pollen, and contact allergens like 3-methyl-2-butenyl caffeate and phenylethyl caffeate (Walgrave et al., 2005). Accordingly, there are reports of contact allergy to beeswax (Garcia et al., 1995; Lucente et al., 1996; Junghans et al., 2002). However, because of the high dilution factor from carryover of beeswax as a previous cargo, the CONTAM Panel considers that allergenicity does not pose any concern when beeswax is used as a previous cargo.

3.35.3. Conclusions

Although specific information on beeswax is very limited, there is sufficient information from its human uses, its poor absorption and on its main component groups of chemicals for the CONTAM Panel to conclude that it will not pose any toxicological concern when used as a previous cargo. There is no evidence that it is genotoxic and there is no allergenic potential of concern. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated.

The CONTAM Panel therefore concludes that beeswax meets the criteria for acceptability as a previous cargo for edible fats and oils.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

- **Wine Lees (vinasses, vinaccia, argol, vini, argil, arcilla, weinstein, crude cream of tartare, crude potassium bitartrate) (CAS No 868-14-4).** The safety evaluation of wine lees as a previous cargo was previously based on the fact that tartrates have a group acceptable daily intake (ADI) of 30 mg/kg body weight (b.w.) per day established by the Joint Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA). However, “wine lees” is a crude mixture, and while (potassium) tartrate is a constituent, there are many others. The mixture (wine lees) has not been evaluated in toxicological studies. The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) considered that materials covered by the term wine lees (vinasses) could not be used as previous cargo because it cannot be excluded that substances of toxicological concern or significant food allergens are present. To ensure that this is not the case would take a careful processing and may even require testing of all batches. Therefore,

the CONTAM Panel concludes that "wine lees" does not meet the criteria for acceptability as a previous cargo for edible fats and oils.

- **Fatty acids (individually specified).** The fatty acids listed, butyric acid, valeric acid, caproic acid, heptanoic acid, caprylic acid, pelargonic acid (*n*-nonanoic acid), capric acid, lauric acid, lauroleic acid (3-dodecenoic acid), myristic acid, myristoleic acid (*n*-tetradecenoic acid), palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid, behenic acid, ricinoleic acid and erucic acid, are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and polychlorinated biphenyls (PCBs). The CONTAM Panel therefore concludes that the fatty acids specified meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels in the fatty acids are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

- **Fatty alcohols (individually specified).** Caproyl alcohol (1-hexanol), myristyl alcohol (1-tetradecanol), stearyl alcohol (1-octadecanol), butyl alcohol (1-butanol), capryl alcohol (1-*n*-octanol), cetyl alcohol (1-hexadecanol), decyl alcohol (1-decanol), lauryl alcohol (*n*-dodecanol), tridecyl alcohol (1-tridecanol) (CAS No 112-70-9) and oleyl alcohol (octadecenol) are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicty. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs. The CONTAM Panel therefore concludes that the fatty alcohols specified meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

- **Fatty alcohol blends (Lauryl myristyl alcohol (C12-C14) and cetyl stearyl alcohol (C16-C18)).** There are no toxicological concerns from the use of the fatty alcohol blends specified when used as previous cargoes for edible fats and oils. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs. The CONTAM Panel therefore concludes that mixtures of lauryl and myristyl alcohol as well as cetyl and stearyl alcohol meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

- **Fatty acid methyl esters (individually specified).** The fatty acid methyl esters methyl laurate (methyl dodecanoate), methyl palmitate (methyl hexadecanoate), methyl stearate (methyl octadecanoate) and methyl oleate (methyl octadecenoate), produced by the combination of the respective fatty acids with methanol, are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs. The CONTAM Panel therefore concludes that the fatty acid methyl esters specified meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

- **Fatty acids esters - any ester produced by the combination of the above listed fatty acids with any of the above listed fatty alcohols. Examples of these are butyl myristate, oleyl palmitate and cetyl stearate.** Fatty acid esters produced by the combination of acceptable fatty acids with acceptable fatty alcohols are of no toxicological concern when used as

previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs. The CONTAM Panel therefore concludes that fatty acid esters produced by the combination of acceptable fatty acids with acceptable fatty alcohols meet the criteria for acceptability as previous cargoes for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

- **Acid oils and fatty acid distillates - from vegetable oils and fats and/or mixtures thereof and animal fats and oils.** Acid oils and fatty acid distillates are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs. The CONTAM Panel therefore concludes that acid oils and fatty acid distillates from vegetable oils and fats and/or mixtures thereof and animal fats and oils meet the criteria for acceptability as previous cargoes or edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

- **Animal, marine and vegetable and hydrogenated oils and fats as specified by the Marine Environment Protection Committee (MEPC) of the International Maritime Organisation (IMO).** Animal, marine and vegetable and hydrogenated oils and fats as specified by the MEPC of the IMO (Annex 6), are of no toxicological concern when used as previous cargoes. Nor is there any concern regarding their possible allergenicity. No reaction products of toxicological concern are known or anticipated. The only impurities of potential concern are the highly lipophilic contaminants, dioxins and PCBs. The CONTAM Panel therefore concludes that animal, marine and vegetable and hydrogenated oils and fats according to the MEPC of the IMO (Annex 6) meet the criteria for acceptability as a previous cargo for edible fats and oils, provided the dioxin and PCB levels are such that the final concentration in the fats and oils as subsequent cargoes complies with the European legislation.

- **Acetic acid (ethanoic acid, vinegar acid, methane carboxylic acid) (CAS No 64-19-7).** On the basis of its low toxicity and its natural occurrence in food and in the body, the CONTAM Panel does not consider it necessary to establish an ADI for acetic acid. It causes adverse effects only when it is present at sufficient concentration to change the H^+ concentration. It will be diluted and buffered by the contents of the gastrointestinal (GI) tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to acetic acid do not give rise to any toxicological concern. Exposure to small amounts of acetic acid locally may cause irritation to the skin or eyes. However, studies in experimental animals and humans have shown that the maximum potential levels of acetic acid arising in fats or oils following its transport as a previous cargo would be of no concern. Acetic acid is not genotoxic at physiological pH, and it is not allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated. The CONTAM Panel therefore concludes that acetic acid meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Sulphuric acid (CAS No 7664-93-9).** No ADI has been established for sulphuric acid. Sulphuric acid is toxic only when it is present at sufficient concentration to change the H^+ concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to sulphuric acid do not give rise to any toxicological concern. Exposure to small amounts of sulphuric acid locally may cause irritation to the skin or eyes. However, studies in experimental animals and humans have shown that the maximum potential levels of sulphuric acid arising in fats or oils following its transport as a previous cargo would be of no concern. Sulphuric acid is not genotoxic at physiological pH, and it is not allergenic. It will not give rise to any reaction

products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated. The CONTAM Panel therefore concludes that sulphuric acid meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Formic acid (methanoic acid; hydrogen carboxylic acid) (CAS No 64-18-6).** A group ADI for formic acid and ethyl formate of 0-3 mg/kg b.w. has been established, and on the basis of available evidence, the CONTAM Panel considers this appropriate. Formic acid is toxic only when it is present at sufficient concentration to change the H^+ concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to formic acid do not give rise to any toxicological concern. Exposure to small amounts of formic acid locally may cause irritation to the skin or eyes. However, the maximum potential levels of formic acid arising in fats or oils following its transport as a previous cargo would be of no concern. Formic acid is not genotoxic at physiological pH, and it is not allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated. The CONTAM Panel therefore concludes that formic acid meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Acetic anhydride (ethanoic anhydride) (CAS No 108-24-7).** No ADI has been established for acetic anhydride, as it is rapidly hydrolysed on contact with water to acetic acid, which is considered sufficiently innocuous that it is not necessary to establish an ADI. The CONTAM Panel considers this appropriate. Acetic anhydride is toxic at site of contact through its chemical reactivity or when the acetic acid formed by hydrolysis is present at sufficient concentration to change the H^+ concentration. Hydrolysis of any intact acetic anhydride in the GI tract will be very rapid and the acetic acid formed will be diluted and buffered by the contents of the GI tract. Hence, the levels that would occur following oral ingestion of fats or oils transported subsequent to acetic anhydride do not give rise to any toxicological concern. Exposure to small amounts of acetic anhydride locally may cause irritation to the skin or eyes. However, the maximum potential levels of acetic anhydride and acetic acid arising in fats or oils following its transport as a previous cargo would be of no concern. Acetic anhydride is not genotoxic at physiological pH. It is not anticipated that unhydrolysed acetic anhydride survives and hence it does not pose a risk of allergenicity when it is transported as a previous cargo. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated. The CONTAM Panel therefore concludes that acetic anhydride meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Acetone (dimethylketone; 2-propanone) (CAS No 67-64-1).** Acetone was considered acceptable as an extraction solvent for food but no ADI has been established. However, the United States Environmental Protection Agency (US-EPA) and the International Program on Chemical Safety (IPCS) have identified 900 mg/kg b.w. per day as the critical no-observed-adverse-effect level (NOAEL), from a 90-day study in rats, in which acetone was administered in drinking water. In the absence of data from chronic exposure, the CONTAM Panel considers this appropriate. This NOAEL would be adequately protective of the toxicological effects of any acetone present in a subsequent cargo of edible fats or oils, using a conventional safety factor of 100 with an additional factor of 10 to allow for possible chronic exposure (i.e. 900 mg/kg b.w. per day divided by 1 000 would result in a health based guidance value of 0.9 mg/kg b.w. per day), albeit chronic exposure is unlikely from the use of acetone as a previous cargo. Acetone is not genotoxic *in vivo* and it is not allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. The toxicological profile of 1,3-dioxolane, and by analogy that of other dioxolanes, is such that there would be no toxicological concern from the use of acetone as a previous cargo to edible fats and oils from any such reaction products. The method for manufacture of acetone gives rise to benzene as a potential impurity. The CONTAM Panel concluded that levels of up to 1 % would not give rise to any toxicological concern from acetone as a previous cargo. The

levels of benzene present in acetone are unlikely to exceed 0.1 %. The CONTAM Panel therefore concludes that acetone meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Heptane (commercial grades) (CAS No 142-82-5).** Although the toxicological database for heptane is limited, available data suggest that the substance is of relatively low systemic toxicity. It is not genotoxic or allergenic. There are no reaction products or impurities of toxicological concern. The CONTAM Panel therefore concludes that heptane meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Hexane (technical grades) (CAS No 110-54-3 / 64742-49-0).** Hexane (CAS No 110-54-3) and petroleum hydrocarbons, covered by CAS No. 64742-49-0, are of low systemic toxicity when administered by the oral route. Subchronic oral studies, although inadequate for establishment of a health based guidance value, did not show clinical signs of neuropathy except at very high doses. There are no adequate carcinogenicity data but the lack of mutagenic effects both *in vitro* and *in vivo* suggests that hexane is not a genotoxic carcinogen. Hexane is not allergenic. No impurities or reaction products with edible fats and oils of concern are known or expected when hexane is used as a previous cargo. The CONTAM Panel therefore concludes that hexane meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Cyclohexane (hexamethylene; hexanaphthene; hexahydrobenzene) (CAS No 110-82-7).** Cyclohexane is of low systemic toxicity via all routes of administration. No adequate observations in humans exposed orally or oral exposure studies in animals exist from which a health based guidance value may be established. There are no adequate carcinogenicity data but the lack of mutagenic effects both *in vitro* and *in vivo* suggests that cyclohexane is not a genotoxic carcinogen. Cyclohexane is not allergenic. There are no reactions of concern with edible fats and oils. However, cyclohexane obtained by hydrogenation may contain residues of benzene. The CONTAM Panel concluded that levels of up to 1 % would not give rise to any toxicological concern from cyclohexane as a previous cargo. The levels of benzene present in cyclohexane are unlikely to exceed 0.1 %. The CONTAM Panel therefore concludes that cyclohexane meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Pentane (CAS No 109-66-0).** *n*-Pentane is of low systemic toxicity via all routes of administration. No adequate observations in humans exposed orally or oral exposure studies in animals exist from which a health based guidance value may be established. No human or animal data are available on the carcinogenicity of *n*-pentane but given the lack of mutagenic effects and of relevant clinical signs in repeated toxicity studies there would be no concern for carcinogenicity when *n*-pentane is used as a previous cargo. *n*-Pentane is not allergenic and there are no impurities or reactions products of toxicological concern. The CONTAM Panel therefore concludes that pentane meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Isopropanol (propan-2-ol; isopropyl alcohol; IPA) (CAS No 67-63-0).** Isopropanol has a low order of acute toxicity. Isopropanol is not genotoxic and is unlikely to be carcinogenic. Maternal and developmental toxicity have been reported in rats and rabbits following oral administration of high doses. The former EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food established an ADI of 2.4 mg/kg b.w. per day from the NOAEL of 240 mg/kg b.w. per day for maternal toxicity in rabbits. The CONTAM Panel considers this ADI appropriate. Isopropanol is not allergenic and there are no impurities or reaction products of toxicological concern. Therefore, the CONTAM Panel concludes that isopropanol meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Propyl alcohol (propan-1-ol; 1-propanol) (CAS No 71-23-8).** Propyl alcohol exhibits low systemic toxicity in animal models. No valid carcinogenicity studies with propyl alcohol are available but the negative results of mutagenicity studies, although limited, do not indicate any concern for carcinogenicity when propyl alcohol is used as a previous cargo. Propyl alcohol is not an allergen. No impurities or reactions products of concern with edible fats and oils are known or expected. Although the toxicological data base is limited, based on the available data, there is no health concern regarding the use of propyl alcohol as a previous cargo for edible fats and oils. Therefore, the CONTAM Panel concludes that propyl alcohol meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Methyl isobutyl ketone (4-methyl-2pentanone) (CAS No 108-10-1).** In subchronic oral exposure studies in animals, methyl isobutyl ketone induced effects associated with the liver, kidney, blood, and nervous system, however there was no clear dose-response relationship and their severity and relevance to effects in humans was uncertain. Recent studies on inhalation carcinogenicity in rats and mice provided some evidence of the carcinogenic activity of methyl isobutyl ketone in kidney and liver, respectively, at the highest dose tested. However, methyl isobutyl ketone was not genotoxic in a variety of *in vitro* and *in vivo* assays suggesting that it is not carcinogenic in animals by a genotoxic mechanism. No impurities of concern are expected. Methyl isobutyl ketone may react with fats and oils and form dioxolanes. The toxicological profile of 1,3-dioxolane, and by analogy that of other dioxolanes, is such that there would be no toxicological concern from the use of methyl isobutyl ketone as a previous cargo to edible fats and oils from any such reaction products. On the basis of the available data there are no toxicological concerns regarding the use of methyl isobutyl ketone as a previous cargo. The CONTAM Panel therefore concludes that methyl isobutyl ketone meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Methyl ethyl ketone (2-butanone) (CAS No 78-93-3).** No animal long term oral toxicity studies are available for methyl ethyl ketone. Methyl ethyl ketone has not been tested for carcinogenicity by the oral or inhalation routes, but the majority of *in vitro* and *in vivo* genotoxicity tests have demonstrated no activity. Methyl ethyl ketone is not an allergen. Although the toxicological database is limited, based on the available data, there are no toxicological concerns regarding the use of methyl ethyl ketone as a previous cargo. No impurities of concern are expected. Methyl ethyl ketone may react with fats and oils and form dioxolanes. The toxicological profile of 1,3-dioxolane, and by analogy that of other dioxolanes, is such that there would be no toxicological concern from the use of methyl ethyl ketone as a previous cargo to edible fats and oils from any such reaction products. Therefore the CONTAM Panel concludes that methyl ethyl ketone meets the criteria for acceptability as a previous cargo for edible fats and oils.

- ***n*-Propyl acetate (CAS No 109-60-4).** No ADI or other toxicological reference value has been established for *n*-propyl acetate. The toxicological database has several data gaps (subacute, subchronic and chronic toxicity, carcinogenicity, reproductive toxicity). It can be concluded from data on the structural analogue ethyl acetate and the hydrolysis products *n*-propyl alcohol and acetic acid, that *n*-propyl acetate is of low concern for these endpoints, with the exception of carcinogenicity, where there are also no data on the structurally similar compounds. The limited data available did not demonstrate any evidence of genotoxicity and there is no concern regarding allergenicity. The CONTAM Panel considers that the available information was sufficient to conclude that the risk from short-term exposure to *n*-propyl acetate when used as a previous cargo would not give raise to any toxicological concern. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that *n*-propyl acetate meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Ammonium hydroxide (ammonium hydrate; ammonia solution; aqua ammonia) (CAS No 1336-21-6).** JECFA has established an ADI "not limited" and the Scientific Committee on Food (SCF) has established an ADI "not specified" for ammonium hydroxide, which the CONTAM Panel considers appropriate. Ammonium hydroxide is not genotoxic or allergenic. Ammonium hydroxide is only toxic when it is present at sufficient concentration that it changes the local OH^- concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to ammonium hydroxide as a previous cargo do not give rise to any toxicological concern. Exposure to small amounts of ammonium hydroxide locally may cause irritation to the skin or eyes. However, the maximum potential levels of ammonium hydroxide arising in fats or oils following its transport as a previous cargo would be of no concern. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that ammonium hydroxide meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Limonene (dipentene) (CAS No 138-86-3).** The WHO established a tolerable intake of 0.1 mg/kg b.w. per day for *d*-limonene based on a no-observed-effect level (NOEL) for hepatic effects in a 13-week study in rats, of 10 mg/kg b.w. per day. The CONTAM Panel noted that the effects for which this NOEL was identified were adaptive changes in the liver, without evidence of histopathological change, and that the NOAEL in this study was 75 mg/kg b.w. per day (the highest dose tested). This dose level was also a NOAEL in female rats in a 2 year carcinogenicity study, while 500 mg/kg b.w. per day was a NOAEL in a 2-year study in mice. The renal tumours seen in male rats in the 2-year carcinogenicity study and the nephropathy seen in shorter-term studies in male rats can be attributed to binding of *d*-limonene and/or its metabolites to α2u-globulin, a phenomenon which is considered not to be relevant for human risk assessment. The CONTAM Panel therefore considered the tolerable intake of 0.1 mg/kg b.w. per day established by IPCS for *d*-limonene to be conservative, and that the toxicological profile of limonene does not raise any toxicological concern when it is used as a previous cargo. The substance is not genotoxic and there is no concern regarding allergenicity. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that limonene meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Methyl tertiary butyl ether (MTBE) (CAS No 1634-04-4).** MTBE is not genotoxic or allergenic. The CONTAM Panel concluded that there is no concern regarding the carcinogenicity, developmental or reproductive toxicity of MTBE at the anticipated levels in food resulting from transport of the substance as a previous cargo. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. The CONTAM Panel also agrees with the previous conclusion of the SCF in 2003, that the solubility of MTBE in water (48 g/L) would allow effective cleaning of the cargoes by water washings at ambient temperature. Therefore, the CONTAM Panel concludes that methyl tertiary butyl ether meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Urea ammonia nitrate solution (UAN).** The CONTAM Panel has previously evaluated calcium ammonium nitrate solution and calcium nitrate (CN-9) solution and concluded that they meet the criteria for acceptability as previous cargoes. Based on the evaluations for urea, ammonium hydroxide and nitrate described above, the CONTAM Panel considers that there are no toxicological concerns regarding urea ammonium nitrate when it is used as a previous cargo. The CONTAM Panel concluded that urea ammonium nitrate is not genotoxic or allergenic. The CONTAM Panel noted that urea ammonium nitrate solution is corrosive, but that it will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to the solution do not give

rise to any toxicological concern. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that urea ammonia nitrate solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Calcium chloride solution (CAS No 10043-52-4).** JECFA has established an ADI not limited and the SCF has established an ADI not specified for calcium chloride, which the CONTAM Panel considers appropriate. The SCF allocated a Tolerable Upper Intake Level (UL) for calcium of 2 500 mg/person per day as a nutrient, and also established a Population Reference Intake of 700 mg calcium per day. The contribution of calcium from previous cargoes is not of safety concern, since the threshold in the criteria of an ADI (or tolerable daily intake (TDI)) above 0.1 mg/kg b.w. per day for previous cargoes is far below the UL of calcium. Calcium chloride is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that calcium chloride solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Magnesium chloride solution (CAS No 7786-30-3).** JECFA has established an ADI not limited and the SCF has established an ADI not specified for magnesium chloride, which the CONTAM Panel considers appropriate. The SCF allocated a UL for magnesium of 250 mg per day in nutritional supplements, water, or added to food and beverages. Magnesium chloride is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that magnesium chloride solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Potable water (CAS No 7732-18-5).** Water must meet specific requirements to be considered potable. Hence, there are no concerns from possible toxicity or allergenicity from the use of potable water as a previous cargo for edible fats and oils. There are no reaction products or impurities of concern. The CONTAM Panel therefore concludes that potable water meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Potassium hydroxide solution (caustic potash) (CAS No 1310-58-3).** JECFA has established an ADI "not limited" and the SCF has established an ADI "not specified" for potassium hydroxide, which the CONTAM Panel considers appropriate. Potassium hydroxide is not genotoxic or allergenic. Potassium hydroxide is toxic only when it is present at sufficient concentration that it changes the local OH^- concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to potassium hydroxide as a previous cargo do not give rise to any toxicological concern. Exposure to small amounts of potassium hydroxide locally may cause irritation to the skin or eyes. However, the maximum potential levels of potassium hydroxide arising in fats or oils following its transport as a previous cargo would be of no concern. There are no reactions of health concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that potassium hydroxide solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Sodium hydroxide solution (caustic soda) (CAS No 1310-73-2).** JECFA has established an ADI "not limited" and the SCF has established an ADI "not specified" for sodium hydroxide, which the CONTAM Panel considers this appropriate. Sodium hydroxide is not genotoxic or allergenic. Sodium hydroxide is toxic only when it is present at sufficient concentration that it changes the local OH^- concentration. It will be diluted and buffered by the contents of the GI tract so that the levels that would occur following oral ingestion of fats or oils transported subsequent to sodium hydroxide as a previous cargo do not give rise to any toxicological concern. Exposure to small amounts of sodium hydroxide locally may cause irritation to the

skin or eyes. However, the maximum potential levels of sodium hydroxide arising in fats or oils following its transport as a previous cargo would be of no concern. There are no reactions of health concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that sodium hydroxide solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Silicon dioxide (microsilica) (CAS No 7631-86-9).** Because silicon dioxide is a solid and essentially insoluble in water, current shipping practices mean that it is not possible to transport this substance by sea in a tanker suitable for the transport of edible fats and oils. This is because of difficulties in transfer and cleaning of the tanker. JECFA has established an ADI "not limited except for good manufacturing practice" and the SCF has established an ADI "not specified" for silicon dioxide, on the basis that there will be negligible absorption from the GI tract. The CONTAM Panel considers this appropriate. Consistent with this, silicon dioxide has negligible systemic toxicity. It is not genotoxic and there is no allergenic potential of concern. There are no reaction products or impurities of toxicological concern. The CONTAM Panel concludes that although silicon dioxide meets the toxicological criteria for acceptability as a previous cargo for edible fats and oils, it is not a suitable cargo on the basis of current shipping practices, due to difficulties in transfer and cleaning of the tanker.

- **Sorbitol solution (D-sorbitol; hexahydric alcohol; D-sorbite) (CAS No 50-70-4).** An ADI for sorbitol was considered unnecessary by the SCF and JECFA, due to its natural occurrence in the diet and low toxicity. The CONTAM Panel considers this appropriate. Sorbitol is not genotoxic or allergenic. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated. The CONTAM Panel therefore concludes that sorbitol solution meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Molasses.** Given its long history of use as a food, and the available information on its components, there are no toxicological concerns regarding the use of molasses obtained from sugar cane, sugar beet, citrus or sorghum, as a previous cargo for edible fats and oils. There is no allergenicity potential of concern for molasses from these sources. The amount of sulphite present in some molasses would not be of concern following dilution in edible fats and oils as subsequent cargo. No other impurities or reaction products of concern are known or anticipated. The CONTAM Panel therefore concludes that molasses, which has been produced from the conventional sugar processing industry using sugar cane, sugar beet, citrus or sorghum, meets the criteria for acceptability as a previous cargo for edible fats and oils.

- **Beeswax (white and yellow) (CAS No 8006-40-4** and **8012-89-3).** Although specific information on beeswax is very limited, there is sufficient information from its human use, its poor absorption and on its main component groups of chemicals for the CONTAM Panel to conclude that it will not pose any toxicological concern when used as a previous cargo. There is no evidence that it is genotoxic and there is no allergenic potential of concern. It will not give rise to any reaction products with fats and oils of toxicological concern. No impurities of toxicological concern are known or anticipated. The CONTAM Panel therefore concludes that beeswax meets the criteria for acceptability as a previous cargo for edible fats and oils.

RECOMMENDATIONS

The CONTAM Panel recommends that a number of amendments be made to the entries of the substances in the annex to Commission Directive 96/3/EC.[5]

- The CONTAM Panel recommends that the entry for "Tridecyl alcohol (1-tridecanol) (CAS No. 27458-92-0 / 112-70-9)" under "Fatty alcohols" be amended to **"Tridecyl alcohol**

(1-tridecanol) (CAS No 112-70-9)" to reflect the chemical composition of the substance of transport.

- The CONTAM Panel recommends that the entry for "Animal, marine and vegetable and hydrogenated oils and fats (other than cashew shell nut and crude tall oil)" be amended to **"Animal, marine and vegetable and hydrogenated oils and fats as specified by the MEPC of the IMO"**, as only those fats and oils have been evaluated by the CONTAM Panel. As the list specified by the MEPC does not include cashew shell nut or crude tall oil, these specific exclusions would no longer be necessary.

- The CONTAM Panel recommends that the entry for "*n*-Heptane (CAS No 142-82-5)" amended to **"Heptane (commercial grades) (CAS No 142-82-5)"**, to reflect the substance of transport.

- The CONTAM Panel recommends that the entry for "*n*-Hexane (technical grades) (CAS No 110-54-3)" be amended to **"Hexane (technical grades) (CAS No 110-54-3 / 64742-49-0)"**, to reflect the substances of transport.

- The CONTAM Panel recommends that the entry for "iso-Propanol (isopropyl alcohol; IPA) (CAS No 67-63-0)" be amended to **"Isopropanol (propan-2-ol; isopropyl alcohol; IPA) (CAS No 67-63-0)"**, to reflect accepted chemical nomenclature.

- The CONTAM Panel recommends that the entry for "Propyl alcohol (propane-1-ol; 1-propanol) (CAS No 71-23-8)" be amended to **"Propyl alcohol (propan-1-ol; 1-propanol) (CAS No 71-23-8)"**, to reflect accepted chemical nomenclature.

- The CONTAM Panel recommends that

  - the entry for "Calcium chloride solution - only where the immediate previous cargo to it is on the list and is not similarly restricted (CAS No 10043-52-4)" be amended to **"Calcium chloride solution (CAS No 10043-52-4)"**;

  - the entry for "Potable water - only where the immediate previous cargo to it is on the list and is not similarly restricted" be amended to **"Potable water (CAS No 7732-18-5)"**;

  - the entry for "Potassium hydroxide (caustic potash) - only where the immediate previous cargo to it is on the list and is not similarly restricted (CAS No. 1310-58-3)" be amended to **"Potassium hydroxide (caustic potash) solution (CAS No 1310-58-3)"**;

  - the entry for "Sodium hydroxide (caustic soda) - only where the immediate previous cargo to it is on the list and is not similarly restricted (CAS No 1310-73-2)" be amended to **"Sodium hydroxide (caustic soda) solution (CAS No 1310-73-2)"**.

  - the entry for "Sorbitol (D-sorbitol; hexahydric alcohol; D-sorbite) (CAS No 50-70-4)" be amended to "**Sorbitol solution (D-sorbitol; hexahydric alcohol; D-sorbite) (CAS No 50-70-4)**".

  - the entry for "Silicon dioxide (microsilica) (CAS No 7631-86-9)" be deleted.

These amendments are recommended because designation of substances on the list reflected contemporary shipping practices and a relative lack of knowledge of the impact of certain cargoes on the material of transport vessels at the time it was put in place. Changes in shipping practices and the

current construction of vessels for the transport of edible fats and oils now make the proposed changes appropriate or necessary.

- The CONTAM Panel recommends that the entry for "Molasses (CAS No 57-50-1)" be amended to **"Molasses"**, omitting the CAS No 57-50-1, because the CAS No refers to D(+)-sucrose, which may be only a minor component in molasses.

The entries in the annex to Commission Directive 96/3/EC[5] for the substances evaluated in this Opinion as previous cargoes for edible fats and oils are listed below, amended as recommended by the CONTAM Panel, in Table 4.

Table 4: Substances in the list to Annex to Commission Directive 96/3/EC[5] listed as acceptable previous cargoes for edible fats and oils with amendments recommended by the CONTAM Panel (**bold entries**).

Substance (synonyms)	CAS Number
Fatty acids:	
Butyric acid (*n*-butyric acid; butanoic acid; ethyl acetic acid; propyl formic acid)	107-92-6
Valeric acid (*n*-pentanoic acid; valerianic acid)	109-52-4
Caproic acid (*n*-hexanoic acid)	142-62-1
Heptoic acid (*n*-heptanoic acid)	111-14-8
Caprylic acid (*n*-octanoic acid)	124-07-2
Pelargonic acid (*n*-nonanoic acid)	112-05-0
Capric acid (*n*-decanoic acid)	334-48-5
Lauric acid (*n*-dodecanoic acid)	143-07-7
Lauroleic acid (dodecenoic acid)	4998-71-4
Myristic acid (*n*-tetradecanoic acid)	544-63-8
Myristoleic acid (*n*-tetradecenoic acid)	544-64-9
Palmitic acid (*n*-hexadecanoic acid)	57-10-3
Palmitoleic acid (cis-9-hexadecenoic acid)	373-49-9
Stearic acid (*n*-octadecanoic acid)	57-11-4
Oleic acid (*n*-octadecenoic acid)	112-80-1
Ricinoleic acid	141-22-0
Linoleic acid (9,12-octadecadienoic acid)	60-33-3
Linolenic acid (9,12,15-octadecatrienoic acid)	463-40-1
Arachidic acid (eicosanoic acid)	506-30-9
Behenic acid (docosanoic acid)	112-85-6
Erucic acid (cis-13-docosenoic acid)	112-86-7
Fatty alcohols:	
Butyl alcohol (1-Butanol; butyric alcohol)	71-36-3
Caproyl alcohol (1-hexanol; hexyl alcohol)	111-27-3
Enanthyl alcohol (1-heptanol; heptyl alcohol)	111-70-6

Table 4: Continued.

Substance (synonyms)	CAS Number
Fatty alcohols (cont.):	
Capryl alcohol (1-*n*-octanol; heptyl carbinol)	111-87-5
Nonyl alcohol (1-nonanol; pelargonic alcohol; octyl carbinol)	143-08-8
Decyl alcohol (1-decanol)	112-30-1
Lauryl alcohol (*n*-dodecanol; dodecyl alcohol)	112-53-8
Tridecyl alcohol (1-tridecanol)	**112-70-9**
Myristyl alcohol (1-tetradecanol; tetradecanol)	112-72-1
Cetyl alcohol (alcohol C-16; 1-hexadecanol; cetylic alcohol; palmityl alcohol, *n*-primary hexadecyl alcohol)	36653-82-4
Stearyl alcohol (1-octadecanol)	112-92-5
Oleyl alcohol (octadecenol)	143-28-2
Fatty alcohol blends:	
Lauryl myristyl alcohol (C12-C14)	
Cetyl stearyl alcohol (C16-C18)	
Fatty acid methyl esters:	
Methyl laurate (methyl dodecanoate)	111-82-0
Methyl palmitate (methyl hexadecanoate)	112-39-0
Methyl stearate (methyl octadecanoate)	112-61-8
Methyl oleate (methyl octadecenoate)	112-62-9
Fatty acids esters — any ester produced by the combination of the above listed fatty acids with any of the above listed fatty alcohols. Examples of these are butyl myristrate, oleyl palmitate and cetyl stearate.	
Acid oils and fatty acid distillates — from vegetable oils and fats and/or mixtures thereof and animal and marine fats and oils	
Animal, marine and vegetable and hydrogenated oils and fats as specified by the MEPC of the IMO	
Acetic acid	64-19-7
Sulphuric acid	7664-93-9
Formic acid (methanoic acid; hydrogen carboxylic acid)	64-18-6
Acetic anhydride (ethanoic anhydride)	108-24-7
Acetone (dimethylketone; 2-propanone)	67-64-1
Heptane (commercial grades)	**142-82-5**
Hexane (technical grades)	**110-54-3** **64742-49-0**
Cyclohexane (hexamethylene; hexanaphthene; hexahydrobenzene)	110-82-7

Table 4: Continued.

Substance (synonyms)	CAS Number
Pentane	109-66-0
Isopropanol (propan-2-ol; isopropyl alcohol; IPA)	**67-63-0**
Propyl alcohol (propan-1-ol; 1-propanol)	71-23-8
Methyl isobutyl ketone (4-methyl-2pentanone)	108-10-1
Methyl ethyl ketone (2-butanone)	78-93-3
n-Propyl acetate	109-60-4
Ammonium hydroxide (ammonium hydrate; ammonia solution; aqua ammonia)	1336-21-6
Limonene (dipentene)	138-86-3
Methyl tertiary butyl ether (MBTE)	1634-04-4
Urea ammonia nitrate solution (UAN)	
Calcium chloride solution	**10043-52-4**
Magnesium chloride solution	7786-30-3
Potable water	**7732-18-5**
Potassium hydroxide (caustic potash) solution	**1310-58-3**
Sodium hydroxide (caustic soda) solution	**1310-73-2**
Silicon dioxide (microsilica)	**7631-86-9** [68]
Sorbitol solution (D-sorbitol; hexahydric alcohol; D-sorbite)	**50-70-4**
Molasses	
Beeswax (white and yellow)	8006-40-4 8012-89-3

DOCUMENTATION PROVIDED TO EFSA

1. **FOSFA International. Response from FOSFA International to questions from the EFSA Working Group on Previous Cargoes. Submitted to EFSA through the EC on 29 September 2011.**

Following a meeting of EFSA Working Group on previous cargoes, various questions were directed to FOSFA International as representing the oils and fats trade, by the representative of the EU Commission, Mr Frank Swartenbroux. The response to these questions is as follows.

ACID OILS AND FATTY ACID DISTILLATES - FROM VEGETABLE OILS AND FATS AND/OR MIXTURES THEREOF AND ANIMAL AND MARINE FATS AND OILS

Question: The WG requested information on what the sources are of such cargoes.

[68] See recommendation above.

Acid oils and fatty acids distillates are by-products of the edible oil refining process.

Acid oils are a by-product obtained from the alkaline refining of oils. An example of the typical details of their production is given in the attached paper, Kuntom et al, JAOCS, 1994. They consist mainly of free fatty acids (FFA) (over 50 %) and neutral oil, with 2-3 % moisture and other impurities. More details of their composition and properties are given in the same journal paper and the attached product data form. Acid oils are used for making laundry soaps, producing calcium soaps, for animal feed formulations and for distilled fatty acid production and as feedstock for the biofuel industry.

The major products of this type which are traded internationally are palm acid oil, palm kernel acid oil, coconut acid oil, maize/soyabean/sunflower acid oil blend and fish acid oil. However, acid oil is produced during the refining of all vegetable, animal and fish oils which are alkali refined.

Fatty acid distillates are a by-product of the physical refining of edible oils. The crude oils are degummed using dilute phosphoric or citric acid, decoloured using bleaching earth and then subjected to a steam distillation process to remove the fatty acids. It is these collected distillates which is traded internationally and carried in bulk in ships' tanks. The distillates are composed of free fatty acids (~70 – 90 %), glycerides, organic compounds such as squalenes, vitamins, sterols and other minor components found in crude oils. Their usual specification states a minimum of 95 % saponifiable matter. More details of their composition and properties are given in the attached product data form. Fatty acid distillates are used in the animal feed and laundry soap industries as well as a raw material for the oleochemicals industry. Vitamin E, squalene and phytosterols are value-added products which can be extracted from Palm FAD and are of potential value for the nutraceutical and cosmetic industries.

The major traded product of this type is palm fatty acid distillate as palm oil is the most abundant vegetable oil worldwide and usually has about 5 % FFA. Other distillates which are traded are palm kernel FAD and coconut FAD.

WINE LEES (VINASSES, VINACCIA, ARGOL, VINI, ARGIL, ARCILLA, WEINSTEIN, CRUDE CREAM OF TARTAR, CRUDE POTASSIUM BITARTRATE) – CAS No 868-14-4

Question: The WG requested information on the origin and composition of this entry.

This is a product which is very rarely carried now in bulk by sea as its value is very low, sometimes less than the freight costs! Lees refers to deposits of dead yeast or residual yeast and other particles that precipitate, or are carried by the action of "fining", to the bottom of a vat of wine after fermentation and ageing. It is the slurry left behind after the racking of the wine. Generally, the term now used for this product is vinasses. The other terms are not widely used. As the potassium tartrates are food additives, they are already included on the acceptable list as foodstuffs. Vinaccia is the Italian name for wine lees and in Italy, it may be used as feedstock for the production of grappa.

It is suggested that this product is amended in the list to read: Wine lees – (vinasses)

GENERIC NAMES FOR OLEOCHEMICALS

Question: On the entries for individual fatty acids and fatty alcohols, not all of the individual fatty acids, alcohols, etc are likely to be transported in bulk. The WG requested information on whether it is possible to refer to these lists more generically.

I have been trying to get an answer from the oleo-chemical industry about the use of generic classes to include all the individual fatty acids which are currently included in the EU List of Acceptable Previous Cargoes. A couple of people have come back to me saying that they think it should be possible and have pointed me to the names used by IMO, the International Maritime Organisation. However, I have spoken to my contact at IMO who also thinks it is possible but also said that even

though IMO introduced the generic terms, the shippers still wanted the original names to be maintained in Chapter 17 of the IBC code!! The reason for this is that they did not want any hold-ups when the ships berthed and the port state authority personnel did not know what the generic terms meant, and whether they individual cargoes were included. This is the same reason that FOSFA has some items on its list, such as "fructose" which is a foodstuff. This is clear to a food scientist, but not necessarily to non-technical port state authority personnel.

For your information, the IMO uses the following terms to cover all the fatty acids which are carried in bulk by sea:

Vegetable fatty acid distillates
Fatty acid (saturated c13+)
Fatty acid methyl esters
Fatty acids, 12+
Fatty acids, c8-c10
Fatty acids, essentially linear (c6 - c18)
Fatty acids, c16+
Saturated fatty acid (c13 and above)

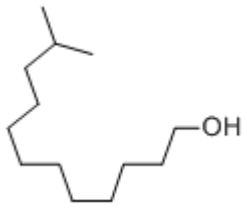
TRIDECYL ALCOHOL

Question: The entry tridecyl alcohol includes two CAS Nos which correspond to two structurally distinct substances. The first CAS No (112-70-9) refers to 1-tridecanol, while the other CAS No (27458-92-0) refers to 11-methyldodecane-1-ol. The SCF opinions (1997a) only evaluated CAS No 112-70-9. The WG requested information on what is the substance currently transported.

The material which was included in the FOSFA List of Acceptable Previous Cargoes in 1996 was tridecyl alcohol. This is also known as 1-tridecanol or C13 linear primary alcohol, and has the CAS number 112-70-9. At that time, it was listed under natural alcohols, but in 1998 it was removed when we included the term "synthetic primary alcohols (C9 – C15)", since this includes the C13 linear primary alcohol.

As you know, the EU List is based on the FOSFA List in force in 1996 and that is why it is on the EU List. In 1996, there was an initiative to have a joint acceptable list for both FOSFA and NIOP (the US trade association which has rules for the trading of vegetable oils in the USA). This initiative came to nothing but I have found a copy of the list in our records and this lists tridecyl alcohol and gives the CAS number 27458-92-0. As you say, this CAS number refers to isotridecanol which is a different product (see below). Thus, I think it was just an error when this provisional joint list was drawn up, and it should be corrected in the EU list by simply removing reference to this CAS number. Clearly, the substance that EFSA should be considering is tridecyl alcohol, CAS number 112-70-9.

1-tridecanol



isotridecanol

POTABLE WATER

Question: Some of the entries have a "disclaimer" reading "only where the immediate previous cargo to it is on the list and is not similarly restricted". This addition was present from the beginning for the entry "potable water", both on the FOSFA list and on the list in the Directive. In the 2004 revision of the Directive, the use of this "disclaimer" was expanded to the entries potassium hydroxide, sodium hydroxide and calcium chloride. In the FOSFA list, this addition is only applicable to "potable water". The WG requested information on the origin, reason/rationale for this restriction.

In a previous email, you asked about the further restriction that FOSFA has on potable water and which the EU List also has on sodium and potassium hydroxides. I have investigated the source of these restrictions. This provision was introduced in the early 1990s when far less was known or understood about the effect of various cargoes on tank coatings, and also before more detailed research work on the cleaning of ships' tanks was carried out. This was also before the rule concerning the quantity of material which constituted a previous cargo was adopted by FOSFA. At that time, oils and fats could be carried in the deep tanks of general product carriers and fresh water was readily obtainable in the majority of the world's ports, and could often be purchased at reasonable prices in many. There was the outside risk that parties could use it as an intermediate cargo in order to meet last cargo requirements.

It should be noted that following the revision by the International Maritime Organisation Annex II of the Marine Pollution regulations, MARPOL, oils and fats must be carried in Chemical Tankers, which are specifically designed to be loaded/(carriage)/unloaded/cleaned, and then loaded/(carriage)/unloaded/cleaned with a different cargo, etc. for the whole of their lives. This has meant that the quality of the fleet which carries oils and fats around the world is much better than in the early 1990s.

All these matters were considered by the group that developed the Codex criteria. Thus, following all the changes which have taken place since the introduction of the first list in 1996, I feel that these further restrictions for all cargoes which comply with the Codex criteria should be removed.

John Hancock

Technical Manager
FOSFA International
28 September 2011 / 3 January 2012 / 8 March 2012 / 16 March 2012 / Collated, 18 April 2012

2. FOSFA International. Response from FOSFA International following a meeting the EFSA Working Group on Previous Cargoes, 3 April 2012. Submitted to EFSA on 18 April 2012.

During a meeting of the EFSA Working Group on previous cargoes held on 3 April 2012, various information was requested from FOSFA international as representing the oils and fats trade. The response to these questions is as follows.

ACETONE

Question: The WG requested information on the potential content of benzene in low quality acetone.

From data on the internet,[69] acetone produced through the cumene process contains benzene at concentrations < 10 ppm. Material Safety Data Sheets (MSDS) received from manufacturers by the

[69] http://www.inchem.org/documents/ehc/ehc/ehc207.htm (accessed 4/4/12).

shippers of this product quote the content as shipped as 100.00 % acetone, which must be one extreme, and another of 99.8 % acetone. Another MSDS states that it lists all other components greater than 0.1 % and it does not list benzene. Other internet references quote < 0.1 % benzene in acetone, but there are also references to "low benzene content acetone" with max 50 ppm. Pharmaceutical grades of acetone are specified as > 2 ppm of benzene. I believe it would be safe to consider the maximum content of benzene in the grade of acetone commonly shipped to be 0.1 %.

CYCLOHEXANE

Question: The WG requested similar information on the potential content of benzene in low quality cyclohexane.

One process for manufacturing cyclohexane is by benzene hydrogenation using a nickel or aluminium catalyst. The quoted product purity is 99.6 %. Only one MSDS has been received so far for the product which is shipped and this states that it lists all other components greater than 0.1 %, and it does not list Benzene. Again, I suggest that the maximum content of benzene in cyclohexane to be 0.1 %.

SORBITOL

Question: The WG requested information on whether sorbitol is transported in solid form in the same type of tanker as used for edible fats and oils, or would it be transported in solution.

All substances which are carried in bulk by sea in Chemical Tankers must be listed in the IBC Code (International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk). Sorbitol solution is included in the IBC Code as pollution category OS – in other words it has been evaluated and found not to pose a safety or pollution risk and therefore does not require carriage in a chemical tanker and is not subject to any of the provisions of MARPOL Annex II. The main Chemical Tanker trade association does not know to what extent, if any, it is carried, but are making enquiries.

MOLASSES

Question: The WG requested information on the origin of molasses transported in tankers, and on the levels of possible contaminants, including sulphite, in molasses.

Sugar Cane Molasses and Sugar Beet Molasses are traded and transported internationally, by sea, by 3 major players, United Molasses, ED&F Man and Peter Cremer, each with broadly similar percentages of the total volume.

Approx. 4,000,000 MT of cane molasses is traded worldwide. Approx. 1,500,000 MT will come to Europe, around 60 % into the animal feed industry and 40 % to fermentation (yeast, Citric acid, ethanol etc.). Asia, primarily Korea and Taiwan, will take 1,500,000 and USA around 1,000,000 MT.

The WG requested information on the level of sulphites found in molasses. This has been measured over the last six months by the industry, also as a result of EFSA requirements. Results are given below and these can be considered as “typical” of the origins.

- Indian <10.0 mg/kg
- Australian <10.0 mg/kg
- Indonesia 25.0 mg/kg
- Belize <5 mg/kg
- Algerian Refinery <10 mg/kg

As regards Sugar Beet molasses, world trade by sea is in the region of 600k, 300k ex Egypt, 200k ex Ukraine/Russia and 80k ex Poland. Internationally traded beet molasses all goes into the fermentation industry, mostly within Europe, but up to 200k may go to Asia.

Any processing aids used in the sugar industry are approved for food production by Codex/FDA/EU. Under current EU Feed law, molasses is routinely tested for sulphites, heavy metals and pesticides. No substances are added to the final molasses produced as this is merely a by-product of the sugar process.

SILICON DIOXIDE

Question: The WG requested information on whether silicon dioxide is transported in the same tankers as used for edible fats and oils.

Silicon dioxide is not in the IBC Code and thus cannot be carried in bulk by chemical tankers. I have asked several shipbrokers and shipping/chemical tanker trade associations and none of them can recall this product ever being carried.

LIST OF OILS AND FATS SHIPPED IN BULK BY SEA

Question: The entry "animal, marine and vegetable and hydrogenated oils and fats (other than cashew shell nut and crude tall oil)" is potentially very broad. The WG requested information on what fats and oils would be included under this entry to the Annex.

Although most animal and vegetable species contain some oil, the vast majority of these oils are not shipped in bulk by sea. It is helpful that the International Maritime Organisation, a UN body which sets the rules for international shipping, has stated that vegetable oil products can only be carried in bulk by sea if the name is included in the MEPC.2/Circ document. I have attached this document which lists the base oils and their synonyms. These are the only oils and fats products (except jatropha oil which we included in our exclusion last year) which could form the previous cargo for another product on this list

The WG had been previously informed that only those oils listed in the IMO (International Maritime Organization) document MEPC.2/Circ could be carried in bulk by sea. It was pointed out at the meeting of the WG that there were two obvious non-oils in the latest version of the document, MEPC.2/Circ.17.

Following investigation of this anomaly, it has been confirmed by the Secretary of the MEPC that the inclusion of these chemical s was an error which has been acknowledged (ref: Report of the IMO Sub-Committee On Bulk Liquids and Gases, paragraph 3.30.3, http://www.uscg.mil/imo/blg/docs/blg16-report.pdf, accessed 18 April 2012), and corrected. This confirms that MEPC.2/Circ is a valid reference for this data.

Dr John N S Hancock
Technical Manager
FOSFA International
18 April 2012

3. FOSFA International. Response from FOSFA International following a meeting the EFSA Working Group on Previous Cargoes, 3 April 2012. Submitted to EFSA on 27 April 2012.

RESPONSE FROM FOSFA CONCERNING THE FORMAT OF PREVIOUS CARGOES

During their recent meeting, the EFSA WG on previous cargoes raised the matter of several of the substances on the trade lists of acceptable previous cargoes being solid in nature, examples of these

being sodium hydroxide, potassium hydroxide and sorbitol. The response from the FOSFA representative was that all the products on the trade lists are actually carried as liquids/solutions. The reason for this is that, when transported in bulk by sea, edible fats and fats must now be carried in chemical tankers. These are vessels with a series of large internal tanks, each tank being filled and emptied through a dedicated system of pipes and pumps. These pipe and pumping systems cannot be used for solids or very viscous liquids. Oils and fats which are solid at room temperature are loaded carried and discharged at temperatures above their melting points, up to 80 °C.

The legislation concerning the carriage of oils and fats in bulk by sea are the MARPOL regulations and the International Code for the Construction and Equipment of Ships Carrying Dangerous Chemicals in Bulk (IBC Code). The references which show that the cargoes are liquids are as follows:

Reg. 1.1 states: "The Code applies to ships regardless of size, including those of less than 500 gross tonnage, engaged in the carriage of bulk cargoes of dangerous chemicals or noxious liquid substances (NLS) other than petroleum……".

1.1.4 "For the purpose of the 1974 SOLAS Convention, the Code applies to ships which are engaged in the carriage of products included in chapter 17 on the basis of their safety characteristics and identified as such by an entry of S or S/P in column d

1.1.5 "For the purposes of MARPOL 73/78, the Code applies only to NLS tankers, as defined in regulation 1.16.2 of Annex II thereof, which are engaged in the carriage of Noxious Liquid Substances identified as such by and entry of X, Y or Z in column c of chapter 17."

1.3.23 "Noxious Liquid Substance means any substance indicated in the pollution category column of chapters 17 or 18 of the IBC Code …… as falling into categories X, Y or Z."

2.1.2.2 "A type 2 ship is a chemical tanker intended to transport chapter 17 products with appreciably severe environmental and safety hazards which require significant preventive measures to preclude an escape of such cargo."

2.1.2.3 "A type 3 ship is a chemical tanker intended for the transportation of products with sufficiently severe environmental and safety hazards which require a moderate degree of containment…."

It can be seen that MARPOL defines edible fats and oils as noxious **liquid** substances and that these must be carried in IMO type 2 or type 3 ships, which are chemical **tankers**.

John Hancock
FOSFA International
27 April 2012

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ABBREVIATIONS

ACGIH	American Conference of Industrial Hygienists
ADH	Alcohol dehydrogenase
ADI	Acceptable daily intake
AFC Panel	Former EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food
ARfD	Acute reference dose
ATSDR	US Agency for Toxic Substances and Disease Registry
b.w.	Body weight
CAC	Codex Alimentarius Commission
CCFO	Codex Committee on Fats and Oils
CHO	Chinese hamster ovary
CoA	Coenzyme A
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
CNS	Central nervous system
DAR	Draft assessment report
DN(M)EL	Derived-no (or minimum)-effect levels
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
EU RAR	European Union Risk Assessment Report
FAO	Food and Agriculture Organization of the United Nations
FDA	United States Food and Drug Administration
FOSFA	Federation of Oils, Seeds and Fats Associations
GD	Gestational day
GI	Gastrointestinal
GRAS	Generally Recognized As Safe
HPV	High Production Volume
IARC	International Agency for Research on Cancer
IMO	International Maritime Organisation
i.p.	Intraperitoneal
IPCS	International Program on Chemical Safety
IRIS	Integrated Risk Information System
IUCLID	International Uniform Chemical Information Database
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LH	Luteinizing hormone
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MEK	Methyl ethyl ketone
MEPC	Marine Environment Protection Committee of the International Maritime Organisation
MIBK	Mehtyl isobutyl ketone
MRL	Maximum residue level
MSDI	Maximised Survey-derived Daily Intake
MTBE	Methyl tertiary butyl ether
NOAEC	No-observed-adverse-effect concentration
NOAEL	No-observed-adverse-effect levels
NOEL	No-observed-effect level
NTP	US National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PAHs	Polycyclic aromatic hydrocarbons
PCBs	Polychlorinated biphenyls
PRI	Population Reference Intake

RfC	Inhalation reference dose
RfD	Reference dose
SCE	Sister chromatid exchange
SCF	Scientific Committee on Food
SCHER	Scientific Committee on Health and Environmental Risks
SHE	Syrian hamster embryo
SIDS	Screening Information Dataset
SO_2	Sulphite
TDI	Tolerable daily intake
TRA	Targeted risk assessments
UAN	Urea Ammonia nitrate solution
UDS	Unscheduled DNA synthesis
UL	Tolerable upper intake level
US-EPA	United States Environmental Protection Agency
WHO	World Health Organization