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SCIENTIFIC OPINION

Scientific Opinion on the evaluation of substances as acceptable previous cargoes for edible fats and oils [1]

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

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ABSTRACT

Shipping of edible fats and oils into Europe is permitted in bulk tanks, in which substances included in a positive list were transported. The European Commission requested EFSA to evaluate a list of substances as acceptable previous cargoes. The Panel on Contaminants in the Food Chain (CONTAM Panel) based this evaluation on its recent review of the SCF criteria for acceptable previous cargoes and criteria proposed by the Codex Committee for Fats and Oils (CCFO). The CONTAM Panel considered that calcium nitrate, ammonium nitrate, the double salt and solutions of these as well as hydrogen peroxide, isobutanol, kaolin slurry and fructose would not be of health concern as previous cargoes. The Panel considered that unfractionated fatty acid/alcohol mixtures or mixtures of fatty acids/alcohols would not cause any health concern as previous cargoes, provided their sources are edible types of oils and fats. Likewise, only fatty ester mixtures produced from fatty acids and fatty alcohols derived from edible types of fats and oils, as well as methanol and ethanol, would not cause any health concern as previous cargoes, provided the sources of fatty esters mixtures are restricted to non-contaminated sources excluding such as oils from waste collection sites. Because of toxicological concern and/or lack of data, the CONTAM Panel considered that cyclohexanol, cyclohexanone and 2,3-butanediol did not meet the criteria for acceptability as previous cargoes. In the case of epoxidised vegetable oils, the Panel had no information about what entities might be covered by the term "epoxidised vegetable oil". Epoxidised soybean oil (ESBO) is already on the list of acceptable previous cargoes. Because there are no toxicological data on other epoxidised vegetable oils, the Panel could not evaluate these epoxidised vegetable oils as previous cargoes.

KEY WORDS

Acceptable previous cargo, edible oils and fats, 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 permitted also in bulk tanks, which have previously been used to transport substances included in a positive list of acceptable previous cargoes. In 1996 and 2003, the Scientific Committee on Food (SCF) evaluated a number of substances as previous cargoes based on a set of criteria for acceptable previous cargoes (SCF criteria). The 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 these substances (SCF, 1996; 2003a). In addition, the Codex Committee for Fats and Oils (CCFO) has also developed a Draft List of Acceptable Previous Cargoes as well as a Proposed Draft List of Acceptable Previous Cargoes (Appendix V to the report Alinorm 09/32/17).

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the evaluation as acceptable previous cargoes for edible fats and oils of the substances included in the Proposed Draft List of Acceptable Previous Cargoes. The Panel on Contaminants in the Food Chain (CONTAM Panel) based its evaluation on the outcome of the CONTAM Panel's recent review of the SCF criteria for acceptable previous cargoes and criteria proposed by the CCFO. In addition, the CONTAM Panel took into account impurities of the chemicals shipped as previous cargoes, since they may be more toxic than the chemical substance itself.

The CONTAM Panel considered that calcium nitrate, ammonium nitrate, the double salt and solutions of these as well as hydrogen peroxide, isobutanol and fructose would not, in the context of the previous cargoes, raise toxicological concerns, particularly in relation to their genotoxic or carcinogenic potential. In addition, the substances were not considered allergenic and the possible reaction products with the fats and oils, if any, as well as possible impurities were considered of no concern. For the kaolin slurry, the CONTAM Panel concluded that it would not be of any health concern as a previous cargo, provided it complies with the European Legislation on dioxins.

In the case of unfractionated fatty acid mixture or mixtures of fatty acids from natural fats and oils, fatty alcohol mixture or mixtures of fatty alcohols, as well as unfractionated fatty ester mixtures or mixtures of fatty esters from natural fats and oils, the CONTAM Panel noted that insufficient information on the sources and specifications of these was provided by industry. Therefore, the CONTAM Panel concluded that the anticipated toxicological profile of unfractionated fatty acid/alcohol mixtures or mixtures of fatty acids/alcohols from fats and oils would generally indicate a low level of concern for human health and therefore would not cause any health concern as previous cargoes, provided their sources are edible types of oils and fats. Likewise, the CONTAM Panel concluded that fatty ester mixtures produced from fatty acids and fatty alcohols, 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, polychlorinated biphenyls).

For cyclohexanol and cyclohexanone, there are uncertainties about the potential carcinogenicity and reproductive toxicity. In addition, the possible toxicity associated with the expected reaction products from cyclohexanone (dioxolane derivatives) needs to be considered. In the case of 2,3-butanediol, there is a lack of chronic and carcinogenicity studies and information about potential genotoxicity is considered insufficient, as well as the potential toxic impurities. The CONTAM Panel therefore considered that these three substances did not meet the criteria for acceptability as previous cargoes.

In the case of epoxidised vegetable oils, the CONTAM Panel had no information about what entities might be covered by the term "epoxidised vegetable oil". Epoxidised soybean oil (ESBO) is already on the list as an acceptable previous cargo. Epoxidised linseed oil (ELO) is the second most commonly used epoxidised vegetable oil as plasticiser, but there are no toxicological data on this or

other epoxidised vegetable oils apart from ESBO. Therefore, the CONTAM Panel could not evaluate these epoxidised vegetable oils as previous cargoes.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Current EU legislation on the hygienic rules to be respected for the transport of bulk liquid oils and fats by sea and the substances that can be accepted as previous cargoes can be summarized as follows:

- Commission Directive 96/3/EC establishes the hygienic rules to be respected as regards the transport of bulk liquid oils and fats by sea[4];
- Commission Directive 2004/4/EC, amending Directive 96/3/EC updates the list of substances of acceptable previous cargoes[5].

In April 2003, the Scientific Committee on Food (SCF) produced an 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.

Fourteen substances were evaluated by the SCF. Seven were considered as acceptable or provisionally acceptable and, consequently, introduced in the EC list of acceptable previous cargoes (Commission Directive 2004/4/EC).

The Codex Alimentarius Commission (CAC) adopted the recommended international code of practice for the storage and transport of edible fats and oils in bulk (www.codexalimentarius.net/download/standards/101/CXP_036e.pdf). This Code applies to the handling, storage and transport of all crude or processed edible oils and fats in bulk.

At its 21st session the CCFO considered the criteria proposed by the Joint FAO/WHO Technical Meeting (Bilthoven, Netherlands, 7-9 November 2006) to determine the acceptability of previous cargoes for edible fats and oils for bulk liquid transport. The CCFO agreed to amend some of the proposed criteria and forward them for adoption at Step 5 at the next session of the Codex Alimentarius Commission (CAC). Further details can be found in the report of the CCFO:

http://www.codexalimentarius.net/dwonload/report/718/al32_17e.pdf

The criteria proposed by the Codex Committee on Fats and Oils are to be adopted by the Codex Alimentarius Commission and only after their adoption can they be used to assess the acceptability of previous cargoes for fats and oils.

The Codex List of Acceptable Previous Cargoes is also under development at the CCFO. At its last session the CCFO agreed to return the Draft List of Acceptable Previous Cargoes to Step 3, for comments and consideration, at the next session. This list can be found in Appendix V to the report (page 39 Alinorm 09/32/17). Some of the substances in the list at Step 3 are also listed in Commission Directive 2004/4/EC. Therefore, they are considered as acceptable and it is not necessary to evaluate them as this stage.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

EFSA is asked to evaluate the substances included in the proposed draft list of acceptable previous cargoes of Appendix V to Alinorm 09/32/17 focusing on the substances which are not included in the Annex to Commission Directive 2004/4/EC amending Directive 96/3/EC.

[4] OJ L 21, 27.01.1996 p 42-46.
[5] OJ L 15, 22.01.2004 p 25.

ASSESSMENT

1. Introduction

The worldwide trade of edible fats and oils in bulk requires their transport by road, railroad, inland waterways and sea. Regulation (EC) 852/2004[6], repealing Council Directive 93/43/EEC[7], requires the transport of bulk liquid, granulate and powdered foods in receptacles and/or containers/tanks reserved for foodstuffs only. According to industry it is not economically viable to operate a fleet of ships engaged only in the carriage of edible fats and oils as they would have to return empty to their original loading ports.

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).

Commission Directive 96/3/EC[4] was developed to allow derogations from certain provisions of Directive 93/43/EEC. It was later on replaced by Regulation (EC) 852/2004. This 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 Directive required a review of the substances included in the list of acceptable previous cargoes to take into account scientific or technical developments. Therefore, 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 of the derogating Directive 96/3/EC (SCF, 1996). 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, Commission Directive 2004/4/EC amended the list of substances acceptable as previous cargoes set out in Annex to Directive 96/3/EC. However, the substances in the list were only considered to be acceptable as long as the provisions of the Hygiene of Foodstuff Directive 93/43/EEC, later on replaced by Regulation (EC) 852/2004, were applied, especially regarding the cleaning and condition of the tanks, as well as the requirement included in the derogating Directive 96/3/EC, where accurate documented evidence relating to the three previous cargoes, and on the efficacy of the cleaning process between cargoes, should 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 Oils and Fats in Bulk, which includes a Draft Codex List of Acceptable Previous Cargoes currently under development (CAC/RCP, 1987). In addition, a set of criteria has been developed to determine the acceptability of substances as previous cargoes. At its 21st session, the CCFO considered the criteria proposed by the

[6] OJ L 139, 30.04.2004 p 1-54.
[7] OJ L 175, 19.07.1993 p 1-11.

Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) (FAO/WHO) Joint Technical Meeting (FAO/WHO, 2007) and agreed to amend some of the proposed criteria and forward them (CCFO criteria) for adoption at Step 5 at the next session of the CAC (Rome, 23-26 June 2009) (CCFO, 2009). At the last CAC session (Rome, 23-26 June 2009), the set of criteria as proposed by CCFO have been adopted at Step 5. Before formal adoption by the CAC, the criteria need to go through Step 6 and 7, where governments and interested parties can comment, and Step 8, where after a final round of comments the CAC adopts the draft as a formal Codex text.

The European Commission 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 oil and fats.

Besides the Codex Draft List of Acceptable Previous Cargoes currently at Step 6, a Proposed Draft List of Acceptable Previous Cargoes has been developed. This includes a number of substances to be evaluated as acceptable previous cargoes. Some of them are already considered acceptable according to Commission Directive 2004/4/EC, amending Directive 96/3/EC. The Proposed Draft List is currently at Step 3 for comments and consideration at the next CCFO session (Malaysia, February 2011).

Therefore, the European Commission has now requested EFSA to evaluate the substances included in the Proposed Draft List of Acceptable Previous Cargoes (Appendix V to the report Alinorm 09/32/17) focusing on the substances which are not included in the Annex of Commission Directive 2004/4/EC, amending Directive 96/3/EC (Table 1).

The substances and mixtures in Table 1 are acceptable previous cargoes in trade conducted under FOSFA rules, except the unfractionated fatty acid/fatty alcohol/fatty esters mixtures or mixtures of fatty acids/fatty alcohols/fatty esters from natural oils and fats and the vegetable oil-epoxidised (FOSFA, 2008).

Table 1: Proposed Draft List of acceptable previous cargoes (at Step 3) (Appendix V of Alinorm 09/32/17) (CCFO, 2009).

Substance (synonyms)	CAS Number
2,3-butanediol (2,3-butylene glycol)	513-85-9
Iso-butanol (2-methyl-1-propanol)	78-83-1
Calcium ammonium nitrate solution	6484-52-2
Calcium nitrate (CN-9) solution	35054-52-5
Cyclohexanol	180-93-0
Cyclohexanone	108-94-1
Fatty acid methyl esters	
These include for example,	
Methyl laureate (methyl dodecanoate) [(a)]	111-82-0
Methyl oleate (methyl octadecenoate) [(a)]	112-62-9
Methyl palmitate (methyl hexadecanoate) [(a)]	112-39-0
Methyl stearate (methyl octadecanoate) [(a)]	112-61-8
Hydrogen peroxide	
Kaolin slurry	1332-58-7
1,3-propylene glycol [(a)]	504-63-2
Unfractionated fatty acid mixture or mixtures of fatty acids from natural oils and fats	
Unfractionated fatty alcohol mixture or mixtures of fatty alcohols from natural oils and fats	
Unfractionated fatty esters or mixtures of fatty esters from natural oils and fats	
Vegetable oil – epoxidised	
Fructose	

(a) Substances included in the Annex of Commission Directive 2004/4/EC, amending Directive 96/3/EC, and therefore not under evaluation in the present opinion.

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, 1996). The Committee was asked to examine the substances given in the Annex of Directive 96/3/EC 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 Directive 96/3/EC 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, 1996; 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): Although 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, later replaced by Regulation (EC) 852/2004, were applied, and especially regarding the cleaning and condition of the tanks, as well as the requirement included in Directive 96/3/EC, where accurately documented evidence relating to the 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, the acceptance was considered only provisional considering mainly 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 and 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 1).

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, 1,3-propanediol) 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).

2.2. EFSA's review of the SCF criteria for acceptable previous cargoes for edible fats and oils

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. 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 at Step 5 at the last CAC session (June 2009).

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./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.

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 Oils and Fats in Bulk.

- With respect to CCFO criterion 2, the CONTAM Panel agrees 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 concludes 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 notes that genotoxic substances would not be acceptable as previous cargoes. Also in relation to CCFO criterion 2, the CONTAM Panel notes 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 is 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 considers 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 endorses CCFO criterion 4 without any further remarks.

3. Evaluation of certain substances as acceptable previous cargoes for edible fats and oils

The CONTAM Panel has evaluated the acceptability of the substances listed in Table 1 as previous cargoes for edible fats and oils. The evaluation is based on its opinion on the review of the criteria for acceptable previous cargoes (see chapter 2.2.) (EFSA, 2009a), as the CCFO criteria are not yet formally adopted by the CAC.

The current evaluation of the substances as acceptable previous cargoes is based on available studies/information from literature searches carried out up to October 2009 on public databases, e.g. PubMed, IUCLID, Toxline, and also evaluations made by international bodies, e.g. World Health Organization (WHO). In addition, a call for data was issued by EFSA in June 2009 asking for any available data/information published in peer-reviewed papers, technical studies or reports related to the physico-chemical properties, toxicity and allergenicity of the target substances or mixtures, as well as information on their reaction products formed when in contact with fats and oils. In response to this call, major trade companies submitted information related to the substances under evaluation (see Documentation Submitted to EFSA).

The toxicological profile of the target substances has been 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 criteria defined in the opinion on the review of the SCF criteria and the proposed CCFO criteria (EFSA, 2009a).

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, which has been shown e.g. for various natural lipids like pollen-associated oxylipins (Traidl-Hoffmann et al., 2009). Besides allergenicity, other influences on the immune system have to be taken into account, in particular promotion of inflammatory responses.

For substances previously assessed by the SCF as previous cargoes, the present opinion does not repeat the detail of the toxicological information already provided in the SCF opinions (SCF, 1996, 2003a), but provides a summary of the SCF's key conclusions as appropriate, and describes any new literature data arising since the SCF's assessments in some more detail. For substances not previously assessed by the SCF as previous cargoes, a more detailed description of the toxicological profile has been provided.

The present criteria for evaluating previous cargoes do not specifically address the presence of potential impurities in the substances evaluated as previous cargoes. The impurities should be taken into consideration since they may be toxicologically more relevant than the substance itself. Therefore, in its evaluation the CONTAM Panel also took into account possible impurities.

3.1. 2,3-Butanediol (2,3-butylen glycol)

2,3-Butanediol ($C_4H_{10}O_2$, CAS no. 513-85-9) has two chiral centres and as a result exists as a meso form with two different enantiomers. 2,3-Butanediol has a large number of industrial applications, including the manufacture of printing inks, perfumes, fumigants, moistening and softening agents,

explosives, plasticizers, foods and pharmaceuticals. 2,3-Butanediol is also used as a flavouring agent [FL-no:02.133].

The CONTAM Panel was not provided with any information on potential impurities in commercial 2,3-butanediol.

2,3-Butanediol is also produced by bacteria following anaerobic fermentation of glucose and occurs naturally in raspberries, certain cheeses and various types of wine.

3.1.1. Previous evaluations

In 1996, the SCF evaluated 2,3-butanediol and considered this substance as not acceptable previous cargo since no toxicological data were presented to the SCF and limited technical data on the ease of cleaning from the tank or removal by the oil refining process was available (SCF, 1996).

In 2003, the information available was inadequate to reconsider the SCF's previous opinion and the compound was again considered a not acceptable previous cargo (SCF, 2003a).

In 2008, EFSA re-evaluated 2,3-butanediol for its use as a flavouring agent (EFSA, 2008d). It was recognised that 2,3-butanediol is also a minor metabolite of ethanol in humans and is classified as a Cramer Class I compound with a TTC value of 1.8 mg/person per day. 2,3-Butanediol has an LD50 of 9,000 mg/kg b.w. (mouse) and was not mutagenic in the Ames test. However, the safety of the use of the compound as a flavouring agent could not be evaluated by EFSA because the estimated levels of intake were higher than the TTC value of 1.8 mg/person per day. In the absence of any information on chirality or stereoisomer composition of commercially available 2,3-butanediol, EFSA concluded in 2008 that no final evaluation of the safety of the compound as a flavouring agent could be undertaken at that time (EFSA, 2008d).

3.1.2. Current evaluation

3.1.2.1. Toxicological profile

Absorption, distribution, metabolism and elimination

2,3-Butanediol (stereoisomers not specified) is a minor metabolite of ethanol and can be detected in plasma and urine in aldehyde dehydrogenase deficient humans (Otsuka et al., 1999), alcoholics (Rutstein et al., 1983) and patients with alcoholic liver cirrhosis (Casazza et al., 1988). Serum levels of 5 to 154 µM 2,3-butanediol have been reported in humans (Xu et al., 1998). The existence of mammalian diacetyl reductases and 2,3-butanediol dehydrogenases has been reported, and in a perfused rat liver model, 2,3 butanediol has been shown to be metabolised to acetyl-CoA via acetoin. Conversely, acetaldehyde reacts with pyruvate to form acetoin which yields diacetyl on oxidation and 2,3-butanediol on reduction.

The potential formation of the α-dicarbonyl metabolite from 2,3-butanediol raises the possibility of generation of a reactive carbonyl metabolite that may be both cytotoxic and genotoxic by DNA adduct formation (the so-called carbonyl stress). This form of stress has also been linked to diabetes, Alzheimer's disease and cancer (Kovacic and Cooksy, 2005; Massari et al., 2008).

Acute toxicity
The acute toxicity of 2,3-butanediol (isomer composition not given) is low and an LD_{50} of 9,000 mg/kg b.w. has been reported for the mouse (EFSA, 2008d). Oral administration of 2,3-butanediol (2.12 g/kg b.w.) to male Sprague-Dawley rats weighing 200-280 g did not induce any liver toxicity based on serum transaminase levels at 40 hours. However, the same dose markedly potentiated carbon tetrachloride-induced hepatic injury (Dietz and Traiger, 1979).

The effect of 2,3-butanediol on whole-body glucose utilisation in rats was studied (Xu et al., 1998). The authors of this study showed that infusion of 2,3-butanediol to give a plasma concentration of 50 µM (equivalent to 4.5 mg/L) caused acute insulin resistance *in vivo*. The use of 2,3-butanediol as a cryopreservant prompted a number of *in vitro* studies on its potential cytotoxicity. Concentrations of 2,3-butanediol up to 100 g/L in a perfused rat liver model did not induce any cytotoxicity or change in resistance and bile production (Eschwege et al., 1993). Likewise, studies in a range of cells maintained in culture showed a lack of cytotoxicity of 2,3-butanediol up to concentrations of 100 g/L.

Sub-chronic and chronic toxicity studies
No multiple dosing toxicity studies on 2,3-butanediol were identified.

Developmental and reproductive toxicity
No studies were identified.

Carcinogenicity and genotoxicity
2,3-Butanediol was described as not mutagenic in the Ames test (*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538, *Escherichia coli* WP2 uvrA) (Iwata et al., 1984). No other genotoxicity or mutagenicity studies were identified. No carcinogenicity studies were identified. Its potential metabolite diacetyl is cytotoxic and genotoxic (Kovacic and Cooksy, 2005; Massari et al., 2008).

3.1.2.2. Allergenicity and immunotoxicity

There is no known association between 2,3-butanediol and allergy.

3.1.2.3. Reactivity and reaction products

As described in Section 3.1.2.3., in fats and oils alcohols are slowly esterified with fatty acids, catalyzed by the free fatty acids present in crude oils. Extrapolated from data on methanol, ethanol, isopropanol and fatty alcohols, the esterification of half of the 2,3-butanediol during transport and storage is possible, primarily forming the monoester.

3.1.2.4. Conclusion

There is a lack of chronic and carcinogenicity studies, and the information about the potential genotoxicity of 2,3-butanediol is considered insufficient. The CONTAM Panel therefore concludes that 2,3-butanediol does not meet the criteria for acceptability as a previous cargo.

3.2. Isobutanol (2-methyl-1-propanol)

Isobutanol ($C_4H_{10}O$, CAS no. 78-83-1) is a colourless compound that is used as an extraction solvent and in the food industry as a flavouring agent. It also occurs naturally during the fermentation of carbohydrates.

Isobutanol usually has a purity of more than 99 % and the main impurity is water (BASF, 2008).

3.2.1. Previous evaluations

Isobutanol has been evaluated by the SCF in 1996. At that time it was considered a not acceptable previous cargo because of the limited toxicological data available (SCF, 1996).

In 2003, the SCF carried out a re-evaluation of isobutanol and considered the information available to be inadequate or needing additional clarification. Therefore, the SCF decided to maintain its previous opinion unchanged and evaluate this compound as a not acceptable previous cargo (SCF, 2003a).

The US-EPA conducted a sub-chronic study in rats (strain not given) by giving oral doses of 0, 100, 316 or 1,000 mg/kg b.w. per day for 13 weeks. Treatment at the high dose (1,000 mg/kg b.w. per day) resulted in a minor and transient decrease in body weight gain, decreased serum potassium levels and hypoactivity and ataxia. Using body weight, clinical and histopathological parameters, a no-observed-adverse-effect (NOEL) of 316 mg/kg b.w. per day was reported for this study. US-EPA derived a reference dose (RfD) for isobutanol of 0-0.3 mg/kg b.w. per day with an uncertainty factor (UF) of 1,000 to account for the fact that the study was of limited duration (EPA, 1991).

In an unpublished study reported by JECFA, male and female Wistar rats were given isobutanol in their drinking-water for three months. The test substance was administered in concentrations corresponding to approximate dose levels of 0, 60, 340 or 1,450 mg/kg b.w. per day. All animals tested were free from adverse clinical effects and no treatment-related adverse effects on gross and histopathology, haematology and clinical chemistry parameters were detected. This study showed a lack of toxicity of isobutanol administered in the drinking-water of rats, and that the NOEL was >1,450 mg/kg b.w. per day (BASF, 1992, cited by JECFA, 1998).

3.2.2. Current evaluation

3.2.2.1. Toxicological profile

Absorption, distribution, metabolism and elimination

Higher alcohols are metabolised to their corresponding aldehydes by alcohol dehydrogenase and microsomal oxidases. Another metabolic pathway is their conjugation to glucuronic acid (Lachenmeier et al., 2008).

Acute toxicity

An early study in rats reported an LD_{50} of 2,460 mg/kg b.w. (Smyth et al., 1954). A study performed using A549 human lung cells and a battery of *in vitro* tests derived half maximal inhibitory concentration IC_{50} values for isobutanol of 149 mM (MTT assay), 37 mM (methylene blue) and 11 mM (colony forming efficiency) (Kreja and Seidel, 2002a).

Sub-chronic and chronic toxicity studies

In addition to the studies described above, the CONTAM Panel identified one additional study. Male and female Wistar rats were given 0.2 % isobutanol in drinking water for 53 to 56 weeks (Johannsen and Purchase, 1969). Clinical chemistry revealed no difference between the treated animals and the corresponding controls. At necropsy, no abnormalities were observed during histological examination. The US Food and Drug Administration (FDA) calculated that this concentration of isobutanol in the drinking water provided the rats with an approximate daily isobutanol intake of 200 mg/kg b.w. (FDA, 1993). Based on this study and the studies on toxicity above, isobutanol would meet the criteria of TDI > 0.1 mg/kg b.w.

Developmental and reproductive toxicity

The developmental toxicity of isobutanol was studied in Wistar rats and Himalayan rabbits following exposure by inhalation (Klimisch and Hellwig, 1995). The rats were exposed on days 6-15 post-coitum and the rabbits on days 7-19 post-coitum, and killed on day 20 and 29, respectively. A

concentration of 10 mg/L caused a slight retardation of body weight gain in the rabbit. No signs of embryo-/fetotoxicity or teratogenicity were observed. The authors derived a no-observed-adverse-effect-level (NOAEL) of 2.5 mg/L for the rabbit and 10 mg/L for the rat.

Carcinogenicity and genotoxicity

Isobutanol was tested in a range of *in vitro* genotoxicity tests, including the alkaline Comet assay (using A549 cells, V79 Chinese hamster fibroblasts and human peripheral blood cells), micronucleus test (using V79 Chinese hamster fibroblasts) and the HPRT test (in V79 Chinese hamster fibroblasts) (Kreja and Seidel, 2002b). The authors reported that isobutanol was negative in all these tests, which confirmed an earlier study by Kapp et al. (1996). However, isobutanol was found to elicit an SOS response in the Luminescent umu Test (Nakajima et al., 2006).

The International Agency for Research on Cancer (IARC) recently issued a report on the carcinogenicity of alcoholic beverages and concluded that the carcinogenicity was primarily due to ethanol itself rather than higher alcohols such as isobutanol (Baan et al., 2007). No specific oral carcinogenicity studies on isobutanol were identified.

3.2.2.2. Allergenicity and immunotoxicity

There is no known association between isobutanol and allergy and from its properties it is not likely that one exists. No influence on inflammation or other immune parameters has been reported.

3.2.2.3. Reactivity and reaction products

In edible oils and fats, isobutanol is slowly esterified, as described in Sections 3.1.2.3 and 3.3.2.3.

3.2.2.4. Conclusion

Based on the negative *in vitro* genotoxicity, the low level of chronic *in vivo* toxicity, as well as the volatility of the compound and ease of cleaning, the CONTAM Panel concludes that isobutanol meets the criteria for acceptability as a previous cargo.

3.3. Calcium Ammonium nitrate solution and Calcium nitrate (CN-9) solution

Solutions of ammonium nitrate (CAS no. 6484-52-2), calcium nitrate (CAS no. 35054-52-5) and their double salt $NH_4NO_3.5Ca(NO_3)_2.10H_2O$, named 'nitric acid, ammonium calcium salt', are nitrogen fertilisers.

No specific information was available on potential impurities.

3.3.1. Previous evaluations

These solutions have never been evaluated as acceptable previous cargo by the SCF.

Many calcium salts such as calcium acetate are permitted food additives. The recommended calcium intake is 700 mg per day (SCF, 1993) and Tolerable Upper Intake Level for adults (including pregnant and lactating women) is 2,500 mg per day (SCF, 2003b).

Nitrate was recently evaluated by the CONTAM Panel (EFSA, 2008e). This evaluation stated that nitrate is a naturally occurring compound that is part of the nitrogen cycle as well as an approved food additive. EFSA reconfirmed the ADI for nitrate of 3.7 mg/kg b.w. per day, equivalent to 222 mg nitrate per day for a 60 kg adult that was previously established by the SCF and confirmed by the JECFA in 2002.

Ammonia and ammonia salts were recently evaluated by EFSA (EFSA, 2009b). The estimated production of ammonia in the human intestine ranges from 10 mg per day in the duodenum to 3 g per day in the colon. Ammonia is readily absorbed from the gastrointestinal tract, after which it enters the portal circulation, is transformed to urea in the liver via the urea cycle and is subsequently excreted as urea by the kidneys. It occurs naturally in many foods, including apples, cabbage and celery. Although specific information on the calcium ammonium nitrate and calcium nitrate salts is not available, information is available on the sodium and potassium salts, and on ammonium chloride. Clinical studies in man show that administration of high doses of ammonium chloride or of sodium nitrate results in changes in the acid-base balance. This is the normal physiological response. Ammonium carbonate and bicarbonate are also used as food additives. Both the levels used in this context and the anticipated worst case exposures from previous cargoes are far below the exposures required to cause physiological changes.

3.3.2. Current evaluation

3.3.2.1. Toxicological profile

Based on the previous evaluations described above, the CONTAM Panel considers that there are no toxicological concerns regarding calcium nitrate, ammonium nitrate and the double salt. 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 tolerable upper intake level of calcium. For nitrate, the threshold in the criteria of an ADI (or TDI) above 0.1 mg/kg b.w. for previous cargoes is well below the ADI. The small amounts of ammonium expected as contamination as a previous cargo is not considered as a safety concern.

3.3.2.2. Allergenicity and immunotoxicity

There is no known influence of these salts on the immune system.

3.3.2.3. Reactivity and reaction products

In an acidic environment (free fatty acids), nitrate reacts with alcohols forming esters of nitric acid, also called nitrates. Since the most abundantly available alcohols in edible oils are the mono- and diglycerides, primarily fatty acid esters of glycerol mononitrate (positions 1 and 3) are expected.

Glycerol nitrates are known as pharmacologically active compounds. However, they are likely to be formed only in small amounts. Therefore, possible formation of these reactants is not of concern.

3.3.2.4. Conclusion

The CONTAM Panel concludes that solutions of calcium nitrate, ammonium nitrate and the double salt, 'nitric acid, ammonium calcium salt', meet the criteria for acceptability as previous cargoes.

3.4. Cyclohexanol

Cyclohexanol ($C_6H_{12}O$, CAS no. 108-93-0) is a colourless to light-yellow liquid mainly used in the polymer industry for the production of adipic acid and caprolactam during the manufacture of nylon and as an intermediate for agricultural chemicals, plasticizers, rubber chemicals and pharmaceuticals. It has limited use as solvent and is also used as a flavouring agent [FL-no: 02.070].

Cyclohexanol is manufactured by oxidation of cyclohexane or hydrogenation of phenol and the main impurities are methanol and water (around 2.5 %).

3.4.1. Previous evaluations

In 1996, the SCF considered cyclohexanol as a not acceptable previous cargo because the data available at that time did not allow an adequate evaluation of its carcinogenicity and genotoxicity. The evaluation was done together with cyclohexanone because of structural similarity and metabolic interconversion between cyclohexanol and cyclohexanone *in vivo*. At that time, there were no carcinogenicity data for cyclohexanol and the limited mutagenicity data were equivocal with respect to clastogenicity (SCF, 1996).

In 2003, the SCF searched for additional information and performed a re-evaluation. Three new studies published since the release of the previous SCF opinion in 1996 were taken into account: a case report in an adolescent (Zuckerman et al., 1998), a human study on metabolism and toxicokinetics (Mraz et al., 1998) and an oral study in rats on enzyme induction (Espinosa-Aguirre et al., 1997). The SCF considered that none of the studies available allowed a re-evaluation of the carcinogenicity or genotoxicity of cyclohexanol. Therefore, the SCF considered its opinion of 1996 as unchanged and proposed the compound should not be accepted as previous cargo (SCF, 2003a).

In 2008, EFSA re-evaluated cyclohexanol as a flavouring agent (EFSA, 2008a,b) and concluded that cyclohexanol [FL-no: 02.070] was not genotoxic in two Ames tests and in an *in vivo* micronucleus assay, which are all considered as valid studies. However, the results of the *in vivo* study are of limited relevance, due to the lack of bone marrow toxicity. Inconclusive results were reported in an *in vitro* chromosomal aberration assay with human leukocytes and negative results were reported in a dominant lethal mutations assay with *Drosophila melanogaster*; both studies were considered inadequate. Cyclohexanol is classified under the Cramer Classification Tree as a structural Class I compound for which the Threshold of Toxicological Concern (TTC) is set to 1.8 mg/person per day. Even though the data on genotoxicity and carcinogenicity were limited, EFSA concluded that the use of cyclohexanol as a flavouring agent would present no safety concern because the levels of intake were not expected to exceed the TTC based on both the Maximised Survey-derived Daily Intake (MSDI) approach and the modified Theoretical Added Maximum Daily Intake (mTAMDI) (EFSA, 2008a). The CONTAM Panel noted that acceptability of cyclohexanol as a flavouring agent is based on an anticipated exposure below a certain threshold of exposure according to the TTC concept.

3.4.2. Current evaluation

3.4.2.1. Toxicological profile

Absorption, distribution, metabolism and elimination

Cyclohexanol is readily absorbed following oral, inhalation or dermal exposure (HSDB, 2005a). In humans, the primary route of metabolism is through glucuronidation. In addition, cyclohexanol can be oxidised to cyclohexanone by alcohol dehydrogenase and to 1,2- and 1,4-cyclohexanediol (Mraz et al., 1998).

Acute toxicity

The oral lethal dose (LD_{50}) of cyclohexanol in rats is 1,500-2,060 mg/kg (Health Council of the Netherlands, 2004).

Sub-chronic and chronic toxicity studies

Only studies of limited validity on the toxicity of cyclohexanol under repeat dose conditions are available. In one study designed to investigate only peripheral neuropathy, rats were given intraperitoneal doses of 200 mg/kg b.w. cyclohexanol once or twice daily for up to six weeks (Perbellini et al., 1981). No effects on the peripheral nervous system were observed, but the experiment was terminated early because the animals were in poor condition, there was a decrease in weight gain and two animals died prematurely. No general gross or histopathological examinations were reported and no NOAEL was established. This study was not considered applicable to the evaluation of the oral toxicity of cyclohexanol.

Cyclohexanol was evaluated in an oral gavage study in Sprague-Dawley rats (Lake et al., 1982). Cyclohexanol was given (455 mg/kg per day) to twelve 30-day old rats for seven days, and control animals received an equivalent 5 ml corn oil/kg b.w. Cyclohexanol significantly increased relative liver weights and the content of hepatic cytochrome P-450 levels and the associated biphenyl 4-hydroxylase, 7-ethoxycoumarin O-deethylase and aniline 4-hydroxylase activities. No effect of cyclohexanol on relative kidney or testes weights was observed.

In another study, cyclohexanol administration (25 mg/kg per day orally for 40 days) in male rabbits produced a moderate elevation of serum cholesterol, phospholipids, triglycerides, bilirubin, and pyruvate transaminase (Dixit et al., 1980). Histopathological examination of the liver did not show any damage.

Developmental and reproductive toxicity

In 2004, the Committee for Compounds Toxic for Reproduction, a committee of the Health Council of the Netherlands, evaluated the effects of cyclohexanol on reproduction, *i.e.* fertility, development and lactation (Health Council of the Netherlands, 2004). A limited number of studies on experimental animals were found, all of them carried out before 1982. In one study, cyclohexanol administration (25 mg/kg per day orally for 40 days) in male rabbits produced a brief period of infertility by inhibiting the process of spermatogenesis at the spermatocyte and spermatid levels (Dixit et al., 1980). No studies were found on the effects of cyclohexanol exposure on human reproduction. No studies were found concerning the excretion of cyclohexanol in human breast milk. The Dutch Committee for Compounds Toxic for Reproduction recommended the classification of cyclohexanol as a substance which causes concern for human fertility (Category 3, according to Directive 93/21/EEC[8]) (Dutch Expert Committee for Occupational Exposure, 1990).

Carcinogenicity and genotoxicity

No carcinogenicity studies have been conducted in accordance with current guidelines. Márquez-Rosado et al. (2007) studied the co-carcinogenicity of cyclohexanol using the hepatocarcinogenesis model of Semple-Roberts to determine whether cyclohexanol favoured the development of hepatic preneoplastic lesions induced by diethylnitrosamine (DEN), and promoted by 2-acetylaminofluorene (2-AAF) and partial hepatectomy (PH). Cyclohexanol was administered at 100 mg/kg b.w. per day to male Fisher rats 334 (180-200 g), and the animals were sacrificed 25 days after initiation of the study.

In this study, the evaluation of cyclohexanol as a tumour co-promoter in animals initiated with DEN and promoted by 2-AAF followed by PH showed (i) a marked increase in gamma-glutamyltranspeptidase (GGT) and glutathione S-transferase P expression (both enzymes are widely used as a tumour marker in the liver during chemical carcinogenesis), (ii) an increased presence of preneoplastic nodules and (iii) evident multinodular alterations leading to the formation of confluent conglomerates. However, (iv) no statistically significant differences of the level of oxidative stress or rates of cell proliferation were observed between animals initiated with DEN and promoted by 2-AAF followed by PH and co-exposed to cyclohexanol versus the corresponding control animals initiated with DEN and promoted by 2-AAF followed by PH. The authors concluded that their results demonstrated the co-carcinogenic effect of cyclohexanol in the development of liver pre-neoplastic lesions. Cyclohexanol administration in the absence of DEN and AAF treatment and PH led to only a very limited number of low intensity stained GGT-positive lesions that were considered to result from hepatic damage.

In a limited study, male ICR mice were exposed by inhalation for six weeks to unknown concentrations of vapours of cyclohexanol (Šiviková et al., 2007). A significant increase in sister chromatid exchanges in bone marrow cells as compared to control animals was reported. No increase in the incidence of chromosomal aberrations or micronucleus formation was observed.

[8] OJ L 110, 4.5.1993 p 20-21.

The metabolic interconversion of cyclohexanol and cyclohexanone raises questions about carcinogenicity of cyclohexanol (see Section 3.2.2.1).

3.4.2.2. Allergenicity and immunotoxicity

There is no known association between cyclohexanol and allergic responses and it is not expected that cyclohexanol could be an allergen or an allergy promoter.

3.4.2.3. Reactivity and reaction products

Alcohols are known to be esterified in edible oils primarily by inter-esterification with the glycerides, but to some extent also by esterification with free fatty acids. This reaction is catalyzed by free fatty acids, as typically present in crude edible oils. Esterification over a few months at ambient temperature was shown to reach 10-20 % for fatty alcohols in olive oil by Mariani and Venturini, (2006). If catalyzed by 1 % free fatty acid (as normally present in raw vegetable oils), some 5 % propyl alcohol was transesterified during 11 days at 40 °C (Biedermann et al., 2008). It is concluded that primary alcohols might be esterified to up to 50 % during storage lasting one year.

No data are available for cyclohexanol regarding its reactivity. However, it should be noted that free sterols are not known to be esterified in significant amounts in edible oils, which is probably due to steric hindrance.

3.4.2.4. Conclusion

There are uncertainties about the potential carcinogenicity, including possible concern arising because of the metabolic interconversion of cyclohexanol to cyclohexanone, and potential reproductive toxicity of cyclohexanol and a lack of chronic studies. The CONTAM Panel therefore concludes that cyclohexanol does not meet the criteria for acceptability as a previous cargo.

3.5. Cyclohexanone

Cyclohexanone ($C_6H_{10}O$, CAS no. 108-94-1) is used as an additive for electronic industry applications, in polyvinyl chloride (PVC) adhesives and in bonding agents for plasticized PVC film, e.g. for roof coverings, swimming pools and tunnels, as a solvent for insecticides/fungicides, as activator in oxidation reactions and for the manufacture of cyclohexanone oxime, caprolactam and nylon 6. It is also used as a flavouring substance (FL-no: 07.148).

The purity of cyclohexanone is usually greater than 99 %.

3.5.1. Previous evaluations

In 1996, the SCF evaluated cyclohexanone in conjunction with cyclohexanol because of structural similarity and metabolic interconversion between cyclohexanol and cylohexanone *in vivo*, as already mentioned. The substance was considered a not acceptable previous cargo since the 2-year carcinogenicity studies in rats and mice evaluated produced equivocal results. Data on genotoxicity were also equivocal indicating a possible clastogenic effect (SCF, 1996).

In 2003, cyclohexanone was again evaluated together with cyclohexanol. The three new studies published after the release of the previous SCF opinion in 1996 did not allow for a re-evaluation of cyclohexanone. It was therefore still considered as a not acceptable previous cargo (SCF, 2003a).

In 2008, EFSA re-evaluated the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluation of cyclohexanone for its use as a flavouring agent (EFSA, 2008c). Cyclohexanone was not

mutagenic in an Ames test considered to be valid. However, the *in vitro* genotoxicity studies conducted in mammalian cells were considered inadequate. In the JECFA evaluation, the Procedure for the Safety Evaluation of Flavouring Agents was applied and the Committee assigned monocyclic alkanones, including cyclohexanone, to structural Class II, under the Cramer classification Tree, with a TTC set to 0.54 mg/person per day. JECFA considered that the use of cyclohexanone as a flavouring agent is of "no safety concern at estimated levels of intake as flavouring substance" based on the estimated levels of intake in the European Union (EU) and the United States of America (USA). EFSA agreed with the JECFA conclusion (EFSA, 2008c). The CONTAM Panel noted that acceptability of cyclohexanone as a flavouring agent is based on an anticipated exposure below a certain threshold of exposure according to the TTC concept.

3.5.2. Current evaluation

3.5.2.1. Toxicological profile

Absorption, distribution, metabolism and elimination

Cyclohexanone is readily absorbed following oral, inhalation or dermal exposure (HSDB, 2005b). In humans, the primary route of metabolism is through reduction to cyclohexanol by cytosolic carbonyl reductases, followed by glucuronidation. In addition, cyclohexanone can be hydroxylated to form 1,2- and 1,4-cyclohexanediol (Mraz et al., 1998).

Acute toxicity

The acute toxicity of cyclohexanone is low and the reported LD_{50} values following oral dosing range from 1,500 to 2,100 mg/kg b.w. for rat and mouse, respectively (JECFA, 2003).

Sub-chronic and chronic toxicity studies

A 13-week toxicity study was performed in which B6C3F1 mice of each sex received drinking-water containing cyclohexanone to provide doses corresponding to 0, 100, 580, 1,600, 3,200, 6,200, 8,500 or 12,000 mg/kg b.w. per day (Lijinsky and Kovatch, 1986). No effects were reported up to 1,600 mg/kg b.w. per day and a 19 % decrease in body-weight gain occurred in male mice given 6,200 mg/kg b.w. per day dose. Higher doses caused a suppression of weight gain in both sexes and at the highest dose, 6/10 males and 3/10 females died; some mice showed focal coagulative liver necrosis and two females showed hyperplasia of the thymus. The NOAEL of this study is 1,600 mg/kg b.w. per day.

A 25-week toxicity study was performed in which groups of five Fischer 344 rats of each sex were given drinking-water containing cyclohexanone to provide doses of up to 1,000 mg/kg b.w. per day (Lijinsky and Kovatch, 1986). All the rats survived to termination of the study at 25 weeks and a no-observed-effect level (NOEL) of 500 mg/kg b.w. per day was reported in male or female rats. Two males dosed with 720 mg/kg b.w. per day showed degenerative changes of the thyroid gland, while animals at the highest dose had a 10 % depression in weight gain.

Developmental and reproductive toxicity

Several studies have investigated the developmental and reproductive toxicity of cyclohexanone. Apart from a decreased live birth weight in mice orally dosed with 2,200 mg/kg b.w. per day on days 8-12 of gestation (Seidenberg et al., 1986), cyclohexanone did not appear to affect development. Two further studies in mice using oral doses of 800 mg/kg b.w. and 2,200 mg/kg b.w. reported in the IUCLID Database (2000) showed no effect of cyclohexanone at the lower dose, but maternal toxicity at the high dose, which appeared associated with an initial but transient reduced weight gain of the neonates. An earlier study using female CF1 mice showed that intraperitoneal administration of 50 mg per day for 28 days had no effect on fertility (Hall et al., 1974).

Carcinogenicity and genotoxicity

A 2-year study was performed by exposing B6C3F1 mice of each sex to dietary intakes of cyclohexanone up to 6,200 mg/kg b.w. per day. Histopathological examination of tissues from male

mice given 1,600 mg/kg b.w. per day showed an increased incidence of proliferative lesions of the liver and lung, combined with a statistically significant increase in the incidence of benign and malignant hepatocellular tumours when compared with controls. No benign or malignant tumours were recorded at the higher doses. Female mice at 1,600 mg/kg b.w. per day had a significant increase in the occurrence of malignant lymphomas (Lijinsky and Kovatch, 1986).

In another 2-year study, groups of 52 Fischer 344/N rats of each sex were given drinking-water containing cyclohexanone to provide doses of cyclohexanone of 0, 330 or 650 mg/kg b.w. per day (Lijinsky and Kovatch, 1986). A statistically significant increase in the incidence of adrenal cortex adenomas was found in males at 330 mg/kg b.w. per day, but not at the higher dose. In addition, a statistically significant increase in the incidence of follicular thyroid tumours (adenomas and carcinomas) occurred in male rats exposed to 650 mg/kg b.w. per day. The authors concluded that in view of the lack of dose-response relationship, the increased incidence of benign tumours did not demonstrate a carcinogenic potential for cyclohexanone (Lijinsky and Kovatch, 1986).

The reports on the *in vitro* genotoxicity of cyclohexanone in the Ames test were negative (EFSA, 2008c; JECFA, 2003; Belsito et al., 2008). Genotoxicity assays, including unscheduled DNA synthesis, mouse lymphoma assays, sister chromatid exchanges in Chinese Hamster Ovary (CHO) cells and chromosomal aberrations in lymphocytes were negative except for a positive result in the hypoxanthine guanine phosphoribosyl transferase gene mutation (HGPRT) assay in CHO cells (IUCLID, 2000). Except for a positive result in one *in vivo* study in *Drosophila melanogaster* that was considered inadequate, all other sex linked recessive lethal mutation studies in *D. melanogaster* were negative (EFSA, 2008c; JECFA, 2003; Belsito et al., 2008). The genotoxicity data are overall inadequate or inconclusive.

3.5.2.2. Allergenicity and immunotoxicity

There are very rare cases of cyclohexanone as an inducer of contact dermatitis upon occupational chronic exposure to pure cyclohexanone (Pazzaglia et al., 2004). In light of this, the cyclohexanone levels due to previous cargoes are unlikely to have immunological effects.

3.5.2.3. Reactivity and reaction products

In acidic environment, cyclohexanone forms 1,3-dioxolane derivatives with vicinal diols (cyclic acetals and ketals). Free fatty acids in the edible oil are probably adequate to support this reaction in view of the long time available. Reaction partners in the edible oil are monoglycerides and dihydroxy fatty acids (e.g. resulting from hydrolyzed epoxy fatty acids).

As dioxolane derivatives are fairly thermostable and stable in alkali media, they will not be removed during the refining process.

Dioxolane derivatives are labile in strongly acidic media and might be hydrolyzed in the stomach. However, as known for epoxy compounds, such as bisphenol A diglycidyl ether (BADGE), compounds in oil tend to be protected from hydrolysis by inclusion in oil droplets.

3.5.2.4. Conclusion

There are uncertainties about the potential carcinogenicity of cyclohexanone. The metabolic interconversion of cyclohexanone to cyclohexanol raises questions about the reproductive toxicity. The potential hazards associated with the dioxolane derivatives, probably formed as reaction products, should also be considered. The CONTAM Panel therefore concludes that cyclohexanone does not meet the criteria for acceptability as a previous cargo.

3.6. Fatty acid methyl esters

In the EU Regulation four specific methyl esters are acceptable as previous cargoes (Commission Directive 2004/4/EC). However, it is usual to transport mixtures of methyl (and ethyl) esters produced from the transesterification of fats and oils, rather than specific methyl esters. The evaluation of such mixtures is covered under chapter 3.11.

3.7. Hydrogen peroxide

Hydrogen peroxide (H_2O_2, CAS no. 7722-84-1) is used to bleach textiles and paper products, as well as to manufacture or process foods, minerals, petrochemicals and consumer products (detergents). It is also used as disinfectant, antiseptic, oxidizer, and in rocketry as a propellant. Hydrogen peroxide is also a normal metabolite in the aerobic cell (concentration 10^{-9}-10^{-7} M) (Chance et al., 1979) and has been detected in whole blood, plasma and serum (ECB, 2003; Li, 1996).

No impurities or additives (i.e. stabilizers) of concern are expected.

3.7.1. Previous evaluations

Hydrogen peroxide has never been evaluated by the SCF as acceptable previous cargo.

3.7.2. Current evaluation

3.7.2.1. Toxicological profile

The toxicology of hydrogen peroxide was reviewed by the European Chemicals Bureau (ECB) in 2003 (ECB, 2003). Hydrogen peroxide is rapidly broken down by enzymes, including glutathione peroxidase and catalase in tissue. The kinetics of hydrogen peroxide are not well described. Hydrogen peroxide causes toxicity at the site of contact, but is not believed to give rise to systemic toxicity (ECB, 2003; HPA, 2009). One of its toxicological mechanisms is the generation of hydroxyl radicals, which together with products of lipid peroxidation can lead to DNA damage and cell death.

Acute toxicity in animals

A variety of values in the range of 500-5,000 mg/kg b.w., have been quoted for the oral LD_{50} of hydrogen peroxide in rats. Signs of toxicity included lethargy, immobility, irregular respiration and hunched posture (ECB, 2003). After inhalation exposure (hydrogen peroxide aerosols and vapours) symptoms reported included decrease in respiration rate, lung congestion, necrosis of bronchial epithelium, and at low concentrations nasal irritation, blinking of the eyes, gasping and loss of muscular coordination (ECB, 2003). The median lethal intravenous dose in rats is 21 mg/kg (Li, 1996; Spector, 1956). The maximum tolerated dose for rats in a prolonged intravenous infusion (up to 30 min) of hydrogen peroxide solutions was approximately 50 mg/kg b.w. The irritancy and corrosivity of hydrogen peroxide solutions to skin, eye and respiratory tract have been well demonstrated (ECB, 2003).

Acute toxicity in humans

The main toxic effect resulting from exposure to hydrogen peroxide is irritation at the site of contact. There are many reports of irritation of the respiratory tract, the skin and the eyes following direct exposure to hydrogen peroxide solutions.

Sub-chronic and chronic toxicity in animals

The repeated dose toxicity of hydrogen peroxide by the oral route has been characterised in several animal studies. Whilst a number of adverse effects have been reported, these are considered to be secondary to local effects on the gastrointestinal tract. Decreased body weight gain was found in

gavage studies in rats employing a dose range of 50-500 mg/kg b.w. per day; other observed symptoms included decreased erythrocyte count, haematocrit, plasma protein concentration, and plasma catalase (ECB, 2003; Ito et al., 1976; Kawasaki et al., 1969). A 90 day study with a catalase-deficient strain of mice indicated that the NOAEL of hydrogen peroxide in drinking water was 100 mg/kg based on dose-related reductions in food and water consumption and observation of duodenal mucosal hyperplasia (ECB, 2003; FMC, 1997). This corresponds to a daily dose of 26 mg/kg b.w. for males and 37 mg/kg b.w. for females. In a study in rats where hydrogen peroxide was administered in drinking water, a decreased body weight gain was found at the lowest dose tested (0.15 %, 1,500 mg/kg) (ECB, 2003; Takayama, 1980).

Sub-chronic and chronic toxicity in humans

No data on chronic toxicity in humans following chronic ingestion are available, ingestion not being a typical route of exposure to hydrogen peroxide.

Reproductive toxicity

No appropriate animal studies are available for a complete evaluation of reproductive and developmental toxicity. There are no data regarding the reproductive or developmental toxicity of hydrogen peroxide in humans.

Genotoxicity and mutagenicity

Hydrogen peroxide causes DNA damage in bacteria and in cultured mammalian cells, and is a mutagen in *Salmonella typhimurium* and *Escherichia coli* particularly in the absence of metabolic activation. It also causes mutations in Chinese hamster V79 cells and mouse lymphoma L5178Y cells (*hpgrt* and TK loci). Positive results were obtained in UDS assays, and chromosomal aberrations and sister chromatid exchanges were induced in human and other mammalian cells *in vitro* (IARC, 1987; ECB, 2003). Negative responses have been observed in a variety of *in vivo* assays, including UDS in liver cells of rats administered hydrogen peroxide by intravenous infusion (CEFIC, 1997) and micronucleus formation in mice after a 2-week drinking water exposure or a single intraperitoneal injection (Du Pont, 1995; CEFIC, 1995). However, two host-mediated assays showed a positive response to hydrogen peroxide (endpoints mutagenicity and chromosome aberrations) (ECB, 2003). To investigate target tissue interactions *in vivo*, solutions of hydrogen peroxide in ethanol (0.2-3.2 %) were applied to the skin of Sencar mice over a period of 4 weeks (Society for the Plastic Industry, 1997). No signs of epidermal hyperplasia were observed. There was no induction of the oxidative DNA damage product 8-OH-dG and also no increase in c-Ha- ras mutations (codon 61). Thus under these conditions there was no indication of induction of local mutagenicity in this tissue model.

No data are available regarding the genotoxicity or mutagenicity of hydrogen peroxide in humans.

Carcinogenicity

Carcinogenicity studies have been carried out on mice treated with hydrogen peroxide by oral administration, skin application and subcutaneous administration, and on hamsters treated by topical application to oral mucosa. Oral administration to mice was associated with increased adenomas and carcinomas of the duodenum. An ECB report (ECB, 2003) noted that a promoting effect by treatment with hydrogen peroxide was reported in rat intestinal carcinogenesis initiated by methylazoxymethanol acetate and in Syrian hamster buccal pouch carcinogenesis initiated by 9,10-dimethyl-1,2-benzanthracene (DMBA). Other studies have not shown promotion activity. However in one of these studies, 1 % hydrogen peroxide in drinking water for 32 weeks induced squamous cell papillomas of the forestomach in rats irrespective of prior initiation.

IARC have concluded that there is limited evidence in experimental animals for the carcinogenicity of hydrogen peroxide (IARC, 1987; 1999) and the ECB report concluded that the mechanism of the carcinogenic effect of hydrogen peroxide is unclear. IARC considered that there was inadequate evidence in humans for the carcinogenicity of hydrogen peroxide and concluded that, overall, it is not classifiable as to its carcinogenicity to humans (group 3) (IARC, 1999).

3.7.2.2. Allergenicity and immunotoxicity

Hydrogen peroxide is not allergenic. It is an important representative of the reactive oxygen species (ROS) produced during innate immune responses against pathogens.

3.7.2.3. Reactivity and reaction products

In edible oils, hydrogen peroxide is likely to react completely with the oil in a matter of days. It primarily reacts with double bonds, which are abundantly available in fatty acids, but also in squalene, sterols and tocopherols. The main reaction products are epoxidised fatty acids. Since epoxides are reactive, they may further react.

The worst case residue of 100 mg/kg of hydrogen peroxide as previous cargo would result in roughly 1,000 mg/kg epoxidised fatty acids. Since the double bonds are in large excess, virtually exclusively monoepoxy fatty acids are to be expected. Such monoepoxy fatty acids are always present in edible oils. High quality edible oils contain some 100 mg/kg epoxidised fatty acids, while heavily oxidized oils reach 10,000 mg/kg (Fankhauser-Noti et al., 2006).

3.7.2.4. Conclusion

The toxicity of hydrogen peroxide is not considered to be of concern, since it reacts completely in contact with oil. The contamination of vegetable oils with up to 100 mg/kg hydrogen peroxide promotes oil oxidation, i.e. deteriorates oil quality in a way and to an extent which also may occur in food processing and storage. The CONTAM Panel therefore concludes that hydrogen peroxide would not be of any health concern as a previous cargo.

3.8. Kaolin slurry

Kaolin is a clay composed of kaolinite, potassium aluminium silicate, feldspar and quartz. Kaolin is used as food additive[9], as an anti-caking feed additive[10], in pharmaceutical preparations (antacids), and for clearing or filtration. The main use is for manufacturing paper.

The kaolin slurry usually contains about 65 % kaolin in water, with less than 1% crystalline silica in the form of quartz, and less than 2 % titanium dioxide. Dioxins have been found in kaolin in amounts up to 910 ng WHO-TEQ/kg (RASFF, 2004). Assuming a worst case contamination of oils and fats with kaolin (100 mg/kg oil) (EFSA, 2009a; FAO/WHO, 2007) this would lead to a contamination of the oil of 0.09 pg/g oil which is below the action level[11] (0.5 pg WHO-TEQ/g fat) and the maximum level[12] (0.75 pg WHO-TEQ/g fat) laid down for the sum of dioxins and furans in vegetable oils and fats. The consumption of such a vegetable oil containing the highest degree of dioxin contamination reported and given a daily consumption of 25 g of vegetable oil (FAO/WHO, 2007), would results in an estimated exposure to dioxins about 2 % of the tolerably weekly intake of 14 pg WHO-TEQ/kg b.w. (SCF, 2001).

3.8.1. Previous evaluations

Kaolin slurry has never been evaluated by the SCF as acceptable previous cargo for edible fats and oils.

[9] OJ L 253, 20.9.2008, pp 1-175.
[10] OJ C 50, 25.2.2004, pp 1-144.
[11] OJ L 42, 14.2.2006, pp 26-28 .
[12] OJ L 364, 20.12.2006, pp 5-24.

Kaolin has been evaluated by JECFA (ADI not specified) and is a permitted anti-caking food additive (up to 2.5 %). Kaolin has GRAS (Generally Recognised as Safe) status under 21 CFR 186.1256 and is generally recognised as safe as an indirect human food ingredient with no limitation other than current good manufacturing practice.

3.8.2. Current evaluation

3.8.2.1. Toxicological profile

No publications describing kaolin-induced detrimental health effects, including carcinogenicity or genotoxicity, following oral administration were identified.

3.8.2.2. Allergenicity and immunotoxicity

Kaolin is not allergenic, although it is known to induce pro-inflammatory responses which have been particularly noticed for the lung following intratracheal administration (Yanagisawa et al., 2007).

3.8.2.3. Conclusion

The CONTAM Panel concludes that kaolin slurry would not be of any health concern as a previous cargo, provided it complies with the European Legislation on dioxins.

3.9. Unfractionated fatty acid mixture or mixtures of fatty acids from natural oils and fats

The CONTAM Panel did not receive any specification of the sources/identity of the fatty acid mixtures from natural oils and fats.

Fatty acids derived from naturals oils and fats are obtained in two ways: by hydrolysis and as a by-product of refining. In the refineries, free fatty acids are classically removed by extraction with hydroxide solutions (chemical refining). The aqueous extract is acidified with sulphuric acid, which liberates the free fatty acids (soap stock). In modern refineries, free fatty acids are removed during deodoration and end up in the condensate (physical refining).

With physical refining of fats and oils, not only the fatty acids, but also contaminants including pesticides and mineral oil, are collected in the condensate. In essence, impurities in the oil are enriched in the fatty acids fraction by up to a factor of 100. However, when edible oils are contaminated through fatty acids transported as previous cargo, the contaminants in the fatty acids are again diluted by a factor of 10,000, which means that in the edible oil or fat transported there will be 100 times less contaminants than in the oil or fat from which the fatty acids were obtained.

Specified risk material of ruminant animals is excluded by law from the human and animal food chain in the EU (Regulation 1774/2002[13]). Therefore, the presence of material that carries possible risk of transmissible spongiform encephalopathy (TSE) infectivity in edible fats of animal origin destined for human consumption can be ruled out.

3.9.1. Previous evaluations

These mixtures have never been evaluated by the SCF as acceptable previous cargoes for edible fats and oils as such. However, there are a number of fatty acids in the list of acceptable previous cargoes in the EU legislation:

[13] OJ L 273, 10.10.2002 p 1-95.

Arachidic acid (eicosanoic acid) 506-30-9, Behenic acid (docosanoic acid) 112-85-6, Butyric acid (butanoic acid) 107-92-6, Capric acid (*n*-decanoic acid) 334-48-5, Caproic acid (*n*-hexanoic acid) 142-62-1, Caprylic acid (*n*-octanoic acid) 124-07-2, Erucic acid (cis-13-docosenoic acid) 112-86-7, Heptoic acid (*n*-heptanoic acid) 111-14-8, Lauric acid (*n*-dodecanoic acid) 143-07-7, Lauroleic acid (dedecenoic acid) 4998-71-4, Linoleic acid (9,12-octadecadienoic acid) 60-33-3, Linolenic acid (9,12,15-octadecatrienoic acid) 463-40-1, Myristic acid (*n*-tetradecanoic acid) 544-63-8, Myristoleic acid (*n*-tetradecenoic acid) 544-64-9, Oleic acid (*n*-octadecenoic acid) 112-80-1, Palmitic acid (*n*-hexadecanoic acid) 57-10-3, Palmitoleic acid (cis-9-hexadecenoic acid) 373-49-9, Pelargonic acid (*n*-nonanoic acid) 112-05-0, Ricinoleic acid (cis-12-hydroxy octadec-9-enoic acid; castor oil acid) 141-22-0, Stearic acid (*n*-octadecanoic acid) 57-11-4, Valeric acid (*n*-pentanoic acid; valerianic acid) 109-52-4.

3.9.2. Current evaluation

3.9.2.1. Toxicological profile

The SCF considered the individual fatty acids in the list of acceptable previous cargoes in the EU legislation acceptable since they are normal constituents of food and many have been evaluated in relation to other food uses, e.g. flavours. Fatty acids are of low oral toxicity, both acute, sub-acute/sub-chronic and chronic (HERA, 2002). They are metabolised to innocuous products, are negative in *in vitro* genotoxicity tests and show no carcinogenic or reproductive toxicity potential. When present as mixtures, the fatty acids do not react with each other, and synergistic or potentiating toxicological reactions are not anticipated.

The CONTAM Panel considers 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. However, the CONTAM Panel noted that not enough information was provided by industry to evaluate as previous cargoes fatty acids from all natural sources of fats and oils.

3.9.2.2. Allergenicity and immunotoxicity

There is no information on allergenicity or immunogenicity of complex fatty acid mixtures. Even if the fatty acids were present as previous cargo at the worst case concentration of 100 mg/kg (EFSA, 2009a; FAO/WHO, 2007), the concentration of any allergenic components ultimately present in the edible oil or fat being transported will be very low and are unlikely to cause any concern.

3.9.2.3. Conclusion

The CONTAM Panel concludes that unfractionated fatty acids mixtures or mixtures of fatty acids from oils and fats would not cause any health concern as previous cargoes, provided their sources are edible types of fats or oils.

3.10. Unfractionated fatty alcohol mixture or mixtures of fatty alcohols from natural oils and fats

The CONTAM Panel did not receive any specification of the sources/identity of the fatty alcohol mixtures.

The fatty alcohols from natural oils and fats are produced by reduction of fatty acids (see chapter 3.9).

3.10.1. Previous evaluations

These mixtures have never been evaluated by the SCF as acceptable previous cargo for edible fats and oils as such. However, there are a number of fatty alcohols in the list of acceptable previous cargoes in the EU legislation:

Butyl alcohol (1-Butanol; butyric alcohol) 71-36-3, Caproyl alcohol (1-hexanol; hexyl alcohol) 111-27-3, Capryl alcohol (1-n-octanol; heptyl carbinol) 111-87-5, Cetyl alcohol (alcohol C-16; 1-hexadecanol; cetylic alcohol; palmityl alcohol, n-primary, hexadecyl alcohol), 36653-82-4, Decyl alcohol (1-decanol) 112-30-1, Enanthyl alcohol (1-heptanol; heptyl alcohol) 111-70-6, Lauryl alcohol (n-dodecanol; dodecyl alcohol) 112-53-8, Myristyl alcohol (1-tetradecanol; tetradecanol) 112-72-1, Nonyl alcohol (1-nonanol; pelargonic alcohol; octyl carbinol) 143-08-8, Oleyl alcohol (octadecenol) 143-28-2, Stearyl alcohol (1-octadecanol) 112-92-5, Tridecyl alcohol (1-tridecanol) 27458-92-0, 112-70-9.

3.10.2. Current evaluations

3.10.2.1. Toxicological profile

The SCF considered that the individual fatty acid alcohols in the list of acceptable previous cargoes in the EU legislation 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.

Fatty acid alcohols from edible types of fats and oils are effectively converted to fatty acids in the body and are generally of low oral toxicity, particularly those of higher molecular weight, both acute, sub-acute/sub-chronic and chronic. Lower molecular weight alcohols have been evaluated individually by the SCF and either included because of lack of toxicological concern at the concentrations expected as residues arising from a previous cargo (e.g. methanol, ethanol, butanol) or excluded because of particular toxicological concerns or lack of data.

Higher fatty acid alcohols are metabolised to innocuous products, are negative in *in vitro* genotoxicity tests, and show no evidence of carcinogenic or reproductive toxicity potential. When present as mixtures, the fatty acids do not react with each other, and synergistic or potentiating toxicological reactions are not anticipated.

The CONTAM Panel considers that the anticipated toxicological profile of fatty alcohol mixtures derived from edible types of fats and oils would generally indicate a low level of concern for human health. However, the CONTAM Panel noted that not enough information was provided by industry to evaluate as previous cargoes fatty alcohols from all natural sources of fats and oils.

3.10.2.2. Allergenicity and immunotoxicity

There is no information on allergenicity or immunogenicity of complex fatty alcohol mixtures.

3.10.2.3. Reactivity and reaction products

Fatty alcohols react with fatty acids in glycerides (trans-esterification) or free fatty acids (esterification) by formation of wax esters of the same type as already exist in edible oils.

3.10.2.4. Conclusion

The CONTAM Panel concludes that unfractionated fatty alcohol mixtures or mixtures of fatty alcohols would not cause any health concern as previous cargoes, provided their sources are edible types of fats or oils.

3.11. Unfractionated fatty esters or mixtures of fatty esters from natural oils and fats

No information was provided by industry to allow the consideration of all possible natural sources of oils and fats. The fatty acids and alcohols taken into consideration are those from natural fats and oils as well as methanol and ethanol.

Fatty acid esters may be produced from heavily contaminated oils. For instance, the Ukrainian sunflower oil mixed with mineral oil was largely converted to methyl/ethyl esters used as biodiesel. Oils from waste collection sites can be used which, in the past, were sometimes contaminated with used motor oils or (the case in Belgium) with polychlorinated biphenyls (PCBs). Although the dilution in the edible oil by a factor 10,000 when transported as a previous cargo in most cases is sufficient to rule out health risks, it would not be sufficient for a waste oil containing PCBs or substantial amounts of mineral oil. Moreover, it should be noted that only white mineral oil is allowed as a previous cargo[14].

3.11.1. Previous evaluations

These mixtures have never been evaluated by the SCF as acceptable previous cargo for edible fats and oils as such. However, there are four fatty acids esters produced from the combination of the acceptable fatty acids with the acceptable fatty alcohols in the EU legislation:

Methyl laurate (methyl dodecanoate) 111-82-0, Methyl palmitate (methyl exadecanoate) 112-39-0, Methyl stearate (methyl octadecanoate) 112-61-8, Methyl oleate (methyl octadecenoate) 112-62-9.

3.11.2. Current evaluation

3.11.2.1. Toxicological profile

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 (APAG, 2009) (see also section 3.9.2.1. and 3.10.2.1.), 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.

3.11.2.2. Allergenicity and immunotoxicity

There is no information on allergenicity or immunogenicity of such mixtures.

3.11.2.3. Conclusion

The CONTAM Panel concludes 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).

[14] OJ L 15, 22.01.2004 p 25.

3.12. Epoxidised vegetable oil

Epoxidised vegetable oils are one of the most effective stabilizers of PVC and other polymers. The most common method for production of epoxidised vegetable oils is based on epoxidation of unsaturated bonds of vegetable oils by peracids.

3.12.1. Previous evaluations

In 1996, epoxidised soybean oil (ESBO) was evaluated by the SCF and considered as acceptable previous cargo for edible fats and oils (SCF, 1996). No further evaluation relating to its use as an acceptable previous cargo was done in the last SCF evaluation of 2003 (SCF, 2003a).

In the category of emulsifiers limited to 'baking purposes only', the maximum level for thermally oxidised soybean oil interacting with mono and diglycerides of fatty acids is 5 g/kg (CCFA, 2007).

The SCF established a TDI for ESBO of 1 mg/kg body weight (SCF, 1999) that was derived from a series of studies performed by the British Industrial Biological Research Association (BIBRA, UK) (BIBRA, 1997). In these studies, ESBO was found to have a very low acute toxicity in the rat. No effect on fertility or offspring development was observed in rats treated with up to 1 g ESBO/kg b.w. per day by gavage before and after mating. There was no evidence of carcinogenicity in rats fed with 2.5 % ESBO in the diet for two years. No evidence of genotoxicity and mutagenicity was obtained in the Ames/Salmonella test, in the forward mutation assay in mouse lymphoma L5178Y cells, or in a chromosomal aberration assay. A NOAEL of 140 mg/kg b.w. was derived from the two year study (SCF, 1999).

3.12.2. Current evaluation

3.12.2.1. Toxicological profile of epoxidised vegetable oils other than ESBO

After ESBO, the second most used epoxidised vegetable oil as plasticiser is epoxidised linseed oil (ELO). ELO is not listed in the EU legislation of authorised plasticizers. It is listed in Italian legislation, although without a toxicological evaluation. There are no toxicity data on ELO and because of different composition the toxicity cannot be deduced from the evaluation of ESBO.

Epoxidised fatty acids, squalene and sterols are present in all vegetable oils and fatty foods. Monoepoxy derivatives of oleic and linoleic acid are frequently present at 100-1,000 mg/kg, with high levels found in frying oil and fried products as well as biscuits (Fankhauser-Noti et al., 2006). Diepoxy derivatives of linoleic acid are encountered in oxidized foods at levels up to 10 mg/kg whereas triepoxy linolenic acid was not detectable at about 10 µg/kg.

It can be speculated that the toxicity of ESBO is due to triepoxy linolenic acid. As this is present in ELO at a roughly 10 times higher concentration than in ESBO, a toxicological evaluation is needed for its assessment as acceptable previous cargo.

3.12.2.2. Allergenicity and immunotoxicity

ESBO has been described as a source of occupational allergy and asthma. For other epoxidised vegetable oils no data have been identified. Epoxidised fatty acids have also been linked with contact allergy due to wearing plastic gloves. However, it is unlikely that there is an allergenic effect due to ingestion of low concentrations in vegetable oils.

3.12.2.3. Conclusion

ESBO is already on the list of acceptable previous cargoes and therefore it was not further considered. The CONTAM Panel had no information about what other entities might be covered by the term "epoxidised vegetable oil". It noted that the second most common epoxidised vegetable oil plasticizer used is ELO. There are no toxicological data on ELO or any other epoxidised vegetable oil and therefore the CONTAM Panel could not evaluate these epoxidised vegetable oils as previous cargoes.

3.13. Fructose

Fructose is a hexose monosaccharide naturally occurring in many fruits and vegetables. It is present in its free form in fruits, together with glucose in the disaccharide sucrose, and in many plants as a part of oligo- and polysaccharides (inulins, fructans).

3.13.1. Previous evaluations

Fructose has never been evaluated by the SCF as a previous cargo.

3.13.2. Current evaluation

3.13.2.1. Toxicity, allergy, immunotoxicity and intolerance

Fructose is a major food compound and a natural metabolite in the carbohydrate metabolism of human cells. It does not interfere with the immune system.

Conditions in humans with fructose intolerance (fructose malabsorption and hereditary fructose intolerance) (EFSA, 2005; Born, 2007; Ali et al., 1998) were considered, but were not found to be of concern with respect to fructose as a previous cargo due to the low residual levels in the oils and fats.

3.13.2.2. Conclusion

The CONTAM Panel concludes that fructose meets the criteria for acceptability as a previous cargo.

CONCLUSIONS

In this opinion, the Panel on Contaminants in the Food Chain (CONTAM Panel) has evaluated the acceptability of a number of compounds and mixtures as previous cargoes for the carriage by sea of edible fats and oils. The evaluation is based on the outcome of the CONTAM Panel's review of the criteria for acceptable previous cargoes (see chapter 2.2.) (EFSA, 2009a).

Evaluation of the compounds and mixtures:

- *2,3-Butanediol*: There is a lack of chronic and carcinogenicity studies, and the information about the potential genotoxicity of 2,3-butanediol is considered insufficient. The CONTAM Panel therefore concludes that 2,3-butanediol does not meet the criteria for acceptability as a previous cargo.

- *Isobutanol*: Based on the negative *in vitro* genotoxicity, the low level of chronic *in vivo* toxicity, as well as the volatility of the compound and ease of cleaning, the CONTAM Panel concludes that isobutanol meets the criteria for acceptability as a previous cargo.

- *Calcium nitrate, ammonium nitrate, the double salt and solutions of these*: The CONTAM Panel concludes that solutions of calcium nitrate, ammonium nitrate and the double salt, 'nitric acid, ammonium calcium salt', meet the criteria for acceptability as previous cargoes

- *Cyclohexanol*: There are uncertainties about the potential carcinogenicity, including possible concern arising because of the metabolic interconversion of cyclohexanol to cyclohexanone, and potential reproductive toxicity of cyclohexanol and a lack of chronic studies. The CONTAM Panel therefore concludes that cyclohexanol does not meet the criteria for acceptability as a previous cargo.

- *Cyclohexanone*: There are uncertainties about the potential carcinogenicity of cyclohexanone. The metabolic interconversion of cyclohexanone to cyclohexanol raises questions about the reproductive toxicity. The potential hazards associated with the dioxolane derivatives, probably formed as reaction products, should also be considered. The CONTAM Panel therefore concludes that cyclohexanone does not meet the criteria for acceptability as a previous cargo.

- *Hydrogen peroxide*: The toxicity of hydrogen peroxide is not considered to be of concern, since it reacts completely in contact with oil. The contamination of vegetable oils with up to 100 mg/kg hydrogen peroxide promotes oil oxidation, i.e. deteriorates oil quality in a way and to an extent which also may occur in food processing and storage. The CONTAM Panel therefore concludes that hydrogen peroxide would not be of any health concern as a previous cargo.

- *Kaolin slurry*: The CONTAM Panel concludes that kaolin slurry would not be of any health concern as a previous cargo, provided it complies with the European Legislation on dioxins.

- *Unfractionated fatty acid mixture or mixtures of fatty acid from natural oils and fats*: The CONTAM Panel concludes that unfractionated fatty acids mixtures or mixtures of fatty acids from oils and fats would not cause any health concern as previous cargoes, provided their sources are edible types of fats or oils.

- *Unfractionated fatty alcohol mixture or mixtures of fatty alcohols from natural oils and fats*: The CONTAM Panel concludes that unfractionated fatty alcohol mixtures or mixtures of fatty alcohols would not cause any health concern as previous cargoes, provided their sources are edible types of fats or oils.

- *Unfractionated fatty esters mixtures or mixtures of fatty esters from natural oils and fats*: The CONTAM Panel concludes 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)

- *Epoxidised vegetable oil*: ESBO is already on the list of acceptable previous cargoes and therefore it was not further considered. The CONTAM Panel had no information about what other entities might be covered by the term "epoxidised vegetable oil". It noted that the second most common epoxidised vegetable oil plasticizer used is ELO. There are no toxicological data on ELO or any other epoxidised vegetable oil and therefore the CONTAM Panel could not evaluate these epoxidised vegetable oils as previous cargoes.

- *Fructose*: The CONTAM Panel concludes that fructose meets the criteria for acceptability as a previous cargo.

RECOMMENDATIONS

- The criteria for evaluating previous cargoes do not address the potential presence of impurities in the substances evaluated. The CONTAM Panel was of the opinion that this should be taken into consideration in future evaluations, since they may be toxicologically more relevant than the substance itself. It is recommended that information regarding potential impurities should be requested for future evaluations.

DOCUMENTATION SUBMITTED TO EFSA

In response to the call for data issued by EFSA in June 2009, the following information was received:

1. FOSFA International. Data summaries for potential additions to the EU previous cargo list (July 2009): 2,3-butanediol (CAS No. 513-85-9), isobutanol (CAS No. 78-83-1), calcium ammonium nitrate solution (CAS No. 6484-52-2), calcium nitrate (CN-9) solution (CAS No. 35054-52-5), cyclohexanol (CAS No. 108-93-0), cyclohexanone (CAS No. 108-94-1), hydrogen peroxide (CAS No. 7722-84-1), kaolin slurry (CAS No. 1332-58-7), unfractionated fatty acid mixture or mixtures of fatty acids from natural oils and fats, unfractionated fatty alcohol mixture or mixtures of fatty alcohols from natural oils and fats, unfractionated fatty esters or mixtures of fatty esters from natural oils and fats, vegetable oil – epoxidised and fructose.

2. YARA International. Concept report concerning the inclusion of three substances on the EU list of acceptable previous cargoes: calcium nitrate (CAS no. 10124-37-5), nitric acid (CAS No. 7697-37-2) and CN-nitcal (CAS No 15245-12-2).

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ABBREVIATIONS

2-AAF	2-acetylaminofluorene
ADI	Acceptable Daily Intake
BADGE	Bisphenol A diglycidyl ether
BIBRA	British Industrial Biological Research Association
b.w.	Body weight
CAC	Codex Alimentarius Commission
CCFO	Codex Committee for Fats and Oils
CONTAM Panel	Panel on Contaminants in the Food Chain
CHO	Chinese Hamster Ovary
DEN	Diethylnitrosamine
DMBA	9,10-dimethyl-1,2-benzanthracene
DNA	Deoxyribonucleic acid
ECB	European Chemicals Bureau
EFSA	European Food Safety Authority
ELO	Epoxidised linseed oil
ESBO	Epoxidised soybean oil
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FOSFA	Federation of Oils, Seeds and Fats Associations
GGT	Gamma-glutamyltranspeptidase
GRAS	Generally Recognised as Safe
HGPRT	Hypoxanthine guanine phosphoribosyl transferase gene mutation assay
IARC	International Agency for Research on Cancer
IC50	Half maximal inhibitory concentration
IUCLID	International Uniform Chemical Information Database
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	Lethal dose – the dose required to kill half the members of a tested animal population

MSDI	Maximised Survey-derived Daily Intake
mTAMDI	Modified Theoretical Added Maximum Daily Intake
MTBE	Methyl tertiary butyl ether
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PCBs	Polychlorinated biphenyls
PH	Partial hepatectomy
PVC	Polyvinyl chloride
RfD	Reference dose
ROS	Reactive oxygen species
SCF	Scientific Committee on Food
TDI	Tolerable Daily Intake
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of Toxicological Concern
UDS	Unscheduled DNA Synthesis
UF	Uncertainty factor
USA	United States of America
US-EPA	United States Environmental Protection Agency
US-FDA	United States Food and Drug Administration
WHO	World Health Organization
WHO-TEQ	World Health Organization – Toxic Equivalents