

SCIENTIFIC OPINION

Scientific Opinion on the evaluation of the substances currently on the list in the Annex to Commission Directive 96/3/EC as acceptable previous cargoes for edible fats and oils – Part I of III¹

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, had been previously transported. The European Commission requested EFSA to evaluate the list of substances in the Annex to Commission Directive 96/3/EC as acceptable previous cargoes for edible fats and oils, taking into account its review of the Scientific Committee on Food (SCF) criteria for acceptable previous cargoes and criteria proposed by the Codex Committee for Fats and Oils. This is the first of three scientific opinions by the Panel on Contaminants in the Food Chain (CONTAM Panel), in which thirteen of these substances have been evaluated. The CONTAM Panel concluded that phosphoric acid, ammonium polyphosphate, benzyl alcohol (pharmaceutical and reagent grades only), epoxidised soyabean oil (with a minimum 7 % - maximum 8 % oxirane oxygen content), ethyl acetate, 2-ethylhexanol, 1,3-butanediol, 1,4-butanediol, propylene glycol, polypropylene glycol (molecular weight greater than 400), methanol and ethanol, would not be of health concern as previous cargoes. In the case of calcium lignosulphonate, there was sufficient information available for the CONTAM Panel to conclude that the risk from short-term exposure to this substance itself, when used as a previous cargo, would not give rise to any toxicological concern. However, the product varies markedly in composition, there is no information on potential impurities, nor is there information on its potential reactivity with fats and oils. The CONTAM Panel therefore concluded that calcium lignosulphonate does not meet the criteria for acceptability as a previous cargo.

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

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

This is the first of three scientific opinions by the CONTAM Panel on the evaluation of the substances listed in the Annex to Commission Directive 96/3/EC. The CONTAM Panel considered that phosphoric acid, ammonium polyphosphate, benzyl alcohol (pharmaceutical and reagent grades only), epoxidised soyabean oil (with a minimum 7 % - maximum 8 % oxirane oxygen content), ethyl acetate, 2-ethylhexanol, 1,3-butanediol, 1,4-butanediol, propylene glycol, polypropylene glycol (molecular weight greater than 400), methanol and ethanol, when used as previous cargoes, would not raise any concerns regarding their acute or longer term toxicity, genotoxicity, carcinogenicity or reproductive toxicity. In addition, there were no concerns regarding possible allergenicity or adjuvant effects. The Panel noted that the majority of these substances, with the exception of 1,4-butanediol and methanol, have been assigned acceptable daily intakes (ADIs) (or tolerable daily intakes (TDIs)) by the FAO/WHO Joint Expert Committee for Food Additives (JECFA), SCF or EFSA and that in all cases these were greater than or equal to 0.1 mg/kg body weight (b.w.) per day. There were no possible reaction products with fats and oils of toxicological concern. The substances could easily be removed by cleaning of the tank. Suitable analytical methods are available or are feasible for all of these substances. Any remaining impurities, either identified or anticipated, were considered of no toxicological concern. The CONTAM Panel therefore concluded that these substances meet the criteria for acceptability as previous cargoes.

In the case of calcium lignosulphonate, there was sufficient information available for the CONTAM Panel to conclude that the risk from short-term exposure to this substance when used as a previous cargo would not give rise to any toxicological concern. However, the product varies markedly in composition, there is no information on potential impurities, nor is there information on its potential reactivity with fats and oils. The CONTAM Panel therefore concluded that calcium lignosulphonate does not meet the criteria for acceptability as a previous cargo.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

General hygiene requirements relating to transport of food applicable to all food business operators laid down in Regulation (EC) No 852/2004⁴ (Annex II, Chapter IV) state, amongst others, that "receptacles in vehicles and/or containers are not to be used for transporting anything other than foodstuffs where this may result in contamination."

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

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

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

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

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

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

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

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

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

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

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

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

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

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Art 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for a scientific opinion on the evaluation of the substances currently on the list in the Annex to Commission Directive 96/3/EC⁵ as acceptable previous cargoes for edible fats and oils. The evaluation should be based on the SCF criteria and the criteria proposed by the CCFO as reviewed by the Panel on Contaminants in Food Chain in 2009¹⁰ for acceptable previous cargoes for edible fats and oils.

¹⁰<http://www.efsa.europa.eu/en/scdocs/scdoc/1110.htm>

ASSESSMENT

1. Introduction

General hygiene requirements relating to transport of food applicable to all food business operators is laid down in Annex II, Chapter IV of Regulation (EC) No 852/2004¹¹ and state, amongst others, that "*receptacles in vehicles and/or containers are not to be used for transporting anything other than foodstuffs where this may result in contamination*". However, the application of this principle to the bulk transport is not practical and imposes an unduly onerous burden on food business when applied to bulk transport in sea-going vessels of liquid oils and fats. Commission Directive 96/3/EC⁵ permits sea transport of fats and oils in bulk tanks, which have previously been used to transport substances included in a positive list of acceptable previous cargoes.

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

In 1996, the Scientific Committee on Food (SCF) assessed the risk to human health arising from potential contamination of oils and fats shipped in tanks, which may have been used to transport the substances as given in the Annex to Commission Directive 96/3/EC⁵ (SCF, 1997). 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, 2003).

Based on the evaluations carried out by the SCF in 1996 and 2003, the list of substances acceptable as previous cargoes set out in Annex to Commission Directive 96/3/EC⁵ was amended by Commission Decision 2004/4/EC.¹² However, the substances in the list were only considered to be acceptable as long as the legal provisions were applied, especially regarding the cleaning and condition of the tanks and the accurate documented evidence relating to the nature of the three previous cargoes, and to the efficacy of the cleaning process between cargoes, to be kept by the captain of the vessel.

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

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

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

previous cargoes and the criteria were adopted by the CAC (Geneva, 4-9 July 2011) (FAO/WHO, 2011).

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

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

The European Commission asked EFSA for a scientific opinion on the evaluation of the substances currently on the list in the Annex to Commission Directive 96/3/EC⁵ as acceptable previous cargoes for edible fats and oils. The evaluation should be based on the review of the criteria performed by the CONTAM Panel in 2009, in order to ensure that the substances currently on the list are evaluated against the same criteria.

The outcome of the evaluation of the substances will be presented in three scientific opinions for practical purposes. In this first output, the evaluation of 13 substances (or groups of) listed in Table 1 is described. Most of these compounds have been assigned a tolerable daily intake (TDI) or acceptable daily intake (ADI) by international bodies, e.g. JECFA, as food additives or flavourings. The evaluation of the remaining substances listed in the Annex to Commission Directive 96/3/EC⁵ will be reported in the other two scientific opinions that will be published by the CONTAM Panel.

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

Table 1: Substances in the list to Annex to Commission Directive 96/3/EC⁵ listed as acceptable previous cargoes for edible fats and oils and re-evaluated in the present opinion.

Substance (synonyms)	CAS Number
Phosphoric acid (ortho phosphoric acid)	7664-38-2
Ammonium polyphosphate	68333-79-9/ 10124-31-9
Benzyl alcohol (pharmaceutical and reagent grades only)	100-51-6
Calcium lignosulphonate	8061-52-7
Epoxidised soyabean oil (with a minimum 7 % - maximum 8 % oxirane oxygen content)	8013-07-8
Ethyl acetate (acetic ether, acetic ester, vinegar naphtha)	141-78-6
2-Ethylhexanol (2-ethylhexyl alcohol)	104-76-7
Glycols:	
1,3-butanediol (1,3 butylene glycol)	107-88-0
1,4-butanediol (1,4 butylene glycol)	110-63-4
Polypropylene glycol (molecular weight greater than 400)	25322-69-4
Propylene glycol (1,2 propylene glycol; propan-1,2-diol; 1,2-dihydroxypropane; monopropylene glycol (MPG); methyl glycol)	57-55-6
Methanol (methyl alcohol)	67-56-1
Ethanol (ethyl alcohol)	64-17-5

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, 1997). The Committee was asked to examine the substances given in the Annex to Commission Directive 96/3/EC⁵ and other substances that may be proposed for addition to the list. The SCF was asked to take into account the information provided by industry concerning (i) the likelihood and potential levels of contamination in the light of the information regarding cleaning procedures, dilution and limits of detection of analytical methods and (ii) the additional processing of oils and fats. The SCF focused its attention on the evaluation of the toxicological properties of the substances without considering other aspects such as the ecotoxicological characteristics, the microbial status or nutritional relevance. The Committee's view on the acceptability of the substances in the list of acceptable previous cargoes from Commission Directive 96/3/EC⁵ was based on the criteria shown in Table 2.

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

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

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

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

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

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

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

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

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

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

2.2. European Food Safety Authority (EFSA)

At the request of the European Commission, the EFSA reviewed the criteria for acceptable previous cargoes for edible fats and oils set by the SCF (Table 2). In doing so, the CONTAM Panel assessed the

appropriateness of the four CCFO criteria (Table 3), one by one, by comparing them with those set by SCF for acceptable previous cargoes for edible fats and oils in 1996.

Table 3: Criteria proposed for immediate previous cargoes by the CCFO during their 21st meeting (CCFO, 2009) and adopted by the CAC (FAO/WHO, 2011).

CCFO Criteria (adopted at Step 5)	
1.	The substance is transported/stored in an appropriately designed system; with adequate cleaning routines, including the verification of the efficacy of cleaning between cargoes, followed by effective inspection and recording procedures.
2.	Residues of the substance in the subsequent cargo of fat or oil should not result in adverse human health effects. The ADI (or TDI) of the substance should be greater than or equal to 0.1 mg/kg b.w./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 ADI (or 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 agreed with the proposed threshold of an ADI (or TDI) of ≥ 0.1 mg/kg body weight (b.w.). For substances for which there is no numerical ADI (or TDI) a case by case evaluation is needed. The Panel also considered the situation of second and third previous cargoes and concluded that for non-genotoxic substances their transport as second and third previous cargoes is not of concern, taking into account their very limited carry over. However, the CONTAM Panel noted that genotoxic substances would not be acceptable as previous cargoes. Also in relation to CCFO criterion 2, the CONTAM Panel noted that as consequence of the above some substances will turn out to be unacceptable as previous cargoes. This could include substances with ADI (or TDI) < 0.1 mg/kg b.w. or substances with genotoxic activity. The Panel was of the opinion that the exclusion of such substances as previous cargoes is appropriate.
- CCFO criterion 3 is sufficient to cover “known food allergens”. However, the CONTAM Panel considered that the scope of the CCFO criterion is too narrow, and should apply to all known allergens, not just to known food allergens, given the fact that the same cargo may be sold for cosmetic use.
- The CONTAM Panel endorsed CCFO criterion 4 without any further remarks.

3. Evaluation of the substances currently on the list in the Annex to Commission Directive 96/3/EC⁵ 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 review of the criteria for acceptable previous cargoes as described in Section 2.2. (EFSA, 2009a) and the experience gained in its subsequent evaluation of 13 substances as previous cargoes which highlighted the importance of addressing any impurities that might be present (EFSA, 2009b):

- The substance is transported/stored in an appropriately designed system; with adequate cleaning routines, including the verification of the efficacy of cleaning between cargoes, followed by effective inspection and recording procedures. The CONTAM Panel was of the opinion that records of the three previous cargoes should be kept, in accordance with the Codex Recommended International Code of Practice for the Storage and Transport of Edible Oils and Fats in Bulk.
- Residues of the substance in the subsequent cargo of fat or oil should not result in adverse human health effects. The ADI (or TDI) of the substance should be greater than or equal to 0.1 mg/kg b.w. per day. Substances for which there is no numerical ADI (or TDI) should be evaluated on a case by case basis. For non-genotoxic substances their transport as second and third previous cargoes is not of concern, taking into account their very limited carry over. However, genotoxic substances would not be acceptable as previous cargoes.
- The substance should not be or contain a known allergen, unless the identified allergen can be adequately removed by subsequent processing of the fat or oil for its intended use. This criterion covers all allergens, not only food allergens.
- If the substance reacts with edible fats and oils, any known reaction products must comply with criteria 2 and 3.
- Analytical methods of sufficient sensitivity to verify the presence of trace amounts of residues or the absence of contamination of oils and fats should be feasible. Generally, nowadays there are sensitive/suitable analytical methods available to determine the presence of relevant levels of the substances under evaluation (previous cargoes) in the subsequent fat and oil, or to verify the cleaning procedure. In those cases where, due to the nature or composition of the substance (or group of) to be evaluated as previous cargo, the feasibility of analytical methods is questioned, it will be indicated when discussing the substance (or group of) in the respective chapter.
- Potential impurities in the previous cargo should be taken into account since they may be toxicologically more relevant than the substance itself. As most products exist in different purities, a reasonable worst-case product within the specification is assumed, the concentration of the impurity estimated from available literature and evaluated in the same way as a listed substance. The source and synthesis of the substance is investigated to identify potential impurities, if no adequate measurements are available for impurities.

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

The safety 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 above (EFSA, 2009a, 2009b).

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

3.1. PHOSPHORIC ACID (*ortho* phosphoric acid) (CAS No 7664-38-2)

Phosphoric acid is a clear syrupy liquid at 42.35 °C, while below this temperature it forms unstable orthorhombic crystals. It is a tribasic acid (pk1=2.15, pk2=7.09 and pk3=12.23).

Phosphoric acid is commonly obtained from phosphate rock deposits by reaction with sulphuric acid. In the "wet process", mined phosphate ores, particularly calcium phosphate, are treated with concentrated sulphuric acid, producing a somewhat diluted phosphoric acid. The reaction mixture is filtered to remove precipitated calcium sulphate and yields a phosphoric acid that contains a wide variety of impurities. The phosphoric acid is subsequently concentrated and used as the starting material in a number of further processes to produce phosphates and phosphate-containing products.

The material transported is a concentrated solution of phosphoric acid with a P₂O₅ concentration of about 52 to 54 % (merchant-grade acid).

Phosphoric acid is mainly used to produce fertilizers and flame retardants for polyolefins and polyurethanes. Purified phosphoric acid may be used as a food additive: as an emulsifier and stabiliser, as nutrient for yeast in bread making or increasing water binding properties, e.g. in meat products (E-545). It is also used in the vegetable oil refining industry as degumming agent.

3.1.1. Previous evaluations

The SCF evaluated phosphoric acid as a previous cargo in 1996 and considered it acceptable (SCF, 1997). This conclusion was based on the facts that phosphoric acid is approved as a food additive (E338) and has a maximum tolerable daily intake (MTDI) of 70 mg/kg b.w. expressed as phosphorous ion (P). In the 2003 SCF evaluation of acceptable previous cargoes, phosphoric acid was not further evaluated as it was already considered acceptable (SCF, 2003).

JECFA evaluated phosphoric acid in 1982, when it established a group MTDI for phosphates, including phosphoric acid, of 70 mg/kg b.w. expressed as phosphorus (JECFA, 1982). This was based on the induction of nephrocalcinosis in the rat at an intake level of 1 % phosphorus in the diet. JECFA established a MTDI, rather than a TDI, as phosphate is an essential nutrient, and hence it would not be appropriate to give a range of values from zero to a maximum, as would be the case when establishing a TDI.

3.1.2. Current evaluation

3.1.2.1. Expected impurities

By-products from the ore are dissolved in the phosphoric acid. They include a wide variety of elements and compounds, such as iron, aluminium, calcium, magnesium and other metals, mainly in the form of their phosphates, sulphates or fluorides, depending on the composition of the phosphate rock. This crude acid normally contains about 30 to 32 % P₂O₅ when produced (filter-grade acid) and is normally concentrated before shipment.

Merchant-grade phosphoric acid contains organic contaminants derived from organic substances originally present in the phosphate rock and organic chemicals utilized in beneficiation of the rock prior to treatment with sulphuric acid. A portion of these impurities is in solid form, mainly black carbonaceous particulate matter. Organic material can be removed by calcination of the phosphate rock, but such processing is becoming increasingly unfeasible as a result of the large energy requirement involved. Consequently, furnace-grade phosphoric acid, prepared from calcinated phosphate rock, is becoming increasingly expensive.

In conclusion, phosphoric acid on the market may be anything between a food-grade, pure substance to a crude product containing 10-25 % impurities. Inorganic impurities are unlikely to be a health risk. In particular, as phosphoric acid can be used as a fertilizer, steps are taken to ensure that heavy metals are not present at elevated levels to avoid possible contamination of soils. The carbonaceous material is likely to include carcinogenic substances like polyaromatic compounds, but these are absorbed into particulate matter.

Phosphoric acid transported in vessels is essentially liquid with suspended material, including most of the organics. It is considered to be easily removed by cleaning and this is why impurities are considered not to be of concern.

3.1.2.2. Reactivity and reaction products

Reaction of phosphoric acid with lipids is not expected to be of concern. Esterification with partial glycerides would form compounds similar to phospholipids.

3.1.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

When ingested, phosphoric acid is present as phosphate, which is under physiological regulation in the body. The gastrointestinal absorption of phosphate is therefore limited, depending on nutritional requirements (reviewed in JECFA, 1965, 1982). Absorbed phosphate from phosphoric acid would undergo the same fate as dietary phosphate. Phosphate is excreted mainly in the faeces, as calcium phosphate.

Acute toxicity

The oral LD₅₀ in rats is greater than 1,000 mg/kg b.w. (summarised in JECFA, 1982). Phosphoric acid is corrosive and mildly irritating to the skin and eyes (OECD, 2009).

Subacute, subchronic and chronic toxicity studies

Studies with phosphate salts were summarised by JECFA (1982). At high levels of phosphate, adverse effects were observed in parathyroids, kidneys and bones. The critical effect observed in these studies, which were performed in rats, was renal calcification (nephrocalcinosis), due to precipitation of calcium phosphate, as the levels of phosphate at the doses used were such that phosphate homeostasis was dysregulated. It was difficult to identify no-observed-adverse-effect levels (NOAELs) in these studies, because there is a background incidence of nephrocalcinosis, determined by dietary intake of calcium and vitamin D. In a study reported on the ECHA website (ECHA, 2011a), rats received gavage doses of phosphoric acid up to 500 mg/kg b.w. per day. Males were dosed for 2 weeks prior to mating, during the 2 weeks of the mating period and 2 for weeks after mating. Females were dosed for 2 weeks before mating to day 4 post partum (approximately 54 days). A few animals in the high dose group showed sign of gastrointestinal irritation and 2 females died. The NOAEL was 250 mg/kg b.w. (79 mg/kg b.w. expressed as phosphorus) per day.

Genotoxicity

Phosphates were negative in a number of tests for genotoxicity *in vitro* and *in vivo* (summarised in JECFA, 1982). Phosphoric acid was negative in the *in vitro* tests undertaken (ECHA, 2011a).

Carcinogenicity

Studies on the carcinogenicity of phosphates have not been identified. However, in view of the physiological roles of phosphate in the body, it is unlikely that oral exposure to phosphoric acid would pose a carcinogenic risk.

Developmental and reproductive toxicity

No effects of dietary administration of phosphoric acid at 0.4 % or 0.75 % were observed in rats over three generations. Studies of phosphate salt showed no developmental effects in mice, at dose levels up to ~300 mg/kg b.w. per day, in rats, at dose levels up to ~170-410 mg/kg b.w. per day, depending on the salt, or hamsters, at dose levels up to 128 mg/kg b.w. per day (JECFA, 1982). In the study described above (ECHA, 2011a), there were no effects on reproduction or development. The NOAEL was the highest dose tested, 500 mg/kg b.w. per day.

3.1.2.4. Allergenicity

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

3.1.3. Conclusion

JECFA has established a group MTDI of 70 mg/kg b.w. for phosphates, including phosphoric acid, expressed as phosphorus, which the CONTAM Panel considers appropriate. Phosphoric acid is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils under normal conditions. Although some grades of phosphoric acid may contain impurities of potential concern, these are considered to be easily removed by cleaning and hence are not considered to be of concern when phosphoric acid is the previous cargo.

Therefore, the CONTAM Panel concludes that phosphoric acid meets the criteria for acceptability as a previous cargo.

3.2. AMMONIUM POLYPHOSPHATE (CAS No 68333-79-9, 10124-31-9)

Ammonium polyphosphate is the salt of polyphosphoric acid and ammonia, containing both linear and branched chains. Its chemical formula is $[\text{NH}_4 \text{PO}_3]_n$. The chain length n is variable, and here includes $n=1$, and the molecular mass can be greater than 1,000. With increasing molecular mass ammonium polyphosphate changes from a liquid to a paste and to a powder. Water solubility decreases and can be low (< 0.1 g/100 mL). Only the liquid forms of ammonium polyphosphate are transported as previous cargoes (FOSFA, 2011, see Documentation provided to EFSA).

Ammonium polyphosphate can be prepared by reacting concentrated phosphoric acid with ammonia. A common way is to react equimolar amounts of ammonium phosphate with phosphorous pentoxide at 170-350 °C under ammonia gas with constant mixing and kneading.

Ammonium polyphosphate is mainly used as fertilizer. It can also be used as a flame retardant for polyolefins and polyurethanes.

3.2.1. Previous evaluations

The SCF evaluated ammonium polyphosphate in 1996 as previous cargo for edible fats and oils and considered this compound as toxicologically acceptable in view of the MTDI of 70 mg/kg b.w. for phosphate expressed as P (SCF, 1997). In the 2003 SCF evaluation of acceptable previous cargoes ammonium polyphosphate was not further evaluated as it was already considered acceptable (SCF, 2003).

JECFA evaluated ammonium polyphosphate in 1982, when it established a group MTDI for phosphates, including ammonium polyphosphate, of 70 mg/kg b.w. expressed as phosphorus (JECFA, 1982). This was based on the induction of nephrocalcinosis in the rat at an intake level of 1 % phosphorus in the diet. JECFA established a MTDI, rather than a TDI, as phosphate is an essential nutrient, and hence it would not be appropriate to give a range of values from zero to a maximum, as would be the case when establishing a TDI.

3.2.2. Current evaluation

3.2.2.1. Expected impurities

The by-products originating from the ore are the same as discussed above for phosphoric acid. Ammonium polyphosphate is also transported in vessels as a liquid with suspended material, including most of the organics. It is considered to be easily removed by cleaning and this is why impurities are considered not to be of concern.

3.2.2.2. Reactivity and reaction products

Reaction of ammonium polyphosphate with lipids is not expected to be of concern.

3.2.2.3. Toxicological profile

There are only very limited data available specifically on the effects of ammonium polyphosphate following oral administration, although there are some data on other polyphosphate salts.

Absorption, distribution, metabolism and elimination

The gastrointestinal absorption of higher polyphosphates is probably low (reviewed by JECFA, 1982). It is likely that ammonium polyphosphate is hydrolysed by gastric acid to phosphate and ammonium ions, which would then be absorbed in the intestinal tract. The rates of hydrolysis and of absorption decrease with increasing length of the polyphosphate (Ebel, 1958, as cited by JECFA, 1982). JECFA (1982) cited data showing that approximately 10-30 % of an orally administered dose of highly polymeric polyphosphates was absorbed. According to the Subcommittee on Flame-Retardant Chemicals of the National Research Council (2000), overall the available data suggest that approximately 50 % of ammonium polyphosphate (as used as flame retardants) would be absorbed as monophosphate. No specific data are available on the metabolism of ammonium polyphosphate, other than it is hydrolysed by acid.

Gastrointestinal bacteria may also contribute to hydrolysis (Schreier and Noller, 1955, as reported by JECFA, 1982). Absorbed monophosphate would undergo the same fate as dietary phosphate. Polyphosphate may be excreted in trace amounts in the urine (Gosselin et al., 1952, as reported by JECFA, 1982), but the extent declines with phosphate chain length, presumably as less will be absorbed intact. Unabsorbed, non-hydrolysed, polyphosphate is excreted in the faeces.

Acute toxicity

Ammonium polyphosphate is not irritating to the skin of either experimental animals or humans (Subcommittee on Flame-Retardant Chemicals, 2000). The LD₅₀ in rats is above 2,000 mg/kg b.w. No deaths or signs of toxicity were observed at the dose used in these studies (summarised in JECFA, 1982).

Subacute, subchronic and chronic toxicity studies

No sub-acute or longer term studies have been performed with ammonium polyphosphate. Studies with other polyphosphate salts were summarised in JECFA (1982). The primary effect observed in these studies, which were performed in rats, was renal calcification (nephrocalcinosis), due to precipitation of calcium phosphate, as the levels of phosphate at the doses used were such that phosphate homeostasis was dysregulated. It was difficult to identify a NOAEL in these studies, because there is a background incidence of nephrocalcinosis, determined by dietary intake of calcium and vitamin D. JECFA (1982) concluded that chronic exposure to 0.5 % polyphosphate in the diet could lead to increased renal weight, but not to histopathological changes, with nephrocalcinosis at higher levels.

Genotoxicity

Ammonium polyphosphate was negative in the Ames test. No other genotoxicity data have been identified (JECFA, 1982; Subcommittee on Flame-Retardant Chemicals, 2000).

Carcinogenicity

Ammonium polyphosphate has not been tested for carcinogenicity. However, in view of the physiological roles of ammonium and phosphate in the body, it is unlikely that oral exposure to polyphosphate would pose a carcinogenic risk.

Developmental and reproductive toxicity

No studies were identified on the effects of ammonium polyphosphate on development or fertility. In studies with other polyphosphates (as cited in JECFA, 1982), no effects on reproduction were observed at dietary concentrations of 0.5 % or less. In one study, at 5 %, there was some decrease in fertility.

3.2.2.4. Allergenicity

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

3.2.3. Conclusion

Ammonium polyphosphate is hydrolysed in the stomach to phosphate, so many of the systemic effects of phosphoric acid would be relevant to ammonium polyphosphates. JECFA has established a group MTDI for phosphates, including ammonium polyphosphate, of 70 mg/kg b.w. expressed as phosphorus, which the CONTAM Panel considers appropriate. Phosphates, including ammonium polyphosphate, are not genotoxic or allergenic. No reactions products of concern with edible fats and oils are anticipated under normal conditions. Although some grades of ammonium polyphosphate may contain impurities of potential concern, these are considered to be easily removed by cleaning and hence are not considered to be of concern when ammonium polyphosphate is used as a previous cargo.

Therefore, the CONTAM Panel concludes that ammonium polyphosphate meets the criteria for acceptability as a previous cargo.

3.3. BENZYL ALCOHOL (pharmaceutical and reagent grades only) (CAS No 100-51-6)

Benzyl alcohol is a colourless liquid with a mild pleasant aromatic odour. Benzyl alcohol is partially soluble in water (4 g/100 mL) and completely miscible in alcohols and diethyl ether.

Benzyl alcohol is produced naturally by many plants and is commonly found in fruits and teas. It is also found in a variety of essential oils including jasmine, hyacinth, and ylang-ylang.

Benzyl alcohol is synthesized by chlorination of toluene followed by hydrolysis of benzyl chloride using sodium hydroxide. An alternative is the catalytic oxidation of toluene in the vapour phase at 300-500 °C. Newer procedures involve lower temperatures (around 200 °C) and liquid toluene. Mixtures containing around 10 % benzyl alcohol are obtained.

Reagent grade benzyl alcohol is ≥ 99 % pure, but there is no official definition of “reagent grade”. Even technical grade benzyl alcohol is available at a purity up to 99 %.

It is a useful solvent due to its polarity, low toxicity, and low vapour pressure. It is used, e.g., for inks, paints, dyes for textiles, lacquers, and epoxy resin coatings. It has many particular uses, such in inks for ball-pens, developer for photography, paint remover, reactive diluent in building materials and disinfectant. It is also a precursor to a variety of esters, used in the soap, perfume, and flavour industries.

3.3.1. Previous evaluations

The SCF evaluated benzyl alcohol in 1996 as a previous cargo for edible fats and oils and considered this compound acceptable in view of the group ADI of 0-5 mg/kg b.w for benzoic acid and benzoates (JECFA, 1997) and its use as an extraction solvent for food (SCF, 1997). In the 2003 SCF evaluation of acceptable previous cargoes benzyl alcohol was not further evaluated as it was already considered acceptable (SCF, 2003).

In the EU, benzyl alcohol is authorised as food additive (E1519) with an ADI of 5 mg/kg b.w. for the sum of benzyl alcohol and benzoic acid.

In its evaluation of benzyl alcohol in 2002, the SCF confirmed the inclusion of benzyl alcohol in the group ADI of 0-5 mg/kg b.w. for benzoic acid and benzoates, taking into account the toxicity data and the fact that benzyl alcohol is metabolised via benzaldehyde to benzoic acid, in agreement with the SCF opinion of 1981 (SCF, 2002).

JECFA reviewed benzyl alcohol at its 46th meeting, in 1996 (JECFA, 1997). The Committee was satisfied that the data reviewed on compounds in this group were sufficient to demonstrate lack of carcinogenic, developmental and reproductive potential. Consequently, it was concluded that further studies were not required, and the group ADI of 0-5 mg per kg b.w. as benzoic acid equivalents was maintained.

JECFA most recently reviewed benzyl alcohol at its 57th meeting, in 2001 (JECFA, 2002). A group ADI of 0-5 mg/kg b.w. for benzoic acid, the benzoate salts (calcium, potassium and sodium), benzaldehyde, benzyl acetate and benzyl alcohol, expressed as benzoic acid equivalents, had been confirmed by the Committee at its 46th meeting (JECFA, 1997) and extended to include benzyl benzoate at the 57th meeting in 2001 (JECFA, 2002). JECFA noted that benzyl alcohol is readily metabolised to benzoic acid, which is endogenous in humans and would therefore not be expected to be of safety concern.

EFSA (2009c) has evaluated benzyl alcohol as a supporting substance in its opinion on benzyl alcohols, benzaldehydes, a related acetal, benzoic acids and related esters from chemical group 23, in which it was concluded on the basis of the default maximised survey-derived daily intake (MSDI)

approach that these substances would not give rise to safety concerns at the estimated levels of intake arising from their use as flavouring substances.

In their evaluation in 1997, the European Medicines Agency (EMA) proposed the inclusion of benzyl alcohol in Annex II of Council Regulation (EC) No 2377/90,¹⁴ for all food-producing species based on the following reasons (EMA, 1997):

- The substance is a normal constituent of some plants such as tea and raspberries. It is an authorised EU food additive and is therefore a normal component of the diet in humans;
- It is rapidly metabolised and excreted in most humans and animals

The OECD (2001a) concluded that benzyl alcohol exhibits low repeated dose toxicity. The available data support the non-reprotoxicity of benzyl alcohol. Overall, it was concluded that benzyl alcohol has low priority for further work.

3.3.2. Current evaluation

3.3.2.1. Expected impurities

The specification of this benzyl alcohol (pharmaceutical and reagent grade only) excludes products with substantial concentrations of impurities. If benzyl alcohol is produced by chlorination of toluene, by-products are formed with chlorine in the ring. The concentrations of such products are unlikely to be of concern.

3.3.2.2. Reactivity and reaction products

As all alcohols, benzyl alcohol may interesterify with triglycerides and form fatty acid benzyl esters. Assuming a worst case of 100 mg/kg residual benzyl alcohol in a rather acidic crude oil, it could interesterify to form 10 mg/kg fatty acid benzyl ester. As this will also occur following consumption of a normal diet which will contain benzyl alcohol naturally, the CONTAM Panel does not consider this to raise any concern.

Benzyl alcohol could be oxidized to form benzaldehyde and benzoic acid, but both of these are of low toxicity, and covered by the group ADI as discussed above.

3.3.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Benzyl alcohol is rapidly absorbed after oral administration (JECFA, 1997). Benzyl alcohol is metabolised to benzaldehyde, a reaction for which there is evidence for the involvement of P450 in human, but apparently not in rat, liver. Benzaldehyde is further metabolised to benzoic acid, with a small amount being conjugated with glutathione and then excreted as the mercapturic acid. Benzaldehyde may be reduced to benzyl alcohol. Benzoic acid is extensively metabolised to hippuric acid, by conjugation with glycine. The conjugate is excreted in the urine. Glucuronidation is a minor pathway of benzoic acid metabolism. Glycine conjugation is saturable at high levels of benzoic acid in neonates (JECFA, 1997). These pathways occur in both experimental animals and in humans.

¹⁴ Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin. OJ L 224, 18.8.90, p. 1-8.

Acute toxicity

The acute toxicity of benzyl alcohol by the oral route is low, with LD₅₀ values in mouse, rat and rabbit all > 1,000 mg/kg b.w. (Adams et al., 2005).

Subacute, subchronic and chronic toxicity studies

In studies in which benzyl alcohol was administered by oral gavage to F344/N rats or B6C3F1 mice for 13 weeks there were a number of deaths, some of which were due to dosing errors. However, there was evidence for compound-related deaths at least in rats (NTP, 1989). The NOAEL in both rats and mice was 100 mg/kg b.w. per day. The only effects observed in mice at higher doses were reduced body weight and, at the highest dose of 800 mg/kg b.w. per day, staggering during the first 2 weeks of the study. In rats, effects observed above the NOAEL included reduced body weight gain and, at the highest dose of 800 mg/kg b.w. per day, reduced body weights. At this dose there were also clinical signs, staggering, laboured breathing and lethargy. Also at this dose, there was necrosis of the CNS (dentate gyrus of the hippocampus) and in some animals of the skeletal muscle, thymic congestion and renal nephrosis, similar to the age-related change observed in rats.

The National Toxicology Program (NTP, 1989) has conducted studies into the chronic toxicity and carcinogenicity of benzyl alcohol by oral gavage, 5 days per week for 103 weeks, in male and female F344/N rats and B6C3F1 mice, at doses of 400 or 200 mg/kg b.w. per day, respectively. Treatment had no effect on body weight or survival of rats or mice in these studies. No significant treatment-related effects were observed either at gross necropsy or histopathologically.

Genotoxicity

Benzyl alcohol has been tested for genotoxicity in a wide range of tests *in vitro* and *in vivo*. In almost all *in vitro* studies, the compound was negative. It was negative in all standard *in vivo* tests (mouse micronucleus, sex-linked recessive lethal and UDS assays) (JECFA, 1997; Adams et al., 2005). The weight of evidence indicates that benzyl alcohol does not pose a genotoxic hazard *in vivo*.

Carcinogenicity

In their study on the carcinogenicity of benzyl alcohol, the NTP (1989) concluded that under conditions of the 2 year gavage study, there was no evidence of carcinogenic activity of benzyl alcohol in male or female F344/N rats or B6C3F1 mice receiving up to 400 or 200 mg/kg b.w. per day, respectively.

Developmental and reproductive toxicity

Benzyl alcohol was administered at a dose of 550 mg/kg b.w. per day by oral gavage to CD-1 mice, five days per week, during days 6-15 of gestation (cited in JECFA, 1997). The dams were allowed to deliver naturally, and pups and dams were observed until day 3, post partum. No treatment related effects were observed, either on the dams or on the offspring. In a second study, CD-1 mice were treated with benzyl alcohol at a dose of 750 mg/kg b.w. per day by oral gavage, five days per week, during days 7-14 of gestation (Hardin et al., 1987; JECFA, 1997). The dams were allowed to deliver naturally, and pups and dams were observed until day 3, post partum. Treatment resulted in maternal deaths (38 %). Maternal body weight was reduced by the treatment. Clinical signs of toxicity were observed in the treated dams. No effects of treatment were observed on mating or gestation indices, the total number of resorptions, the number of live pups per litter, or on pup survival. Pup body weight and weight gain, both per litter and per offspring were reduced following treatment, during PND1-3.

3.3.2.4. Allergenicity

Benzyl alcohol is considered as an agent causing contact allergy for example in moisturizers (Curry and Warshaw, 2005; Zirwas and Stechschulte, 2008). There is no indication that the agent could be a type I allergen.

OECD considers benzyl alcohol to be not a sensitizing agent, but discusses some skin responses in human as non-immunological urticaria (OECD, 2001a). This is in disagreement with multiple literature reports which describe benzyl alcohol as an agent causing allergic contact dermatitis. Benzyl alcohol as a compound of cosmetics and fragrances has received significant attention with respect to effects on humans, including allergic contact dermatitis.

Since the compound is present in consumer products it has to be considered what concentrations may be reached via previous cargoes. Its widespread use in consumer products shows that the level of allergenicity is very low. The same is argued by absence of sensitization in workers (OECD, 2001a).

3.3.3. Conclusion

SCF has established a group ADI of 0-5 mg/kg b.w. for benzyl alcohol and related substances, which the CONTAM Panel endorses. Benzyl alcohol does not pose any concern for genotoxicity or allergenicity. There are no reactions of concern with edible fats and oils. There are no impurities of concern.

Therefore, the CONTAM Panel concludes that benzyl alcohol (pharmaceutical and reagent grades only) meets the criteria for acceptability as a previous cargo.

3.4. CALCIUM LIGNOSULPHONATE (CAS no 8061-52-7)

Calcium lignosulphonate is an anionic surfactant. After purification, it is a light brown powder and the bulk is soluble in water. Lignosulphonates have very broad ranges of molecular mass (they are polydisperse). A range of from 1,000 to 140,000 Da has been reported for soft wood lignosulphonates, with lower values reported for hard woods.

Lignosulphonates are recovered from the spent sulphite pulping liquids (red or brown liquor) from sulphite pulping. Delignification in sulphite pulping involves acidic cleavage of ether bonds. Sulphonates are formed which are precipitated by addition of excess calcium hydroxide.

The largest use for lignosulphonates is as plasticizers in concrete improving workability. Lignosulphonates allow concrete to be made with less water (giving stronger concrete) while maintaining the ability of the concrete to flow. They are applied during the production of cement, where they act as grinding aids in the cement mill and as a raw mix slurry deflocculant (that reduces the viscosity of the slurry). Lignosulphonates are also used for the production of plasterboard to reduce the amount of water required to make the stucco flow and form the layer between two sheets of paper. The reduction in water content allows lower kiln temperatures to dry the plasterboard, saving energy. Calcium lignosulphonates are also used in petroleum drilling (blocking agent, improvement of mud fluidity), asphalt emulsification, tanning leather, dispersant of chemicals and pesticides (improves the suspensibility and wettability of powders), additive of slurry mixture of water and coal, and as additive for feedstuff processing (deflocculant). They were traditionally used to suppress dust on unpaved roads.

A large amount of lignosulphonate is burned in cellulose factories to produce heat.

3.4.1. Previous evaluations

The SCF evaluated calcium lignosulphonate in 1996 and considered this substance as acceptable previous cargo, noting that it was likely to be toxicologically inert and easily removed by tank cleaning, also that it was acceptable as an animal feedstuff¹⁵ (SCF, 1997). In the 2003 SCF evaluation of acceptable previous cargoes calcium lignosulphonate was not further evaluated as it was already considered acceptable (SCF, 2003).

An ADI of 0-20 mg/kg b.w. per day for calcium lignosulphonate (40-65)¹⁶ as a food additive has been established by JECFA (JECFA, 2009) and JECFA has also prepared specifications.

Lignosulphonic acid was evaluated as a food contact material with a specific migration limit (SML) of 0.24 mg/kg only to be used as dispersant for plastic dispersion¹⁷ (SCF, 1999).

Lignosulphonates (E565) are approved as feed additives in the EC and may be used in all animal species and animal categories without maximum levels specified.¹⁸ Calcium lignosulphonate (40-65) has been evaluated by EFSA as a food additive (EFSA, 2010). EFSA concluded that the available data on calcium lignosulphonate (40-65) were insufficient to establish an ADI. EFSA have further considered their evaluation in 2011 and have reached the same conclusion (EFSA, 2011).

3.4.2. Current evaluation

3.4.2.1. Expected impurities

Without purification, calcium lignosulphonate is a crude mixture of materials, essentially a waste of low value, used for purposes for which impurities are of little concern. The material might often contain substances that would be undesirable in food. It would be difficult to develop analytical methods enabling identification of all the potentially toxic components.

3.4.2.2. Reactivity and reaction products

Lignosulphonates include a variety of functional groups for which it will be difficult to rule out chemical reaction with lipids.

3.4.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

As reported by EFSA and JECFA, calcium lignosulphonate (40-65) is poorly absorbed by the oral route, as shown by both *in vitro* and *in vivo* studies (JECFA, 2009; EFSA, 2010).

Acute toxicity

The acute toxicity of calcium lignosulphonate is low. An acute oral LD₅₀ of greater than 31.6 g/kg b.w. has been reported in rats (EFSA, 2010). In another study in rats the LD₅₀ was estimated to lie between 10 and 20 g/kg b.w. (EFSA, 2010).

¹⁵ Council Directive 70/524/EEC of 23 November 1970 concerning additives in feeding-stuffs. OJ L 270, 14. 12.1970, p. 1-17.

¹⁶ The descriptor (40-65) refers to the average molecular weight of the calcium lignosulphonate form assessed as a food additive, which is between 40 000 to 65 000 g/mol.

¹⁷ Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1-89.

¹⁸ Commission list of the authorised additives in feedingstuffs published in application of Article 9t (b) of Council Directive 70/524/EEC concerning additives in feedingstuffs *2005/C 50/01(. OJ C 50, 25.2.2004, p. 1-144.

Subacute and subchronic studies

In a 28-day oral toxicity study in rats with calcium lignosulphonate (40-65) at dose levels of 0, 500, 1,500 and 4,000 mg/kg b.w. per day the only adverse effect related to treatment was a higher incidence of chronic inflammation in the rectum of males at the high dose group. In a 90-day oral toxicity study in rats at dose levels of 0, 500, 1,000 and 2,000 mg/kg b.w. per day, there were no treatment-related effects of biological significance other than signs of lymphoid hyperplasia or lymphoid infiltration in different organs, a dose-related histiocytosis in the mesenteric lymph nodes in all treatment groups and renal tubular vacuolation in female at the two highest doses tested (EFSA, 2010). EFSA concluded that this study could not be used for the safety evaluation of calcium lignosulphonate (40-65) due to a possible poor health status of the animals, also considering that longer-term toxicity studies are needed to elucidate whether the histiocytosis in the mesenteric lymph nodes in the rats could progress into a more adverse state with time (EFSA, 2010).

Genotoxicity

The results of one *in vitro* bacterial reverse mutation assay and one mammalian chromosomal aberration assay indicated an absence of genotoxic potential for calcium lignosulphonate (40-65) (EFSA, 2010).

Chronic toxicity and carcinogenicity

No long-term or carcinogenicity studies have been conducted with calcium lignosulphonate (40-65).

Developmental and reproductive toxicity

In a developmental toxicity study (21 days) in the rat, no treatment-related effects in dams or foetuses were reported up to the highest dose tested (1,000 mg/kg b.w. per day) (EFSA, 2010).

3.4.2.4. Allergenicity

Contact allergy to calcium lignosulphonate has been described for one single case (Andersson and Göransson, 1980), as previously noted by EFSA (EFSA, 2010). Since there are no further reports the substance can be considered to be of no concern regarding allergenicity.

3.4.3. Conclusion

Although JECFA has established an ADI of 0-20 mg/kg b.w. per day for calcium lignosulphonate with defined specifications, the EFSA ANS Panel concluded that the available data were insufficient to establish an ADI (EFSA, 2010). The toxicological database has several data gaps (long-term toxicity, carcinogenicity, limited data on reproductive toxicity). The limited data available did not demonstrate any evidence of genotoxicity or significant concern regarding allergenicity. The CONTAM Panel considers that the available information was sufficient to conclude that the risk from short-term exposure to calcium lignosulphonate when used as a previous cargo would not give rise to any toxicological concern.

The CONTAM Panel noted however that the product varies markedly in its grade. There is no information on impurities in crude quality material (the form most in use), nor is there information on the reactivity of calcium lignosulphonate with fats and oils.

The CONTAM Panel therefore concludes that calcium lignosulphonate does not meet the criteria for acceptability as a previous cargo.

3.5. EPOXIDISED SOYABEAN OIL (with a minimum 7 % - maximum 8 % oxirane oxygen content) (CAS No 8013-07-8)

Epoxidized soyabean oil (ESBO) is manufactured from soyabean oil through the process of epoxidation, using acetic acid and hydrogen peroxide (forming the peracid as an intermediate). Soyabean oil is used as starting material because of the high number of double bonds.

ESBO is used as plasticizer in polyvinyl chloride (PVC) materials, such as sealing masses of lids, cling films and toys. At the same time it serves as a scavenger for hydrochloric acid liberated from PVC when the PVC undergoes heat treatment, being converted to chlorohydrins and cyclic chlorinated fatty acids.

3.5.1. Previous evaluations

The SCF evaluated ESBO with a maximum of 8 % oxirane oxygen content acceptable as a previous cargo for edible fats and oils (temporary TDI of 1 mg/kg b.w., established by the SCF/Food Contact Material Working Group at its 44th meeting) (SCF, 1997). The TDI was temporary because of the lack of data on genotoxicity. Note that in its compilation of evaluations of food contact materials in 1999, the SCF listed the health based guidance value for ESBO as a TDI. In the 2003 SCF evaluation of acceptable previous cargoes ESBO was not further evaluated as it was already considered acceptable (SCF, 2003).

The former EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC Panel) in 2004 concluded the TDI of 1 mg/kg b.w. previously established by the SCF for ESBO (SCF, 1999) remains valid in view of the negative results provided by genotoxicity assays, not available to SCF at the time of its evaluation (1995-1996) (EFSA, 2004a).

In the OECD Screening Information Dataset (SIDS) evaluation of ESBO in 2006, it was concluded that the compound is currently of low priority for further work for human health and the environment because of its low hazard profile (OECD, 2006).

3.5.2. Current evaluation

3.5.2.1. Expected impurities

From the production, hydroperoxides may be expected as impurities, but since edible oils and fats contain these in more substantial amounts, they are not of concern.

3.5.2.2. Reactivity and reaction products

No relevant reaction products are expected, since edible oils and fats normally contain epoxidised fatty acids.

3.5.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Fatty acid esters, such as ESBO, are readily hydrolysed in the gastrointestinal tract by pancreatic lipases. The resultant free fatty acids and glycerides are readily absorbed and enter the normal nutritional pools (JECFA, 1974).

Acute toxicity

ESBO is of very low acute oral toxicity, with an LD₅₀ of at least > 5 g/kg b.w. in rat. ESBO is slightly irritating to the skin and eyes in rabbits (OECD, 2006).

Subacute, subchronic and chronic toxicity studies

ESBO was administered to rats at doses of up to 5 % in the diet for 15 weeks (OECD, 2006). Growth was reduced for part of the treatment period and enlargement of the liver and kidney was observed at dietary concentrations of greater than 1.5 %. Fatty infiltration of the liver was observed at and above 2.5 % (~1.3 g/kg b.w. per day). The lowest-observed-adverse-effect level (LOAEL) was above 1.5 % ESBO (> 375 mg/kg b.w. per day).

Rats were administered ESBO in their diets at concentrations up to 5 % (1.25 g/kg b.w. per day) for 90 days (OECD, 2006). Animals in the higher dose groups showed some changes in weight gain and food intake. Liver weights were increased in both sexes at the highest dose and in females at 1 %. Effects were also observed on the kidneys of males at 1 % and 5 %. The NOAEL was 0.2 % (50 mg/kg b.w. per day).

Dogs were fed ESBO in their diet for 12 months, at concentrations of up to 5 % (Larsen et al., 1960; OECD, 2006). Dogs in the high dose group lost weight and had reduced food intake. No other clinical signs, macroscopic or histopathological changes were observed, other than fatty infiltration of the liver of one dog in the high dose group. The LOAEL was 5 % ESBO (1,250 mg/kg b.w. per day).

In a somewhat limited study (15 animals/sex/dose group), rats received ESBO at doses of up to 5 % in the diet (1.25 g/kg b.w. per day) for 2 years (Larsen et al., 1960; OECD, 2006). Body weight gain was impaired at the highest dose. Liver and kidney weights were increased from the mid-dose onwards. No histopathological changes were observed. The NOAEL was 0.5 % (~120 mg/kg b.w. per day).

Groups of rats were administered diets containing up to 2.5 % (1,000 mg/kg b.w. per day in males) ESBO for 2 years (OECD, 2006). Survival was not affected by treatment. Body weight was slightly increased in males and decreased in females receiving the highest dose. There were also some slight changes in food and water consumption in this group. In the high dose group, there were indications of some effects of kidney and uterus.

Genotoxicity

ESBO was negative in a range of *in vitro* tests of mutagenicity and in an *in vitro* test for chromosomal aberrations. It is concluded that ESBO is unlikely to be genotoxic (OECD, 2006).

Carcinogenicity

Groups of rats were administered diets containing up to 2.5 % ESBO for 2 years (OECD, 2006). Survival was not affected by treatment. There were some signs of toxicity at the highest dose. There was no evidence for any effect of treatment on the incidence of tumours in rats. In a limited study in rats, administered up to 5 % ESBO in the diet, there was no evidence for a carcinogenic effect of ESBO (Larsen et al., 1960; OECD, 2006).

Developmental and reproductive toxicity

ESBO has been tested for effects on reproduction in a rat one-generation study. Doses of up to 1,000 mg/kg b.w. per day were administered by gavage. ESBO had no toxic effects on the parental animals, on any of the reproductive parameters or on the development of the F1 offspring up to the highest dose tested, 1,000 mg/kg b.w. per day, which was therefore the NOAEL for the study. Similar findings were reported in a range finding study, up to the same maximum dose (OECD, 2006).

Rats were treated with ESBO by oral gavage at dose up to 1,000 mg/kg b.w. per day during days 6-15 of pregnancy. Treatment had no effect on the number of corpora lutea, implantation sites, live fetuses, postimplantation loss or fetal body weight. No effects of treatment were observed on the incidence of external malformations, soft tissue malformations or anomalies, or on the skeleton of fetuses (OECD, 2006).

3.5.2.4. Allergenicity

Soyabean is a significant source of type 1 allergens, but these protein allergens are not present in the oil under question. Studies conducted on albino guinea pigs did not reveal any sign of sensitization (OECD, 2006). There is a single report on epoxidized soyabean oil as a secondary agent in an occupational asthma (Pauli et al., 1980). Since there are no further reports the substance can be considered not to be of concern regarding allergenicity.

3.5.3. Conclusion

EFSA confirmed the TDI of 1 mg/kg b.w. for ESBO established by the SCF, which the CONTAM Panel endorses. ESBO is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any toxicologically relevant impurities anticipated.

Therefore, the CONTAM Panel concludes that ESBO (with a minimum 7 % - maximum 8 % oxirane oxygen content) meets the criteria for acceptability as a previous cargo.

3.6. ETHYL ACETATE (acetic ether, acetic ester, vinegar naphtha) (CAS No 141-78-6)

Ethyl acetate is manufactured on a large scale for use as a solvent. The combined annual production in 2004 was 1.3 million tons.

Ethyl acetate is synthesized industrially mainly via the classic Fischer esterification reaction of ethanol and acetic acid using catalysts such as sulphuric acid, *p*-toluene sulphonic acid or ion exchange resins. The equilibrium can be shifted to the ester by removal of water. It is also prepared industrially using the Tishchenko reaction, by combining two equivalents of acetaldehyde in the presence of an alkoxide catalyst. Other routes entail the catalytic dehydrogenation of ethanol or the reaction of ethylene and acetic acid with a solid acid catalyst.

Ethyl acetate is the most common ester in wine, occurring at concentrations of around 100 mg/L.

Ethyl acetate is used as solvent for many purposes. A main use is as solvent and thinner in the manufacture of paints, nitrocellulose lacquers and varnishes. It is also an important solvent for extraction in chemical industry. Substantial quantities are used in the manufacture and printing of flexible packaging, such as polyester and bi-axially oriented polypropylene (BOPP) films. Ethyl acetate is used in adhesives, cleaning fluids, inks, nail-polish removers, coated papers, explosives, artificial leather, photographic films and plates.

3.6.1. Previous evaluations

The SCF evaluated ethyl acetate in 1996 as previous cargo for edible fats and oils and considered it acceptable as previous cargo, since it is acceptable as an extraction solvent for food (SCF 29th report) (SCF, 1997). In the 2003 SCF evaluation of acceptable previous cargoes ethyl acetate was not further evaluated as it was already considered acceptable (SCF, 2003).

JECFA evaluated ethyl acetate at its 46th meeting, in 1996 (JECFA, 1997). They concluded that there was no safety concern at current levels of intake when it is used as a flavouring agent. The 1967 ADI of 0-25 mg/kg b.w. (JECFA, 1967) was maintained at the 46th meeting (JECFA, 1997).

In their evaluation, JECFA (1997) noted that ethyl acetate is completely hydrolysed in the human body to ethanol and acetic acid, which are endogenous intermediates in human metabolism. Hence, ethyl acetate is predicted to be metabolised to innocuous products and the Committee therefore concluded that it would not present a safety concern at the estimated levels of current intake.

In their evaluation of 2002, the OECD concluded that ethyl acetate is currently of low priority for further work (OECD, 2002).

3.6.2. Current evaluation

3.6.2.1. Expected impurities

Depending on the synthetic pathway, by-products of the dehydrogenation include diethyl ether, acetaldehyde and its aldol products; higher esters; and ketones. These are not considered to be of concern at the levels that would arise from ethyl acetate as previous cargo.

3.6.2.2. Reactivity and reaction products

No reaction products of toxicological concern are expected.

3.6.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

There are few specific data on the toxicokinetics of ethyl acetate. However, based on information on structurally similar compounds and on its physicochemical properties, it can be assumed that it will be absorbed rapidly from the gastrointestinal tract. It is soluble in plasma and will be extensively distributed throughout the body. It is readily hydrolysed in liver and plasma by esterases, to produce ethanol and acetic acid (acetate). These will then enter the endogenous pool of such compounds and undergo a similar fate, other than at very high doses, when saturation of one or more enzymes will occur (JECFA, 1967). The blood elimination of ethyl acetate *in vivo* is 33-37 s (< 1 min) (OECD, 2002).

Acute toxicity

Ethyl acetate is of low acute toxicity, with lowest reported LD₅₀ values of 10,170 mg/kg in rats and ~4,900 mg/kg in rabbits (OECD, 2002). At doses approaching the LD₅₀, ethyl acetate produces narcosis and other clinical signs (loss of corneal reflexes, dyspnoea, involuntary eye movements and bradycardia). Ethyl acetate is not irritating to the skin, and is slightly irritating to the eyes (OECD, 2002).

Subacute, subchronic and chronic toxicity studies

Ethyl acetate was fed daily to rats at doses of 13-115 mg (possibly ~50-450 mg/kg b.w.) for 5-9 days. Treated animals developed fatty infiltration of the liver. No further details are available of this study (JECFA, 1967).

Rats were treated by oral gavage with doses of ethyl acetate up to 3,600 mg/kg b.w. per day, for 90 days. High dose males exhibited a decrease in body weight and organ weights, most likely

secondary to the observed depression in food consumption at this dose. No effects were observed at 900 mg/kg b.w. per day, which was therefore the NOAEL for this study (IRIS, 1988).

Ethyl acetate given to rats in drinking water for 56 weeks had no adverse effects at dose corresponding to 4 mg/kg b.w. per day (JECFA, 1997). Ethyl acetate has been evaluated for neurotoxicity in rats following single and repeat dose exposure. The only signs of effects on the central nervous system (CNS) occurred at doses that were sedative. No persistent effects were observed in repeat dose studies (up to 90 days).

Genotoxicity

Ethyl acetate was negative in *in vitro* tests of mutagenicity. There are some reports of aneugenicity and clastogenicity *in vitro* at very high concentrations, but the significance of these findings to predicting genotoxicity *in vivo* is not clear. Ethyl acetate was consistently negative in micronucleus tests *in vivo* (OECD, 2002). It is concluded that ethyl acetate is unlikely to be genotoxic *in vivo*.

Carcinogenicity

No data were identified.

Developmental and reproductive toxicity

No data were identified. It has been argued that ethanol could be used for read across to ethyl acetate, due the rapid metabolism of ethyl acetate (OECD, 2002).

3.6.2.4. Allergenicity

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

3.6.3. Conclusion

JECFA established an ADI of 0-25 mg/kg b.w. for ethyl acetate, which the CONTAM Panel endorses. Ethyl acetate is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that ethyl acetate meets the criteria for acceptability as a previous cargo.

3.7. 2-ETHYLHEXANOL (2-ethylhexyl alcohol) (CAS No 104-76-7)

2-Ethylhexanol is a fairly viscous liquid produced in large scale (about 2,500,000 tons per year).

2-Ethylhexanol is produced industrially by the aldol condensation of n-butyraldehyde, followed by hydrogenation of the resulting hydroxyaldehyde. The n-butyraldehyde is made by hydroformylation of propylene (carbon monoxide and hydrogen).

2-Ethylhexanol is largely used in the production of di(2-ethylhexyl) phthalate and some other plasticizers, but also some acrylates.

3.7.1. Previous evaluations

The SCF evaluated 2-ethylhexanol in 1996 as a previous cargo for edible fats and oils and considered it acceptable as a previous cargo (SCF, 1997). This was based on its acceptability as a flavouring in

food and that it had an ADI of 0-0.5 mg/kg b.w (JECFA, 1993). In the 2003 SCF evaluation of acceptable previous cargoes, 2-ethylhexanol was not further evaluated as it was already considered acceptable (SCF, 2003).

In the OECD SIDS assessment of 1995, 2-ethylhexanol was considered a candidate for further work, especially regarding the reprotoxicity end-point (OECD, 1995).

JECFA evaluated 2-ethylhexanol at its 49th meeting, in 1997 (JECFA, 1998). The Committee had no concerns regarding its safety at current levels of intake when used as a flavouring agent. The ADI of 0-0.5 mg/kg b.w. established in 1993 was maintained at the 49th meeting.

3.7.2. Current evaluation

3.7.2.1. Expected impurities

Major impurities are ethyl methyl pentanol (resulting from isobutyraldehyde), 2-ethylhexenal, C4-alcohols and 2-ethylhexanoic acid. These are not considered to be of concern at the levels that would arise from 2-ethylhexanol as previous cargo.

3.7.2.2. Reactivity and reaction products

Transesterification is likely to produce 2-ethylhexanol esters of fatty acids. These are also industrially produced and sometimes applied in printing inks and as plasticizers. The CONTAM Panel does not consider that these would be of any greater toxicological concern than 2-ethylhexanol itself.

3.7.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

2-Ethylhexanol is well absorbed from the gastrointestinal tract following oral administration and rapidly eliminated. The main metabolic pathway is via 2-ethylhexanoic acid, followed by conjugation with glucuronic acid. 2-Ethylhexanoic acid can also undergo further metabolism by β -oxidation and decarboxylation to give 2- and 4-heptanone and CO₂. Only a small amount of the parent compound is excreted unchanged. There is evidence that metabolic saturation can occur at high doses (JECFA, 1993, 1998).

Acute toxicity

2-Ethylhexanol is not acutely toxic, with LD₅₀ values > 3,000 mg/kg following oral administration to rats. High doses administered by oral gavage, either undiluted or in corn oil have been reported to cause gastrointestinal irritation. 2-Ethylhexanol was moderately irritating to the skin and very irritating to the eyes of rabbits (JECFA, 1993).

Subacute, subchronic and chronic toxicity studies

Mice received doses of ethylhexanol up to 1,500 mg/kg b.w. per day by oral gavage, for 9-11 days (JECFA, 1993). At all doses above the lowest, reversible CNS signs were observed, including ataxia and piloerection. Other effects observed were increased liver weights and signs of irritation to the stomach mucosa.

Mice received doses of up to 500 mg/kg b.w. per day of 2-ethylhexanol by oral gavage for 90 days (JECFA, 1993). In mice receiving 250 and 500 mg/kg b.w. clinical signs were evident, together with damage to the mucosa of the stomach. The NOAEL was 125 mg/kg b.w. per day.

Rats were administered 2-ethylhexanol by oral gavage at dose of up to 1,500 mg/kg b.w. per day, for 9 days (JECFA, 1993). Kidney-to-body weight ratio was increased in animals receiving 330 mg/kg b.w. and at this dose thymus size was decreased in a few animals. At higher doses, clinical signs of CNS depression, reduced food consumption, body weight and body weight gain, hepatic enlargement, irritation to the stomach and effects on several immune system tissues, such as the thymus and spleen were observed. The NOAEL was 100 mg/kg b.w. per day.

In a 90 day study, rats received doses of up to 500 mg/kg b.w. per day 2-ethylhexanol by oral gavage (JECFA, 1993). At 250 mg/kg b.w. per day, treatment related findings included increased liver to body weight ratio and increased stomach to body weight ratio. In the high dose animals, additional observations included decreased body weight and body weight gain, foci in the gastric mucosa and other signs of gastric irritation and decreased fat deposition in the liver. The NOAEL was 125 mg/kg b.w. per day.

Mechanistic studies suggest that at high doses, 2-ethylhexanol can induce peroxisomal proliferation in rat liver. A gavage dose of 500 mg/kg b.w. per day for 90 days results in 6.5-fold and a 3.4-fold increase in hepatic cyanide-insensitive palmitoyl CoA in male and female rats, respectively (Lake et al., 1975; JECFA, 1993).

2-Ethylhexanol was administered to mice by oral gavage for 18 months, at doses of up to 750 mg/kg b.w. per day, 5 days/week (JECFA, 1993). Effects were observed only at the highest dose tested. Mortality was higher in this group, although it was not such that it prevented interpretation of the study. Reduced body weight gain, associated with reduced food consumption, was observed. Other treatment-related effects included focal hyperplasia of the stomach, increased liver and stomach weights and a number of haematological changes. The NOAEL was 200 mg/kg b.w. per day (JECFA, 1993). Rats were administered 2-ethylhexanol by oral gavage at doses of up to 150 mg/kg b.w. per day for 2 years, 5 days/week. Mortality in high dose females was increased. Reduced body weight and body weight gain were observed in mid and high dose animals, with occasional reduced food consumption in high dose animals. The incidence of animals with clinical signs increased with dose in mid and high dose groups. Relative liver, stomach, brain, kidney and testes weights were increased in animals in these groups. The NOAEL was 50 mg/kg b.w. per day.

Genotoxicity

2-Ethylhexanol was in general negative in a range of assays for genotoxicity *in vitro* and *in vivo*. It is concluded that 2-ethylhexanol is unlikely to be genotoxic (JECFA, 1993).

Carcinogenicity

2-Ethylhexanol was tested for carcinogenicity in rats and mice in the studies described above for chronic toxicity (JECFA, 1993). The compound was administered by oral gavage at doses up to 750 mg/kg b.w. per day in mice for 18 months and up to 150 mg/kg b.w. per day in rats for 2 years, 5 days/week. At the highest dose, 750 mg/kg b.w., in mice there was a slight increase in the incidences of hepatic basophilic foci and hepatocellular carcinomas. In males, these differences were not statistically significant increase. In females, the incidence of hepatocellular carcinomas was not statistically significantly different from that in water controls, but was statistically different ($P < 0.05$) from that in the vehicle (aqueous Cremophor EL) controls. Administration of 2-ethylhexanol did not result in an increase in the incidences of tumours in either male or female mice.

Developmental and reproductive toxicity

No valid studies on the reproductive toxicity of 2-ethylhexanol have been identified.

2-Ethylhexanol was administered in the diet, in a microencapsulated form, to give doses of up to 191 mg/kg b.w. per day to mice from gestation day 0-17 (ECHA, 2011b). There was no treatment-

related toxicity to the dams in this study. None of the gestational parameters were affected by ethylhexanol in this study, nor was there any evidence for effects on the incidence of fetal anomalies or malformations. The NOAEL was the highest dose tested, 191 mg/kg b.w. per day. In other studies, higher doses produced maternal and fetotoxicity (Hardin et al., 1987).

Pregnant rats were administered 2-ethylhexanol by oral gavage at doses up to 1,300 mg/kg b.w. per day from gestation day (GD)6-15 (ECHA, 2011b). The highest dose was maternally toxic, with increased mortality, clinical signs of toxicity, reduced food consumption and reduced food consumption. There was some slight toxicity in the mid-dose dams. The NOAEL for maternal toxicity was 130 mg/kg b.w. per day. In the mid-dose group, fetal weight was slightly decreased and the incidence of fetuses with skeletal variations and retardations was increased. In the high dose group, there was an increase in early resorptions and appreciable postimplantation loss. Fetal body weights were markedly reduced and there was an increase in the incidences of skeletal malformations, variations and retardations. The NOAEL for teratogenicity was 650 mg/kg b.w. per day. The NOAEL for developmental toxicity was 130 mg/kg b.w. per day.

3.7.2.4. Allergenicity

Available data give no indication that 2-ethylhexanol is an allergen or an adjuvant.

3.7.3. Conclusion

SCF established an ADI of 0-0.5 mg/kg b.w. for 2-ethylhexanol, which the CONTAM Panel endorses. 2-Ethylhexanol is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that 2-ethylhexanol meets the criteria for acceptability as a previous cargo.

3.8. 1,3-BUTANEDIOL (1,3-Butylene glycol) (CAS No 107-88-0)

1,3-butanediol is a colourless, viscous liquid, miscible with water and very hygroscopic (it absorbs 38.5 % w/w of water in 144 hours at 81 % relative humidity). It has a boiling point of 207.5 °C, ignition temperature 440 °C (DIN 51794) and a flash point (open cup) of 121 °C.

It is obtained by catalytic hydrogenation of alcohol using Raney Nickel. Biotechnological synthesis has been reported by purified dehydrogenase obtained from a cell free extract of *Candida parapsilosis* as well as of *Escherichia coli* recombinant strain.

It is used as intermediate for synthesizing optically active products as azetidinone derivatives, an intermediate for production of antibiotics, pheromones, fragrances and insecticides. It is used as wetting agents for regenerated cellulose film, tobacco. Some activity in inhibition of mould development has been reported.

3.8.1. Previous evaluations

The SCF evaluated 1,3-butanediol in 1996 and considered this substance as acceptable previous cargo (SCF, 1997). In the 2003 SCF evaluation of acceptable previous cargoes 1,3-butanediol was not further evaluated as it was already considered acceptable (SCF, 2003).

JECFA at its 23rd meeting in 1979 established an “Estimate of acceptable daily intake for man” of 0 to 4 mg/kg b.w. for 1,3-butanediol and also published specifications (JECFA, 1980).

1,3-butanediol is listed in Commission Regulation 10/2011¹⁷ as an acceptable substance in plastics, without restrictions on migration (acceptable food contact material).

1,3-butanediol is included in the EU register of flavouring substances used in or on foodstuffs,¹⁹ and has been evaluated by EFSA for its use as a flavouring agent (EFSA, 2009d). EFSA concluded that the substance was of no safety concern as a flavouring at the estimated level of intake based on the MSDI approach (EFSA, 2009d). 1,3-butanediol is permitted by the US FDA as a food additive in several direct and indirect applications.

3.8.2. Current evaluation

3.8.2.1. Expected impurities

Crude 1,3-butanediol often contains acetaldehyde, butyraldehyde, crotonaldehyde, various oligomers of the aldehydes, as well as several acetals. The majority of these compounds are not considered to be of concern at the levels that would arise from 1,3-butanediol as previous cargo. Crotonaldehyde has been reported to be genotoxic in some test systems, but the available evidence does not suggest that it is carcinogenic (IARC, 1995).

3.8.2.2. Reactivity and reaction products

Because 1,3-butanediol is an alcohol, it can esterify free fatty acids leading to mono- or di-esters. The CONTAM Panel does not consider that these would be of any greater toxicological concern than 1,3-butanediol itself.

3.8.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

Available studies indicate that 1,3-butanediol is well absorbed from the gastrointestinal tract following oral administration. Following absorption, it is metabolised to β -hydroxybutyraldehyde, which in turn is oxidised to β -hydroxybutyrate (JECFA, 1980). Ultimate metabolic products are acetoacetate and acetyl CoA, the latter entering the tricarboxylic acid cycle to produce carbon dioxide and reducing equivalents that are converted to ATP by the electron transport chain. As cited by JECFA, several metabolic tests and acute and chronic feeding studies in mice, rats, dogs and cattle have demonstrated that 1,3-butanediol can be utilised as a source of energy, although at high dietary levels it can produce ketosis (JECFA, 1980). Short-term metabolic studies in man indicate that 1,3-butanediol can supply up to 10 % of total dietary energy without toxic effects (Tobin et al., 1975, as cited by JECFA, 1980).

Acute toxicity

The acute toxicity of 1,3-butanediol is low. As cited by JECFA (1980), studies have been carried out in rats, mice and guinea pigs, providing LD₅₀ values of between 11,460 mg/kg b.w. (guinea pigs; Smyth et al., 1941) and 23,120-25,130 mg/kg b.w. (mice; Dominguez-Gil and Cadorniga, 1971), LD₅₀ values for rats lay within this range.

¹⁹ Commission Decision of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs drawn up in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council of 28 October 1996. OJ L 84, 27.3.1999, p. 1-74.

Subacute, subchronic and chronic toxicity studies

As cited by JECFA (1980), dietary exposure of rats to 0, 5, 10, 20, 30 or 40 % 1,3-butanediol (equivalent to 0, 2,500, 5,000, 10,000, 15,000 or 20,000 mg/kg b.w. per day) in the diet for 8 weeks did not produce any signs of toxicity (Schlüssel, 1954).

In a subchronic (13-week) feeding study dogs were fed with a diet containing 1,3-butanediol, resulting in intake levels of 0, 3,000, 6,000, 9,000 and 12,000 mg/kg b.w. per day (Reuzel et al., 1978, as cited by JECFA, 1980). Reduction in body weight gain was observed at 9,000 and 12,000 mg/kg b.w. per day and was accompanied by organ weight, blood biochemistry, haematology, and behavioural changes. These two doses also produced epilepsy-like seizures in dogs of both sexes, and the highest dose, 12,000 mg/kg per day produced slight ketonuria at week 12. The 6,000 mg/kg level was a NOAEL.

JECFA reported the results of a two-year feeding study in groups of 30 male and 30 female rats (60 males and 60 females in controls), using levels of 0, 1, 3 or 10 % 1,3-butanediol (Scala et al., 1967, as cited by JECFA, 1980). In this study, 1,3-butanediol-treated animals did not show any adverse effects compared with controls. Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasms and organ histopathology were unaffected by the two-year treatment at levels up to 10 % in feed. The same authors carried out a two-year study in groups of 4 beagle dogs using levels of 0, 0.5, 1 or 3 % 1,3-butanediol in the diet. Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasms and organ histopathology were unaffected by the two-year treatment at levels up to 3 % in feed (Scala et al., 1967, as cited by JECFA, 1980).

A number of nutritional studies have also been carried out with 1,3-butanediol in several species, including humans, which provide more information on the metabolism and effects on physiological parameters at high doses, and confirm the low toxicity of the substance (JECFA, 1980).

Genotoxicity

No *in vitro* genotoxicity tests have been carried out on 1,3-butanediol. The structurally-related 1,4-butanediol has yielded negative results *in vitro*, however, as have the metabolites of 1,3-butanediol, β -hydroxybutyraldehyde, β -hydroxybutyrate and acetoacetate. *In vivo* no dominant lethal effects were reported in the multigeneration study in rats carried out by Hess et al. reported below (Hess et al., 1981). Analysis of the femur bone marrow of at least two animals per sex and dose revealed no increase in chromosomal aberrations (Hess et al., 1981).

Carcinogenicity

No evidence of carcinogenicity was seen in the 2-year feeding study in rats carried out by Scala et al. (1967, as cited by JECFA, 1980)

Developmental and reproductive toxicity

As reported by JECFA (1980), in a multigeneration study twenty five rats of both sexes were fed either control diet or diets containing 1,3-butanediol at dose levels of 5, 10 or 24 % of the diet (equivalent to 2,500, 5,000 or 12,000 mg/kg b.w. per day). No treatment-related effects were seen on reproduction and lactation parameters for four of the five generations. The pregnancy rate of F1A rats decreased during five successive mating cycles, and no pups were born at the high-dose level group of the fifth series of litters (F2E generation). Excluding this group, the viability of F2 generation pups revealed no significant differences between litters or between control and test groups. Body weight gains of male rats in all four generations were slightly depressed with an apparent dose relationship. Body weight gain of females was not affected (Hess et al., 1981). Fertility was not affected in a three generation study in rats which received 20 % 1,3-butanediol in the diet (10,000 mg/kg b.w. per day).

Adult body weight gain decreased with each generation in treated animals (Dymaza and Adams, 1969). A developmental toxicity study conducted as part of this multigeneration study showed no substantive evidence of developmental toxicity of 1,3-butanediol, although some fetotoxicity (e.g., delayed ossification of sternbrae) was noted at dietary levels of 10 and 24 %, levels associated with metabolic disturbances due to the nutritional value of 1,3-butanediol (Hess et al., 1981).

In another developmental toxicity study, pregnant Long-Evans rats were treated by gavage with 1,3-butanediol at levels of 0, 7,060, 4,236, or 706 mg/kg b.w. per day on days 6-15 of gestation (Mankes et al., 1986). Transient maternal sedation was observed at 7,060 and 4,236 mg/kg b.w. per day, but feed consumptions and maternal body weights were unaffected. A significant, dose-dependent decrease in pup birth weights was observed. At the highest dose, birth weights were preferentially and significantly decreased in male pups not contiguous in utero to female siblings. Other offspring of the highest dose group were not affected and did not differ significantly from controls. Skeletal changes observed were considered by the authors to reflect the birth weight reductions, rather than being indicative of developmental toxicity (Mankes et al., 1986).

3.8.2.4. Allergenicity

Available data give no indication that 1,3-butanediol is an allergen or an adjuvant.

3.8.3. Conclusion

JECFA established an ADI of 0 to 4 mg/kg b.w. for 1,3-butanediol, which the CONTAM Panel endorses. The limited evidence available suggests that 1,3-butanediol is unlikely to be genotoxic. It is not carcinogenic or developmentally toxic. 1,3-butanediol is not allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that 1,3-butanediol meets the criteria for acceptability as a previous cargo.

3.9. 1,4-BUTANEDIOL (1,4-Butylene glycol) (CAS No 110-63-4)

1,4-butanediol is an odourless and colourless liquid, with a melting point of 18 °C, a boiling point of 230 °C, and miscible with water.

1,4-butanediol is industrially prepared by several processes: 1) the “Reppe synthesis” is carried out by reaction of acetylene with formaldehyde that leads to 1,4-butyndiol, this undergoes to hydrogenation to obtain 1,4-butanediol; 2) Another pathway involves the conversion of propylene oxide to allyl alcohol, then it is hydroformylated to 4-hydroxybutyraldehyde. Hydrogenation of the 4-hydroxybutyraldehyde yields 1,4-butanediol; 3) from maleic anhydride, which is first converted to the methyl maleate ester, then hydrogenated; 4) a biotechnological approach uses an engineered *Escherichia coli* strain to produce 1,4-butanediol from sugars.

1,4-Butanediol is used industrially as a solvent and in the manufacture of some types of plastics, elastic fibers and polyurethanes. In organic chemistry, 1,4-butanediol is used for the synthesis of γ -butyrolactone.

3.9.1. Previous evaluations

The SCF evaluated 1,4-butanediol in 1996 and considered this substance as acceptable previous cargo (SCF, 1997), noting that it had previously been considered as a substance intended for use in materials in contact with food (SCF, 1986). The SCF noted that there were some toxicological data on short

term effects and developmental toxicity of 1,4-butanediol, and that from its chemical structure the substance was unlikely to be genotoxic. The SCF also noted the availability of technical data indicating that 1,4-butanediol could be considered to be highly soluble in water and therefore easily cleaned from tanks. In the 2003 SCF evaluation of acceptable previous cargoes 1,4-butanediol was not further evaluated as it was already considered acceptable (SCF, 2003).

1,4-butanediol was evaluated by the SCF in 1986 as a food contact material and placed in list 7²⁰ (SCF, 1986). It was considered again in 2001 as a substance intended for use in materials in contact with food according to Council Directive 89/109/EEC²¹ relating to materials and articles intended to come into contact with foodstuffs (SCF, 2001). The SCF established a migration limit for the substance of 0.05 mg/kg of food, based on a reduced core set of toxicological data, and placed it in List 3²² (SCF, 2001). 1,4-butanediol was re-evaluated by EFSA by the former EFSA AFC Panel, also as a substance intended for use in materials in contact with food, and on the basis of additional toxicological data, EFSA established a migration limit for the substance of 5 mg/kg of food, based on a comprehensive set of toxicological data (EFSA, 2004b).

1,4-butanediol has been evaluated under the OECD SIDS programme on High Production Volume (HPV) chemicals (OECD, 2000). It was concluded that the substance was a candidate for further work, specifically more work on characterising human exposure from various sources.

3.9.2. Current evaluation

3.9.2.1. Expected impurities

There are no data on anticipated impurities in 1,4-butanediol. It is not anticipated that any of the synthetic intermediates used in the synthesis of 1,4-butanediol or other potential impurities present would be at a level such that they would be a toxicological concern from the use of 1,4-butanediol as a previous cargo.

3.9.2.2. Reactivity and reaction products

Because 1,4-butanediol is an alcohol, it can esterify free fatty acids leading to mono- or di-esters. The CONTAM Panel does not consider that these would be of any greater toxicological concern than 1,4-butanediol itself.

3.9.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

1,4-butanediol can be anticipated to be well absorbed from the gastrointestinal tract following oral administration based on analogy to similar compounds. Following absorption, it is metabolised to γ -hydroxybutyraldehyde, which in turn is oxidised to γ -hydroxybutyric acid and then to the γ -butyrolactone and ultimately to carbon dioxide (EFSA, 2004b; OECD, 2000). A metabolism and disposition study conducted in F344/N rats by the NTP confirmed the rapid and extensive conversion of 1-(¹⁴C)-1,4-butanediol to ¹⁴CO₂ (NTP, 1996a).

²⁰ Substance for which some toxicological data exist, but for which an ADI or TDI could not be established. The additional specified information should be furnished.

²¹ Council Directive 89/109/EEC of 21 December 1988 on the approximation of the laws of the Member States relating to materials and articles intended to come into contact with foodstuffs. OJ L 40, 11.2.1989, p. 38-44.

²² Substances for which an ADI or TDI could not be established, but where the continued use could be accepted.

Acute toxicity

As reported in the OECD SIDS evaluation document, acute toxicity studies on 1,4-butanediol have been carried out in rats, mice and guinea pigs, providing LD₅₀ values of between 1,200 mg/kg b.w. in guinea pigs and 2,060 mg/kg b.w. in mice (OECD, 2000). LD₅₀ values for rats lay within this range.

1,4-butanediol is mildly irritant to the skin, eyes and respiratory tract (OECD, 2000).

Subacute, subchronic and chronic toxicity studies

In a 28-day oral toxicity study in Wistar rats 1,4-butanediol was administered by gavage at doses of 5, 50 or 500 mg/kg per day (Jedrychowski et al., 1990a, as reported by OECD, 2000). A statistically significant increase in activities of sorbitol dehydrogenase and alanine aminotransferase was observed at 500 mg/kg per day in males. Mild to moderate inflammatory change, characterised by proliferation of bile ducts and periportal infiltration with fibroblasts and mononuclear cells were observed in the liver of a number of treated animals at all dose levels compared with controls. The authors considered that the proliferation of bile ducts and periportal mononuclear cell infiltrations were indicative of chronic toxic inflammation of the liver (Jedrychowski et al., 1990a). The OECD SIDS evaluation noted that the reliability of this study is questionable, since histopathology was only carried out on five of the eight animals in each group and the severity of the bile duct changes in treated animals was not statistically significantly different from that in controls. The CONTAM Panel agreed with the view of OECD and concluded that since similar hepatic changes have not been seen in 90-day studies with γ -butyrolactone, results which are considered to be relevant to 1,4-butanediol on metabolic grounds (see below) and the reliability of the study is questionable, this study should not be used to identify a NOAEL.

As reported in the OECD SIDS evaluation, in a combined repeat dose and reproductive/developmental toxicity screening test, 1,4-butanediol was administered at doses of 200, 400 or 800 mg/kg b.w. per day by gavage for 45 days in males and from 14 days before mating to day 3 of lactation in females (OECD, 2000). Acute and transient dose-related central nervous system effects were observed in both sexes, consisting of hyperactivity at 200 mg/kg b.w. per day and CNS depression at higher doses. Body weight gains were reduced at 400 and 800 mg/kg b.w. per day during the early period of administration, and food consumption was also reduced in parallel. Epithelial hyperplasia and fibrosis of the lamina propria was seen in the bladder of animals receiving 400 or 800 mg/kg b.w. per day on histopathological examination. While the authors of the study considered that the hyperactivity seen at 200 mg/kg b.w. per day was not an adverse effect, the Japanese Expert Committee to whom the study was submitted were not in agreement, and considered that a NOAEL could not be identified. Based on the description provided in the OECD SIDS evaluation, the CONTAM Panel considered that the transient hyperactivity seen at a dose level of 200 mg/kg b.w. per day could be considered non-adverse, and that 200 mg/kg b.w. per day was likely to represent a NOAEL in this study. The Panel was not however able to review the original Japanese report.

Ninety day studies in rats and mice with γ -butyrolactone have been performed by the National Toxicity Program (NTP, 1996a), and are considered to be relevant to 1,4-butanediol on metabolic grounds (NTP, 1996a; EFSA, 2004b). Rats were dosed by gavage with 0, 56, 112, 225, 450 or 900 mg γ -butyrolactone/kg b.w. per day, while mice received doses of 0, 65, 131, 262, 525, or 1,050 mg/kg b.w. per day. Mortality was seen at the highest dose tested in both rats and mice, while body weight and body weight gain were significantly lower in male rats receiving 450 mg/kg compared with controls; no such effect was seen in female rats or in mice with the exception of high dose males. Histopathological examination revealed an increased incidence of focal inflammation of the nasal mucosa in rats administered γ -butyrolactone. No lesions related to the administration of γ -butyrolactone occurred in mice (NTP, 1996a). The CONTAM Panel concluded that NOAELs of 225 mg/kg b.w. per day in rats and 525 mg/kg b.w. per day could be identified for γ -butyrolactone in this study, which can be extrapolated to 1,4-butanediol.

Genotoxicity

Negative results have been obtained for 1,4-butanediol in an *in vitro* bacterial mutagenicity study, a chromosome aberration test using V79 Chinese hamster lung cells and a gene mutation assay using CHO cells (OECD, 2000; EFSA, 2004b). An *in vivo* study in *Drosophila melanogaster* was also negative (OECD, 2000). 1,4-butanediol is considered not to be genotoxic.

Carcinogenicity

No data are available on 1,4-butanediol itself. However, as reported by EFSA (EFSA, 2004b), NTP stated “that because the toxicity and carcinogenicity of γ -hydroxybutyric acid was fully evaluated in the NTP pre-chronic and chronic studies of γ -butyrolactone, with a lack of toxic or carcinogenic potential being demonstrated, it is concluded that there is a high likelihood that 1,4-butanediol would be negative in a similar set of studies” (NTP, 1996a).

Developmental and reproductive toxicity

In the combined repeat dose and reproductive/developmental toxicity screening test described under “Subacute, subchronic and chronic toxicity studies” above, the parental animals exhibited no treatment-related effects on reproductive parameters. Pup viability or incidence of morphological abnormalities were not affected by administration of the compound, however pup body weight was slightly but significantly decreased in the 800 mg/kg group, and there was an increase in skeletal defects. This change was considered to be secondary to maternal toxicity (reduced food consumption and body weight gain) (OECD, 2000).

As reported in the OECD SIDS evaluation (OECD, 2000), pregnant Swiss (CD-1) mice (28-32/group) were given 1,4-butanediol (0, 100, 300 or 600 mg/kg b.w. per day) by gavage during gestational days 6-15 (Price et al., 1993). No maternal or developmental effects were observed at the low dose. Dams at the mid and high doses exhibited symptoms of central nervous system intoxication (hypoactivity, immobility, loss of righting reflex and/or prone posture) during the first 4 hr following daily administration. Maternal effects at the mid and high doses also included reduced food intake, reduced body weight, and reduced weight gain. The only definitive expression of developmental toxicity was a reduction in average foetal body weight at the middle and high doses (92 % and 83 % of control weight, respectively). However, this effect was considered to be secondary to maternal toxicity.

3.9.2.4. Allergenicity

The maximization test in guinea pigs produced no sensitization (Jedrychowski et al., 1990b), and skin patch test in 200 persons similarly revealed no sensitization (GAF, 1967, as cited by OECD, 2000). Therefore, 1,4-butanediol is not considered a sensitizer for contact dermatitis.

Available data give no indication that 1,4-butanediol is an allergen or an adjuvant.

3.9.3. Conclusion

The CONTAM Panel noted that no ADI or TDI has been established for 1,4-butanediol. The toxicological studies carried out either on the substance itself or on γ -butyrolactone generally indicate a lack of organ-specific toxicity and carcinogenicity. NOAELs in the region of 200 mg/kg b.w. per day could be identified in 90-day studies in rats on the substance itself or on γ -butyrolactone (NTP, 1996a; OECD, 2000). Application of an uncertainty factor of 100 or 1,000 to a NOAEL of 200 mg/kg b.w. per day would result in health based guidance values greater than 0.1 mg/kg b.w. per day. An additional uncertainty factor of 10 might be considered necessary due to limitations in the database (there were few studies on the substance itself, with reliance on data for the metabolite γ -butyrolactone). The CONTAM Panel noted that the health based guidance value would meet

criterion 2, that the ADI (or TDI) of the substance should be greater than or equal to 0.1 mg/kg b.w. per day. The evidence suggests that 1,4-butanediol is not genotoxic and it is not allergenic. Overall, the CONTAM Panel considered that 1,4-butanediol is not of toxicological concern when used as a previous cargo, also noting the SCF's conclusion that 1,4-butanediol is soluble in water and therefore easily cleaned from tanks. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that 1,4-butanediol meets the criteria for acceptability as a previous cargo.

3.10. PROPYLENE GLYCOL (1,2 propylene glycol; propan-1,2-diol; 1,2-dihydroxypropane; monopropylene glycol (MPG); methyl glycol) (CAS No 57-55-6)

Propylene glycol (molecular weight 76.09 Da) is optically active but appears to be used as the racemic mixture, although specific information is rarely given. It is a hygroscopic, viscous liquid, miscible with water, acetone, chloroform and diethyl ether. It is a good solvent for many essential oils, but immiscible with fats and oils.

Propylene glycol is obtained by hydrolysis of propylene oxide under pressure at high temperature without a catalyst. It is used in the manufacturing of synthetic resins and de-icing solutions. It is used in pharmaceuticals, as a drug vehicle (for example as a Food and Drug Administration (FDA)-approved solvent for intravenous diazepam) and preservative. It is also used in personal lubricants, in semi-moist pet food and as a humectant for tobacco. In the food industry it is used as a solvent for colorants and flavours, as a humectant, preservative and emulsifier.

3.10.1. Previous evaluations

The SCF evaluated propylene glycol in 1996 and considered this substance as acceptable previous cargo, noting that the substance was a food additive with an ADI previously established by JECFA of 0-25 mg/kg b.w. per day (SCF, 1997). In the 2003 SCF evaluation of acceptable previous cargoes, propylene glycol was not further evaluated as it was already considered acceptable (SCF, 2003).

In 1993, the SCF had also evaluated propylene glycol as a food additive, and concluded that “the uncertainty with regard to potential mutagenic effects at the germ cell level, the fact that most studies at the chromosomal level used limited protocols, that there is no *in vitro* assay for gene mutation in cultured mammalian cells as well as the absence of a carcinogenicity study in a second species leads the Committee to change the established full ADI into a temporary ADI of 25 mg/kg b.w.” (SCF, 1996). Propylene glycol is currently authorised as a food additive (E1520).

The JECFA at its 17th meeting in 1973 established an “Estimate of acceptable daily intake for man” of 0 to 25 mg/kg b.w. for propylene glycol (JECFA, 1974), following several previous evaluations, and specifications were also prepared (JECFA, 2006). JECFA also evaluated propylene glycol as a flavouring substance in 2001. The evaluation was not finalised as further information was required whether propylene glycol is currently in use as a flavouring agent (JECFA, 2001).

Propylene glycol was evaluated by the SCF in 1978 as a substance intended for use in the manufacture of regenerated cellulose films (SCF, 1978). The Committee considered the substance toxicologically acceptable for the use intended on the basis of the JECFA ADI of 0-25 mg/kg b.w. per day and assigned it to List 1, substances with ADIs established by JECFA or SCF. In 1984, propylene glycol

was evaluated by the SCF as a substance intended for use in materials in contact with food and considered acceptable on the basis of the JECFA ADI. It was placed in list 1.²³

The US Agency for Toxic Substances and Disease Registry (ATSDR) has prepared a toxicological profile on propylene glycol (ATSDR, 1997). There was insufficient information to establish an oral reference value.

3.10.2. Current evaluation

3.10.2.1. Expected impurities

There are no data on anticipated impurities in propylene glycol. It is not anticipated that starting substances or intermediates from the synthesis of propylene glycol or other potential impurities would be present at a level which could be a toxicological concern for the use of propylene glycol as a previous cargo.

3.10.2.2. Reactivity and reaction products

Under ordinary conditions, propylene glycol is stable, but at high temperature it tends to oxidise, forming propionaldehyde, lactic acid, pyruvic acid and acetic acid. There are no concerns regarding reactivity of propylene glycol with fats and oils when used as a previous cargo.

3.10.2.3. Toxicological profile

Absorption, distribution, metabolism and elimination

According to JECFA (JECFA, 1974), propylene glycol is rapidly absorbed after oral administration and appears in the blood-stream. After a dose of 8 mL/kg b.w. (equivalent to 8,284 mg/kg b.w.) had been administered to dogs approximately 24 hours were required for complete elimination from the blood-stream. Conversion to lactic acid has been shown to be the normal metabolic pathway, via two biochemical pathways (JECFA, 2001). Phosphorylated propylene glycol can be converted to acetol phosphate, lactaldehyde phosphate, lactyl phosphate, and then lactic acid. Non-phosphorylated propylene glycol is successively oxidized to lactaldehyde, methylglyoxal, and lactic acid (JECFA, 2001). High doses are likely to be excreted largely unchanged in the urine (JECFA, 2001).

Acute toxicity

As reported by JECFA, acute toxicity studies on propylene glycol have been carried out in rats, mice, rabbits and guinea pigs, providing LD₅₀ values of greater than 19,000 mg/kg b.w. in all these species (JECFA, 1974).

Subacute, subchronic toxicity studies

Short-term oral toxicity studies of propylene glycol in rats, rabbits and dogs have shown no adverse effects at levels approximating 10 % in the diet (SCF, 1996; ATSDR, 1997). Haematological effects have been seen at high dose levels in some species, notably cats. Cats appear to be uniquely sensitive to haematological effects of ingested propylene glycol, manifest as an increase of Heinz bodies in circulating erythrocytes (ATSDR, 1997).

²³ Substances, e.g. food additives, for which an ADI (=Acceptable Daily Intake), a t-ADI (=temporary ADI), a MTDI (=Maximum Tolerable Daily Intake), a PMTDI (=Provisional Maximum Tolerable Daily Intake), a PTWI (=Provisional Tolerable Weekly Intake) or the classification "acceptable" has been established by this Committee or by JECFA.

Genotoxicity

Propylene glycol has been extensively evaluated in a range of genetic toxicity test systems. The existing studies provide convincing evidence that it is not genotoxic (ATSDR, 1997; JECFA, 2001).

Chronic toxicity studies and carcinogenicity

As cited by JECFA (2001), in a study in which rats were given propylene glycol in the diet at a concentration of 2.45 % or 4.9 % (equivalent to 900 and 1,800 mg/kg b.w. per day) for 2 years no treatment-related adverse effects were found on growth, and histological examination revealed no treatment-related effects (Morris et al., 1942).

As cited by JECFA (2001), in a study in which rats received propylene glycol in the diet at a concentration of 0, 310, 630, 1,300 or 2,500 mg/kg b.w. per day for 2 years no treatment-related adverse effects on body weight gain, haematological, urinary, or clinical chemical end-points, or organ weights were found. The NOEL was 1,300 mg/kg b.w. per day (Gaunt et al., 1972).

As cited by JECFA (2001), in a study in which dogs received propylene glycol in the diet at a concentration of 0, 2000, or 5000 mg/kg b.w. per day for 2 years increased erythrocyte destruction was found at 5,000 mg/kg b.w. per day. No significant treatment-related effects on haematological, clinical chemical, or urinary end-points, or on gross or histological appearance were found (Weil et al., 1971).

Developmental and reproductive toxicity

In rats and mice, no adverse effects on reproductive performance were observed after oral treatment at doses as high as 10,000 mg/kg b.w. per day during gestation of 1 generation or for multiple litters and 2 generations of mice (Kavlock et al., 1987; NTP, 1985, as cited by ATSDR, 1997) or inhalation exposure to 112 ppm for 18 months (Robertson et al., 1947, as cited by ATSDR, 1997). ATSDR considered that further evaluation of the reproductive toxicity of propylene glycol was not necessary (ATSDR, 1997). As reported by JECFA, in a study to examine the potential of di(2-ethylhexyl) phthalate and its metabolites to cause testicular damage in rats after oral administration, a control group of six male Sprague Dawley rats were given propylene glycol orally at a dose of 2,000 mg/kg b.w. per day for 5 days. Histopathological examination of testis, prostate and liver was done following sacrifice on day 6. The testes of animals given propylene glycol were reported to contain occasional degenerated cells, most of which were in early meiotic prophase or undergoing meiotic division (Sjoberg et al., 1986). In another study cited by JECFA (2001), in which the effects of 15 chemicals, including propylene glycol, on differential ovarian follicle counts and reproductive performance were compared, propylene glycol was reported to have no effect on reproductive function (Bolon et al., 1997).

3.10.2.4. Allergenicity

There is evidence from clinical studies that propylene glycol is a weak irritant and skin sensitizer (challenge with 2 % solution or stronger), and may increase the reaction to some contact allergens (i.e. adjuvant-like effect), if there is co-exposure, for example when propylene glycol is used as a vehicle (for references, see Andersen, 1994). Taking into account that the worst case residue levels of a previous cargo in the oils and fats is considered to be 100 mg/kg, and additionally that propylene glycol is only a weak or very weak irritant, allergen or adjuvant, the CONTAM Panel considers that there would be no significant risk for adverse reactions due to irritancy or allergy from the use of propylene glycol as a previous cargo.

3.10.3. Conclusion

JECFA established an ADI of 0-25 mg/kg b.w. for propylene glycol, which the CONTAM Panel endorses. Propylene glycol is not genotoxic. Its use as previous cargo would not give rise to any concerns regarding possible irritancy or allergenicity. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance.

Therefore, the CONTAM Panel concludes that propylene glycol meets the criteria for acceptability as a previous cargo.

3.11. POLYPROPYLENE GLYCOL (molecular weight greater than 400) (CAS No 25322-69-4)

Polypropylene glycol (PPG) is a polyether obtained by polymerization of propylene glycol. It is a clear, viscous liquid with a low pour point. Viscosity increases and water solubility decreases with increasing molecular weight.

PPG is produced by anionic ring-opening polymerization of propylene oxide. The initiator is an alcohol and the catalyst a base, usually potassium hydroxide. When the initiator is ethylene glycol or water the polymer is linear. With a multifunctional initiator like glycerol, pentaerythritol or sorbitol the polymer branches out.

PPG is used in many formulations for polyurethanes. It is used as a rheology modifier, as well as a surfactant, wetting agent and a dispersant.

3.11.1. Previous evaluations

The SCF evaluated PPG (molecular weight greater than 400) in 1996 and considered this substance as acceptable previous cargo (SCF, 1997). In the 2003 SCF evaluation of acceptable previous cargoes, PPG was not further evaluated as it was already considered acceptable (SCF, 2003).

PPG was evaluated by the SCF in 1978 as a substance intended for use in the manufacture of regenerated cellulose films (SCF, 1978). On the basis of the available toxicological information, the Committee established a TDI of 1.5 mg/kg b.w. (as a group TDI with 1,2-polypropylene oxide and dipropylene glycol) and considered the substance toxicologically acceptable for the use intended, while noting data gaps on effects on reproduction including developmental toxicity and mutagenicity potential. This latter comment was intended to cover all the substances evaluated by the SCF in their opinion, not specifically PPG. In 1984, PPG was evaluated by the SCF as a substance intended for use in materials in contact with food and considered acceptable on the basis of the TDI established by SCF in 1978. It was placed in list 2²⁴ (SCF, 1986).

PPG is listed in Commission Regulation 10/2011¹⁷ as an acceptable substance in plastics, without restrictions on migration (acceptable food contact material) and no specifications on molecular mass.

3.11.2. Current evaluation

3.11.2.1. Expected impurities

Anticipated impurities include propylene glycol, its impurities (see Section 3.10.2.1.) and oligomers of molecular weight < 400 Da. These oligomers may include cyclic structures with the dioxane skeleton. However, PPG has been approved for various applications in the food sector and the toxicological evaluation occurred on a material that included these oligomers. Therefore it is not anticipated that

²⁴ Substances for which a TDI has been established by the SCF or EFSA.

PPG would contain low molecular mass substances at a level that these would be of toxicological concern for PPG as a previous cargo.

3.11.2.2. Reactivity and reaction products

There are no concerns regarding any possible reaction products of PPG with fats and oils when used as a previous cargo.

3.11.2.3. Toxicological profile

Limited toxicological data are available on PPG (molecular weight greater than 400). PPGs range in molecular weight from 200 to 2000 g/mol or greater, and the toxicity of the lower molecular weight PPGs (200-1,200 g/mol) can be anticipated to be broadly similar to propylene glycol (see above), while the higher molecular weight PPGs can be anticipated to be comparatively inert, as found for the polyethylene glycols (PEGs).

Absorption, distribution, metabolism and elimination

Toxicokinetic studies on PPGs 425, 1025, and 2025 (nomenclature reflecting the molecular weights of the PPGs tested) indicate that they are readily absorbed from the gastrointestinal (GI) tract and are excreted in the urine and faeces (Andersen, 1994).

Acute toxicity

Low molecular weight PPGs are reported to be moderately acutely toxic by the oral route, with LD₅₀ values in rats reported to range from 500 mg/kg b.w to over 40,000 mg/kg b.w. (BIBRA, 1990; Andersen, 1994; HSDB, 2011). Effects following acute intake in humans or experimental animals include CNS effects and cardiac arrhythmias, also tissue damage in the liver, kidney and spleen (BIBRA, 1990; HSDB, 2011). The latter are recognised target organs for the glycols.

The lower molecular weight PPGs are mildly irritating to skin and eyes (BIBRA, 1990; Andersen, 1994).

Subacute, subchronic and chronic toxicity studies

In subchronic oral toxicity studies, administration of PPG 2000 resulted in slight reduction in growth and body weight of rats, while administration of PPG 750 to rats and dogs resulted in slight increases in liver and kidney weights in rats (Andersen, 1994). No other treatment-related effects were reported.

Genotoxicity

BIBRA reported that PPG of undefined specification was mutagenic in an Ames bacterial test (BIBRA, 1990). The CONTAM Panel considered this result could be disregarded given the negative genotoxicity database on propylene glycol.

Carcinogenicity

No information is available on the carcinogenicity of PPG. However an ether of PPG, PPG Butyl Ether, having a chain length approximately 9 to 13 (molecular weight range approximately 300 to 500) was not carcinogenic in a 2-year feeding study in rats when incorporated in the diet at levels up to 2,600 ppm (equivalent to 130 mg/kg b.w. per day) (Andersen, 1994). The CONTAM Panel also noted that there was no evidence of a carcinogenic effect of propylene glycol in two chronic toxicity studies (see Section 3.10).

Developmental and reproductive toxicity

No information is available on the developmental or reproductive toxicity of PPG. The CONTAM Panel noted that propylene glycol is considered not to have adverse effects on reproduction (see Section 3.10)

3.11.2.4. Allergenicity

Neither skin irritation nor sensitization reactions were observed in 300 subjects who received continuous and repeated dermal applications of undiluted PPG 2000 (Andersen, 1994).

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

3.11.3. Conclusion

The SCF established a TDI of 1.5 mg/kg b.w. for PPG, which was endorsed by the CONTAM Panel. There are limited toxicological data on PPG, in particular on chronic toxicity and reproductive toxicity. The CONTAM Panel considered however that information on these endpoints could be read across from the monomer propylene glycol. PPG is considered not to be genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are there any toxicologically relevant impurities.

Therefore, the CONTAM Panel concludes that PPG (molecular weight greater than 400) meets the criteria for acceptability as a previous cargo.

3.12. METHANOL (methyl alcohol) (CAS No 67-56-1)

Methanol is a low molecular mass, colourless liquid miscible with water. It is largely produced from carbon monoxide and hydrogen, using catalysts. Carbon monoxide is produced from coal or mineral oil derivatives, and in smaller amounts also from organic materials such as wood, peat, sludge and other organic wastes.

A large proportion is converted to basic chemicals, like formaldehyde (more than half of the production), MTBE (e.g. added to gasoline) and many types of methyl esters and ethers.

3.12.1. Previous evaluations

The SCF evaluated methanol in 1996 and considered it as an acceptable previous cargo on the basis of its acceptability as an extraction solvent for food (SCF, 1997). In the 29th report the SCF gave its opinion that methanol may be present up to levels of 5-10 mg/kg food when used as an extraction solvent. Although there were insufficient data to establish an ADI, the Committee considered the residues arising from its use to be minimal, constituting no safety problem, and therefore set no ADI. The substance is readily removed by tank cleaning, and is easily removed by the oil refining process.

In the SCF evaluation of acceptable previous cargoes in 2003, methanol was not further evaluated as it was already considered acceptable (SCF, 2003).

JECFA (1970) concluded that the use of methanol as an extraction solvent “should be restricted to that determined by good manufacturing practice which is expected to result in minimal residues unlikely to have any significant toxicological effects”.

The International Program on Chemical Safety (IPCS) published an evaluation of the toxicity of methanol in 1997. It was concluded that it was not feasible to conduct a conventional risk assessment

for methanol, for a number of reasons. An alternative approach was adopted, on the basis of blood formate levels. As formate is present normally in blood, IPCS identified exposures that would not increase blood formate above the normal background level. On this basis, occupational exposure to methanol vapour around 260 mg/m³ or single oral exposures of approximately 20 mg/kg b.w. were considered to pose negligible risk (IPCS/WHO, 1997).

A draft US Environmental Protection Agency Integrated Risk Information System (US EPA IRIS) assessment (2011) has proposed a reference dose (cf TDI) for methanol by the oral route of 0.4 mg/kg b.w. per day, based on route to route extrapolation of the NOAEL for developmental effects observed in an inhalational study. However, this has yet to pass review.

3.12.2. Current evaluation

3.12.2.1. Expected impurities

No relevant impurities expected.

3.12.2.2. Reactivity and reaction products

Methanol readily interesterifies with lipids, but the resulting methyl esters also exist normally in edible oils or in fats from interesterification at concentrations which may exceed 100 mg/kg.

3.12.2.3. Toxicological profile

Methanol is produced as an endogenous metabolite in the body, present in trace amounts as a result of intermediary metabolism and the fermentation of carbohydrates in the diet by gastrointestinal organisms (see Lindinger et al., 1997).

Absorption, distribution, metabolism and elimination

Methanol is rapidly and completely absorbed from the gastrointestinal tract following oral ingestion, reaching peak serum levels within 30-60 minutes, depending on the presence or absence of food in the stomach. Methanol distributes readily and uniformly to organs and tissues in direct proportion to their water content, and has a volume of distribution of 0.6-0.7 L/kg b.w. (IPCS/WHO, 1997). Methanol is rapidly and extensively metabolised in the liver, first to formaldehyde, by alcohol dehydrogenase in humans, then to formic acid or formate (depending on pH), primarily by formaldehyde dehydrogenase and finally to carbon dioxide, catalysed by formyl-tetrahydrofolic acid (THF) synthetase. Formic acid combines with THF to give 10-formyl-THF which is then converted into carbon dioxide by formyl-THF dehydrogenase. Almost 97 % of an oral dose of methanol is eliminated as CO₂ (IPCS/WHO, 1997; Cruzan, 2009). The rate of formate oxidation depends on the availability of folate, which varies amongst species. This is a key determinant in species differences in sensitivity to acute methanol toxicity. In general folate levels are lower in primates than in rodents (Johlin et al., 1987). The elimination half-life of methanol in humans is 2.5-3.0 h, although at high doses saturation of elimination results in more prolonged half-lives (Jones, 1987). In contrast, the elimination of formaldehyde is extremely rapid, with a half-life of approximately 1.5 min, in *Cynomolgus* monkeys (McMartin et al., 1979). A small amount of methanol (~2 %) is excreted unchanged in urine and expired air.

Acute toxicity

Methanol is of low acute oral toxicity, with LD₅₀ values of >5,000 mg/kg b.w. However, as methanol is a liquid (density ~ 0.8 g/mL) it is not difficult to ingest high doses either deliberately or accidentally, as 1 ml is equivalent to >10 mg/kg b.w. and methanol is sometimes consumed as a cheap substitute for

ethanolic beverages. Acute effects of methanol intoxication are initially similar to those caused by ethanol (inebriation and sleepiness) followed, after a few hours, by vomiting, vertigo, abdominal pain, diarrhoea, dyspnoea, acidosis, blurred vision, hyperaemia of the optic disc, blindness, dilated pupils and, in rare cases, delirium. It has been estimated that the minimum lethal dose of methanol in humans is between 0.3 and 1 g/kg. The minimum dose causing permanent visual defects is not known (IPCS/WHO, 1997), but may be as low as 10 mL (8 g or 133 mg/kg b.w.) (Vale, 2007).

Methanol is not irritating to the skin in conventional tests in animals. It is moderately irritating to rabbit eyes. It has been reported to cause minor irritation to the skin and eyes at atmospheric concentrations well above 200 ppm (260 mg/m³) in humans. It is not a skin sensitiser (IPCS/WHO, 1997).

Subacute, subchronic and chronic toxicity studies (US EPA, 2011)

There are a limited number of case reports that prolonged exposure to methanol may cause effects qualitatively similar to those arising from acute exposure, including CNS and visual disorders (IPCS/WHO, 1997). There are few experimental studies of the effects of repeated exposure by the oral route on the toxicity of methanol, most being by the inhalation route. In a study following oral gavage with methanol to rats at doses up to 2,500 mg/kg b.w. for 90 days, clinical chemical changes suggestive of effects on the liver were observed at the top dose, but there were no histopathological correlates. There was a reduction in brain weight at this dose. The NOAEL was 500 mg/kg b.w. per day (IRIS, 1993). Mice were exposed chronically to methanol in their drinking water to give doses up to ~2,000 mg/kg b.w. per day (Apaja, 1980, cited in US EPA, 2011). At the highest dose, females showed decreased survival and a slight increase in hepatocellular necrosis. There was an increase in acute pancreatitis in the high dose males. The NOAEL was 970 mg/kg b.w. per day. Rats were exposed throughout their life to methanol in the drinking water, to provide doses up to ~2,000 mg/kg b.w. per day (Soffritti et al., 2002; Cruzan, 2009). Methanol produced no obvious toxicity in any of dose groups in this study, although reporting of non-cancer effects was limited. The NOAEL was therefore 1,840 mg/kg per day, the highest dose tested.

Genotoxicity

The genotoxicity of methanol has been assessed in a wide range of tests both *in vitro* and *in vivo*. In general results were negative, with a few equivocal positives *in vitro* and uniformly negative results *in vivo*. The weight of evidence is that methanol is not genotoxic (IPCS/WHO, 1997; Cruzan, 2009; ECHA, 2011c).

Carcinogenicity

The carcinogenicity of methanol following exposure by the oral route has been evaluated in only one study (Soffritti et al., 2002; Cruzan, 2009). Rats were exposed throughout their lifetime to methanol in the drinking water, to provide doses up to ~2,000 mg/kg b.w. per day. Interpretation of this study was compromised, to some extent, by intercurrent infection. Soffritti et al. (2002) reported an increase in the incidence of lympho-immunoblastic lymphoma in high dose males and in high and mid-dose females. The design and interpretation of this and similar studies from the laboratory involved have been criticised by a number of groups including EFSA (EFSA, 2006, 2009e; Cruzan, 2009). Regardless of interpretation, in view of the general lack of genotoxicity of methanol and the doses required to produce any carcinogenic response in rats by the oral route, it is very unlikely that methanol would pose a risk of carcinogenicity at the levels of exposure that would occur following its use as a previous cargo.

Developmental and reproductive toxicity

Maternal occupational exposure to methanol was not associated with any increase in the occurrence of cleft lip and palate (Lorente et al., 2000). In rodents, very high doses of methanol (generally > 2 g/kg

b.w. per day) are associated with a range of teratogenic effects when administered by inhalation or orally (US EPA, 2011). There is evidence that the metabolite formaldehyde is responsible for these effects, particular neural tube defects, in fetuses. In a study in *Cynomolgus* monkeys, exposure to methanol vapour at concentrations equivalent to doses of up to 96 mg/kg b.w. per day had no effect on the health of the offspring (Burbacher et al., 2004).

3.12.2.4. Allergenicity

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

3.12.3. Conclusion

Despite the fact that there is no ADI or TDI established for this substance, the CONTAM Panel considered that methanol does not pose any toxicological concern when used as a previous cargo. Methanol is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any toxicologically relevant impurities anticipated. The Panel also noted that methanol will be readily removed by tank cleaning.

Therefore, the CONTAM Panel concludes that methanol meets the criteria for acceptability as a previous cargo.

3.13. ETHANOL (ethyl alcohol) (CAS No 64-17-5)

Ethanol (Molecular weight 46.07) is a clear, colourless, flammable liquid, with a boiling point of 78.5 °C, a flash point of 13 °C (closed cup), miscible with water and many organic solvents and acids. The CAS number 64-17-5 refers to undenatured ethanol.

Several kind of liquids can be traded under the description “Ethanol” or similar ones: 95 % alcohol or alcohol alone is used to identify a ca 95 % solution in water (boiling point 78.15 °C), while absolute alcohol indicates 100 % ethanol. Denatured ethanol/alcohol (CAS No 9003-99-0) refers to ethyl alcohol to which certain substances had been added soon after its production (for distillery alcohol, at the distillery), in order to make it unsuitable for human consumption.

The present opinion refers only to undenatured ethanol (CAS No 64-17-5), which is the product that is shipped as “ethanol” (FOSFA, 2011, see Documentation provided to EFSA).

Ethanol is obtained by fermentation of carbohydrates, simple sugars or starch, previously hydrolyzed to glucose. Chemical synthesis is also carried out from ethylene, acetylene and methane. Ethylene can be hydrated to form ethanol both directly by using phosphoric acid as catalyst and by means of ethyl bisulphate as intermediate.

Ethanol is produced by fermentation of sugars, followed by distillation. The so-called “absolute ethanol” is produced by making it anhydrous by means of molecular sieves (zeolytes) that reduce water content to 0.1 %.

Ethanol is used in the food industry as a base for alcoholic beverages as well as a carrier for colourants, flavourings and preservatives, and it is used as a preservative itself, both as a covering liquid and sprayed on to the surface (e.g. white bread slices).

Ethanol is used as chemical intermediate or solvent in the industry of plastics, resins, dyes, and in pharmaceutical industry as antiseptic, cosmetic as lotions, perfumery etc.

3.13.1. Previous evaluations

The SCF evaluated ethanol in 1996 and considered this substance as acceptable previous cargo (SCF, 1997), noting that ethanol had previously been considered as an extraction and carrier solvent for food (SCF, 1992). The SCF also noted that in view of the large amount of toxicological data available it was not necessary to establish an ADI or to set residue limits for ethanol in food. In the 2003 SCF evaluation of acceptable previous cargoes, ethanol was not further evaluated as it was already considered acceptable (SCF, 2003).

Ethanol was considered by JECFA in 1970 as an extraction solvent. The Committee concluded that the use of this solvent should be restricted to that determined by Good Manufacturing Practice (JECFA, 1970).

Ethanol is included in the EU register of flavouring substances used in or on foodstuffs.¹⁹

Ethanol has been evaluated under the OECD SIDS programme on HPV chemicals (OECD, 2004). OECD concluded that ethanol was currently of low priority for further work.

3.13.2. Current evaluation

3.13.2.1. Expected impurities

Raw ethanol obtained by fermentation can be accompanied by limited concentrations of alcoholic fermentation byproducts such as glycerol, methanol and acetic acid. Because of its capability to form an azeotrope, water can be present.

According to Commission Regulation 110/2008,²⁵ for ethanol for food industry, admitted impurities and related limits are as follows: Organic acids ($\leq 1,5$ as grams of acetic acid/100 L ethanol), esters ($\leq 1,3$ as grams of ethyl acetate/100 L ethanol), aldehydes (≤ 0.5 as grams of acetaldehyde /100 L ethanol), alcohols with more than 3 carbon atoms (≤ 0.5 as grams of 2-methyl-1-propanol /100 L ethyl alcohol), methyl alcohol (≤ 30 g/100 L ethanol), nitrogen volatile basis (≤ 0.1 as grams of nitrogen/100 L ethanol).

3.13.2.2. Reactivity and reaction products

Ethanol readily interesterifies with fatty acids, but the resulting ethyl esters also exist normally in edible oils.

3.13.2.3. Toxicological profile

The CONTAM Panel noted that ethanol is an endogenous metabolite in the body, present in trace amounts in body tissues as a result of fermentation of carbohydrates in the diet by gastrointestinal organisms, particularly yeasts (Logan and Jones, 2000).

Absorption, distribution, metabolism and elimination

Ethanol is absorbed from the gastrointestinal tract following oral administration and metabolised via alcohol dehydrogenase in the liver to acetaldehyde, then to acetic acid and ultimately to carbon dioxide (OECD, 2004).

²⁵ Regulation (EC) No 110/2008 of the European Parliament and of the Council of 15 January 2008 on the definition, description, presentation, labelling and the protection of geographical indications of spirit drinks and repealing Council Regulation (EEC) No 1576/89. OJ L 39, 13.2.2008, p. 16-54.

Acute toxicity

Acute toxicity studies on ethanol have been carried out in rats, mice, rabbits, guinea pigs, cats and dogs. LD₅₀ values of 8,300 mg/kg b.w. in mice and 15,061 mg/kg b.w. in rats have been reported in the OECD SIDS evaluation document (OECD, 2004). In humans ethanol produces intoxication (drowsiness, ataxia, loss of concentration) and can be fatal in large doses.

Sub-acute, subchronic and chronic toxicity studies

As reported in the OECD SIDS evaluation document (OECD, 2004), NTP has carried out 90-day studies in rats with 5 % ethanol in drinking water, equivalent to doses of at least 4,000 mg/kg b.w. per day in rats and 7,500 mg/kg b.w. per day in mice (NTP, 1996b). Male rats showed minor changes to organ weights and haematology/biochemistry; female rats showed minor biochemistry changes and increased length of oestrus cycle along with liver nodules; male mice showed increased organ weights and some fatty changes to the liver and a decrease in sperm concentration (NTP, 1996b). The authors concluded that 5 % ethanol in drinking water was a NOAEL (NTP, 1996b). As reported by OECD, a NOAEL of 2,400 mg/kg b.w. was reported in another subchronic toxicity study with ethanol in rats (Holmberg, 1986).

Genotoxicity

As reported by OECD, negative results have been obtained for ethanol in a range of *in vitro* genotoxicity assays including bacterial mutagenicity tests and chromosome aberration studies, while in L5178Y mouse lymphoma cells a weak mutagenic effect was reported at high ethanol concentrations (OECD, 2004). Ethanol did not induce micronucleus formation *in vivo* in rats, and *in vivo* tests for chromosome aberrations in both rats and Chinese hamsters have similarly given negative results (OECD, 2004). Dominant lethal assays with ethanol have provided equivocal results, indicating that ethanol may have a very limited capacity to induce genetic changes *in vivo* at very high doses (Phillips and Jenkinson, 2001). Overall, however, the CONTAM Panel concluded that ethanol does not have genotoxic potential.

Chronic toxicity and carcinogenicity

In a 2-year study in mice, ethanol at levels of 2.5 % and 5 % in drinking water caused a slight increase in survival in males but had no effect on the survival of females. There was equivocal evidence of carcinogenicity in male mice based on increased incidences of liver tumours, but no evidence of carcinogenicity was seen in female mice exposed to either concentration (NTP, 2002). The International Agency for Research on Cancer (IARC) has concluded that there is inadequate evidence for the carcinogenicity of ethanol in experimental animals (IARC, 1988). In humans, there is considered to be a causal relationship between consumption of ethanol in alcoholic beverages and cancers of the oral cavity, pharynx, larynx and oesophagus (IARC, 1988). Ethanol is also a liver carcinogen in humans, tumours normally being associated with cirrhosis following chronic alcohol abuse in excess of 80 g ethanol per day (Greim, 1999).

Developmental and reproductive toxicity

Ethanol is a recognised developmental toxicant, and also adversely affects fertility (OECD, 2004). The developmental effects of ethanol have been widely studied both in humans and experimental models. In humans excessive alcohol consumption (greater than 5 units per day, although abnormalities have occurred in the offspring of women consuming as low as 2 units per day) during pregnancy causes foetal facial and skeletal malformations, brain damage, impairment in learning and reduction in body size, the so called Foetal Alcohol Syndrome (FAS). FAS causes a distinctive pattern of physical and behavioural anomalies in human fetuses characterized by craniofacial, limb, central nervous system, and cardiovascular effects, in addition to growth delay and mental retardation (Ahmed, 1995).

3.13.2.4. Allergenicity

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

3.13.3. Conclusion

An ADI “not specified” was established by JECFA because of the low toxicity of the substance. The CONTAM Panel concluded that there are no toxicological concerns when ethanol is used as a previous cargo. Ethanol is not genotoxic or allergenic. There are no reaction products of concern with edible fats and oils. There are no impurities that would be of toxicological concern at the levels occurring from ethanol as a previous cargo. The Panel also noted that ethanol will be readily removed by tank cleaning.

Therefore, the CONTAM Panel concludes that ethanol 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 substances (or groups of) 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 Section 2.2.).

In considering the issue of efficacy of cleaning between cargoes, the CONTAM Panel concluded that all of the substances evaluated could easily be removed by cleaning of the tank. Considering the issue of analytical methods of sufficient sensitivity to verify the presence of trace amounts of residues or the absence of contamination of oils and fats, with the exception of calcium lignosulphonate, the CONTAM Panel concluded that suitable analytical methods are available or are feasible for the substances evaluated.

The CONTAM Panel also noted that the majority of the substances evaluated in this opinion, with the exception of 1,4-butanediol and methanol, have been assigned acceptable daily intakes (ADIs) (or tolerable daily intakes (TDIs)) by the FAO/WHO Joint Expert Committee for Food Additives (JECFA), the Scientific Committee on Food (SCF) or the European Food Safety Authority (EFSA) and that in all cases these were greater than or equal to 0.1 mg/kg b.w. per day.

Evaluation of the substances (or groups of):

- *Phosphoric acid*: JECFA has established a group maximum TDI (MTDI) of 70 mg/kg b.w. for phosphates, including phosphoric acid, expressed as phosphorus, which the CONTAM Panel considers appropriate. Phosphoric acid is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils under normal conditions. Although some grades of phosphoric acid may contain impurities of potential concern, these are considered to be easily removed by cleaning and hence are not considered to be of concern when phosphoric acid is the previous cargo. Therefore, the CONTAM Panel concludes that phosphoric acid meets the criteria for acceptability as a previous cargo.
- *Ammonium polyphosphate*: Ammonium polyphosphate is hydrolysed in the stomach to phosphate, so many of the systemic effects of phosphoric acid would be relevant to ammonium polyphosphates. JECFA has established a group MTDI for phosphates, including ammonium polyphosphates, of 70 mg/kg b.w. expressed as phosphorus, which the CONTAM Panel considers appropriate. Phosphates, including ammonium polyphosphate, are not genotoxic or allergenic. No reactions products of concern with edible fats and oils are anticipated under normal conditions. No anticipated impurities are likely to be present at

levels of toxicological relevance when ammonium polyphosphate is used as a previous cargo. Therefore, the CONTAM Panel concludes that ammonium polyphosphate meets the criteria for acceptability as a previous cargo.

- *Benzyl alcohol (pharmaceutical and reagent grades only)*: SCF has established a group ADI of 0-5 mg/kg b.w. for benzyl alcohol and related substances, which the CONTAM Panel endorses. Benzyl alcohol does not pose any concern for genotoxicity or allergenicity. There are no reactions of concern with edible fats and oils. There are no impurities of concern. Therefore, the CONTAM Panel concludes that benzyl alcohol (pharmaceutical and reagent grades only) meets the criteria for acceptability as a previous cargo.
- *Calcium lignosulphonate*: Although gaps in the toxicological database were such that the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) was unable to establish an ADI for calcium lignosulphonate as a food additive, the CONTAM Panel considers that the available information was sufficient to conclude that the risk from short-term exposure to calcium lignosulphonate when used as a previous cargo would not give rise to any concern regarding its toxicity, genotoxicity or allergenicity. Tank cleaning would not present a problem. The CONTAM Panel noted however that the product varies markedly in quality and composition. There is no information on impurities in crude quality material (the form most in use), nor is there information on the reactivity of calcium lignosulphonate with fats and oils. The CONTAM Panel therefore concludes that calcium lignosulphonate does not meet the criteria for acceptability as a previous cargo.
- *Epoxidised soyabean oil (ESBO) (with a minimum 7 % - maximum 8 % oxirane oxygen content)*: The former EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food confirmed the TDI of 1 mg/kg b.w. for ESBO established as “temporary TDI” in 1997 because of the lack of data on genotoxicity and listed as “TDI” in 1999 by the SCF. The CONTAM Panel endorses this value. ESBO is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any toxicologically relevant impurities anticipated. Therefore, the CONTAM Panel concludes that ESBO (with a minimum 7 % - maximum 8 % oxirane oxygen content) meets the criteria for acceptability as a previous cargo.
- *Ethyl acetate*: JECFA established an ADI of 0-25 mg/kg b.w. for ethyl acetate, which the CONTAM Panel endorses. Ethyl acetate is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that ethyl acetate meets the criteria for acceptability as a previous cargo.
- *2-ethylhexanol*: SCF established an ADI of 0-0.5 mg/kg b.w. for 2-ethylhexanol, which the CONTAM Panel endorses. 2-Ethylhexanol is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that 2-ethylhexanol meets the criteria for acceptability as a previous cargo.
- *1,3-Butanediol*: JECFA established an ADI of 0-4 mg/kg b.w. for 1,3-butanediol, which the CONTAM Panel endorses. The limited evidence available suggests that 1,3-butanediol is unlikely to be genotoxic. It is not carcinogenic or developmentally toxic. 1,3-butanediol is not allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that 1,3-butanediol meets the criteria for acceptability as a previous cargo.
- *1,4-Butanediol*: Toxicological studies carried out either on the substance itself or on the toxicologically relevant metabolite γ -butyrolactone generally indicate a lack of organ-specific

toxicity and carcinogenicity. Although no ADI or TDI has been established for 1,4-butanediol, no-observed-adverse-effect levels (NOAELs) in the region of 200 mg/kg b.w. per day could be identified in 90-day studies in rats on the substance itself or on γ -butyrolactone. Application of an uncertainty factor of 100 or 1,000 to a NOAEL of 200 mg/kg b.w. per day would result in health based guidance values greater than 0.1 mg/kg b.w. per day, which meets one of the toxicological criteria. The evidence suggests that 1,4-butanediol is not genotoxic and it is not allergenic. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that 1,4-butanediol meets the criteria for acceptability as a previous cargo.

- *Propylene glycol*: JECFA established an ADI of 0-25 mg/kg b.w. for propylene glycol, which the CONTAM Panel endorses. Propylene glycol is not genotoxic. Its use as a previous cargo would not give rise to any concerns regarding possible irritancy or allergenicity. There are no reactions of concern with edible fats and oils, nor are any anticipated impurities likely to be present at levels of toxicological relevance. Therefore, the CONTAM Panel concludes that propylene glycol meets the criteria for acceptability as a previous cargo
- *Polypropylene glycol (PPG) (molecular weight greater than 400)*: The SCF established a TDI of 1.5 mg/kg b.w. for PPG, which was endorsed by the CONTAM Panel. There are limited toxicological data on PPG, in particular on chronic toxicity and reproductive toxicity. The CONTAM Panel considered however that information on these endpoints could be read across from the monomer propylene glycol. PPG is considered not to be genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are there any toxicologically relevant impurities. Therefore, the CONTAM Panel concludes that PPG (molecular weight greater than 400) meets the criteria for acceptability as a previous cargo.
- *Methanol*: Despite the fact that there is no ADI or TDI established for this substance, the CONTAM Panel considered that methanol does not pose any toxicological concern when used as a previous cargo. Methanol is not genotoxic or allergenic. There are no reactions of concern with edible fats and oils, nor are any toxicologically relevant impurities anticipated. Therefore, the CONTAM Panel concludes that methanol meets the criteria for acceptability as a previous cargo.
- *Ethanol*: An ADI “not specified” was established by JECFA because of the low toxicity of the substance. The CONTAM Panel concluded that there are no toxicological concerns when ethanol is used as a previous cargo. Ethanol is not genotoxic or allergenic. There are no reaction products of concern with edible fats and oils. There are no impurities that would be of toxicological concern at the levels occurring from ethanol as a previous cargo. Therefore, the CONTAM Panel concludes that ethanol meets the criteria for acceptability as a previous cargo.

DOCUMENTATION PROVIDED TO EFSA

1. FOSFA International. Clarification on a number of substances and entities in the Annex of Commission Directive Annex to Commission Directive 96/3/EC.⁵ Submitted to EFSA through EC on 29 September 2011.

Information relating to some substances on the FOSFA list of acceptable previous cargoes

Ammonium polyphosphate – CAS No 68333-79-9 / 10124-31-9

This substance is carried as a liquid. Oils and fats are carried in ships' tanks of between 500 - 6 000 tonnes, and thus they must be pumpable (viscosity between 1 – 70 mPas) so that they can

be loaded or discharged at about 150 – 300 tonnes per hour. Thus, pastes are not carried as previous cargoes.

Ethanol (ethyl alcohol) – CAS No 64-17-5

The ethanol listed in the FOSFA List of Acceptable Previous Cargoes is undenatured ethanol. Denatured ethanol within the shipping fraternity, and within FOSFA, is considered as a blend of ethanol and the denaturing substance, and is not FOSFA acceptable and not carried under the term "ethanol".

As stated, the ethanol indicated in the list refers to undenatured ethanol and covers both 96 % ethanol and absolute ethanol. However, the industrial-grade 96 % vol ethanol (also called REN or Sekunda-grade) contains about 4 % water. A typical analysis is given in the following table.

Test	Result
Ethanol strength	min 96 % vol
Water content	max 4 % vol
Methanol	max 50 mg/kg
Higher alcohols	max 100 mg/kg
Acetone	max 50 mg/kg
Methylethylketone	max 10 mg/kg
Aldehydes (acetaldehyde)	max 100 mg/kg
Diethylether	max 10 mg/kg
Esters (ethylacetate)	max 50 mg/kg
Acidity (acetic acid)	max 20 mg/kg
SO ₄ , NO ₃	max 0.4 mg/l

The specific type of ethanol (industrial grade or absolute) is generally stated in the ships' documentation but the difference is not distinguished within the FOSFA list.

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ABBREVIATIONS

ADI	Acceptable daily intake
AFC Panel	Former EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food
ANS Panel	EFSA Scientific Panel on Food Additives and Nutrient Sources added to Food
ATSRD	US Agency for Toxic Substances and Disease Registry
BIBRA	British Industrial Biological Research Association
b.w.	Body weight
CAC	Codex Alimentarius Commission
CCFO	Codex Committee for Fats and Oils
CNS	Central nervous system
CONTAM Panel	EFSA Scientific Panel on Contaminants in the Food Chain
EC	European Commission
ECHA	European Chemicals Agency,
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESBO	Epoxidized soyabean oil
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FAS	Foetal Alcohol Syndrome
FDA	Food and Drug Administration
FCM	Food Contact Material
FOSFA	Federation of Oils, Seeds and Fats Associations
GD	Gestational day
GI	Gastrointestinal
HPV	High Production Volume
IARC	International agency for research on cancer
IPCS	International Program on Chemical Safety
IRIS	Integrated Risk Information System
IUCLID	International Uniform Chemical Information Database
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD ₅₀	Lethal dose – the dose required to kill half the members of a tested animal population
LOAEL	Lowest-observed-adverse-effect level
MSDI	Maximised Survey-derived Daily Intake
MTBE	Methyl tertiary butyl ether
MTDI	Maximum tolerable daily intake
NOAEL	No-observed-adverse-effect levels
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PEG	Polyethylene glycol
PPG	Polypropylene glycol
PVC	Polyvinyl chloride
SCF	Scientific Committee on Food
SIDS	Screening Information Dataset
SML	Specific Migration Limit
TDI	Tolerable daily intake
THF	Formyl-tetrahydrofolic acid
US-EPA	United States Environmental Protection Agency
WHO	World Health Organization