

Evaluation of certain contaminants in food

Ninetieth report of the Joint
FAO/WHO Expert Committee on
Food Additives



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List of abbreviations

ADI	acceptable daily intake
bw	body weight
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCCF	Codex Committee on Contaminants in Foods
CCFO	Codex Committee on Fats and Oils
CIFOCoss	Chronic Individual Food Consumption Database – Summary statistics
CHO	Chinese hamster ovary
CONTAM	European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain
CPSC	Consumer Product Safety Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
ELSO	epoxidized linseed oil
EPA	(United States) Environmental Protection Agency
ESBO	epoxidized soybean oil
ETBE	ethyl tertiary butyl ether
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GC-FID	gas chromatography with flame ionization detection
GC-MS	gas chromatography–mass spectrometry
FCID	Food Commodity Intake Database (US Environmental Protection Agency)
GEMS/Food	Global Environment Monitoring System, Food Contamination Monitoring and Assessment Programme
HBGV	health-based guidance value
IMO	International Maritime Organization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LC-GC-FID	on-line coupled liquid chromatography-gas chromatography-flame ionization detection
LC-HRMS	liquid chromatography-high resolution mass spectrometry
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD ₅₀	median lethal dose
MTBE	methyl tertiary butyl ether
MOAH	mineral oil aromatic hydrocarbons
MOE	margin of exposure
MOH	mineral oil hydrocarbons
MOSH	mineral oil saturated hydrocarbons

MTDI	maximum tolerable daily intake
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PBTK	physiologically based toxicokinetic
PCB	polychlorinated biphenyl
QSAR	quantitative structure-activity relationship
RP	reference point
SCF	EU Scientific Committee on Food
SIDS	Screening Information Dataset
TBA	tertiary butyl alcohol
TDI	tolerable daily intake
TRS	Technical Report Series
UL	upper intake level
USA	United States of America
WHO	World Health Organization



1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) met by video-conference from 26 October – 6 November 2020. The meeting was opened on behalf of the Director-General of the World Health Organization (WHO) by Dr Francesco Branca and on behalf of the Director-General of the Food and Agriculture Organization of the United Nations (FAO) by Dr Markus Lipp. Dr Branca preceded his opening remarks by welcoming all meeting participants, especially during the COVID-19 pandemic. Dr Branca highlighted the roles and responsibilities of the Committee in the framework of the international food safety standard development work of the Codex Alimentarius Commission (CAC). He reminded the JECFA experts about their responsibility to impart the most unbiased and best scientific advice possible. Dr Lipp emphasized that participants had been invited not as representatives of their employer or country, but to serve solely in their capacity as scientific experts to provide sound and independent scientific advice to generate food standards designed to be protective of health for all consumers and trade in all regions and countries. He finished by urging the attendees to be as open and transparent as possible and emphasizing that scientific excellence requires input from all and the courage to ask critical questions.

1.1 Procedural matters

The ninetieth meeting of JECFA was originally scheduled to be held from 27 October – 5 November 2020 at WHO headquarters in Geneva, Switzerland. Owing to the travel restrictions and lockdowns due to the COVID-19 pandemic in many countries, it was not possible to convene the meeting as scheduled and it was decided to hold the meeting online by video-conferencing. In view of the time differences in the countries of origin of the invited experts, the only possible time for a video-conference was restricted to a 4-hour time slot (12:00–16:00 CET) each day. This allowed only 40% of the usual daily length (8–10 hours) of a JECFA meeting, precluding complete evaluation of all the scheduled compounds. In an effort to regain some additional meeting time, the ninetieth JECFA meeting was extended by 3 days, adding Monday 26 October, Friday 6 November 2020 and Tuesday 24 November 2020.

Although the experts participated fully, they noted that an online meeting does not permit the necessary in-depth, robust scientific discussions and that online meetings are therefore not a suitable substitute for face-to-face meetings for JECFA. In particular, the experts felt that the online format did not foster the atmosphere of trust, inclusiveness and openness that has marked all JECFA meetings. The experts considered that the success of the ninetieth meeting was

due to a large extent to the cohesion between them, which resulted from the trust generated during previous face-to-face meetings.

The experts decried the significant difficulty of meeting informally outside the scheduled meeting times because of the widely differing time zones. They noted that such informal interactions during physical meetings are instrumental to solving problems and to discussing issues in depth, bilaterally or in small groups, and added that such informal meetings often gave rise to solutions to stubborn problems. The inability to hold such meetings was considered to have impeded progress at the current meeting, as lack of sufficient time for discussion had slowed progress in developing safety evaluations.

The experts emphasized further that an invitation to a physical JECFA meeting at FAO or WHO headquarters gives rise to significantly more recognition by the expert's employer of the weight, reach, responsibility and workload required for full participation. The same degree of recognition was not granted by employers for this online meeting, as the experts remained available locally. This lack of recognition of the workload and significance of participation in a JECFA meeting led to an increase in other demands on experts, resulting in distraction and more frequent scheduling conflicts. The experts concluded that, cumulatively, such factors would be counterproductive for participation in future JECFA meetings if FAO and WHO maintained the online-only format.

In recognition of the difficulties and the tremendous effort made, the Joint FAO/WHO Secretariat expresses its deep gratitude to all the experts for their commitment and flexibility, not least as the scheduled meeting times were exceedingly inconvenient for many.

The meeting report was adopted on 24 November 2020.

1.2 Declarations of interests

The Secretariat informed the Committee that all experts participating in the ninetieth JECFA meeting had completed a declaration of interest form. The declarations were assessed as to the extent to which any interest could be reasonably expected to influence the experts' judgement. The declared interests were considered unlikely to impair the individual's objectivity or have any significant influence on the impartiality, neutrality and integrity of the work. Neither FAO nor WHO received any public comments in response to the online posting of the names and brief biographies of the individuals considered for participation in the expert meeting. The interests of all participants were disclosed at the beginning of the meeting to all attendees.

1.3 Adoption of the agenda

Owing to the shortage of time, monographs on the following group of compounds were not considered at the ninetieth meeting: previous cargoes: solvents and reactants, and the toxicological evaluation of trichothecenes (T2 and HT2). These substances will be rescheduled for evaluation at a future meeting.



2. General consideration

2.1 Dietary exposure assessment for previous cargo chemical substances

As a consequence of considering a range of previous cargo chemical substances at its ninetieth meeting, the Committee concluded that it was appropriate to review the approach to estimating dietary exposure set out in the 2006 document *Development of criteria for acceptable previous cargoes for fats and oils* (criteria document) (1).

The Committee noted that since the 2006 criteria document was drafted, newer and better-quality data on the consumption of fats and oils by adults, infants and young children have become available.

The Committee also noted that some of the previous cargo chemical substances assessed have additional sources of dietary exposure and expressed the view that it may be necessary to consider this in the exposure assessment.

2.2 Exposure estimates in the 2006 criteria document

Based on the best available data at that time, the 2006 criteria document set out the following approach to dietary exposure assessment of previous cargo chemical substances present in fats and oils:

- Estimated mean per capita consumption of 0.025 kg/day of a single type of fat or oil. The value was rounded up from the maximum per capita consumption of refined soybean oil of 22 g/person per day from the GEMS/Food cluster diets.
- A factor of 2.5 to cover children and high consumers was derived from a rounded ratio between the mean and 97.5th percentile consumption of total vegetable oil from a food consumption survey in the United Kingdom (20 and 52 g/person per day for the population aged > 18 years). The criteria document also noted that dietary exposure of children to contaminants is frequently 2.5 times that of adults.
- A worst-case concentration of 100 mg/kg for a previous cargo contaminant in fats or oils.
- A body weight of 60 kg.

These data were used to define a worst-case dietary exposure estimate:

$$\frac{\text{Consumption of oil (0.025 kg/day)} \times 2.5 \times \text{concentration (100 mg/kg fat or oil)}}{60 \text{ kg body weight}}$$

= 0.1 mg/kg bw per day

Based on the **mean per capita consumption of fats and oils, and a factor of 2.5**, there would be no health concern to the general population from exposure to previous cargoes if the acceptable daily intake (ADI) or tolerable daily intake (TDI) is sufficiently protective, for example, the ADI or TDI is greater than, or equal to **0.1 mg/kg bw per day**.

2.3 Exposure estimates based on up-to-date consumption data for adults

Since 2006, the GEMS/Food cluster diets have been revised, and the FAO/WHO Chronic Individual Food Consumption – summary statistics database (CIFOcOss) has become available (2). The 2006 criteria document noted that food consumption information from dedicated surveys would be more appropriate than the food consumption estimates from the GEMS/Food cluster diets (3). However, it used the cluster diets, as food consumption survey data were only available from a very limited number of countries at that time. CIFOcOss currently contains food consumption data from 37 countries.

From the current version of CIFOcOss, the maximum mean consumption for a single fat or oil type is 35 g/person per day for consumption of virgin or extra-virgin olive oil by elderly Italians. The maximum 95th percentile (p95) consumption of a single fat or oil is 138 g/person per day for edible cottonseed oil by women (age 15–49 years) from Burkina Faso. This group also has the highest 97.5th percentile consumption of 189 g/person per day.

Based on the protocols currently used by JECFA for veterinary drugs, the number of consumers of cottonseed oil in the Burkina Faso survey (n = 116) would suggest that the 95th percentile is the highest reliable percentile (4, 5).

These data suggest that for adults, a mean fat or oil consumption of 35 g/person per day and a high consumption of fat or oil of 140 g/person per day would be a conservative estimate consistent with available data.

The use of updated food consumption data will result in a revised estimated worst-case dietary exposure for adults:

$$\frac{\text{p95 consumption of oil (0.140 kg/day)} \times \text{concentration (100 mg/kg fat or oil)}}{60 \text{ kg body weight}}$$

= 0.2 mg/kg bw per day

2.4 Exposure estimates for infants and young children

Potentially vulnerable population groups, like infants and young children, were not specifically considered in the 2006 criteria document. Since then, individual consumption data for several population groups, including infants and young children, have become available through CIFOcOss and other sources. Infants and young children should be considered in the risk assessment because they could potentially experience high exposure to previous cargo chemical substances per kg body weight during their growth and development.

Information on consumption of food oils by infants and young children was also available from the US Environmental Protection Agency's Food Commodity Intake Database (FCID) (6), which in turn is based on data from the US National Health and Nutrition Survey/What We Eat in America, 2005–2010 cycles. The highest oil consumption for infants and young children based on FCID is comparable to those in the CIFOcOss database; however, oil consumption information based on FCID takes into account individual body weights.

The highest reported consumption of a specific fat or oil type was for palm oil. Estimated mean and p95 consumption by infants and young children were 7.6 and 19 g/day, respectively. Estimated mean and p95 consumption on a body weight basis were 1 g/kg bw per day and 3 g/kg bw per day, respectively.

These data were used to define a worst-case dietary exposure estimate for infants and young children:

$$\text{p95 consumption of oil (0.003 kg/kg bw per day)} \times \text{concentration (100 mg/kg fat or oil)}$$

= 0.3 mg/kg bw per day

2.5 Exposure from other dietary sources

For some previous cargo chemical substances potentially present in food oils, there are additional sources of dietary exposure, such as contamination (for example, contaminated drinking-water) or food additive uses (Table 1). Dietary exposures from these different sources should be considered in exposure assessment.

Table 1

List of substances for evaluation by JECFA arising from the development of a list of acceptable previous cargoes by the Codex Committee on Fats and Oils: other sources of exposure

Substance (synonyms)	Other sources of exposure
1,4-Butanediol (1,4-butylene glycol)	Used in food contact material
Calcium ammonium nitrate solution	Calcium, nitrate and ammonium are ubiquitous in the human diet
Calcium lignosulfonate liquid (lignin liquor; sulfite lye), molecular weight not specified	Calcium lignosulfonate (40-65) is used as a food additive, an additive in animal feed and as an ingredient in pesticides
Calcium nitrate (CN-9) solution	Calcium and nitrate are ubiquitous in the human diet
<i>iso</i> Decyl alcohol (isodecanol)	None
Myristyl alcohol (1-tetradecanol; tetradecanol)	Flavouring agent, formulation agent, lubricant, release agent
<i>iso</i> Nonyl alcohol (isononanol)	None
<i>iso</i> Octyl alcohol (isooctanol)	Used in food contact material
Tridecyl alcohol (1-tridecanol)	Used in food contact material
Unfractionated fatty alcohol mixture or mixtures of fatty alcohols from natural oils and fats ^a	Occurs naturally in foods
Methyl tertiary butyl ether (MTBE)	Drinking-water
Mineral oil, medium and low viscosity, class II and III	Used in food contact material, direct food additive
Montan wax	Food additive
1,3-Propylene glycol	Used in place of 1,2-propanediol as a food additive
Propylene tetramer (tetrapropylene, dodecene)	None
Soybean oil epoxidized	Used in food contact material
Ethyl tertiary butyl ether (ETBE)	Drinking-water

^a Discussed with Group 2 – Alcohols.

2.6 Conclusion

The Committee concluded that, based on up-to-date data on consumption of single fats and oils in the general population, which have become available since 2006, the generic human exposure value of 0.1 mg/kg bw per day used in the 2006 criterion no. 2 to determine the acceptability of a previous cargo should be revised. Consequently, the updated, more conservative generic human exposure value of 0.3 mg/kg bw per day should be used in the evaluation of these substances.

The Committee noted that these estimates of dietary exposure were derived from a more conservative approach to using data on consumption of single fats and oils and a worst-case concentration of previous cargo chemicals in a single fat or oil of 100 mg/kg.

The Committee also concluded that additional sources of dietary exposure need to be considered in exposure assessment of previous cargo chemical substances.

2.7 Recommendations

The Committee recommended that the Codex Committee on Fats and Oils (CCFO) consider revising criterion no. 2 in RCP-36-1987 as adopted by CAC 34 (2011).

- 1) Based on the consumption of fats and oils by infants and young children, there is no health concern for the general population from dietary exposure to previous cargo chemical substances if the ADI or TDI is sufficiently protective, for example, the ADI or TDI is greater than, or equal to 0.3 mg/kg bw per day. Substances for which there is no numerical ADI or TDI should be evaluated on a case-by-case basis (e.g. margin of exposure (MOE) approach).
- 2) Where there are additional sources of dietary exposure to the previous cargo chemical substances, they should be considered in the exposure assessment.

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3. Assessment of substances proposed as previous cargoes

3.1 Introduction

Fats and oils destined to be used as food are transported and stored in large volumes. Transportation in large volumes by sea is exempted from many land-based regulations as it is not practical to have fleets of ships solely dedicated to the transportation of food in large tanks, since the trade is generally unidirectional from producer to consumer. Furthermore, the construction and dependency on the availability of a limited number of single-use carriers would make the transport of fats and oils extremely expensive. To address the economic realities, certain types of ships are permitted to carry different classes of cargo in their tanks on their outbound and onward journeys. A non-food item may be carried in a tank in one direction and a single type of fat or oil on the further voyage. Since ships are constructed to have several individual tanks, each may contain a cargo destined for a different location and may be used to carry either a food or non-food item depending on the contract.

A number of organizations have been involved in the development of codes of practice, transportation contracts, ship construction, cargo segregation, environmental issues and food safety. The Codex Alimentarius Commission (CAC) adopted and published a code of practice for the storage and transport of edible fats and oils in bulk, which was developed by CCFO in 1987 (1). At that time, CCFO recognized the need to assess the acceptability of previous cargoes transported in a tank subsequently used for the transportation of an edible fat or oil. Commercial trade contracts recognized the need to specify that certain chemicals should never be acceptable previous cargoes for subsequent cargoes of edible fats or oils. These substances formed the basis of the “banned lists” of previous cargoes. In 2001, a combined list of chemicals banned as previous cargoes was developed by CCFO and adopted by CAC (2); it was added to the Codex code of practice as Appendix 1. Other substances carried in bulk were considered to pose a low risk to public health as a contaminant in edible fats or oils; these formed the basis of “acceptable lists” of previous cargoes. The development of a CCFO acceptable list of previous cargoes was also based on trade experience. A preliminary list was reviewed by the Scientific Committee on Food and their findings were reported to CCFO in 1999; 14 substances were identified for which there were insufficient data to make a safety determination. After further discussion at subsequent CCFO meetings, a list of 23 potentially safe previous cargoes that require evaluation was developed. CCFO asked for scientific advice from FAO/WHO on these 23 substances that lacked safety evaluations. The present evaluation by JECFA addresses 18 of the

23 substances on the current list of chemicals considered acceptable as previous cargoes by CCFO.

3.2 Background

3.2.1 Global production and consumption of fats and oils

The global trade in edible fats and oils is more than 200 million metric tonnes annually and valued at approximately US\$ 120 billion (3). By far the largest contributors are palm (36%) and soybean oil (28%), followed by rapeseed/canola (14%), sunflower seed (10%), palm kernel (4%), peanut (3%), cottonseed (3%), coconut (2%) and olive oils (2%).

Many vegetable oils are produced in regions (for example: soybean – Argentina, Brazil, USA; rapeseed – Australia, Canada; sunflower seed – Ukraine; palm – Indonesia and Malaysia; and coconut – equatorial latitudes) far from the major sites of consumption. Olive oil is produced in regions with a Mediterranean climate in both the northern and southern hemispheres. International trade in fats and oils uses the most economical method of ocean transportation since global trade in edible fats and oils is primarily unidirectional. Soybean oil from Argentina and Brazil, for example, is shipped to both Asian and European markets, but there is unlikely to be a complementary cargo of fat or oil available for transportation in the reverse direction. Similarly, oils from tropical regions are traded globally, often without reciprocal trade in fats and oils.

3.2.2 Regulations affecting fats and oils

Shipment of fats and oils is described in numerous national and international regulations and agreements. Land-based transportation is regulated by local and national guidelines and/or legislation, whereas international trade is subject to commercial agreements, international shipping regulations and various codes of practice. The development of banned lists and acceptable lists of previous cargoes is founded on existing trade contracts.

About 85% of the fats and oils are traded globally using FOSFA (The Federation of Oils, Seeds and Fats Associations, London) contracts. The balance is traded under contracts issued by NIOP (National Institute of Oilseed Products) or other organizations. A contract under “banned list terms” requires that fats and oils are not shipped in tanks that have contained a substance on the banned list as the immediate previous cargo. For certain chemicals, this requirement is extended to the three previous cargoes. Alternatively, a contract may state that “the immediate previous cargo shall be a product on the FOSFA List of Acceptable Previous Cargoes”. In this case, the receiver will only accept the cargo if the previous cargo is on FOSFA’s acceptable list. These two lists only cover a small

proportion of the chemicals transported by sea; thus many substances appear on neither list and their acceptability as a previous cargo is subject to agreement by the contracting parties.

3.2.3 Global transport of fats and oils

Transportation by sea is regulated by the International Maritime Organization (IMO). The International Convention for the Prevention of Pollution from Ships (MARPOL) aims to prevent operational and accidental pollution from ships. MARPOL limits the carriage of different classes of liquid cargoes to specific tanker vessels based on ship construction and the class of chemical. Under this convention, fats and oils may not be transported in vessels designated to carry cargoes of crude oil, fuel oil, heavy diesel oil or lubricating oil. The International Code for the Construction and Equipment of Ships Carrying Dangerous Chemicals in Bulk (IBC Code) lists chemicals carried as bulk liquids, their pollution category, the type of ship design and any relevant restrictions or derogations. The previous cargoes under consideration (see [Table 2](#)) are in the medium- or low-risk categories for marine pollutants. The single exception is propylene tetramer, which is considered a high-risk marine pollutant. MARPOL also deals with tank washing and material discharge. Pentane falls into an additional category of oil-like substances requiring additional attention between cargoes.

3.2.4 The interrelationship of national, regional and trade interests

The practice of Acceptable List trading was discussed in line with regional initiatives to protect consumer health. The adoption of the hazard analysis and critical control point (HACCP) principles and their inclusion in the Codex Alimentarius approach to the safe trade of food and food products can be applied to the transport of oils and fats by sea. The CAC adopted the *Code of Practice for the Storage and Transport of Fats and Oils in Bulk* developed by CCFO in 1987 (CAC-RCP 36-1987) (1). The code has been revised periodically and a banned list of substances was added in 2001. The list of acceptable previous cargoes adopted by the European Union (EU) and based on existing trade lists, was evaluated by EFSA.

3.2.5 Development of the Codex Code of Practice for Storage and Transport of Edible Fats and Oils in Bulk

CCFO discussions highlighted the need for lists of banned and acceptable previous cargoes. The topic of contamination by previous cargoes led to the incorporation of the FOSFA and NIOP trade lists into the code by reference only. In 2001, CAC adopted the “Banned List” and it appears in the current code of practice as Appendix 3.

Table 2

List of substances submitted by CCFO for evaluation by JECFA for addition to the list of acceptable previous cargoes

Substance (synonyms)	CAS number	Assessment group ^a
Acetic anhydride (ethanoic anhydride)	108-24-7	1
1,4-Butanediol (1,4-butylene glycol)	110-63-4	2
Butyl acetate, <i>sec</i> -	105-46-4	1
Butyl acetate, <i>tert</i> -	540-88-5	1
Calcium ammonium nitrate solution	15245-12-2	4
Calcium lignosulfonate liquid (lignin liquor; sulfite lye)	8061-52-7	4
Calcium nitrate (CN-9) solution	35054-52-5	4
Cyclohexane	110-82-7	1
Fatty alcohols		
<i>iso</i> Decyl alcohol (isodecanol)	25339-17-7	2
Myristyl alcohol (1-tetradecanol, tetradecanol)	112-72-1	2
<i>iso</i> Nonyl alcohol (isononanol)	27458-94-2	2
<i>iso</i> Octyl alcohol (isooctanol)	26952-21-6	2
Tridecyl alcohol (1-tridecanol)	112-70-9	2
Unfractionated fatty alcohol mixture or mixtures of fatty alcohols from natural oils and fats ^b		3
Methyl tertiary butyl ether (MTBE)	1634-04-4	5
Mineral oil, medium and low viscosity, class II		3
Mineral oil, medium and low viscosity, class III		3
Montan wax	8002-53-7	3
Pentane	109-66-0	1
1,3-Propanediol (1,3-propylene glycol)	504-63-2	2
Propylene tetramer (tetrapropylene, dodecene)	6842-15-5	3
Soybean oil epoxidized	8013-07-08	3
Ethyl tertiary butyl ether (ETBE)	637-92-3	5

^a Group 1 was not considered at this meeting.

^b Discussed with Group 2 – alcohols.

The development of a List of Acceptable Previous Cargoes by CCFO began with attempts to harmonize the FOSFA and NIOP trade lists with an EU list. The Acceptable List was further refined in 1999 when CCFO considered a list of substances proposed by the EU that had been reviewed by the Scientific Committee on Food (SCF). Having developed a list of acceptable previous cargoes, it was determined that there were 14 substances on it that required further evaluation; these 14 substances formed the basis of the CCFO Proposed Draft List of Acceptable Previous Cargoes, which was adopted by CAC 34 in 2011. For consideration at this meeting a list of 23 substances was proposed to FAO/WHO (Table 2) by CCFO for scientific advice on their suitability as previous cargoes for the carriage of fats and oils by sea-going vessels upon its evaluation

against the four criteria. Each substance on the list has been assigned to Groups 1–5 (1 – solvents/reactants; 2 – alcohols; 3 – oils and waxes; 4 – solutions; 5 – butyl ethers). Substances in Group 1 were not evaluated at the present meeting.

3.3 Development of criteria

As a result of the CCFO request to FAO/WHO for scientific advice on the development of criteria for the assessment of the safety of residues of previous cargoes in the tanks of sea-going vessels carrying edible fats and oils, a technical meeting was convened (in November 2006) at the Dutch National Institute of Public Health and the Environment (RIVM). RIVM prepared a technical background document (Appendix II (4)) and drafted the meeting report with FAO/WHO (5).

Discussions were limited to the assessment of previous cargoes in the transport of edible fats and oils in bulk by sea and the consideration of safety implications in terms of human health. The experts accepted that the quality of the fats and oils cargo could change as a result of hydrolysis and oxidation, but they acknowledged that these changes were already taken into account in trade contracts.

The experts considered a list of parameters originating from discussions at CCFO meetings, noting that previous cargoes are generally liquid chemical substances, slurries of solid particles or aqueous solutions. To further frame the deliberations, the experts decided to consider only a generic worst-case scenario since developing criteria to cover every possible combination of previous cargo, type of tank, cleaning regime and possible further processing of the subsequent cargo of fat or oil would not be a realistic approach.

The experts developed the following worst-case scenario: the smallest commercially viable tank size (200 m³), coated with a polymer that absorbs the previous cargo, is filled to 60% capacity (as required by contract), and the cargo of fat or oil is not to be further processed or refined. The model also assumed that the tank and associated pipework has been cleaned according to defined standards, inspected and considered clean and dry. Under these circumstances, the maximum level of contamination in the subsequent fat or oil cargo by the previous cargo was calculated to be 100 mg/kg. This value was used to determine a single estimate of worst-case human exposure of 0.1 mg/kg bw per day. Based on this generic exposure value, the experts considered that for the evaluation of previous cargoes, the ADI (or TDI) should be greater than or equal to 0.1 mg/kg bw in order to provide sufficient protection for children and high-intake consumers. Negligent or fraudulent practices were not considered to be part

Table 3

Criteria adopted by CAC 34 and included in RCP-36-1987

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 bw per day. Substances for which there is no numerical ADI (or TDI) should be evaluated on a case-by-case basis.
3.	The substance should not be or contain a known food allergen, unless the identified food allergen can be adequately removed by subsequent processing of the fat or oil for its intended use.
4.	Most substances do not react with edible fats and oils under normal shipping and storage conditions. However, if the substance does react with edible fats and oils, any known reaction products must comply with criteria 2 and 3.

of the criteria. The experts identified four criteria necessary to determine the acceptability of a previous cargo (see (4)).

The criteria as adopted by CAC 34 (2011) are listed in [Table 3](#).

3.4 Basis of evaluation

3.4.1 Chemistry/reactivity

Edible fats and oils are normally chemically stable; however, there may be potential for reactions with residues of previous cargoes that could give rise to products that are hazardous to human health. Consideration should be given to chemical substances that can react with edible fats and oils under normal transportation conditions. Minor oxidation and hydrolysis are normally anticipated in trade contracts and are not considered a consequence of contact with a previous cargo, unless accelerated degradation occurs. Although many possible reactions require the presence of specific catalysts or temperatures well in excess of those anticipated during transportation, potential reactions of the previous cargo with triglycerides and free fatty acids or other minor components present in the fat or oil should still be considered.

3.4.2 Methods of analysis

In a few cases where contamination is considered critical there has been an international effort to develop specific analytical methods. Cases of contamination with diesel fuel (alkanes) and mineral oils (mineral oil saturated hydrocarbons, MOSH; mineral oil aromatic hydrocarbons, MOAH) led to the development of relevant international standards. Although many of the substances under review at the present meeting can be analysed by gas or liquid chromatography using appropriate detector systems, little progress has been made in the application

of these technologies to their contamination of oils and fats. It is assumed that available methods with suitable modifications will be capable of determining the maximum anticipated level of 100 mg/kg of previous cargo in the subsequent cargo of fats or oils.

3.4.3 Occurrence and exposure

For information on occurrence and exposure see [section 2](#) (General consideration).

3.4.4 Approach to toxicological evaluation

The Committee received no submitted data and, therefore, reviewed monographs from previous evaluations of individual substances conducted by JECFA, WHO, International Agency for Research on Cancer (IARC), and national and regional governmental authorities to retrieve additional relevant references for completing the present assessment. The Committee also conducted literature searches. The details are included in the consideration of individual substances.

At its present meeting, the Committee revised the generic value for assumed worst-case human dietary exposure from 0.1 to 0.3 mg/kg bw per day and used this revised generic exposure value for the evaluation of previous cargoes. The Committee also considered data on exposure to the substances from sources other than previous cargoes. Thus, the ADI (or TDI) should be greater than or equal to the estimated dietary exposure (0.3 mg/kg bw per day plus exposure from other possible dietary sources) in order to provide sufficient protection for infants, children and high-intake consumers. In situations where no appropriate numerical ADI (or TDI) was available from JECFA, the Committee considered other previously established health-based guidance values or calculated a margin of exposure (MOE) based on a reference point characterizing the toxicological hazard (such as a no-observed-adverse-effect level (NOAEL), etc.) identified from the available data divided by the estimated dietary exposure. Interpretation of this MOE is a matter of expert judgement that takes into account limitations in the available toxicological database.

References

1. CAC-RCP 36-1987: Code of Practice for the Storage and Transport of Edible Fats and Oils in Bulk (Rev. 2015) (http://www.fao.org/fao-who-coexalimentarius/codex-texts/codes-of-practice/en/CXP_036e_2015%20.pdf, accessed 5 November 2020).
2. Codex Alimentarius: CCFO and CAC Reports (<http://www.fao.org/fao-who-codexalimentarius/meetings/archives/pt/>, accessed 5 November 2020).

3. World vegetable oils supply and distribution, 2012/13-2018/19 [Online]. Washington (DC): United States Department of Agriculture; 2019 (<https://www.ers.usda.gov/data-products/oil-crops-yearbook/>, accessed 5 November 2020).
4. Development of criteria for acceptable previous cargoes for fats and oils. Report of a Joint FAO/WHO Technical Meeting, Bilthoven, Netherlands, 7–9 November 2006.
5. Development of criteria for acceptable previous cargoes for fats and oils. Rome: FAO/WHO in collaboration with the National Institute for Public Health and the Environment; 2007 (<http://www.fao.org/3/a-a1090e.pdf>, accessed 5 November 2020).

3.5 Evaluation of substances

3.5.1 Alcohols (Group 2)

3.5.1.1 Tridecyl alcohol, myristyl alcohol and unfractionated fatty alcohols

Explanation

Tridecyl and myristyl alcohol were considered acceptable previous cargoes by the EU Scientific Committee on Food (SCF) (1, 2).

The primary linear and saturated fatty alcohols C4 to C24 as well as oleyl alcohol have been evaluated by the SCF as substances intended for use in materials in contact with food and are listed without a specific migration limit in Commission Regulation 10/2011. Butyl, caproyl, capryl, nonyl, decyl, lauryl, tridecyl, myristyl, cetyl, stearyl and oleyl alcohols were all placed in the list (List 3) of substances for which an ADI or a TDI could not be established but where the present use could be accepted (3).

Tridecyl alcohol (CAS number 27458-92-0 corresponding to 11-methyldodecan-1-ol) and myristyl alcohol (CAS 112-72-1) were included in the list of acceptable previous cargoes in European Commission Directive 96/3/EC of 26 January 1996 (4).

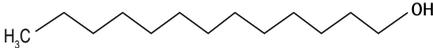
In 2009, the EFSA Panel on Contaminants in the Food Chain (CONTAM) concluded that unfractionated fatty alcohol mixtures, or mixtures of fatty alcohols from natural oils and fats, would not cause any health concern as previous cargoes, provided their sources are edible types of oils and fats (5).

Tridecyl and myristyl alcohol were evaluated by the EFSA CONTAM Panel in 2012 and considered acceptable as previous cargoes for edible fats and oils (6).

For the current review, previous assessments by SCF, EFSA and the European Chemicals Agency (ECHA) were considered. A search by CAS number and name synonyms for additional toxicological studies in animals in humans was undertaken to identify any critical new data for the assessment of human health risk. Searches of PubMed, PubChem and Embase were conducted. The cut-off date for inclusion in this report was 25 October 2020.

Table 4

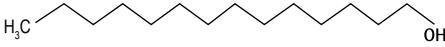
Chemical and technical considerations for tridecyl alcohol

Name: tridecyl alcohol (1-tridecanol)	
CAS number	Alternative CAS numbers
112-70-9	26248-42-0 (tridecanol); 80206-82-2 (alcohols C12–14)
Chemical details	Tridecyl alcohol; 1-tridecanol White, low melting point solid
	
	Molar mass: 200.37 g/mol Melting point: 32 °C Boiling point: 274 °C
Route(s) of synthesis	Insoluble in water; soluble in ether, hexanes and other organic solvents Manufactured by different processes: by the oxo process in which propylene tetramer is reacted with carbon monoxide and hydrogen using a catalyst, followed by hydrogenation; by a second type of oxo process using C15 hydrocarbons; or by a modified oxo process in which C11–C14 linear olefins are reacted with hydrogen and carbon monoxide over a modified cobalt catalyst
Composition	Occurs as a mixture of mainly <i>n</i> -alcohols with minor amounts of iso-alcohols such as 2-tridecanol, 3-tridecanol, 4-tridecanol, 5-tridecanol, 6-tridecanol and isotridecanol
Uses	Used as a processing aid in polyvinyl chloride resin production; as a lubricant and as an ingredient in the manufacture of surfactants and plasticizers
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils may require saponification, extraction and derivatization followed by GC-FID or GC-MS
Potential reaction(s) with a subsequent cargo of fat or oil	Transesterification with glycerides or esterification with free fatty acids present in the cargo may occur, but are likely to be slow at ambient temperature

GC-FID, gas chromatography with flame ionization detection; GC-MS, gas chromatography–mass spectrometry.

Table 5

Chemical and technical considerations for myristyl alcohol

Name: myristyl alcohol (1-tetradecanol)	
CAS number	Alternative CAS numbers
112-72-1	67762-30-5 (alcohols C14–18); 67762-41-8 (alcohols C10–16); 68002-95-9 (alcohols C14–22 and C16–22-unsaturated); 68333-80-2 (alcohols, C14–16); 68855-56-1 (alcohols C12–16); 71750-71-5 (alcohols C>14); 75782-87-5 (alcohols C14–15); 6338-82-8 (alcohols C12–15); 63393-82-8 (alcohols C12–15)
Chemical details	Myristyl alcohol; 1-tetradecanol White, low melting point solid
	
	Molar mass: 214.39 g/mol Melting point: 38 °C Boiling point: 290 °C
	Insoluble in water; soluble in diethyl ether; slightly soluble in ethanol

Route(s) of synthesis	Manufactured by different processes: sodium reduction of fatty acid esters; lithium aluminium hydride reduction of fatty acids; and from acetaldehyde plus dimethylamine. May also be produced from ethylene in the presence of aluminium and hydrogen, and is coproduced with <i>n</i> -hexanol, <i>n</i> -octanol, <i>n</i> -decanol, <i>n</i> -alkanol (C8–C10) and lauryl alcohol (C12). Fractionation also gives “narrow-cuts” such as <i>n</i> -alkanol (C12–C14), cetyl alcohol or stearyl alcohol; or “broad-cuts” such as <i>n</i> -alkanol (C12–C18), cetyl stearyl alcohol or <i>n</i> -alkanol (C20+).
Composition	Occurs as a mixture and may contain by-products such as isoocetyl and isononyl alcohols, trimethyl-1-heptanols, and dimethyl-1-octanols depending on the olefin feedstock.
Uses	Used as a flavouring agent, release agent, lubricant, food contact material, perfume fixative for soaps and cosmetics and in many personal care items. Also used in specialty cleaning products, as an anti-foam agent and in some plastics.
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils may require saponification, extraction and derivatization followed by GC-FID or GC-MS.
Potential reaction(s) with a subsequent cargo of fat or oil	Transesterification with glycerides or esterification with free fatty acids present in the cargo may occur but are likely to be slow at ambient temperature.

GC-FID, gas chromatography with flame ionization detection; GC-MS, gas chromatography–mass spectrometry.

Table 6

Chemical and technical considerations for unfractionated fatty alcohol mixtures of fatty alcohols from natural oils and fats (herein referred to as unfractionated fatty alcohols)

Name: unfractionated fatty alcohols	
CAS number	Alternative CAS numbers
None	None
Chemical details	Mixture of fatty alcohols derived from triglycerides by saponification and reduction of the fatty acids
Route(s) of synthesis	Manufactured from natural oils and fats by either saponification and reduction of the fatty acids released or by direct reduction of fatty acids recovered from deodorizer distillates. Other manufacturing processes involve sodium reduction with cyclohexanol, hydrogenolysis or methanolysis plus hydrogenation.
Composition	Occurs as a mixture of fatty alcohols representative of the oil and/or fat used as feedstock. Chain lengths may range from C4 to C20. The fatty alcohols may be saturated or retain unsaturation depending on the method of manufacture.
Uses	Used as plasticizers (shorter chains); in surfactants, detergents and cosmetic formulations (longer chains)
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils may require saponification, extraction and derivatization followed by GC-FID or GC-MS.
Potential reaction(s) with a subsequent cargo of fat or oil	Transesterification with glycerides or esterification with free fatty acids present in the cargo may occur but are likely to be slow at ambient temperature.

GC-FID, gas chromatography with flame ionization detection; GC-MS, gas chromatography–mass spectrometry.

Chemical and technical considerations

Chemical and technical considerations for tridecyl alcohol, myristyl alcohol and unfractionated fatty alcohols are summarized in [Tables 4, 5 and 6](#).

Assessment

Biochemical aspects

There is no specific information on absorption, metabolism, distribution and excretion of tridecyl alcohol, myristyl alcohols and unfractionated alcohols. Based on data on primary aliphatic alcohols (C6–C22), they are expected to be absorbed by all common routes of exposure. They are metabolized in mammals by alcohol dehydrogenase and the aldehyde formed is further oxidized to carboxylic acid that undergoes mitochondrial β -oxidation. Absorbed aliphatic alcohols could potentially be widely distributed within the body. However, as a result of the rapid metabolism, it is anticipated that aliphatic alcohols would be rapidly removed from the body (7).

Toxicological studies

There are no new data in the literature regarding the toxicological properties of tridecyl and myristyl alcohol since the 2012 EFSA evaluation. For unfractionated fatty alcohols, there are no specific toxicological data available on these mixtures of substances. Most of the toxicological evaluation was therefore based on the long chain alcohols category (C6–C22 primary aliphatic alcohols) as proposed by the Organisation for Economic Co-operation and Development (OECD) in 2006 (7). Some of the studies are described in detail on the ECHA website and in the previous OECD Screening Information Dataset (SIDS) report (8).

Tridecyl alcohol has very low acute oral toxicity with a reported oral LD₅₀ in rats of 17 200 mg/kg bw.¹ Myristyl alcohol is of very low acute oral toxicity with a median lethal dose (LD₅₀) exceeding 5000 mg/kg bw (9).

No repeated-dose study was available for tridecyl alcohol. Rhodes et al. (10) administered branched tridecyl alcohol by gavage for 14 days to five male Alderley Park Wistar-derived rats (single dose level of 184 mg/kg bw per day). The Committee noted that this experiment has major limitations for the purposes of risk assessment (small group size, single species, single dose level, single sex and limited duration). No changes were reported in body, liver or testicular weight relative to controls and peroxisome proliferation and hypolipidaemia were not observed (10). No major pathological features of hepatotoxicity were noted. Mild liver histological changes were reported: slight centrilobular hypertrophy, slight/moderate glycogen vacuolation and slight/moderate centrilobular lipid vacuolation. The Committee did not consider these changes to be adverse.

No repeated-dose study was available for myristyl alcohol. In a 90-day study in Wistar rats (11 males and females per group), C14–16-branched and linear alcohol was administered via the diet at 0%, 0.2%, 1% and 5% (equal to 0,

¹ <https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID2021947#toxicity-values>, accessed 5 November 2020.

171, 759 and 3626 mg/kg bw per day in males and 0, 167, 736 and 3491 mg/kg bw per day in female rats). No effects were observed at the dose of 167 mg/kg bw per day and reduced body weight gain was reported at the two higher doses. This reduction in growth was accompanied by a reduction of food and water intake, and was reported to be probably due to decreased food consumption related to unpalatability of the diet (Ito et al. (11) described in (8)). The Committee concluded that 167 mg/kg bw per day is a NOEL for myristyl alcohol.

No data were identified on the repeated-dose toxicity of unfractionated fatty alcohols. The saturated linear alcohols C4, C6, C8, C10, C12, C14, C16 and C18, as well as oleyl alcohol are, or may be, the predominant components of these mixtures (6). NOAELs recorded for alcohols with chain length C6–C22 range from 200 mg/kg bw per day to 1000 mg/kg bw per day in the rat upon subchronic administration via the diet (7).

No studies on reproductive and developmental toxicity were identified for tridecyl, myristyl and unfractionated fatty alcohols. Branched tridecanol did not induce testicular atrophy in male Alderley Park Wistar-derived rats treated with 184 mg/kg per day (single dose) for 2 weeks (10). In a 90-day repeated-dose study conducted in male and female Wistar rats, C14–16 branched and linear alcohols did not induce alterations in the gonads (weight and histology) when administered via the diet at 0.2%, which was equal to 167 mg/kg bw per day in the females ((11) described in (8)). 1-Dodecanol and 1-octadecanol, selected by the OECD as supporting substances for fertility evaluation of the linear long chain alcohols category, were tested for reproductive toxicity. Fertility was not affected; no alterations were observed in reproductive organs and no adverse effect on the offspring was observed at 2000 mg/kg bw per day (highest dose tested) (7). The Committee concluded that tridecyl alcohol, myristyl alcohol and the unfractionated fatty alcohols are unlikely to induce toxic effects on reproduction and development.

Based on the data from the SIDS report (7) for genotoxicity of the long chain alcohols category and taking into account that the long chain alcohols contain no structural alerts, which may be of concern for potential mutagenic activity, the Committee concluded that tridecyl alcohol and myristyl alcohol and the unfractionated fatty alcohols do not have genotoxicity potential.

No long-term exposure studies were identified for tridecyl alcohol, myristyl alcohol or unfractionated fatty alcohols.

Allergenicity

The Committee did not identify any reports of allergenicity upon oral exposure to tridecyl and myristyl alcohols or to unfractionated fatty alcohols that would indicate that they are, or they contain a known food allergen.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo chemical substances (see [section 2](#), General consideration).

Tridecyl alcohol has no direct food uses but is listed as an indirect additive used in food contact substances without limitations by the FDA. No data were identified on concentrations in foods from these uses.

Myristyl alcohol is permitted as a flavouring agent (02.126) (12). In the USA, myristyl alcohol is permitted as a formulation agent, lubricant or release agent and is generally recognized as safe (GRAS) (13). No data were identified on concentrations of myristyl alcohol in foods from these uses.

No food uses for unfractionated fatty alcohols were identified.

Worst-case human dietary exposures to previous cargo chemical substances in food oils have been estimated at 0.3 mg/kg bw per day (see [section 2](#), General consideration).

No other data on dietary exposure to 1-tridecanol, myristyl alcohol or unfractionated fatty alcohols were identified.

Evaluation

The Committee noted the limitations of the current dataset of toxicological evaluations, and the need to use a read-across approach where appropriate. Based on the weight of evidence across long chain fatty alcohols, tridecyl and myristyl alcohol and unfractionated fatty alcohols can be considered not to raise concerns for genotoxicity.

For **tridecyl alcohol**, the Committee used the dose level of 184 mg/kg bw per day, at which mild histopathological changes were reported in the liver following a 14-day study of oral gavage exposure in rats (10), as a reference point (RP) supported by the data on other long chain alcohols, for which the NOAELs recorded in the rat upon subchronic administration via the diet range from approximately 200 to 1000 mg/kg per day (7). The Committee noted limitations in the study design, but concluded that it could be used to establish a MOE in the absence of longer-term studies. Considering the estimated human dietary exposure of 0.3 mg/kg bw per day, the MOE is 610, which is adequate to address the uncertainties in the database.

For **myristyl alcohol**, the Committee identified a NOEL of 167 mg/kg bw per day as the reference point from a 90-day dietary study with C14–16 branched and linear alcohols in rats ((11) described in (8)), based on decreased body weight gain at 702 mg/kg bw per day, possibly attributable to reduced palatability of the diet. Considering the estimated human dietary exposure of 0.3 mg/kg bw per day, the MOE is 560, which is adequate to address the uncertainties in the database.

For **unfractionated fatty alcohols**, the Committee adopted a read-across approach, using data on two representative fatty alcohols, tridecyl alcohol and myristyl alcohol, and long chain alcohols. NOAEL values of between 200 mg/kg bw per day and 1000 mg/kg bw per day have been reported for fatty alcohols with chain lengths in the C6–C22 range, based upon subchronic dietary studies in rats (7). Based upon read-across, plus the fact that unfractionated fatty alcohols are present in natural food sources, the Committee concluded that the unfractionated fatty alcohols with components in the C6–C22 range are not of toxicological concern at the estimated dietary exposure level of 0.3 mg/kg bw per day.

There are no reports of allergenicity following oral exposure to tridecyl and myristyl alcohols and to unfractionated fatty alcohols that would indicate that they are or contain a known food allergen.

Tridecyl alcohol, myristyl alcohol and unfractionated fatty alcohols may react with a previous cargo in transesterification reactions with glycerides or esterification reactions with free fatty acids present, but the rates of reaction are likely to be slow at ambient temperature and any products would be naturally occurring waxes.

Therefore, the Committee concluded that tridecyl alcohol, myristyl alcohol and unfractionated fatty alcohols meet the criteria for acceptability as previous cargoes.

3.5.1.2 Isodecyl alcohol, isononyl alcohol and isoctyl alcohol

Explanation

The SCF evaluated isodecyl alcohol, isononyl alcohol and isoctyl alcohol as previous cargoes in 1997 and they were listed in [Annex 2](#) of its Opinion as substances provisionally acceptable because of a lack of toxicological data and uncertainty as to their composition. It was also noted that they can be easily removed if vegetable oil is refined (1).

In 2003, the SCF re-evaluated a series of provisionally accepted previous cargoes, including isodecyl alcohol, isononyl alcohol and isoctyl alcohol. The information available was still considered inadequate or in need of additional clarification. On this basis, the SCF decided to maintain its previous opinion, including isodecyl alcohol, isononyl alcohol and isoctyl alcohol in the list in [Annex 2](#) of its Opinion as substances provisionally acceptable as previous cargoes (2).

The CONTAM Panel of EFSA undertook an assessment of substances listed as acceptable previous cargoes for edible fats and oils in 2012 (6). The Panel noted the sparse data available to form an opinion and used a read-across approach to fill data gaps, where possible. They concluded that isodecyl alcohol, isononyl alcohol and isoctyl alcohol were of a low order of acute toxicity, and

there was no evidence of genotoxicity or allergenicity. EFSA concluded that isodecyl alcohol, isononyl alcohol and isoocetyl alcohol met the criteria for acceptability as previous cargoes for edible fats and oils.

For **isodecyl alcohol**, PubChem was used to identify common synonyms, namely: 25339-17-7, iso-decyl alcohol, 8-methylnonan-1-ol and 8-methyl-1-nonanol. These terms were used as the input for a Web of Science literature search (1900–2020). The cut-off date for the search was 30 September 2020.

Common synonyms for **isononyl alcohol** identified using PubChem were: 2430-22-0, isononanol, iso-nonanol, isononyl alcohol, iso-nonyl alcohol, 7-methyl-1-octanol, 7-methyloctan-1-ol and 7-methyl-octanol. These terms were used as the input for a Web of Science literature search (1900–2020). The cut-off date for the search was 30 September 2020.

Common synonyms for **isoocetyl alcohol** identified using PubChem were: 1653-40-3, isoocetanol, iso-octanol, isoocetyl alcohol, iso-octyl alcohol, 6-methyl-heptan-1-ol and 6-methylheptanol. The cut-off date for the search was 30 September 2020.

Other reference sources included PubChem, European Chemicals Bureau, IUCLID Dataset, ECHA and the National Institute for Occupational Safety and Health (NIOSH).

Chemical and technical considerations

Chemical and technical considerations for isodecyl alcohol, isononyl alcohol and isoocetyl alcohol are summarized in [Tables 7, 8 and 9](#).

Assessment

Biochemical aspects

No studies have been identified for isodecyl alcohol, isoocetyl alcohol and isononyl alcohol with respect to absorption, distribution, biotransformation and excretion, or formal pharmacokinetic analysis.

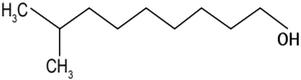
Iso-alcohols all show similar patterns of absorption, distribution, excretion and biotransformation. They are readily absorbed from the gastrointestinal tract and are rapidly cleared from the plasma due to extensive distribution around the body. They are initially converted to the respective carboxylic acid, which is subsequently metabolized to carbon dioxide via mitochondrial beta-oxidation pathways and the tricarboxylic acid cycle, in the same way as dietary fatty acids (7).

Toxicological studies

There are limited references in the literature regarding the toxicological assessment of isodecyl alcohol, isoocetyl alcohol and isononyl alcohol. In many

Table 7

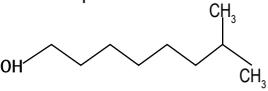
Chemical and technical considerations for isodecyl alcohol

Name: isodecyl alcohol (isodecanol)	
CAS number	Alternative CAS numbers
25339-17-7	68551-08-6 (alcohols C9–11-branched), CAS number 68526-85-2 (alcohols C9–11-iso-, C10-rich)
Chemical details	Isodecyl alcohol, isodecanol Colourless, slightly viscous liquid
	
	Molar mass: 158.28 g/mol Melting point: –2.8 °C Boiling point: 220 °C Insoluble in water; soluble in ethanol, ether, mineral oil, propylene glycol and most fixed oils
Route(s) of synthesis	Manufactured by two different mechanisms: by the oxo process in which nonenes are reacted with carbon monoxide and hydrogen using a cobalt catalyst, followed by hydrogenation; or by polymerization of propylenes and butenes with phosphoric acid to yield a mixture of branched olefins, which give isodecyl alcohol upon alkaline hydrolysis.
Composition	Occurs as a mixture of isomeric C10 alcohols and typically contains by-products of the propylene-butylene polymerization such as isooctyl and isononyl alcohols. May also contain small amounts of trimethyl-1-heptanols and dimethyl-1-octanols depending on the olefin feedstock used.
Uses	Used in the manufacture of plasticizers (about 70%), lubricants, surfactants and solvents; as an antifoaming agent in textile processing and as a flavouring agent
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils may require saponification, extraction, and derivatization followed by GC-FID or GC-MS.
Potential reaction(s) with a subsequent cargo of fat or oil	Transesterification with glycerides or esterification with free fatty acids present in the cargo may occur but are likely to be slow at ambient temperature.

GC-FID, gas chromatography with flame ionization detection; GC-MS, gas chromatography–mass spectrometry.

Table 8

Chemical and technical considerations for isononyl alcohol

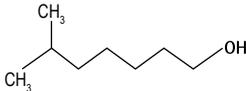
Name: isononyl alcohol (isononanol)	
CAS number	Alternative CAS numbers
27458-94-2	2430-22-0 (7-methyl-1-octanol); 68526-84-1 (alcohols, C8–10-iso-, C9-rich); 3452-97-9 (3,5,5-trimethylhexanol)
Chemical details	Isononyl alcohol, isononanol Colourless liquid
	
	Molar mass: 144.25 g/mol Melting point: –64.5 °C Boiling point: 206 °C Insoluble in water; soluble in alcohol

Route(s) of synthesis	Manufactured by the oxo process in which olefins are reacted with carbon monoxide and hydrogen in the presence of a catalyst, followed by hydrogenation
Composition	Produced as a mixture of isomeric primary C ₉ alcohols, consisting mainly of 3,5,5-trimethyl-1-hexanol, isomeric dimethyl-1-heptanols and isomeric methyl-1-octanols (e.g. 7-methyloctan-1-ol). It can be up to 99% pure. Isononyl alcohol is characterized as a primary alcohol and is a mixture of isomers of different branched structures with both odd- and even-numbered carbon chains ranging from C ₈ to C ₁₀ , predominantly C ₉ . The exact composition depends on the starting materials, the manufacturing process used, the reaction conditions and the purification method.
Uses	Used as an ingredient in plasticizers, stabilizers and lubricants.
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils may require saponification, extraction and derivatization followed by GC-FID or GC-MS.
Potential reaction(s) with a subsequent cargo of fat or oil	Transesterification with glycerides or esterification with free fatty acids present in the cargo may occur but are likely to be slow at ambient temperature.

GC-FID, gas chromatography with flame ionization detection; GC-MS, gas chromatography–mass spectrometry.

Table 9

Chemical and technical considerations for isooctyl alcohol

Name: isooctyl alcohol (isooctanol)	
CAS number	Alternative CAS numbers
26952-21-6	1653-40-3-9 (6-methyl-1-heptanol); 68526-83-0 (alcohols C ₇ –9-iso-, C ₈ -rich); 68551-09-7 (alcohols C ₇ –9-branched); 104-76-7 (2-ethylhexanol)
Chemical details	Isooctyl alcohol, isooctanol Clear colourless liquid  Molar mass: 130.23 g/mol Melting point: –106 °C Boiling point: 188 °C
Route(s) of synthesis	Insoluble in water; soluble in ether or alcohol Manufactured by the oxo process in which heptenes are reacted with carbon monoxide and hydrogen in the presence of a catalyst, followed by hydrogenation
Composition	Occurs as a mixture of isomeric C ₈ alcohols and typically consists of methyl-1-heptanols and/or dimethyl-1-hexanols. The composition depends on the olefin feedstock.
Uses	Used as a solvent; in the manufacture of cutting and lubricating oils and hydraulic fluids; in the production of other chemicals; as an ingredient in plasticizers; an intermediate in nonionic detergent and surfactant production; in synthetic drying oils and resin solvents; and in emulsifiers and antifoaming agents
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils may require saponification, extraction, and derivatization followed by GC-FID or GC-MS
Potential reaction(s) with a subsequent cargo of fat or oil	Transesterification with glycerides or esterification with free fatty acids present in the cargo may occur but are likely to be slow at ambient temperature.

GC-FID, gas chromatography with flame ionization detection; GC-MS, gas chromatography–mass spectrometry.

cases, experiments were undertaken with mixed isomers and/or combinations of iso-alcohols (C9–13). In addition, as might be expected for chemicals used in industrial processes, many of the citations are from unpublished reports, and access to the original data is often limited. As such, caution is needed in interpreting data to refer to a single pure chemical.

For **isodecyl alcohol**, an acute oral LD₅₀ value of 6500 mg/kg bw has been reported for rat (14). For **isononyl alcohol**, an acute oral LD₅₀ value of 2980 mg/kg bw has been reported in rat (15). For **isooctyl alcohol**, acute oral LD₅₀ values of 1670 mg/kg bw and 1480 mg/kg bw have been reported for mouse and rat, respectively (15, 16).

Rhodes et al. (10) administered groups of five male Alderley Park Wistar-derived rats isodecyl alcohol, isononyl alcohol and isooctyl alcohol at a dose of 1 mmol/kg bw per day for 14 days, equivalent to approximately 158, 130 and 144 mg/kg bw per day, respectively. The Committee noted limitations in the study design, including a small group size, single species, single sex, single dose level and limited duration. No changes were observed in body, liver or testicular weight relative to controls. No major pathological features of hepatotoxicity were observed. Mild histological changes in the liver were noted with all three chemicals, including slight centrilobular hypertrophy, slight/moderate glycogen vacuolation, and slight/moderate centrilobular lipid vacuolation (10). The Committee did not consider these changes to be adverse.

In a comparative developmental toxicity study with Wistar rats, **isodecyl alcohol** was administered by gavage at doses of 0, 158, 790 and 1580 mg/kg bw per day during gestation days 6 to 15 (17). Maternal toxicity was observed at 790 and 1580 mg/kg bw per day, with mortality (4/10) observed at the highest dose. Significantly reduced fetal weights were observed in the highest dose group, alongside a low incidence of retardations and rare malformations (17). The Committee concluded that NOAELs of 158 mg/kg bw and 790 mg/kg bw could be identified for maternal and fetal effects, respectively.

In the same comparative developmental toxicity study with Wistar rats, **isononyl alcohol** was administered by gavage to rats during gestation days 6 to 15 (17). Type 1 isononyl alcohol (isomers with a medium degree of branching including approximately 16% isodecyl alcohol) was administered at doses of 0, 144, 720 and 1440 mg/kg bw per day, and type 2 isononyl alcohol (isomers with a low degree of branching) at 0, 130, 650 and 975 mg/kg bw per day.

For type 1 isononyl alcohol, maternal toxicity was observed at 720 and 1440 mg/kg bw per day, with mortality (10/10) observed in the highest dose group. An additional dose group, 1080 mg/kg bw per day, showed maternal toxicity, but no mortality. An increased incidence of fetal retardations and rare malformations was reported for the 720 and 1080 mg/kg bw per day dose groups

(17). The Committee identified a NOAEL of 144 mg/kg bw per day for both maternal and fetal toxicity from isononyl alcohol type 1.

For type 2 isononyl alcohol, maternal toxicity was observed at 650 and 975 mg/kg bw per day, with mortality (3/10) observed in the highest dose group. Significantly reduced fetal weights, compared to controls, were observed in the highest dose group, alongside a low incidence of retardations and rare malformations (17). The Committee concluded that the NOAELs were 130 mg/kg bw per day and 650 mg/kg bw per day for maternal and fetal effects, respectively, for isononyl alcohol type 2.

No studies on reproductive or developmental toxicity have been identified for **isooctyl alcohol**.

Bacterial mutagenicity studies for individual chemicals and mixtures of iso-alcohols in the C9–C13 category showed a consistent lack of mutagenic activity. Negative results, with or without metabolic activation, have been reported for *Salmonella* Typhimurium strains TA98, TA100, TA1535 and TA1537 (18). **Isononyl alcohol** and **isooctyl alcohol** were negative in the Ames test, with and without metabolic activation, cited in (19), and ECHA, 1986.¹ Mutagenic activity for **isodecyl alcohol** has not been reported. Clastogenic activity was not observed in the in vitro mammalian chromosome aberration test in Chinese hamster ovary (CHO) cells with and without metabolic activation (20).

No carcinogenicity studies have been identified for **isodecyl alcohol**, **isononyl alcohol** or **isooctyl alcohol**.

Allergenicity

The Committee did not identify any reports of allergenicity upon oral exposure to **isodecyl alcohol**, **isononyl alcohol** or **isooctyl alcohol** that would indicate that they are, or they contain a known food allergen.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo chemical substances (see [section 2](#), General consideration).

Isodecyl alcohol and **isononyl alcohol** have no food uses. **Isooctyl alcohol** has no direct food uses but is listed as an indirect additive used in food contact substances without limitations by the FDA. No data were identified on concentrations in foods from these uses.

Worst-case human dietary exposures to previous cargo chemical substances in food oils have been estimated at 0.3 mg/kg bw per day (see [section 2](#), General consideration).

¹ <https://echa.europa.eu/registration-dossier/-/registered-dossier/13404/7/3/2>, accessed 14 November 2020.

No other data on dietary exposure to isodecyl alcohol, isononyl alcohol and isooctyl alcohol were identified.

Evaluation

The Committee noted the limitations of the current dataset of toxicological evaluations, and the need to use a read-across approach where appropriate.

The Committee also noted the negative data for mutagenic activity for isooctyl alcohol and isononyl alcohol, lack of clastogenic activity of isodecyl alcohol, and the weight of evidence across long chain fatty alcohols for a lack of mutagenic potential. The Committee considered that isodecyl alcohol, isononyl alcohol and isooctyl alcohol can be considered non-genotoxic. The Committee noted that no carcinogenicity studies have been identified for isodecyl alcohol, isononyl alcohol and isooctyl alcohol. Based upon the weight of evidence across several aliphatic alcohols, including the linear alcohol 1-dodecanol, the Committee concluded that isodecyl alcohol, isononyl alcohol and isooctyl alcohol are unlikely to possess carcinogenic potential.

For **isodecyl alcohol**, the Committee concluded that a NOAEL of 158 mg/kg bw per day for maternal toxicity from a comparative developmental toxicity study on rats (17) was a suitable reference point. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the MOE is approximately 520, which the Committee concluded is sufficient to address the uncertainties in the database.

For **isononyl alcohol**, the Committee considered a NOAEL of 158 mg/kg bw per day for maternal toxicity from a comparative developmental toxicity study on rats (17) was a suitable reference point. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the MOE is approximately 520, which the Committee concluded is sufficient to address the uncertainties in the database.

For **isooctyl alcohol**, no studies on reproductive or developmental toxicity were identified. Using read-across from isodecyl alcohol and isononyl alcohol, the Committee concluded that it is highly unlikely that isooctyl alcohol possesses significant reproductive or developmental toxicity. The Committee considered that the dose of 130 mg/kg bw per day, which resulted in mild histopathological changes in the liver following a 14-day oral gavage exposure in rats, was a suitable reference point (RP) (10). The Committee noted limitations in the study design but concluded that it could be used to establish a MOE in the absence of longer-term studies. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the MOE is approximately 430, which the Committee concluded is sufficient to address the uncertainties in the database.

There are no reports of allergenicity upon oral exposure to isodecyl alcohol, isononyl alcohol and isoocetyl alcohol that would indicate that they are or contain a known food allergen.

Isodecyl alcohol, isononyl alcohol and isoocetyl alcohol may react with a previous cargo in transesterification reactions with glycerides or esterification reactions with free fatty acids present, but the rates of reaction are likely to be slow at ambient temperature and any products would be naturally occurring waxes.

Therefore, the Committee concluded that isodecyl alcohol, isononyl alcohol and isoocetyl alcohol meet the criteria for acceptability as previous cargoes.

3.5.1.3 1,3-Propanediol (1,3-PD)

Explanation

In 1996, SCF concluded that 1,3-PD was not acceptable as a previous cargo owing to inadequate toxicological data (1). In 1998, SCF considered 1,3-PD for use as a co-monomer in polyesters and, based on new mutagenicity and developmental toxicity studies (unpublished data), it was classified as acceptable (21).

Based on a subchronic toxicity study showing low oral toxicity, the SCF considered 1,3-PD acceptable as a previous cargo, providing that residues would be low after tank cleaning (2).

In 2012, the EFSA CONTAM Panel concluded that 1,3-PD was acceptable as a previous cargo (6).

For the current review, previous assessments by SCF, EFSA and ECHA were considered. A search by CAS number and name synonyms for additional toxicological studies in animals and humans was undertaken to identify any critical new data for the assessment of human health risk. Searches were conducted on PubMed, PubChem and Embase. The cut-off date for inclusion in this report was 25 October 2020.

Chemical and technical considerations

Chemical and technical considerations for 1,3 propanediol are summarized in [Table 10](#).

Assessment

Biochemical aspects

No studies on absorption and distribution of 1,3-PD were identified. 1,3-PD can be metabolized by alcohol dehydrogenase. It is suggested that malondialdehyde can be formed as an intermediate metabolite that would be further metabolized to 3-hydroxypropionic and malonic acid and finally carbon dioxide (22–24).

Table 10

Chemical and technical considerations for 1,3 propanediol

Name: 1,3-propanediol (1,3-propylene glycol)	
CAS number	Alternative CAS numbers
504-63-2	None
Chemical details	1,3-propanediol, 1,3-propylene glycol, 1,3-PD Colourless to pale yellow very viscous liquid
	
	Molar mass: 76.09 g/mol Melting point: -27 °C Boiling point: 214.4 °C
	Miscible with water and ethanol
Route(s) of synthesis	Manufactured by classical oleochemical processes from acrolein, ethylene oxide; or by fermentation.
Composition	The final product depends on the manufacturing process. From acrolein, the final product may contain up to 500 mg/kg residual carbonyl compounds including saturated aliphatic carbonyl compounds such as propionic aldehyde and acetylated products such as 2-(2'-hydroxyethyl)-1,3-dioxane. From ethylene oxide, by-products include ethanol, acetaldehyde, propanol and propionaldehyde. By-products in fermentation from glycerol include acetate, acetic acid, butyric acid, lactic acid, formic acid, ethanol, 2,3-butanediol, succinic acid, lactate and butanol.
Uses	Used in polymer applications such as composites, adhesives, laminates, powder and UV-cured coatings, mouldings, novel aliphatic polyesters, copolyesters, solvents and lubricants; as a component in polytrimethylene terephthalate polymers; as a component of cosmetics and personal care items
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils may require extraction and clean-up steps prior to analysis by GC-MS/MS or LC-MS/MS.
Potential reaction(s) with a subsequent cargo of fat or oil	1,3-Propanediol is a very stable liquid at room temperature; unlikely to polymerize or participate in hydrogenation or dehydrogenation reactions without the presence of a catalyst or microorganism.

GC-MS/MS, gas chromatography with tandem mass spectrometry; LC-MS/MS, liquid chromatography with tandem mass spectrometry.

Toxicological studies

1,3-PD has been reported to possess very low acute toxicity. The lowest oral dose to induce death in rats was determined by Van Winkle as 10 mL/kg bw (approximately 10 000 mg/kg bw per day) (25).

In a 13-week study in male and female rats (10 animals of each sex per dose) 1,3-PD was administered by gavage at 1, 100, 300 and 1000 mg/kg bw per day. No treatment-related effects were observed (24).

In a developmental toxicity study, rats were treated with 0, 250 and 1000 mg/kg bw per day of 1,3-PD ((26) reported in EPA HPVIS (27) and ECHA¹). The available data indicated dose-dependent effects of 1,3-PD on fetal skeletal retardations at the high dose and incomplete ossification of the skull at

¹ <https://echa.europa.eu/registration-dossier/-/registered-dossier/2099/7/9/3>, accessed 14 November 2020.

both doses. The Committee noted the limitations of the design (two dose groups only) and the incomplete data reporting (not accounting for the litter effects in the developmental study evaluation), which prohibited a robust dose–response assessment. Therefore, effects of 1,3-PD on the development of the rat fetus could not be discounted even at the low dose. No other alterations were observed in the mothers or fetuses. A NOAEL for maternal toxicity of 1000 mg/kg bw and a LOEL of 250 mg/kg bw per day for marginal fetal effects was determined.

1,3-PD was not genotoxic *in vitro* or *in vivo*. No long-term exposure studies were identified for 1,3-PD.

Allergenicity

The Committee did not identify any reports of allergenicity upon oral exposure to 1,3-PD that would indicate that it is, or it contains a known food allergen.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo chemical substances (see [section 2](#), General consideration).

1,3-PD has no registered food uses but can be used in place of 1,2-propanediol at levels not exceeding good manufacturing practice (GMP) (13).

No data were identified on actual concentrations in food from these uses. However, given the high levels permitted for inclusion in processed foods, dietary exposure to 1,3-PD from this source is potentially much greater than that resulting from the carryover from previous cargoes into food oils. Worst-case human dietary exposures to previous cargo chemical substances in food oils have been estimated at 0.3 mg/kg bw per day (see [section 2](#), General consideration).

No other data on dietary exposure to 1,3-PD were identified.

Evaluation

1,3-PD is not genotoxic.

The Committee considered that the LOEL of 250 mg/kg bw per day, based on marginal fetal effects observed in the study by Mitterer should be used as the reference point ((26), cited in (27)). Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the MOE is 830, which is adequate to address the uncertainties in the databases.

There are no reports of allergenicity upon oral exposure to 1,3-PD that would indicate that it is or contains a known food allergen.

1,3-PD is a very stable liquid at room temperature, and it is unlikely to polymerize or participate in hydrogenation or dehydrogenation reactions without the presence of a catalyst or microorganism.

Therefore, the Committee concluded that 1,3-propanediol meets the criteria for acceptability as a previous cargo.

3.5.1.4 1,4-butanediol (1,4-BD)

Explanation

SCF evaluated 1,4-BD in 1997 and considered it acceptable as a previous cargo, also noting that 1,4-BD is soluble in water and therefore easily cleaned from tanks (1). The CONTAM Panel of EFSA undertook an assessment of substances currently listed in the Annex to Commission Directive 96/3/EC as acceptable previous cargoes for edible fats and oils (28). They concluded that 1,4-BD is not of toxicological concern when carried as a previous cargo.

SCF first evaluated 1,4-BD as a substance intended for use in materials in contact with food (29). It concluded that 1,4-BD was a substance for which some toxicological data exist, but that an ADI or TDI could not be established. In 2001, the SCF re-evaluated 1,4-BD for this use, and again concluded that an ADI or TDI could not be established. It concluded that continued use as a substance intended for use in materials in contact with food could be accepted, and established a migration limit for 1,4-BD of 0.05 mg/kg of food. The Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC Panel) of EFSA re-evaluated 1,4-BD in 2004 for use in materials in contact with food. Based on additional toxicological data, a migration limit of 5 mg/kg of food was established (30).

PubChem was used to identify common synonyms for 1,4-butanediol, namely: 110-63-4, 1,4-butanediol, 1,4-butylene glycol, tetramethylene glycol, 1,4-dihydroxybutane, 1,4-tetramethylene glycol and tetramethylene 1,4-diol. These terms were used as the input for a Web of Science literature search (1900–2020), which was further refined with the search terms: toxic*, metaboli*, mutagen*, genotoxic*, carcinogen*, sensiti*, allerg* and ADI. The cut-off date for the search was 30 September 2020.

Other reference sources included PubChem, European Chemicals Bureau, IUCLID Dataset, ECHA and NIOSH.

Chemical and technical considerations

Chemical and technical considerations for 1,4-butanediol are summarized in [Table 11](#).

Assessment

Biochemical aspects

1,4-BD is rapidly metabolized to γ -hydroxybutyraldehyde and subsequently γ -hydroxybutyric acid (31, 32). Maximum plasma concentrations of

Table 11

Chemical and technical considerations for 1,4-butanediol

Name: 1,4-butanediol (1,4-butylene glycol)	
CAS number	Alternative CAS numbers
110-63-4	None
Chemical details	1,4-butanediol, 1,4-butylene glycol, 1,4-BD Colourless viscous liquid or crystals
	 <chem>OCCCCO</chem>
	Molar mass: 90.12 g/mol Melting point: 20 °C Boiling point: 230 °C
Route(s) of synthesis	Soluble in water and ethanol Manufactured by different mechanisms: by the Reppe process from formaldehyde plus acetylene; from maleic anhydride; from propylene oxide; or from butadiene plus acetic acid.
Composition	<ul style="list-style-type: none"> • Reppe process: 1,4-BD > 99%; 2-methyl-1,4-butanediol maximum 0.4%, and 2-(4-hydroxybutoxy) tetrahydrofuran maximum, 0.2% • maleic anhydride process: 1,4-BD 90–95%; <i>n</i>-propanol and <i>n</i>-butanol 5–10% • propylene oxide process: 1,4-BD 86–91%; <i>n</i>-propanol and propionaldehyde 0.5–3.5%; methyl propanediol typically < 13.5% • butadiene-acetic acid process: 1,4-BD > 99%; 2-(4-hydroxybutoxy)tetra- hydrofuran 0.3%
Uses	Used in the manufacture of tetrahydrofuran (THF) and polytetramethylene ether glycol, polybutylene terephthalate, gamma-butyrolactone, polyurethane and other chemical reagents. THF production represents the largest use.
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils may require extraction of 1,4-BD using a mixture of methanol and acetonitrile, followed by clean-up using a polymeric strong cation exchanger and analysis by LC-MS/MS or GC-MS/MS.
Potential reaction(s) with a subsequent cargo of fat or oil	1,4-Butanediol is unlikely to polymerize or participate in hydrogenation or dehydrogenation reactions without the presence of a catalyst or microorganism. There is a small possibility of ester formation with free fatty acids.

LC-MS/MS, liquid chromatography with tandem mass spectrometry; GC-MS/MS, gas chromatography with tandem mass spectrometry.

γ -hydroxybutyric acid are approximately equivalent in humans following administration of 1,4-BD or γ -hydroxybutyric acid (33).

γ -Hydroxybutyric acid can also be rapidly formed from γ -butyrolactone. Thus, data on γ -butyrolactone can be used as a read-across for γ -hydroxybutyric acid, and by extension 1,4-BD (34).

Further metabolism of γ -hydroxybutyric acid yields succinic acid, which is converted to carbon dioxide via the tricarboxylic acid cycle (34).

Toxicological studies

1,4-BD has been noted to possess very low oral acute toxicity. Acute oral LD₅₀ values have been reported for mouse (2062 mg/kg bw), rat (1525 mg/kg bw), guinea-pig (1200 mg/kg bw) and rabbit (2531 mg/kg bw) (35).

In a 28-day oral toxicity study in male and female Wistar Imp:DAK rats, 1,4-BD was administered by gavage at doses of 0, 5, 50 and 500 mg/kg bw per day. No alterations in body or organ weight were reported, and only mild levels of liver histopathology with no overt hepatotoxicity at any dose (36).

In a US National Toxicity Program (NTP)-sponsored developmental toxicity study with CD1 mice, 1,4-BD was administered by gavage at doses of 0, 1, 100, 300 and 600 mg/kg bw per day from gestation day 6 to day 15 ((37), as cited in (34)). No maternal deaths were reported, but acute central nervous system (CNS) intoxication was reported in the maternal 300 and 600 mg/kg bw per day dose groups, with all symptoms reported usually to resolve within 4 hours of dosing. In addition, body and liver weight, and food consumption were lower than control levels for the 300 and 600 mg/kg bw dose groups, while kidney weights were lower than control weights for the 600 mg/kg bw dose group. Significant reductions in fetal weights were reported in the 300 and 600 mg/kg bw dose groups ((37), as cited in (34)). Based upon these observations, the Committee identified a NOAEL of 100 mg/kg bw per day for both maternal and fetal toxicity.

In a combined repeat-dose and reproductive and developmental toxicity study, 1,4-BD was administered to rats at doses of 0, 200, 400 or 800 mg/kg bw per day by oral gavage for 45 days in males and from 14 days before mating to day 3 of lactation in females (38). No effects on parental reproductive parameters, fetal survival or incidence of morphological abnormalities was reported. Epithelial hyperplasia and fibrosis of the lamina propria has been reported in the bladder of animals receiving 400 or 800 mg/kg bw per day 1,4-BD (38). Acute and transient dose-related CNS effects were reported in male and female rats exposed to 1,4-BD, namely hyperactivity at a dose of 200 mg/kg bw per day and CNS depression at higher doses (400 or 800 mg/kg bw per day). The authors of the study considered that the hyperactivity seen at a dose of 200 mg/kg bw per day was not an adverse effect. The Committee, however, noted that hyperactivity would generally be considered adverse, but was not able to reach a conclusion on this study without access to the original data.

Both 1,4-BD and γ -butyrolactone are negative in the Ames test using *Salmonella* Typhimurium strains TA98, TA100, TA1535 or TA1537, with or without metabolic activation (34, 38). The results of an in vitro mammalian chromosome aberration assay of 1,4-BD were reported as negative, while γ -butyrolactone was reported to cause significant increases in chromosomal aberrations in one study at high concentrations (2580 and 3990 $\mu\text{g/mL}$) (38).

No chronic toxicity or carcinogenicity studies were identified for 1,4-BD. However, γ -butyrolactone has been assessed in a 2-year study reported by NTP in 1992 (39). γ -Butyrolactone was administered to F133 rats at doses of 0, 112 and 225 mg/kg bw (males) or 0, 225 and 450 mg/kg bw (females). In male and female F344 rats, exposure to γ -butyrolactone was not reported to increase the incidence of tumours. In contrast, the incidence of mammary gland fibroadenomas and pituitary gland cysts was reported to show a negative trend with dose in female rats, while mononuclear cell leukaemia was reported to show a negative trend with dose in male rats. In mice, hepatocellular adenomas or carcinomas (combined) were reported to show a dose-dependent negative trend for incidence. NTP considered that these dose-dependent negative trends were due to high incidence levels in the control groups, which were significantly higher than historical values (34). In the same study, B6C3F1 mice were administered γ -butyrolactone at doses of 0, 262 and 450 mg/kg bw (males and females). A significantly increased incidence of focal hyperplasia of the adrenal medulla was reported in male mice given the low dose, but this was not a dose-dependent effect (34). The Committee concluded that 1,4-BD was unlikely to possess genotoxic carcinogenic potential.

Allergenicity

The Committee did not identify any reports of allergenicity upon oral exposure to 1,4-BD that would indicate that it is, or it contains a known food allergen.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo chemical substances (see [section 2](#), General consideration).

1,4-BD has no direct food uses but is listed as an indirect additive used in food contact substances without limitations by the FDA. No data were identified on concentrations in foods from this use, and the Committee concluded that this would most likely represent a minor contribution to total exposure and did not consider this route further.

Worst-case human dietary exposures to previous cargo chemical substances in food oils have been estimated at 0.3 mg/kg bw per day (see [section 2](#), General consideration).

No other data on dietary exposure to 1,4-BD were identified.

Evaluation

The Committee noted that both 1,4-BD and γ -butyrolactone are rapidly metabolized to γ -hydroxybutyric acid, whereupon they share metabolic fates and data on γ -butyrolactone could therefore be used for read-across to fill data gaps concerning 1,4-BD.

The Committee concluded that 1,4-BD is not genotoxic, and that the data for γ -butyrolactone are consistent with 1,4-BD being unlikely to possess carcinogenic potential.

The Committee noted that a range of toxic end-points have been reported for 1,4-BD and γ -butyrolactone from various studies. It concluded that acute and transient CNS effects, most notably hyperactivity, provided the most relevant end-point. A NOAEL of 100 mg/kg bw was identified by the NTP ((37), as cited in (34)), and the Committee considered that this was appropriate as a reference point in the current evaluation. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the MOE is approximately 330, which the Committee concluded is sufficient to address the uncertainties in the database.

There are no reports of allergenicity upon oral exposure to 1,4-BD that would indicate that it is or contains a known food allergen.

1,4-BD is unlikely to polymerize or participate in hydrogenation or dehydrogenation reactions without the presence of a catalyst or microorganism. There is a small possibility of ester formation with free fatty acids.

Therefore, the Committee concluded that 1,4-butanediol meets the criteria for acceptability as a previous cargo.

A toxicological monograph on alcohols including dietary exposure and chemical and technical considerations was prepared.

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3.5.2 Butyl ethers (Group 5)

3.5.2.1 Methyl tertiary butyl ether (MTBE)

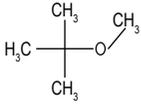
Explanation

MTBE was evaluated for acceptability as a previous cargo by SCF in 1996 and 2003 (1, 2). SCF concluded that MTBE could be accepted as a previous cargo based on the determination that the solubility of MTBE in water (48 g/L) would enable effective cleaning of the cargoes by water washings at ambient temperature. More recently, EFSA's CONTAM Panel reviewed the available data on MTBE to evaluate its acceptability as a previous cargo for edible oils and fats (3). The CONTAM Panel concluded that there was no concern regarding the carcinogenicity, developmental or reproductive toxicity of MTBE at the anticipated exposure levels from its use as a previous cargo, no reactions of concern with edible fats and oils, and no impurities likely to be present at levels with toxicological relevance. Therefore, the CONTAM Panel concluded that MTBE met the criteria for acceptability as a previous cargo for edible oils and fats. No health-based guidance values were established for MTBE under previous evaluations.

For the present assessment, the Committee identified and reviewed previous evaluations (monographs) by the WHO International Programme on Chemical Safety (WHO/IPCS), EFSA, IARC, SCF, and the United States Agency for Toxic Substances and Disease Registry (US ATSDR) and located additional references from these evaluations. This was followed by comprehensive searches for toxicological data on MTBE on PubMed and PubChem. The cut-off date for the searches was 31 August 2020. Some recent publications that described application of physiologically based toxicokinetic (PBTK) modelling of MTBE and its major metabolite, tertiary butyl alcohol (TBA), were reviewed and included in the present assessment. These studies examined internal dose metrics of MTBE and/or TBA in various MTBE exposure scenarios, and the contribution of their binding with alpha (α)-2-globulin in the kidneys of male rats to the observed renal

Table 12

Chemical and technical considerations for methyl tertiary butyl ether (MTBE)

Name: methyl tertiary butyl ether (2-methoxy-2-methylpropane)	
CAS number	Alternative CAS numbers
1634-04-4	None
Chemical details	<i>t</i> -Butyl methyl ether, <i>tert</i> -butoxymethane, 1,1-dimethylethyl methyl ether, MTBE Colourless liquid with terpene-like odour
	
	Molar mass: 88.15 g/mol Melting point: -108.6 °C Boiling point: 55.2 °C Solubility in water (25 °C): 48 g/L; very soluble in ethanol and diethyl ether
Route(s) of synthesis	Manufactured by reacting isobutylene with methanol in the presence of acidic ion-exchange resin catalysts or strong acids. An alternative two-step route of synthesis includes catalytic oxidation of isobutene with hydrogen peroxide followed by etherification with methanol.
Composition	Commercially available in two grades: gasoline grade (95–99% pure) and solvent grade (>99.8% pure); minor impurities may include methanol, isobutylene, 1-butylene, isopentanes and tertiary butyl alcohol.
Uses	Used to oxygenate gasoline to improve octane number. Minor uses include chemicals, petrochemicals, pharmaceuticals, paints and coatings.
Analytical methods	None reported for previous cargoes. Potential methods for its determination in fats and oils include head space, purge and trap or solid-phase micro-extraction techniques coupled with GC-FID/PID/ELCD or GC-MS.
Potential reaction(s) with a subsequent cargo of fat or oil	MTBE is not expected to react with edible fats and oils to form any reaction products.

GC-FID/PID/ELCD, gas chromatography with flame ionization detection/photo-ionization detection/electrolytic conductivity detection; GC-MS, gas chromatography-mass spectrometry.

toxic effects. The Committee also considered some data on TBA to conduct the toxicological evaluation of MTBE.

Chemical and technical considerations

The chemical and technical considerations for MTBE are summarized in [Table 12](#).

Assessment

Biochemical aspects

Following oral exposure, MTBE is rapidly absorbed such that the peak plasma concentration is observed as early as within 15 minutes after administration (4). Even though MTBE is soluble in water, it has a low molecular weight and is

lipophilic enough to be extensively distributed in human tissues. MTBE initially undergoes oxidation catalysed by the enzyme cytochrome P450 2A6 (CYP2A6) to form TBA and formaldehyde (5–7). The elimination of MTBE in humans after acute oral exposure is triphasic with elimination half-lives ($t_{1/2}$) of 0.25 to 0.8 hours, 1–2 hours and 7–8 hours (8). The $t_{1/2}$ of the generated TBA ranges from 8 to 12 hours (8). TBA is further metabolized, first to form 2-methyl-1,2-propanediol and then 2-hydroxyisobutyrate; both metabolites are primarily eliminated in the urine (7). TBA is also eliminated in the urine as TBA-glucuronide and, in trace amounts, as TBA-sulfate (7, 9). Formaldehyde is not detected in significant amounts in the blood upon exposure to MTBE, possibly owing to its rapid and spontaneous non-enzymatic conjugation with glutathione to form an adduct S-hydroxymethylglutathione, followed by hydrolysis to formic acid and reduced glutathione catalysed by S-formylglutathione hydrolase (10). The Committee also reviewed studies that described application of PBTK modelling for investigating the accumulation of MTBE and TBA in the male rat kidney due to specific binding to α 2-globulin and its association with the incidence of male-rat-specific renal tumours, α 2-globulin nephropathy and similar effects in the kidneys (11–14). However, the Committee considered this mechanism of renal effects as male-rat-specific, and, therefore, as not relevant to humans.

Toxicological studies

There are extensive toxicological datasets on MTBE exposure via different exposure routes. The Committee evaluated relevant toxicological data on oral exposure to MTBE in animals and humans, and from genetic toxicity studies conducted with MTBE using in vitro and in vivo systems.

The Committee concluded that the potential for acute toxicity of MTBE after oral exposure is low based on reported oral LD₅₀ values of 3866 mg/kg bw in rats (15) and about 4000 mg/kg in mice (16). The Committee reviewed the available short-term and subchronic oral toxicity studies of MTBE and noted that some common findings between most studies included effects on kidney weights and kidney morphology in the form of hyaline droplets in renal proximal tubule cells (17–19). As these effects can be attributed to binding of MTBE and/or TBA to α 2u-globulin in the kidneys of male rats, as stated above, the Committee considers this mechanism to be male-rat-specific and not relevant to humans.

The Committee reviewed a 90-day oral toxicity study of MTBE conducted in male and female Sprague-Dawley rats at doses of 0, 100, 300, 900 and 1200 mg/kg bw per day (19). It noted some treatment-related effects in the kidney and the liver, which included statistically significant increases in relative kidney weights in females treated with 300, 900 and 1200 mg/kg bw per day of MTBE and in the relative liver weights in males treated with 900 mg/kg bw per day and 1200 mg/

kg bw per day. The Committee also noted that no changes in clinical chemistry parameters or microscopic observations in organs were reported with relative weight increases in the kidneys of females. The Committee considered that no significant increases in kidney weights were observed in female Sprague-Dawley rats following oral exposure to MTBE at 250 mg/kg bw per day and 1000 mg/kg bw per day in the 104-week chronic toxicity/carcinogenicity study discussed below (20, 21). In contrast, the increases in the relative liver weights reported in males in the study by Robinson et al. were accompanied by elevated cholesterol levels (19). Therefore, based on statistically significant increases in the relative liver weights and elevated cholesterol levels in males, the Committee identified a NOAEL of 300 mg/kg bw per day from this study (19).

The Committee also reviewed another 90-day oral toxicity study of MTBE, conducted in male rats only, at dose levels of 200, 600 and 1000 mg/kg bw per day, which reported significant increases in absolute and relative liver weights, and dose-related microscopic findings in the liver were reported at all tested doses (22). The Committee considered the reported hypertrophic changes in the liver and subsequent weight increases observed in this study as adaptive responses and not adverse findings, particularly in the absence of data that would indicate an association with altered liver function or progression to long-term adverse effects (22).

The Committee evaluated the potential for reproductive toxicity of oral MTBE exposure based on two reproductive studies, both of which looked at the effects of subacute MTBE exposure on the male reproductive system in rodents. The first study did not report any treatment-related effects of oral MTBE exposure in mice (23). In contrast, the second study reported some treatment-related effects on the male reproductive system, including a significant increase in the percentage of abnormal sperm, an irregular and disordered arrangement of the seminiferous epithelium indicated by a histopathological examination, changed serum levels of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and decreased levels of androgen binding protein in the high-dose groups (24). However, the Committee noted that these effects were mainly reported in the high-dose groups. The Committee did not identify any studies examining the potential for reproductive or developmental toxicity in response to oral exposure to MTBE in both male and female animals.

The Committee concluded that MTBE is not genotoxic based on negative responses reported in most of the *in vivo* and *in vitro* genetic toxicity studies reviewed, and genotoxicity data on TBA, its major metabolite, indicating that TBA is non-genotoxic (25).

The Committee reviewed a 104-week oral (gavage) chronic toxicity/carcinogenicity assay of MTBE conducted on male and female rats at dose levels of 0, 250 and 1000 mg/kg bw per day (20, 21). It also reviewed a 2-year oral

carcinogenicity assay of TBA in drinking-water in male and female rats (0, 1.25, 2.5 and 5 mg/ml equal to 0, 90, 200 and 420 mg/kg bw per day in males and 0, 2.5, 5 and 10 mg/ml equal to 0, 180, 330 and 650 mg/kg bw per day in females) and mice (0, 5, 10 and 20 mg/ml equal to 0, 540, 1040 and 2070 mg/kg bw per day in males and 0, 510, 1020 and 2110 mg/kg bw per day in females) (25) to evaluate the potential for carcinogenicity of MTBE following oral exposure. Both reported some tumour incidences; however, the Committee noted that the observed tumour incidences in rodents lacked human or toxicological relevance, and these effects were reported at exposure levels much higher than those expected from oral exposure to MTBE as a previous cargo.

The Committee noted that MTBE has been used clinically for dissolution of gallstones by instillation through a transhepatic or nasobiliary catheter (26–31). However, no adverse effects of the treatment were reported in the studies reviewed.

Allergenicity

The Committee did not identify any reports that indicated that MTBE elicits an allergic response upon oral exposure. There are also no data available that indicate that MTBE would contain a known food allergen.

Impurities

The Committee noted that impurities, namely methanol, isobutylene, 1-butylene, isopentanes and TBA may be expected in MTBE. As MTBE products are of high purity, the percentage contribution of these impurities to the total composition of the substance is minor. The Committee noted that these impurities were non-genotoxic and studies of oral exposure to these impurities in animals did not report tumour incidences of human or toxicological relevance. The Committee also did not identify any reports that indicated that these impurities elicit an allergic response upon oral exposure or would contain a known food allergen. Therefore, the Committee concluded that these compounds would not be expected to cause any adverse health effects at their anticipated levels of exposure as minor impurities in MTBE.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo substances (see [section 2](#), General consideration). MTBE has been found in drinking-water in areas where MTBE-containing gasoline has leaked into groundwater aquifers and surface waters. The worst-case exposures to previous cargo substances in food oils have been estimated as 0.3 mg/kg bw per day (see [section 2](#), General consideration). The maximum daily MTBE exposure from

drinking-water was estimated to be 0.008 mg/kg bw per day based on drinking-water consumption of 190 mL/kg bw per day by infants and children (the maximum estimated by EFSA (32)), and an MTBE concentration of 40 µg/L (the maximum level the US EPA determined would not have an unpleasant taste or odour (33)).

Evaluation

Upon evaluating the available toxicity studies and examining the toxicological relevance of the effects reported, the Committee considered that the NOAEL of 300 mg/kg bw per day identified from the 90-day oral subchronic study of MTBE in rats was the most appropriate RP (19). The Committee concluded that the estimated exposure to MTBE from drinking-water is a minor contributor (0.008 mg/kg bw per day) as compared with the estimated exposure to MTBE in food oil commodities from previous cargoes (0.3 mg/kg bw per day), and that there are no other known potential sources of dietary exposure to MTBE. A comparison of the RP of 300 mg/kg bw per day with the estimated exposure of 0.3 mg/kg bw per day for MTBE as a previous cargo yields a MOE of 1000, which is sufficient to address the uncertainties in the database.

There are no data on allergenicity upon oral exposure to MTBE that indicate that it is, or it contains a known food allergen.

MTBE as a previous cargo is not expected to react with edible fats and oils to form any reaction products.

Therefore, MTBE meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.5.2.2 Ethyl tertiary butyl ether (ETBE)

Explanation

The acceptability of ETBE as a previous cargo was evaluated by the CONTAM Panel based on the assessment of toxicological data on both MTBE and ETBE (34). The CONTAM Panel established a TDI of 1 mg/kg bw per day based on a NOAEL of 100 mg/kg per day from a 180-day rat study (35) after application of an uncertainty factor of 100. The CONTAM Panel concluded that ETBE was neither genotoxic nor allergenic, and considered that ETBE would not pose a risk for carcinogenicity at levels of exposure anticipated from its use as a previous cargo. Therefore, the CONTAM Panel concluded that ETBE met the criteria for acceptability as a previous cargo for edible oils and fats. The United States Environmental Protection Agency (US EPA) conducted a toxicological review of ETBE and established a chronic oral reference dose of 0.5 mg/kg bw per day based on effects in the kidneys, such as urothelial hyperplasia, reported in a long-term study in rats (36).

For the present assessment, the Committee reviewed previous evaluations completed by EFSA and US EPA and located additional references from these evaluations. This was followed by comprehensive searches for toxicological data on ETBE on PubMed and PubChem. The cut-off date for the inclusion criteria on all searches was 31 August 2020. Some recent publications on PBTK modelling of ETBE and its major metabolite TBA, which investigated the contribution of binding of ETBE and/or TBA with α 2-globulin in the kidneys of male rats to the observed renal toxic effects, were retrieved. The relevant toxicological data from these publications were included in the present assessment. The Committee also considered some data on TBA to conduct the toxicological evaluation of ETBE.

Chemical and technical considerations

The chemical and technical considerations for ETBE are summarized in [Table 13](#).

Assessment

Biochemical aspects

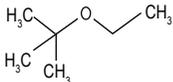
The toxicokinetic profiles of ETBE and MTBE are expected to be similar owing to the similarities in their chemical structures. The $t_{1/2}$ estimates of TBA generated upon metabolism of MTBE and ETBE are also expected to be in the same range. Based on oral exposure studies with MTBE (8), ETBE is expected to be rapidly absorbed following oral exposure. Given its high lipophilicity and low molecular weight, ETBE is extensively distributed in human tissues (37). It undergoes oxidation catalysed by CYP2A6 to form TBA and acetaldehyde (6, 38). The terminal $t_{1/2}$ of ETBE in humans is predicted to be about 24–33 hours (38). The $t_{1/2}$ of the generated TBA in humans is predicted to range from 8 to 12 hours. TBA is further metabolized, first to form 2-methyl-1,2-propanediol and then 2-hydroxyisobutyrate; both metabolites are primarily eliminated in the urine (38). TBA is also eliminated in the urine as TBA-glucuronide and, in trace amounts, as TBA-sulfate (9, 38). No measurements of acetaldehyde after exposure to ETBE have been reported; however, the oxidation of acetaldehyde by aldehyde dehydrogenases (ALDH) to form acetic acid is expected (38). The Committee reviewed studies that described application of PBTK modelling to investigate specific binding of ETBE and/or TBA to α 2-globulin in the male rat kidneys after ETBE exposure via different exposure scenarios, including oral administration (39, 40). However, the Committee considered this mechanism of renal effects to be male-rat-specific, and, therefore, as not relevant to humans.

Toxicological studies

There are extensive toxicological datasets on ETBE exposure via different routes. The Committee evaluated relevant toxicological data on oral exposure to ETBE

Table 13

Chemical and technical considerations for ethyl tertiary butyl ether (ETBE)

Name: ethyl tertiary butyl ether (2-ethoxy-2-methylpropane)	
CAS number	Alternative CAS numbers
637-92-3	None
Chemical details	Ethyl tert-butyl oxide, methyl-2-ethoxypropane, tert-butyl ethyl ether, ETBE Colourless liquid with strong objectionable odour
	
	Molar mass: 102.17 g/mol Melting point: -94 °C Boiling point: 73 °C Solubility in water (25 °C): 12 g/L; very soluble in ethanol and diethyl ether
Route(s) of synthesis	Manufactured by reacting isobutylene with ethanol in the presence of acidic ion-exchange resin catalysts or strong acids.
Composition	ETBE > 95%; minor impurities may include ethanol, isobutylene, 1-butylene, isopentanes and tertiary butyl alcohol
Uses	Used to oxygenate gasoline to improve octane number. Minor uses include chemicals, petrochemicals, pharmaceuticals, paints and coatings.
Analytical methods	None reported for previous cargoes. Potential methods for its determination in fats or oils may include head space, purge and trap or solid-phase micro-extraction techniques coupled with GC-FID/PID/ELCD or GC-MS.
Potential reaction(s) with a subsequent cargo of fat or oil	ETBE is not expected to react with edible fats and oils to form any reaction products.

GC-FID/PID/ELCD, gas chromatography with flame ionization detection/photo-ionization detection/electrolytic conductivity detection; GC-MS, gas chromatography-mass spectrometry.

in animals and humans, and from genetic toxicity studies conducted with ETBE in *in vitro* and *in vivo* systems.

The Committee concluded that the potential for acute toxicity of ETBE after oral exposure is low based on the reported oral LD₅₀ value of > 5000 mg/kg bw in rats (38). The Committee reviewed a 180-day oral toxicity study conducted in male and female Sprague-Dawley rats at exposure levels of 0, 5, 25, 100 and 400 mg/kg bw per day and identified a NOAEL of 100 mg/kg bw per day (35). This was based on an increase in relative mean liver weights and microscopic findings in the livers of males and females treated with 400 mg/kg bw per day, and the increase in cholesterol levels reported in males treated with 400 mg/kg bw per day of ETBE. The Committee concluded that ETBE did not show selectively reproductive or developmental toxicity in the absence of other manifestations of general parental toxicity based on an evaluation of some reproductive and developmental toxicity studies conducted in rats (41–44).

The Committee concluded that ETBE is not genotoxic based on negative responses reported in the in vivo and in vitro genetic toxicity studies reviewed, and genotoxicity data on TBA, its major metabolite, reporting that TBA is non-genotoxic (25).

The Committee evaluated a 104-week oral (gavage) chronic toxicity/carcinogenicity assay of ETBE conducted on male and female rats given doses of 0, 250 and 1000 mg/kg bw per day to assess the potential for carcinogenicity of ETBE upon oral exposure (45). In addition, the Committee reviewed the 2-year oral carcinogenicity assay of TBA in drinking-water conducted in male and female rats and mice at different dose levels (25). Both studies reported some tumour incidences; however, the Committee noted that the observed tumours in rodents lacked human or toxicological relevance, and these effects were reported at exposure levels much higher than those expected from oral exposure to ETBE as a previous cargo.

The Committee did not identify any reports of oral exposure to ETBE in humans.

Allergenicity

The Committee did not identify any reports that indicated that ETBE elicits an allergic response upon oral exposure. There are also no data available that indicate that ETBE would contain a known food allergen.

Impurities

The Committee noted that impurities, namely ethanol, isobutylene, 1-butylene, isopentanes and TBA, may be expected in ETBE. As ETBE products are of high purity, the percentage contribution of these impurities to the total composition of the substance is minor. The Committee noted that these impurities were non-genotoxic and studies of oral exposure to these impurities in animals did not report tumour incidences of human or toxicological relevance. The Committee also did not identify any reports that indicated that these impurities elicit an allergic response upon oral exposure, or would contain a known food allergen. Therefore, the Committee concluded that these compounds would not be expected to cause any adverse health effects upon oral exposure at their anticipated levels of exposure as minor impurities in ETBE.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo substances (see [section 2](#), General consideration). ETBE, used in many areas as a substitute for MTBE in gasoline, has been found in drinking-water (46). The worst-case exposures to previous cargo substances in food oils have been

estimated as 0.3 mg/kg bw per day (see [section 2](#), General consideration). The estimated maximum daily ETBE exposure from drinking-water was estimated to be 0.01 mg/kg bw per day based on drinking-water consumption of 190 mL/kg bw per day by infants and children (the maximum estimated by EFSA (32)), and an ETBE concentration of 50 µg/L (47).

Evaluation

Upon evaluating the available toxicity studies and examining the toxicological relevance of effects reported therein, the Committee concluded that the NOAEL of 100 mg/kg bw per day identified from the 180-day oral subchronic study of ETBE in rats was the most appropriate RP (35). The Committee concluded that the estimated exposure to ETBE from drinking-water is a minor contributor (0.01 mg/kg bw per day) compared with the estimated exposure to ETBE in food oil commodities from previous cargo (0.3 mg/kg bw per day), and that there are no other known potential sources of dietary exposure to ETBE. A comparison of the RP of 100 mg/kg bw per day with the estimated exposure of 0.3 mg/kg bw per day for ETBE as a previous cargo yields a MOE of 330, which is sufficient to address the uncertainties in the database.

There are no data on allergenicity upon oral exposure to ETBE that indicate that it is, or it contains a known food allergen.

ETBE as a previous cargo is not expected to react with edible fats and oils to form any reaction products.

Therefore, ETBE meets the criteria for acceptability as a previous cargo for edible fats and oils.

A toxicological monograph on the butyl ethers including dietary exposure and chemical and technical considerations was prepared.

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3.5.3 Oils and waxes (Group 3)

3.5.3.1 Mineral oil, medium and low viscosity, class II and class III

Explanation

White mineral oil, edible grade, contains complex mixtures of paraffinic and naphthenic liquid hydrocarbons. Medium and low viscosity mineral oil class II and III contains mineral oil saturated hydrocarbons (MOSH). These include paraffins (straight chain or n-alkanes and branched alkanes) and naphthenes (cyclic alkanes), with a minimal content of mineral oil aromatic hydrocarbons (MOAH). For class II, the average relative molar mass is 400–480 g/mol, with a viscosity of 7.0–8.5 mm²/s at 100 °C. For class III, the average relative molar mass is 300–400 g/mol, with a viscosity of 3.0–7.0 mm²/s at 100 °C. Commercial mineral oil products range from being free of MOAH (food-grade mineral

oil) to containing 30% MOAH (crude mineral oil). The Committee noted that crude mineral oil is banned as a previous cargo and MOAH, which contains mutagenic and carcinogenic substances, would be unacceptable as a previous cargo. The current evaluation was conducted under the assumption that mineral oil products shipped as previous cargoes are highly refined food-grade products free of MOAH.

The previous Committee established a temporary group ADI of 0.01 mg/kg bw per day, based on an increase of histiocytosis in the mesenteric lymph nodes, for mineral oil (medium and low viscosity) classes II and III in 1995, which was extended on a number of occasions. As data supporting establishment of a full ADI had not been made available, the previously established temporary group ADI was withdrawn in 2012 ([Annex 1](#), reference 211).

In 2012, the CONTAM Panel (1) evaluated substances for their acceptability as previous cargoes for edible fats and oils (Part III of III) and concluded that white mineral oils met the criteria for acceptability as a previous cargo. White mineral oils include class II and class III mineral oils.

In 2012, the CONTAM Panel also evaluated mineral oil hydrocarbons (MOH) in food (2) and considered it inappropriate to establish a common health-based guidance value (HBGV) for MOSH owing to the absence of toxicological studies on MOSH mixtures typical of those humans are exposed to. The Panel used an MOE approach to the risk assessment and selected a NOAEL of 19 mg/kg bw per day for granuloma formation as a RP for background exposure.

For the current review, previous assessments by the Committee and EFSA were used to identify relevant information, and a search for additional relevant toxicological data in animals or humans was undertaken on the PubMed, PubChem and Medline websites.

The following sources and databases were also queried to obtain data on chemical specifications, route(s) of synthesis, composition and uses of mineral oil, medium and low viscosity, class II and class III, as well as information on analytical methods and potential reactions with edible fats and oils: Embase, Food Science and Technology Abstracts (FSTA), Global Health and Medline.

The cut-off date for inclusion in this report was 30 September 2020.

Chemical and technical considerations

Chemical and technical considerations for mineral oil, medium and low viscosity, class II and class III are summarized in [Table 14](#).

Table 14

Chemical and technical considerations for mineral oil, medium and low viscosity, class II and class III

Name: mineral oil, medium and low viscosity, class II and III		
CAS number	Alternative CAS numbers	
8042-47-5	None	
Chemical details	White mineral oil (liquid paraffin oil)-edible grade Liquid hydrocarbons (paraffinic and naphthenic) Structure: complex mixture	
	Average relative molar mass (g/mol)	Viscosity at 100 °C (mm ² /s)
	Class II 400–480	7.0–8.5
	Class III 300–400	3.0–7.0
Route(s) of synthesis	Insoluble in water; soluble in nonpolar solvent (e.g. hexane) Manufactured from crude oil by distillation and refining (extraction, crystallization, dewaxing, acid treatments, clay treatments, etc.)	
Composition	Complex mixtures of hydrocarbons Medium and low viscosity mineral oils class II and III contain saturated hydrocarbons (MOSH (paraffins: straight chain or n-alkanes and branched alkanes or iso-alkanes; and naphthenes: cyclic alkanes)) with minimal content of mineral oil aromatic hydrocarbons (MOAH). Commercial products range from being free of MOAH (food-grade mineral oil) to containing 30% MOAH (crude mineral oil).	
Uses	Used as releasing agents, anticaking agents, glazing agents, lubricants, in food packaging, as anti-dust agents, and as diluents in printing inks and in cosmetic products.	
Analytical methods	An official method for the determination of mineral oils in crude and refined edible oils and fats is available (ISO, 2015). ^a A method for the determination of MOSH and MOAH (C10–C50) is also available (CEN, 2017). ^b Other analytical methods include LC-GC-FID, LC-GC/MS, GCxGC-FID, GCxGC-MS, LC-GC-MS/MS-FID, LC-GC-ToF MS.	
Potential reaction(s) with a subsequent cargo of fat or oil	No potential reactions were identified, although mineral oils are known to migrate into fats and oils.	

LC-GC-FID, on-line coupled liquid chromatography-gas chromatography-flame ionization detection; LC-GC/MS, liquid chromatography-gas chromatography/mass spectrometry; GCxGC-FID, two-dimensional gas chromatography with flame ionization detection; GCxGC-MS, two-dimensional gas chromatography-mass spectrometry; LC-GC-MS/MS-FID, liquid chromatography-gas chromatography-tandem mass spectrometry-flame ionization detection; LC-GC-ToF MS, liquid chromatography-gas chromatography-time-of-flight mass spectrometry.

^a ISO (2015). Determination of aliphatic hydrocarbons in vegetable oils. International Standard 17780: 2015.

^b CEN. Foodstuffs – vegetable oils and foodstuff on basis of vegetable oils – determination of mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH) with on-line HPLC-GC-FID analysis. Brussels: European Committee for Standardization; 2017.

Assessment**Biochemical aspects**

Absorption of alkanes, which decreases with increasing carbon number, may occur through the liver portal and the lymphatic system (2). Alkanes are oxidized to the corresponding fatty alcohols through cytochrome P450 and then generally biotransformed to fatty acids. In experimental animals, MOSH having carbon numbers C16 to C35 may accumulate in various tissues, including adipose tissue, lymph nodes, spleen and liver.

Similarly, in humans, MOH and MOSH accumulation has been reported in various tissues, including liver, spleen, lung, adipose tissue, brain, heart and kidney tissues. MOSH accumulated were mostly branched and cyclo-alkanes with a molecular mass range from C20 to C40. The accumulated fractions in human livers showed low levels of n-alkanes, suggesting that n-alkanes are not well absorbed and/or efficiently metabolized and eliminated (3–6). MOSH in human liver samples appear as a cloud of unresolved (in the chromatogram) and highly isomerized hydrocarbons, mainly naphthenes.

Animal studies to determine MOSH accumulation in terms of molecular mass and structure were carried out on MOSH mixtures (C14–C50) representative of the whole MOSH range to which humans are exposed via the diet (7–10). Rats were given daily dietary doses of 0, 2, 22 and 222 mg/kg bw for up to 120 days. Accumulation of MOSH occurred predominantly in the liver and to a lesser extent in adipose tissue and spleen. In liver and spleen, the maximum relative retention was at n-C29, and hydrocarbons below n-C19 and above n-C40 were virtually absent. Testing with MOSH subfractions showed MOSH in the mass range of C26–30 were more strongly accumulated than those between C20 and C25. In liver and spleen, n-alkanes up to C25 were eliminated, but accumulated at around C30.

Toxicological studies

Aliphatic hydrocarbons generally show low to moderate acute oral toxicity in laboratory animals with LD₅₀ values reported for some hydrocarbons at >5000 to >64 000 mg/kg in rats for MOH (C9–C50) (3).

In subchronic studies in F344 rats, the main findings following repeated exposure to MOH were organ weight changes, especially increased absolute and relative liver weights, and formation of liver granulomas/microgranulomas associated with inflammatory response (7, 10–14). The study by Baldwin et al. (11) was the first to report on granulomas described as focal changes composed of macrophages, lymphocytes, epithelioid cells, fibroblasts and occasional multinucleate Langhans-type giant cells. More severe lesions showed areas of necrosis. There are strain and species differences in liver granuloma formation following MOH exposure in experimental studies. Granulomas were found in F344 rats (females were more sensitive), but not in Sprague-Dawley rats, Long-Evans rats, mice, guinea-pigs and dogs (11–17).

In a recent subchronic study, Cravedi and co-workers (7–10) used a MOSH mixture representative of human exposures to MOSH from food (C14–C50) and MOSH subfractions to investigate the effects on the liver, and the relationship between MOSH accumulation in the liver and the formation of hepatic granulomas. MOSH concentrations in food were 0, 40, 400 and 4000 mg/kg, equivalent to

dietary doses of 0, 2, 22 and 222 mg/kg bw per day for a study duration of 120 days. Five female F344 rats were assigned to each experimental group and for each sampling period of 30, 60, 90 and 120 days (20 groups in total). Additionally, three groups were assigned to a 90-day treatment followed by a recovery period of 30 days. Significant changes in organ weights were noted, especially increased absolute and relative liver weights, and granuloma formation at 222 mg/kg bw per day. Increased organ weights seemed to be associated with accumulation of iso-alkanes, substituted cycloalkanes and wax n-alkanes, while granuloma formation mainly appeared to be related to n-alkanes >C₂₅ and not total accumulated MOSH (10). Granuloma formation and increase in liver weight were not seen at 22 mg/kg bw per day. The effects were observed after 90 or 120 days of treatment, but not after 30 or 60 days, and the hepatic granulomas formed were not reversible within a 30-day recovery period. Granuloma density was significantly higher in the group of rats exposed to the highest dose level compared to the control group after 90 and 120 days. Inflammatory cell aggregates increased along with strong granuloma formation. The increase in granuloma formation at the highest dose appeared to be accompanied by an increased number of lymphoid clusters in the liver parenchyma, reaching statistical significance after 90 days of exposure. A similar trend was observed after treatment for 120 days or treatment for 90 days followed by 30 days on control feed.

A study on mineral oil accumulation in human autopsy tissues collected in 2013 at the Medical University of Vienna did not find granulomas (18). The authors noted that granulomas linked to MOH by chemical analysis had been reported in the literature between 1970 and 1985 (see also (2)). The lipogranulomas reported in humans are characterized by the presence of histiocytic clusters around oil droplets, which were markedly different from the epithelioid granulomas often seen in F344 rats, which are characterized by the presence of activated, cytokine-secreting giant cells (19–21). Lipogranulomas in human livers are largely asymptomatic, do not progress over the years and are not associated with abnormalities of clinical relevance.

There was limited information on reproductive and developmental toxicity of MOSH (2). In a reproductive/developmental toxicity screening test, undecane (n-alkane) was given orally by gavage to CD rats at doses of 0, 100, 300 and 1000 mg/kg bw per day (22). Females were treated from 14 days before mating to day 3 of lactation, and killed on day 4 of lactation. Males were treated for 46 days and killed at day 47. Changes were observed in salivation, body weight gain, food consumption, haemoglobin levels, relative liver weights and clinical serum parameters at the highest or the two highest dose levels. No effects on reproductive ability, reproductive organ weights, gross or histopathological findings were observed in either sex, and there was no apparent influence on delivery or maternal behaviour of dams. Body weight gain was decreased in male

and female offspring of animals in the highest dose group. No effects were noted in terms of viability, general condition or autopsy findings in offspring.

Generally, white highly refined paraffinic and naphthenic mineral oil mixtures with a very low content of aromatic hydrocarbons were not mutagenic in the *Salmonella* Typhimurium mutagenicity tests, with or without metabolic activation, and they did not produce DNA adducts upon painting of mouse skin (23–25).

In the study by Shubik et al. (15), five petroleum waxes were tested by feeding them to male and female Sprague-Dawley rats at a level of 1% in the diet for 2 years; no carcinogenic or toxic effect was detected. These five petroleum waxes were also tested by repeated skin application, after dissolution in benzene solution, to mice and rabbits and by subcutaneous implantation in mice; no carcinogenic effects were found.

Two-year dietary studies were conducted to determine the chronic toxicity and reversibility and carcinogenicity of high-viscosity P70(H) and P100(H) white mineral oils in F344 rats (26). Mineral hydrocarbon deposition in liver, kidneys, mesenteric lymph nodes and spleen of female rats, and reversibility of deposition following cessation of exposure were evaluated. Dietary intakes were 60, 120, 240 and 1200 mg/kg per day. MOH were detected in the liver following exposure to either oil, and the maximal concentrations were similar for both oils but occurred more rapidly with the P70(H) oil. Liver mineral hydrocarbon content returned to near-background levels during the reversibility phase. No treatment-related mortality, neoplastic lesions or changes in clinical health, haematology, serum chemistry or urine chemistry were seen in any treated group. A statistically significant increase in food consumption was noted in the highest dose groups of either oil for both males and females, and statistically significantly higher body weights were noted in the males in the highest dose group from week 33 until study termination in the P100(H) study. Higher mesenteric lymph node weights were accompanied by increased severity of infiltrating histiocytes. This occurred to a greater extent with the P70(H) than the P100(H) oil. No other histopathology of significance was observed.

The carcinogenicity of dietary administration of a mixture of eight medium-viscosity liquid paraffin oils meeting Japanese food additive and Japanese Pharmacopoeia standards was investigated in F344 rats (27). Groups of 50 rats per sex per dose group were fed 0, 2.5 or 5% of this oil mixture in the diet for 104 weeks, equivalent to overall intakes of 0, 962.2 or 1941.9 mg/kg per day for males and 0, 1135.4 or 2291.5 mg/kg per day for females. Slight increases in food consumption and body weight were observed in both high-exposure groups. There were no effects on mortality, clinical signs and haematology; no differences in survival between the groups; and no statistically significant differences in the incidences of any tumour type between the test groups and the control animals.

Studies to determine whether oral exposure to a MOSH mixture in the diet at doses of 0, 2, 22 or 222 mg/kg bw per day had an impact on the immune response, measured as keyhole limpet haemocyanin (KLH)-specific IgM antibody production in response to antigen challenge, showed that MOSH did not have any effect (7, 10). Effects of mineral oils on autoimmunity in animals, based mainly on high concentrations of the inducing agent (typically 500 mL of pristane administered intraperitoneally), have been reported following parenteral administration, and at presumed high levels of exposure via inhalation or the skin in humans (28). Therefore, an evaluation of autoimmune arthritis was performed in dark Agouti rats exposed to a MOSH mixture in the diet at 0, 40, 400 and 4000 mg/kg, to pristane (4000 mg/kg diet), or injected pristane as a positive control. None of the rats fed MOSH or pristane developed arthritis symptoms or showed any significant increase in serum markers of arthritis, while this occurred in the positive controls (7, 29).

Allergenicity

The Committee did not identify any reports of allergenicity upon oral exposure to mineral oil, medium and low viscosity, class II and class III, or MOSH, that would indicate that they are or contain a known food allergen.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo substances (see [section 2](#), General consideration). Mineral oils are used as coatings for fruit, vegetables and confectionary, and as processing aids, lubricants, release agents, plasticizers and adhesives. MOSH may also be present in foods due to migration of printing inks on food packaging, from the packaging itself (e.g. jute bags used in Africa and Asia, wax paper or recycled cardboard), pesticide residues, or environmental pollution from motor oils and other sources. A number of studies conducted in the past 10 years have measured concentrations of MOSH in foods (e.g. (30–35)). MOSH has been found in foods at levels as high as 133 mg/kg (32).

Worst-case human dietary exposures to previous cargo substances in food oils have been estimated at 0.3 mg/kg bw per day (see [section 2](#), General consideration).

Estimates of MOSH exposures from sources other than previous cargoes vary widely. These estimates cover MOSH exposures from all sources, not just low- and medium-viscosity oils. Upper-level exposures to MOSH for infants whose parents are brand-loyal to formulae containing high MOSH concentrations were estimated at 2 mg/kg bw per day (35). However, for other populations, recent estimates of median or mean exposures to MOSH from sources other

than previous cargoes are 0.1 mg/kg bw per day or lower, and recent estimates of upper-level exposure to MOSH from these sources are 0.12 mg/kg bw per day or lower (35–37). The Committee therefore selected 0.1 mg/kg bw per day as the best estimate of exposure to MOSH from sources other than previous cargoes.

Evaluation

The critical toxicological end-point for evaluation of MOSH is liver granuloma formation and increase in liver weight in F344 rats. The Committee acknowledged that F344 rats represent the only strain and species that have shown liver granulomas accompanied by an inflammatory response due to MOSH exposure. In humans, lipogranulomas in the liver associated with exposure to MOSH have been observed, but these have not been associated with inflammatory reactions or other adverse consequences of clinical relevance. Given the lack of sufficient information on the mechanism of liver granuloma formation in F344 rats, the Committee concluded that it could not dismiss the human relevance of these liver granulomas and used them and the increase in liver weight in its assessment of MOH as previous cargoes.

The Committee decided to use the NOAEL of 22 mg/kg bw per day of a MOSH mixture (C14–C50, including class II and class III mineral oil, medium and low viscosity) from the study by Cravedi et al. as a RP (7). The Committee applied an MOE approach to assess the acceptability of MOSH as a previous cargo. Considering the estimated dietary exposure of 0.4 mg/kg bw per day (0.3 mg/kg bw per day from previous cargoes, plus 0.1 mg/kg per day from other sources), the MOE is 55. In its judgement of this MOE, the Committee took into account that the end-point of granuloma formation is determined in the most sensitive species, sex and strain, that the RP used is one tenth of the dose showing the effect and the uncertainty of the human health significance of the end-point. Furthermore, the exposure estimate is conservative. Based on these considerations the Committee concluded that the MOE of 55 was sufficient to address the uncertainties in the database.

There are no data on allergenicity upon oral exposure to the mineral oil, medium and low viscosity, class II and class III, or MOSH that would indicate that they are or contain a known food allergen.

No potential information has been identified with respect to the reaction of mineral oil with edible fats and oils, although migration studies have confirmed that mineral oil migrates into fats and oils.

The Committee concluded that mineral oils, medium and low viscosity, class II and class III meet the criteria for acceptability as previous cargoes provided the MOH is food-grade.

Commercial MOH products range from being free of MOAH (food-grade mineral oil) to containing 30% MOAH (crude mineral oil). The Committee noted that crude mineral oil is banned as a previous cargo and MOAH, which contain mutagenic and carcinogenic substances, would be unacceptable as previous cargoes. The current evaluation is based on the assumption that MOH products shipped as previous cargoes are highly refined food-grade products free of MOAH.

3.5.3.2 Montan wax

Explanation

Montan wax as a previous cargo was evaluated in 1996 by the EU SCF (38) and determined to be provisionally acceptable. The conclusion was based on the fact that montan wax itself is highly insoluble and that montan acid esters derived from montan wax were temporarily authorized as food additives for the surface treatment of certain fruits (1). Montan wax was re-evaluated in 2011 by EFSA's CONTAM Panel based on revisions to the criteria for the acceptability of previous cargoes as proposed by the Codex Committee on Fats and Oils in 2009 (1). The CONTAM Panel noted that montan wax is an ill-defined material and that there was insufficient information on the composition and toxicological profile of the substance to determine that it does not contain constituents that would be a human health concern when used as a previous cargo. Taking into account these deficiencies, the Committee concluded that montan wax does not meet the criteria for acceptability as a previous cargo for edible fats and oils.

For the current review, previous assessments by EFSA and a recent review by Health Canada were considered (39). A search by CAS number and name for additional relevant toxicological studies in animals or humans was undertaken to identify any critical new data for the assessment of risk to human health. REACH registration data from the ECHA dissemination website were accessed, and targeted searches were conducted on the PubMed and PubChem websites as well as using the Google Scholar search engine.

The following sources and databases were also queried to obtain data on chemical specifications, route(s) of synthesis, composition and uses of montan wax, as well as information on analytical methods and potential reactions with edible fats and oils: Agricola, CAB Abstracts, Embase, FSTA, Global Health, Medline, Scopus, the grey literature and PubMed. The cut-off date for inclusion in this report was 30 September 2020.

Chemical and technical considerations

Chemical and technical considerations for montan wax are summarized in [Table 15](#).

Table 15
Chemical and technical considerations for montan wax

Name: montan wax	
CAS number	Alternative CAS numbers
8002-53-7	None
Chemical details	Creamy white, light yellow, light brown or dark brown solid depending on grade Structure: complex mixture Melting point: 80–89 °C Insoluble in water; soluble in toluene and other organic solvents
Route(s) of synthesis	Montan wax is formed during coalification and is present in lignite or brown coal. It is extracted from dried, crushed particles of lignite using toluene.
Composition	Esters (43–60%) Fatty acids (0.1–25%) Alcohols (1–13%) n-Alkanes (1–10%) Ketones (1–1.5%) Resin acids (10–15%) Terpenes (0.1–3.5%) Hydroxy acids (1%) Ash (0.5%) Resin + asphalt (25%) Sterols, alkenes, aldehydes and ethers (not defined)
Uses	Used in shoe polish, floor wax, car wax, etc. (as a replacement for carnauba wax). Used as an insulator, road asphalt additive, in paper making, leather finishing and lubricant manufacture, as a chemical dispersant in agricultural applications, and in waterproofing of wood products; minor use as a food additive
Analytical methods	None found for previous cargoes. Possible means of detection in fats and oils by GC-FID or GC-MS
Potential reaction(s) with a subsequent cargo of fat or oil	No specific information is available on the reactions of montan wax with edible fats and oils

GC-FID, gas chromatography with flame ionization detection; GC-MS, gas chromatography–mass spectrometry.

Assessment

Biochemical aspects

No data specific to the disposition of montan wax following oral exposure were identified. The composition of montan wax varies according to the geographical region, plant material that has undergone coalification and the period in which it was formed. Crude montan wax, deresinated montan wax and refined montan wax from lignite have long chain fatty acids (C14–C34), wax alcohols (C24–C32) and normal alkanes (C23–C33). Several studies have identified individual constituents of montan wax, which vary according to the source and degree of refinement. Despite this variability, most constituents identified tended to be large, hydrophobic molecules that are anticipated to have low oral bioavailability.

Alkane constituents of montan wax that are absorbed are expected to be metabolized to the corresponding fatty alcohols and fatty acids.

Toxicological studies

Although assessments are based on limited information, montan wax is anticipated to be of low acute oral toxicity, with an estimated rat oral $LD_{50} > 12\,000$ mg/kg bw (40).

In an OECD guideline-compliant subchronic oral toxicity study, male and female F344/DuCrj rats (10 per sex per group) were administered montan wax in the diet for 90 days at levels of 0, 0.56, 1.67 or 5% (equivalent to 0, 260, 835 or 2500 mg/kg bw per day) for 90 days (41). The authors did not specify whether the test article was a crude, deresinated or refined montan wax, nor its geographical source. No deaths occurred in any group and there were no remarkable changes in general condition. However, haematological and serum biochemical changes were observed at all doses tested, as were diffuse liver granulomas accompanied by hepatocyte effects, as well as lymphocytic infiltration and granulomatous lesions in mesenteric lymph nodes. In addition to effects occurring from the lowest dose tested, most of the lesions observed, including the liver granulomas, showed no clear dose–response relationship. A NOAEL for subchronic oral toxicity could therefore not be established on the basis of these findings. There is some evidence to suggest that the F344 rat is particularly sensitive to certain mineral waxes and oils and that adverse effects may be more severe and consequential in this strain (Annex 1, reference 211) (42–45). However, these observations are based on studies of long-chain MOH generally and are not specific to montan wax.

No chronic toxicity or carcinogenicity studies were located for montan wax and no data on end-points such as developmental or reproductive toxicity, immunotoxicity or neurotoxicity were identified. Montan wax in ethanol was non-mutagenic and non-cytotoxic in guideline-compliant bacterial reverse mutation assays using *Salmonella* Typhimurium strains TA97a, 98, 100, 102 and 1535 with and without metabolic activation (46).

Allergenicity

The Committee did not identify any reports of allergenicity upon oral exposure to montan wax that would indicate that it is or contains a food allergen.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo substances (see section 2, General consideration).

Montan wax substances are used for the protection of fruit surfaces and as additives for food packaging in some countries and regions; however, no data are available on concentrations resulting from these uses.

Worst-case human dietary exposures to previous cargo contaminants in food oils have been estimated at 0.3 mg/kg bw per day (see [section 2](#), General consideration).

Health Canada (39) evaluated the potential for exposure to montan wax substances from food packaging and concluded that exposure related to this use is negligible.

Evaluation

While oral bioavailability of montan wax is expected to be limited and the material appears to be of low acute toxicity, in the only repeat-dose study available (41), montan wax produced toxicity at all doses tested. The Committee noted that montan wax is a highly variable and poorly defined material. Given the high degree of variability in composition, the extent to which the particular test article in the subchronic study is representative of the diversity of the various forms of crude, desinated or refined montan wax currently in commerce is unknown. Therefore, the Committee could not characterize the hazard of montan wax shipped as a previous cargo.

No specific information was found on the reactions of montan wax with edible fats and oils.

The Committee determined that the available evidence was not sufficient to characterize the risk of montan wax; as a result, it was concluded that montan wax does not meet the criteria for acceptability as a previous cargo for edible fats and oils.

Recommendations

The Committee recommended that sufficient chemical and toxicological information that allows the evaluation of montan wax as shipped are made available prior to the next evaluation. At a minimum this information should address the following:

- degree of refinement and chemical constituents;
- repeat-dose toxicological data on representative products in a relevant animal model.

3.5.3.3 Propylene tetramer

Explanation

Propylene tetramer was evaluated by SCF in 1996, at which time it was determined to be acceptable as a previous cargo, subject to the results of ongoing genotoxicity testing ((38) as cited in (1)). At the time of the evaluation, only limited toxicity data were available, but no specific concerns based on chemical structure were identified. Moreover, it was anticipated that propylene tetramer residue levels would be low, as the substance is easily removed by cleaning as well as during refinement of oils.

In 2011, EFSA (1) evaluated the acceptability of propylene tetramer as a previous cargo, to ensure continued alignment with the revised criteria for acceptable previous cargoes proposed by the Codex Committee for Fats and Oils (47). The expert panel concluded that propylene tetramer would not be of toxicological concern at the levels that would occur when used as a previous cargo for edible fats and oils, and therefore the substance met the criteria for acceptability. Although it was acknowledged that studies on carcinogenicity were lacking, the panel concluded that in the absence of genotoxicity or evidence of pathological changes in subchronic studies, which might indicate carcinogenic potential, there was no concern for carcinogenicity from the use of propylene tetramer as a previous cargo.

For the current review, previous assessments by SCF, OECD and EFSA were considered, as were recent toxicological studies conducted by the Japanese National Institute of Health Sciences. A search by CAS number and name for additional relevant toxicological studies in animals or humans was undertaken to identify any critical new data for the assessment of human health risk. Targeted searches were conducted on the PubMed and PubChem websites as well as using the Google Scholar search engine.

The following sources and databases were also queried to obtain data on chemical specifications, route(s) of synthesis, composition and uses of propylene tetramer, as well as information on analytical methods and potential reactions with edible fats and oils: Embase, FSTA, Global Health, Medline, Scopus and PubMed.

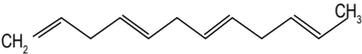
The cut-off date for inclusion in this report was 30 September 2020.

Chemical and technical considerations

Chemical and technical considerations for propylene tetramer are summarized in [Table 16](#).

Table 16

Chemical and technical considerations for propylene tetramer

Name: propylene tetramer	
CAS number	Alternative CAS numbers
6842-15-5	None
Chemical details	4E,7E,10E)-dodeca-1,4,7,10-tetraene Colourless liquid
	
	Molar mass: 162.27–168.32 g/mol Melting point: –33.6 to –31 °C Boiling point: 213 °C
	Insoluble in water; soluble in ethanol, ether and acetone
Route(s) of synthesis	Manufactured by polymerization of propene using phosphoric acid or sulfuric acid as catalysts
Composition	C12 alkenes (>71%) C10/C11 alkenes (<22%) C13–C15 alkenes (<15%)
Uses	Used in the production of alcohols, surfactants, detergents, plasticizers, anti-rust agents, and petroleum and lubricating oil additives
Analytical methods	None found for previous cargoes. Possible means of analysis in fats and oils by GC-FID (methods applied to 12-carbon alkenes)
Potential reaction(s) with a subsequent cargo of fat or oil	No specific information is available on reactions of propylene tetramer with edible fats and oils

GC-FID, gas chromatography with flame ionization detection.

Assessment**Biochemical aspects**

No studies were identified that investigated the toxicokinetics of propylene tetramer specifically. However, propylene tetramer is a crude mixture largely of olefins and some information on the disposition of these substances following oral administration is available (1). On the basis of physicochemical properties (average molecular weight of 168 to 160, high lipid solubility), EFSA determined that the main olefins present in propylene tetramer are “likely to be absorbed from the gastrointestinal tract to a reasonable extent and distributed throughout the body” (1). The initial step in the metabolism of olefinic compounds appears to be cytochrome P450-dependent oxidation in the liver to form unstable electrophilic epoxides, which are subsequently inactivated by the formation of protein adducts, hydrolysed to the corresponding diol by epoxide hydrolases or form glutathione conjugates that are ultimately excreted in urine in the form of mercapturic acids (1, 48, 49). Henderson has shown important species-specific differences in the subcellular location and activity of these enzymes that mediate

the potential toxicity of olefins (49). Notably, activity of the hydrolysis pathway appears to be far more prominent in primates than in rats or mice, suggesting humans may be less sensitive to olefin toxicity than are rodents (49).

Toxicological studies

Propylene tetramer and its constituents consistently demonstrate low oral acute toxicity. A recent study conducted by the Japanese National Institute of Health Sciences in accordance with OECD test guideline 423 (Acute Toxic Class Method) estimated the acute oral LD₅₀ of propylene tetramer in rats to be approximately 5000 mg/kg bw (50). The low acute oral toxicity of propylene tetramer is consistent with previous studies of the individual alkenes and mixtures of alkenes that comprise this substance; in most cases oral LD₅₀ values were observed to be greater than 10 g/kg bw in mice and rats (1).

Similarly, studies of olefins administered via the oral route indicate that these substances are generally of low toxicity upon repeat administration. The most sensitive end-point is kidney effects in male rats; however, the mechanism of action is attributed to induction of α 2u-globulin and hyaline droplet accumulation in proximal tubule cells. As humans lack an analogous protein at levels sufficient to produce a similar response, α 2u-globulin-mediated nephropathy is widely acknowledged as male-rat-specific and therefore not relevant to the evaluation of toxicological risk in humans.

Propylene tetramer was evaluated in a combined repeated-dose oral toxicity study with a reproduction/developmental toxicity screening test similar to OECD test guideline 422 (50). Male and female CrI:CD(SD) rats (12 animals per sex and dose) were administered propylene tetramer daily by oral gavage at doses of 0 (vehicle control), 40, 150 or 600 mg/kg bw per day from 14 days pre-mating to day 4 of lactation (40–45 days). Five of 12 males in the 0 and 600 mg/kg bw per day groups were evaluated as a 14-day recovery group, and 10 females per dose were treated with 0 or 600 mg/kg bw per day and kept as a satellite group (without mating) to be evaluated after the administration period or following a 14-day recovery period.

Haematotoxicity (anaemia) was observed in male rats administered propylene tetramer at doses of 150 mg/kg bw per day and higher as well as in satellite females at 600 mg/kg bw per day. Hepatotoxicity was observed in both sexes; liver weights were increased in animals given the dose of 150 mg/kg bw per day and higher, and hypertrophy of centrilobular hepatocytes occurred at 600 mg/kg bw per day. Alterations in clinical chemistry parameters (α 2-globulin fraction, γ -glutamyl transpeptidase, total cholesterol and glucose levels) were observed in both sexes. Thyroid effects (increased thyroid weight and thyroxin level as well as hypertrophy of follicular cells) were seen in females at the highest

dose tested. Following cessation of treatment, the liver, kidney and haematological parameters resolved during the recovery period, whereas the thyroid effects, which were limited to females at the highest dose tested, persisted throughout the 14-day recovery period. No reproductive or developmental toxicity effects were described. The results of this study indicate an absence of lesions such as proliferative effects, hyperplasia or hyperplastic foci that would give rise to concerns of carcinogenicity. The Committee determined that the lowest NOAEL for repeated-dose systemic effects not attributable to α 2u-globulin induction was 40 mg/kg bw per day, based on increased liver weights in rats at the next highest dose of 150 mg/kg bw per day.

The *in vitro* genotoxic potential of propylene tetramer was evaluated in bacterial reverse mutation assays using *Salmonella* Typhimurium strains TA100, TA1535, TA98 and TA1537 and *Escherichia coli* WP2uvrA with and without metabolic activation (50). Propylene tetramer in acetone with or without S9 mix did not produce revertant colonies when tested at concentrations up to 5000 μ g/plate. Likewise, an *in vitro* cytotoxicity/chromosomal aberration test conducted in Chinese hamster lung (CHL/IU) cells produced no evidence of genotoxicity with or without metabolic activation.

Allergenicity

The Committee did not identify any reports of allergenicity upon oral exposure to propylene tetramer that would indicate this substance is or contains a known food allergen.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo substances (see [section 2](#), General consideration).

Worst-case human dietary exposures to previous cargo substances in food oils have been estimated at 0.3 mg/kg bw per day (see [section 2](#), General consideration).

Evaluation

Although no chronic or carcinogenic studies were identified, the Committee concluded that propylene tetramer does not have genotoxic potential *in vitro* nor any structural alerts for carcinogenicity. These findings are consistent with other individual olefins present in propylene tetramer or mixtures thereof (51, 52). The Committee noted the availability of a recent guideline-compliant subchronic study in rats and decided to use the NOAEL from this study of 40 mg/kg bw per day based on increased liver weights as an RP in a MOE approach to evaluate the acceptability of propylene tetramer as a previous cargo for edible fats and oils.

Comparison of the generic maximum anticipated oral exposure to propylene tetramer from previous cargoes of 0.3 mg/kg bw per day with the RP of 40 mg/kg bw per day yields a MOE of approximately 130. This margin is considered adequate to address uncertainties in the health effects database. Therefore, and given that this substance is not known or anticipated to be a food allergen, the Committee concluded that propylene tetramer meets the criteria for acceptability as a previous cargo for edible fats and oils.

3.5.3.4 Soybean oil epoxidized (ESBO)

Explanation

Soybean oil epoxidized (ESBO) was reviewed by the EU SCF in 1996 and assigned a provisional TDI (pTDI) of 1 mg/kg bw per day based on a chronic study in rats. The HBGV was deemed provisional pending the results of genotoxicity testing although the SCF concluded at the time that ESBO was acceptable as a previous cargo for edible fats and oils (38). In 2004, having reviewed the results of genotoxicity assays and concluding that ESBO is neither carcinogenic nor genotoxic, the TDI was affirmed by EFSA and the provisional designation was removed (53). ESBO was also evaluated within the framework of the OECD Screening Information Dataset (SIDS) and determined to be a low priority for further assessment owing to its low hazard profile (54).

A review of ESBO in food contact applications was published in a peer-reviewed journal by scientists from the US Food and Drug Administration (US FDA) (55). In addition, a toxicity review of ESBO was commissioned by the US Consumer Product Safety Commission (CPSC) in 2019 (56).

For the current review, previous assessments by SCF, EFSA, US FDA and CPSC were considered. A search by CAS number and name for additional relevant toxicological studies in animals or humans was also undertaken to identify any critical new data for the assessment of human health risk. Targeted searches were conducted on the PubMed and PubChem websites as well as using the Google Scholar search engine, and relevant databases from competent authorities were searched.

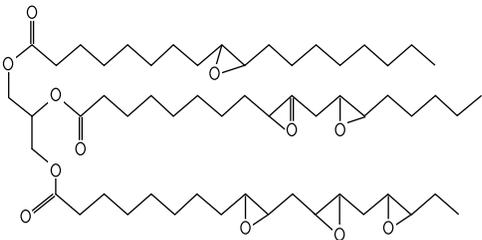
The following sources and databases were also queried to obtain data on chemical specifications, route(s) of synthesis, composition and uses of ESBO, as well as information on analytical methods and potential reactions with edible fats and oils: Embase, FSTA, Global Health and Medline. The cut-off date for inclusion in this report was September 2020.

Chemical and technical considerations

Chemical and technical considerations for ESBO are summarized in [Table 17](#).

Table 17

Chemical and technical considerations for soybean oil epoxidized (ESBO)

Name: Soybean oil epoxidized	
CAS number	Alternative CAS numbers
8013-07-8	None
Chemical details	ESBO Oil, mixture of epoxy compounds of triglycerides Pale yellow, viscous liquid Approximate contribution of fatty acids: linolenic (7%) oleic (25%) linoleic (53%) saturated fatty acids (15%) Representative structure for ESBO: 
	Insoluble in water; soluble in hydrocarbons, ketones, esters and higher alcohols; slightly soluble in ethanol; miscible in edible fats and oils
Route(s) of synthesis	Manufactured via epoxidation of soybean oil with carboxylic acid and hydrogen peroxide in the presence of sulfuric or phosphoric acid catalysts; using enzymes; using inorganic and organic peroxides; and using halohydrins in the presence of hypohalous acids and oxygen with a silver catalyst.
Composition	Occurs as a mixture with no single composition depending on the soybean oil used as feedstock. All double bonds in the fatty acid chains of ESBO are epoxidized.
Uses	Used as a plasticizer, lubricant, cross-linking agent and stabilizer in polyvinyl chloride, etc.
Analytical methods	None found for previous cargoes. From studies performed to determine ESBO migration into foods including olive oil, recommended approaches are GC-FID, LC-GC-FID, GC-MS, LC-MS/MS and LC-HRMS.
Potential reaction(s) with a subsequent cargo of fat or oil	No specific information was found on the reaction of ESBO with edible fats and oils, although migration studies have confirmed that ESBO migrates into oily foods and oil-based food simulants (e.g. olive oil).

GC-FID, gas chromatography with flame ionization detection; LC-GC-FID, on-line coupled liquid chromatography-gas chromatography-flame ionization detection; GC-MS gas chromatography-mass spectrometry; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LC-HRMS, liquid chromatography-high resolution mass spectrometry.

Assessment
Biochemical aspects

Although no studies specific to the toxicokinetics of ESBO were identified, ESBO is a mixture of triglycerides and therefore its absorption and metabolism are anticipated to be similar to that of other vegetable oils (54, 56, 57). Therefore,

following emulsification by bile salts, pancreatic lipases in the gastrointestinal tract are expected to readily hydrolyse triglycerides into mono- and diglycerides, which may then be absorbed in the duodenum. Further metabolism by esterases is expected to yield glycerol and the corresponding free fatty acids. The oral bioavailability of epoxidized fatty acids was evaluated by Wilson et al. in healthy adult female volunteers (58). In this study, in which the women consumed triglycerides containing uniformly labelled [¹³C]-monoepoxy or diepoxy fatty acids, oral bioavailability decreased as the degree of epoxidation increased.

Toxicological studies

Although the underlying mode of action of ESBO toxicity is unknown, the substance is likely to enter normal metabolic pools and the effects observed at high doses are consistent with the general effects of high dietary lipid intake (56, 59). The toxicity of ESBO is relatively well characterized, although most of the studies are dated and only available through summaries published in secondary sources. In general, studies in experimental animals indicate that ESBO produces growth suppression as well as increased liver and kidney weights when administered at relatively high doses, with increased toxicity associated with higher epoxide numbers. ESBO has low acute oral toxicity, with a reported rat oral LD₅₀ exceeding 5 g/kg bw (54).

Several subchronic oral toxicity studies of ESBO in both rats and dogs have been reported. Administration of ESBO to Holtzman albino rats (10 animals per sex and dose) at concentrations of 0, 0.1, 0.5, 1.0, 5.0 or 10% in the diet (equivalent to 0, 50, 250, 500, 2500 or 5000 mg/kg bw per day) for 90 days suppressed growth and increased liver and kidney weights at the highest dose tested ((60) as cited in (55)). In another subchronic study, albino rats (10 animals per sex and dose; strain not reported) were fed diets containing 0, 0.04, 0.2, 1 or 5% ESBO (equivalent to 0, 20, 100, 500 or 2500 mg/kg bw per day) for 90 days ((61) as cited in (55)). Changes in body weight and food intake were observed in higher dose groups, with liver weight increases at 500 mg/kg bw per day in females and 2500 mg/kg bw per day in males. ESBO also produced treatment-related kidney effects in males at doses of 500 mg/kg bw per day and higher. In studies in which rats were administered five variants of ESBO with varying epoxide content in the diet for 8 or 10 weeks, effects were reported to be more severe in rats exposed to test articles with higher epoxide content (62 as cited by the British Industrial Biological Research Association BIBRA (63)).

Two subchronic studies in which ESBO was administered to dogs ((64) as cited in (55); (65)) for 14 weeks or 1 year, respectively, demonstrated reduced food intake, weight loss and growth suppression at the highest dose tested (5% in diet, equivalent to 1250 mg/kg bw per day), which was attributed to food

palatability. No additional adverse effects were reported other than minimal fatty liver infiltration in one animal in the highest dose group in one study (65). However, the applicability of these findings in the evaluation of the safety of ESBO is limited by the small group sizes, high variances and reporting deficiencies.

The results of two chronic rodent bioassays are available in which ESBO was administered to rats in the diet for 2 years. In the first study, Larson and colleagues conducted chronic feeding studies of two ESBO products with differing epoxide content in albino rats (15 animals per sex and dose; strain not specified) at doses up to the equivalent of 2500 mg/kg bw per day (65). Two-year survival was unaffected and no significant treatment-related effects on haematological or histopathological end-points were detected at terminal sacrifice, although reporting is limited. In animals exposed to the test article with a higher epoxide content, elevated relative liver weights were observed in both sexes as well as elevated relative kidney weights in females, although the organ weight effects were not accompanied by histopathological changes (65).

In a second chronic study, Wistar rats (48 animals per sex and dose) were administered a diet containing ESBO at 0%, 0.025%, 0.25% or 2.5% (equivalent to dose levels of 0, 12.5, 125 or 1250 mg/kg bw per day) for 2 years ((66) as cited in (55)). No treatment-related effects on survival were noted. In the highest dose group, slightly increased body weights in males and slightly decreased body weights in females were observed, accompanied by increased uterus weights in females and increased liver and kidney weights in males. It is not clear, however, whether the organ weight changes observed were absolute or relative. Although the complete study report was not available, a “comprehensive” range of tissues were said to have been examined and the observed changes in organ weights were not accompanied by histopathological changes (56). The Committee identified a NOAEL of 125 mg/kg bw per day on the basis of organ weight changes in this chronic study.

The results of the two chronic rodent bioassays provide no evidence of increased tumour incidence in rats administered ESBO in the diet for up to 2 years. ESBO has also been evaluated in a range of in vitro tests for mutagenicity and consistently produced negative results with or without metabolic activation. ESBO was not mutagenic in Ames bacterial reverse mutation assays using various strains of *Salmonella* Typhimurium nor in mammalian gene mutation assays using CHO cells. ESBO was also evaluated for clastogenicity in human and mouse lymphoma cells, and no evidence of chromosomal alterations was observed with or without metabolic activation. Based on this information, the Committee did not consider ESBO to have genotoxic potential.

The reproductive and developmental toxicity of ESBO has also been evaluated in male and female Sprague-Dawley rats in a one-generation study ((67) as cited in (55)). No adverse effects were observed on any reproductive or

developmental end-points and the NOAEL was reported to be the highest dose tested, which was 1000 mg/kg bw per day.

Allergenicity

Refined soya bean oil (non-epoxidized) has very low levels of allergenic proteins and is not regarded as a food allergen even though soya bean allergy is relatively common (68). Similarly, the Committee did not identify any reports of allergenicity upon oral exposure to ESBO that would indicate that this substance is or contains a food allergen.

Assessment of dietary exposure

A worst-case concentration of 100 mg/kg has been assumed for all previous cargo substances (see [section 2](#), General consideration).

ESBO is used in Europe, the USA, and in other parts of the world as a stabilizer in PVC-based food contact materials, such as gaskets for glass jar lids and film wraps. It may also be used in adhesives.

Worst-case human dietary exposures to previous cargo substances in food oils have been estimated at 0.3 mg/kg bw per day (see [section 2](#), General consideration).

Estimates of exposure to ESBO from food packaging sources have varied from 0.13 mg/kg bw per day to 0.64 mg/kg bw per day (54, 69, 70). The estimate of 0.13 mg/kg bw per day (55) is a deterministic estimate of mean exposure from food packaging sources based on the most recently available ESBO migration data, and was considered by the Committee to best represent likely exposure to ESBO from sources other than previous cargoes.

Evaluation

The overall toxicity database for ESBO is relatively complete, including acute, subchronic and chronic toxicity studies. ESBO is not genotoxic or carcinogenic and is not a reproductive or developmental toxicant. The overall systemic toxicity of ESBO is considered to be low and no toxicologically relevant impurities or reaction products with edible fats or oils are anticipated. The Committee decided to use the NOAEL of 125 mg/kg bw per day based on organ weight changes at the next highest dose in a 2-year rat oral bioassay as a RP to evaluate the acceptability of ESBO as a previous cargo for edible fats and oils. It should be noted that ESBO is also used in a variety of food packaging applications, which may contribute significantly to exposure. Recently, Bandele et al. estimated the cumulative daily intake of ESBO from its use in PVC-based food contact articles to be 0.13 mg/kg bw per day for the general US population (55). A worst-case exposure estimate of 0.43 mg/kg bw per day can therefore be derived by combining the maximum

estimated exposure from ESBO as a previous cargo (0.3 mg/kg bw per day) with other sources associated with food packaging. Comparison of the RP with this estimate yields a MOE of approximately 290. The Committee considered this margin adequate to account for uncertainties in the health effects and exposure databases.

ESBO is not known or anticipated to be a food allergen.

No specific information has been identified on the reaction of ESBO with edible fats and oils, although migration studies have confirmed that ESBO migrates into oily foods and oil-based food simulants (e.g. olive oil).

Therefore, ESBO meets the criteria for acceptability as a previous cargo for edible fats and oils.

A toxicological monograph on oils and waxes including dietary exposure and chemical and technical considerations was prepared.

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3.5.4 Solutions (Group 4)

3.5.4.1 Calcium nitrate and calcium ammonium nitrate

Explanation

The toxicological datasets on oral exposure to calcium nitrate and calcium ammonium nitrate are sparse; therefore, available toxicological data on calcium, ammonium and nitrate were reviewed to conduct a toxicological evaluation of calcium nitrate and calcium ammonium nitrate as previous cargoes for edible fats and oils. Given that dolomite and phosphate rock could be used in the manufacture of calcium ammonium nitrate and calcium nitrate, respectively, toxicological data on magnesium and phosphate were also reviewed to complete their toxicological evaluation.

The Committee has previously evaluated many calcium salts, including calcium sulfate, calcium chloride, calcium carbonate, calcium acetate and calcium gluconate for use as food additives. The Committee allocated an ADI “not specified”¹ to these salts based on their low toxicity determined from a review of data available at the time of the evaluations. SCF (1) established a tolerable upper intake level (UL) for calcium of 2500 mg/day for adults, including pregnant and lactating women. This UL was confirmed by EFSA (2, 3).

The toxicological data on nitrate were reviewed by the Committee at its sixth, eighth, seventeenth, forty-fourth (Annex 1, reference 116) and fifty-ninth meetings (Annex 1, reference 160). At its sixth meeting, the Committee established an ADI of 0–5 mg/kg bw for sodium nitrate, based on a NOAEL² of 500 mg/kg bw per day for body weight gain at a higher dose in a long-term study in rats and a short-term study of toxicity in dogs and by applying an uncertainty factor of 100. This ADI was retained at the eighth and seventeenth meetings. At the forty-fourth (Annex 1, reference 116) and fifty-ninth meetings (Annex 1, reference 160), the Committee concluded that the rat was an unsuitable model for evaluating toxicity of nitrate owing to quantitative differences in conversion of nitrate to nitrite between rats and humans. However, owing to limited toxicity data on nitrate and nitrite in other animal species, the Committee used toxicokinetic modelling of the rat data to estimate a conversion rate of nitrate to nitrite in humans of about 5–7% in average individuals and 20% in individuals with a high rate of conversion. Based on a re-evaluation of a long-term study in rats, and consideration of the available epidemiological data, the Committee concluded that a NOAEL of 370 mg/kg bw per day was most appropriate for the

¹ A term applicable to a food substance of very low toxicity that does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary (Environmental Health Criteria No. 240).

² At the time called NOEL.

safety evaluation of nitrate and established an ADI of 0–3.7 mg/kg bw for nitrate, expressed as nitrate ion, by applying an uncertainty factor of 100 to the NOAEL ([Annex 1](#), reference 160).

The Committee has previously evaluated many ammonium salts, such as ammonium carbonate, ammonium bicarbonate, ammonium chloride and ammonium acetate, and allocated an ADI “not specified” to these salts based on their low toxicity determined upon review of the data available at the time of the evaluations.

The Committee has also previously evaluated many magnesium salts, including magnesium carbonate, magnesium hydrogen carbonate, magnesium sulfate, magnesium chloride, magnesium DL-lactate, magnesium gluconate, magnesium acetate, magnesium citrate, magnesium adipate, magnesium succinate, monomagnesium phosphate and magnesium stearate. Given their widespread occurrence in food from natural sources and their low toxicity assessed based on a review of available toxicological data, the Committee allocated an ADI “not specified” to the evaluated magnesium salts. The Institute of Medicine in the USA established recommended dietary allowances of magnesium at 80–420 mg/day for different age groups, which are considered to meet the nutrient needs of 97–98% of the individuals in a population (4). SCF established an upper level of 250 mg/day for readily dissociable magnesium salts, such as magnesium chloride, magnesium sulfate, magnesium carbonate, magnesium lactate, and compounds in nutritional supplements, in water or added to food and beverages (5).

At its twenty-sixth meeting, the Committee established a maximum tolerable daily intake (MTDI) for phosphates, diphosphates and polyphosphates of 70 mg/kg bw, expressed as phosphorus ([Annex 1](#), reference 59). More recently, at its seventy-sixth meeting, the Committee stated that the approach taken to derive the MTDI of phosphates from the toxicological data was unclear. This was because the end-point considered (nephrocalcinosis in rats) for deriving this value may not be relevant to humans, leading to an overly conservative value of the MTDI. The Committee, therefore, acknowledged the need to review the toxicological basis of the MTDI for phosphate salts ([Annex 1](#), reference 211).

The EFSA CONTAM Panel concluded that calcium nitrate and calcium ammonium nitrate met the criteria for acceptability as previous cargoes (2), as the criterion for an ADI or TDI at that time, i.e. 0.1 mg/kg bw per day, was below the existing UL for calcium and the ADI for nitrate, and no numerical ADI was considered necessary for most ammonium salts.

For the present assessment, the Committee identified and reviewed its previous evaluations (monographs) as well as those of SCF and EFSA on calcium nitrate and calcium ammonium nitrate, or calcium, nitrate, ammonium, magnesium and phosphates, and located additional references from these evaluations. This was followed by comprehensive searches for data on calcium

nitrate and calcium ammonium nitrate, or calcium, nitrate, ammonium, magnesium and phosphates on PubMed and PubChem. The cut-off date for the searches was 20 August 2020. Some retrieved references contained relevant toxicological information not detailed under previous evaluations. These included a report of contact dermatitis upon dermal exposure to calcium ammonium nitrate and recently published articles on PBTK modelling of nitrate from dietary sources, and the potential of nitrate to be converted into carcinogenic nitrosamines and its possible implications for human health.

Chemical and technical considerations

Chemical and technical considerations for calcium nitrate and calcium ammonium nitrate solutions are summarized in [Tables 18](#) and [19](#).

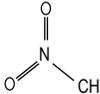
Assessment

Biochemical aspects

Calcium: The Committee noted that calcium is an essential nutrient. In the soluble ionized form, calcium is absorbed by the intestine in humans via active transport across cells mainly in the duodenum and the upper jejunum, and through passive diffusion mainly in the ileum and to a lesser extent in the large intestine (6–8). Most of the absorbed calcium is stored in the skeleton (about 99% of the body's calcium), depending on the physiological needs related to growth and health conditions, including pregnancy and lactation (8). Absorbed calcium that is not retained by the body is excreted in urine, faeces and sweat (1, 8).

Nitrate: The Committee revisited its previous evaluation of nitrates conducted at the fifty-ninth meeting ([Annex 1](#), reference 160) (9) to examine its toxicokinetic profile for the present assessment. The Committee had previously concluded that nitrate is rapidly absorbed after oral administration such that its concentration increases in the plasma within 10 minutes ([Annex 1](#), reference 160) (9). The elimination half-life ($t_{1/2}$) of nitrate in the plasma is 6.5 hours and 70% of the dose is excreted in the urine within 10 hours of oral administration. Some of the dietary nitrate is converted to nitrite through non-enzymatic processes and to nitric oxide by symbiotic bacteria in the oral cavity and stomach. The nitric oxide generated plays a protective role in the cardiovascular system and the gastric mucosa as well as against metabolic diseases (10, 11). The Committee also concluded that the rat was an unsuitable model for examining toxicokinetics of nitrate as the rat does not convert nitrate into nitrite in a quantitatively similar way to humans ([Annex 1](#), reference 160) (9). Toxicokinetic modelling based on a simple one-compartment approach (12) as well as on a multi-compartment framework (13) was used to examine the kinetics of nitrate. The Committee determined that the range of nitrate to nitrite conversion in humans is about

Table 18
Chemical and technical considerations for calcium nitrate solution

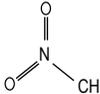
Name: Calcium nitrate solution	
CAS number	Alternative CAS numbers
35054-52-5 (hydrate)	10124-37-5 (anhydrous), 13477-34-4 (tetrahydrate)
Chemical details	Nitric acid, calcium salt, CN CN is a colourless or white to grey crystalline or granular material. Structure: multiple different but closely related formulations exist.
	 <ul style="list-style-type: none"> • 1/2 Ca • × H₂O <p>Molar mass, anhydrous: 164.09 g/mol Molar mass, tetrahydrate: 236.15 g/mol Melting point, anhydrous: 560 °C Melting point, tetrahydrate: ~ 44 °C</p>
Route(s) of synthesis	Readily soluble in water Manufactured by dissolution of limestone in nitric acid or as a by-product of the nitrophosphate fertilizer manufacturing process.
Composition	Variable formulations exist in commerce – amounts of Ca and N vary. Specific composition depends on the final use of the product.
Uses	Used as fertilizer – source of nitrogen. Additionally, used in wastewater treatment and in production of concrete.
Analytical methods	None found for previous cargoes: possible means of detection in fats and oils by inductively coupled plasma (ICP) analysis for Ca residues.
Potential reaction(s) with a subsequent cargo of fat or oil	Formation of calcium salts of free fatty acids is possible; reaction conditions are not expected to be present in a cargo of edible fats or oils.

5–7% in average individuals and 20% in individuals with a high rate of conversion ([Annex 1](#), reference 160) (9). The model developed by Zeilmaker et al. (13) also predicted that a single dose of nitrate from vegetables as well as repeated intake of nitrate in drinking-water up to 44 mg/kg bw would not induce clinical methaemoglobinaemia and that lethal toxicity would occur at doses > 440 mg/kg bw. The Committee also reviewed recent reports on the potential of nitrate to be converted to carcinogenic nitrosamines in the body under certain conditions, such as acidic gastric environment (11, 14). However, recent epidemiological cohort studies concluded that there is no clear evidence of an association of dietary nitrates with increased incidence of cancers, such as stomach cancer (15).

Ammonium: The Committee noted that ammonia is produced in the gut of all mammalian species by bacterial degradation of nucleic and amino

Table 19

Chemical and technical considerations for calcium ammonium nitrate solution

Name: Calcium ammonium nitrate solution	
CAS number	Alternative CAS numbers
15245-12-2	None
Chemical details	Nitric acid, calcium ammonium salt, CAN CAN is a white to pale yellow granule or prilled solid. Structure: multiple different but closely related products exist.  <ul style="list-style-type: none"> • × Ca • × NH₃ Molar mass (as H ₄ CaN ₂ O ₆): 120.12 g/mol Melting point: 170 °C
Route(s) of synthesis	Readily soluble in water Manufactured by addition of ground limestone, dolomite or calcium nitrate to molten ammonium nitrate.
Composition	Variable formulations exist in commerce – amounts of Ca and N vary, as do the forms of N (as ammoniacal nitrogen or nitrate nitrogen). Specific composition depends on the final use of the product.
Uses	Used as a fertilizer – source of ammoniacal nitrogen and nitrate nitrogen. Minor use in disposable cold packs is also reported.
Analytical methods	None found for previous cargoes. Possible means of detection in fats and oils by inductively coupled plasma (ICP) analysis for Ca residues.
Potential reaction(s) with a subsequent cargo of fat or oil	Formation of calcium, magnesium or ammonium salts of free fatty acids is possible; reaction conditions are not expected to be present in a cargo of edible fats or oils.

acids from ingested foods. The estimated production of ammonia in the human intestine ranges from 10 mg per day in the duodenum to 3 g per day in the colon (cited in (16)). Ammonia is readily absorbed by the gastrointestinal tract upon oral ingestion in foods, followed by its entry into the portal circulation and its transformation to urea in the liver via the urea cycle. It is then excreted by the kidneys as urea.

Magnesium: The Committee noted that magnesium is an essential nutrient. It is commonly found in foods, such as lettuce, spinach, turnip greens and collard, and it is an essential mineral that serves as a cofactor for more than 300 enzyme systems (4). It contributes to energy metabolism, protein and nucleotide synthesis, and metabolism and activation of vitamin D and parathyroid hormone (Annex 1, reference 224). The net absorption of dietary magnesium in a typical diet is between 40 and 60% (17). Upon ingestion, magnesium salts, such as magnesium carbonate, magnesium sulfate, magnesium chloride and

magnesium stearate are dissolved under acidic gastric conditions and separate into the magnesium ion (cation) and the anion (carbonate, sulfate, chloride, stearate, etc., respectively). Magnesium is absorbed all along the intestinal tract, but the sites of maximal absorption are the ileum and jejunum (18). Magnesium is excreted mainly in the urine and the kidney is the principal organ involved in its homeostasis (4).

Phosphates: The Committee considered its previous evaluation of phosphates conducted at the twenty-sixth meeting to assess their toxicokinetic profile (Annex 1, reference 59). Phosphorus is an essential nutrient and a constituent of bones, teeth and several enzyme systems. Phosphates play an important role in carbohydrate, fat and protein metabolism. Phosphates (or phosphorus) are mainly absorbed from the diet as free orthophosphate after enzymatic hydrolysis. The intestinal absorption of phosphates depends on the requirements of the body and their levels are regulated by certain physiological mechanisms. The amounts of inorganic phosphates in the blood are stabilized by exchange with the mineral deposit in the skeleton by parathyroid hormone. The parathyroid hormone inhibits renal tubular reabsorption of phosphates causing demineralization of the bone tissue, and the concentrations of circulating parathyroid hormone are regulated by blood calcium concentrations. Phosphates are mainly excreted in the faeces.

Toxicity

Given the sparse availability of toxicological datasets on calcium nitrate and calcium ammonium nitrate, the Committee considered health-based guidance values for calcium, nitrate, ammonium, magnesium and phosphates, established under previous evaluations and briefly summarized below, to conduct the toxicological evaluation of calcium nitrate and calcium ammonium nitrate at the anticipated exposure level as previous cargoes for edible oils and fats.

Calcium: The Committee had previously evaluated many calcium salts, including calcium sulfate, calcium chloride, calcium carbonate, calcium acetate and calcium gluconate, among others, for use as food additives. It allocated an ADI “not specified” to these salts based on their low toxicity determined from a review of the data available at the time of the evaluations. The UL of 2500 mg per day for adults (equivalent to about 40 mg/kg bw), based on different intervention studies in humans, of long duration, in which total daily calcium intakes of 2500 mg from both diet and supplements were tolerated without adverse effects, was established by SCF in 2003 (1) and confirmed by EFSA (2, 3).

Nitrates: At its forty-fourth and fifty-ninth meetings (Annex 1, references 116 and 160), the Committee concluded that nitrate was not genotoxic and the carcinogenicity studies on nitrates were negative, except when extremely high

doses of both nitrate and nitrosable precursors were administered. A review of available epidemiological data provided no evidence of an association between human exposure to nitrite and risk of cancer. Based on a re-evaluation of a long-term study in rats and consideration of the available epidemiological data, the Committee concluded that a NOAEL of 370 mg/kg bw per day was most appropriate for the safety evaluation of nitrate, and established an ADI of 0–3.7 mg/kg bw for nitrate, expressed as nitrate ion, by applying an uncertainty factor of 100 to the NOAEL of 370 mg/kg bw per day ([Annex 1](#), reference 160).

Ammonium: The Committee had previously evaluated toxicological data on several ammonium salts, including ammonium carbonate, ammonium bicarbonate, ammonium chloride and ammonium acetate and concluded that these salts would not cause significant toxic effects, except for alteration of acid-base balance. At its previous meetings, the Committee decided not to establish a numerical ADI and allocated an ADI “not specified” for most ammonium salts, based on their low toxicity determined upon review of data available at the time of the evaluations.

Magnesium: The Committee had previously evaluated available toxicological data on several magnesium salts, including magnesium carbonate, magnesium hydrogen carbonate, magnesium sulfate, magnesium chloride, magnesium DL-lactate, magnesium gluconate, magnesium acetate, magnesium citrate, magnesium adipate, magnesium succinate, monomagnesium phosphate and magnesium stearate, for their use as food additives. The Committee noted the possibility of diarrhoea and similar gastrointestinal effects due to excessive intake of magnesium salts; however, no other adverse effects had been reported after long-term exposure to magnesium salts ([Annex 1](#), reference 160). Given their widespread occurrence in food from natural sources and no indication of significant toxic effects from human exposure to most magnesium salts, the previous Committees did not establish a numerical ADI and allocated an ADI “not specified” for the magnesium salts evaluated.

Phosphate: The Committee considered its previous evaluation of phosphates ([Annex 1](#), reference 59) conducted at the twenty-sixth meeting. At that time, it concluded that the phosphates are not genotoxic and the only consequence of excessive intake of phosphates in animals is an effect on calcium and magnesium homeostasis, which could potentially lead to bone loss, calcification of soft tissues and nephrocalcinosis. Upon evaluating the available toxicological data, the previous Committee established an MTDI for phosphates, diphosphates and polyphosphates of 70 mg/kg bw ([Annex 1](#), reference 59). More recently, at the seventy-sixth meeting, while evaluating magnesium dihydrogen diphosphate for use as an alternative to sodium-based acidifiers and raising agents, the Committee stated that the approach taken to derive the MTDI of phosphates from the toxicological data was unclear, as the end-point considered

(nephrocalcinosis in rats) for deriving this value may not be relevant to humans, leading to an overly conservative value of the MTDI ([Annex 1](#), reference 211). While there was no indication from the available toxicological data that the MTDI of 70 mg/kg bw for phosphates was insufficiently health protective, the Committee acknowledged the need to review the toxicological basis of the MTDI for phosphate salts expressed as phosphorus ([Annex 1](#), reference 211).

No data on oral exposure to calcium nitrate and calcium ammonium nitrate in humans have been reported. However, the Committee located a report of a case of contact dermatitis in a farmer in India after using urea and calcium ammonium nitrate as fertilizers (19). The recurrent episodes of dermatitis that followed visits to the field, and positive patch tests with calcium ammonium nitrate on two occasions suggested that the allergic response was associated with the use of the fertilizer; however, these effects were not further evaluated to confirm whether they were specifically caused by exposure to calcium ammonium nitrate.

Allergenicity

The Committee did not locate any reports of allergenicity upon oral exposure to calcium nitrate and calcium ammonium nitrate that would indicate that these substances are, or contain known food allergens.

Assessment of dietary exposure

Calcium, magnesium, nitrate, phosphates and ammonium are ubiquitous in the human diet. The generic human dietary exposure value for previous cargoes of 0.3 mg/kg bw per day indicates that any potential dietary exposure to calcium, magnesium, nitrate, phosphates and ammonium from previous cargoes in food oils would be a minor contributor to the overall dietary exposure to these substances.

Evaluation

Given that toxicological datasets on calcium nitrate and calcium ammonium nitrate are sparse, the Committee evaluated available toxicological data on calcium, ammonium and nitrate to conduct their toxicological evaluation. The Committee also reviewed available toxicological data on magnesium and phosphates, as dolomite and phosphate rock could be used in the manufacture of calcium ammonium nitrate and calcium nitrate, respectively.

The Committee estimated exposure to calcium nitrate and calcium ammonium nitrate from previous cargoes for edible fats and oils as 0.3 mg/kg bw per day each, which is much less than the exposures to calcium, nitrate, ammonium, magnesium and phosphates expected from dietary sources. The Committee considered health-based guidance values for calcium,

nitrate, ammonium, magnesium and phosphates, established under previous evaluations, to conduct the toxicological evaluation of calcium nitrate and calcium ammonium nitrate at the anticipated exposure level from previous cargoes for edible oils and fats. The estimated exposure value for calcium nitrate and calcium ammonium nitrate as previous cargoes for edible fats and oils is 0.3 mg/kg bw each, which does not exceed the ADI for nitrate of 0–3.7 mg/kg bw, expressed as nitrate ion ([Annex 1](#), reference 160), and the MTDI of 70 mg/kg bw for phosphates, diphosphates and polyphosphates ([Annex 1](#), reference 59). The previous Committees did not assign a numerical ADI but allocated an ADI “not specified” for most calcium, ammonium and magnesium salts based on their low oral toxicity profiles. Furthermore, the Committee considered that human exposure to these substances resulting from their use as previous cargoes would be a minor contributor to the total dietary exposure.

There are no data on allergenicity upon oral exposure to calcium nitrate and calcium ammonium nitrate that would indicate that these substances are, or contain, known food allergens.

The Committee concluded that the formation of calcium, ammonium or magnesium salts of free fatty acids is possible. However, owing to the anticipated absence of alkaline conditions and an insufficient concentration of counter ions and free fatty acids (necessary for the reactions to occur), these reaction products are not expected to be formed in detectable amounts in a cargo of edible fats and oils.

Therefore, calcium nitrate and calcium ammonium nitrate meet the criteria for acceptability as previous cargoes for edible fats and oils.

3.5.4.2 Calcium lignosulfonate

Explanation

Calcium lignosulfonate is a complex mixture of polymers with variable degrees of cross-linking and a wide range of molecular weights, derived from the sulfite pulping of wood. Calcium lignosulfonate 40-65 is one fractionated product from sulfite pulping and is used in food applications. Calcium lignosulfonate 40-65 (a purified lignosulfonate product with an average molecular weight range of 40 000–65 000 Daltons) was evaluated by the Committee at its sixty-ninth meeting as a food additive, intended for use as a carrier for encapsulated food ingredients ([Annex 1](#), reference 190) (20). The Committee identified a NOAEL of 2000 mg/kg bw per day based on the results of a 90-day dietary study of calcium lignosulfonate (40-65) in rats (21). The study authors reported a dose-dependent increase in incidence of histiocytosis in the mesenteric lymph nodes. However, the Committee concluded that such histiocytosis would not be expected to progress to any adverse effect. Based on this NOAEL and an uncertainty factor

of 100, the Committee established an ADI of 0–20 mg/kg bw for calcium lignosulfonate (40-65) ([Annex 1](#), reference 190). Calcium lignosulphonate (or calcium lignosulfonate) was evaluated by SCF. It was considered acceptable as a previous cargo and also as an additive to animal feedstuff, based on the conclusion that it is toxicologically inert and easily removable by tank cleaning (22). The Panel for Food Additives and Nutrient Sources added to Food (ANS Panel) evaluated the available data and concluded that the 90-day feeding study in rats (21) was inadequate for evaluating the safety of calcium lignosulfonate (40-65). This was due to a possible poor health status of the animals in this study (high incidence of lymphoid hyperplasia and lymphoid infiltration in the mandibular and mesenteric lymph nodes, in the Peyer's patches and in the livers of the animals, including controls) (23). The CONTAM Panel evaluated calcium lignosulfonate as an acceptable previous cargo in 2016 and 2019 (24, 25). Based on a report of a re-evaluation of the 90-day dietary study in rats (26), the CONTAM Panel agreed with the JECFA-identified NOAEL of 2000 mg/kg bw per day for calcium lignosulfonate (40-65) derived from this study (24). However, owing to data gaps regarding the composition and toxicity of the low molecular weight fraction (LMWF) of technical grade calcium lignosulfonate, the CONTAM Panel concluded that calcium lignosulfonate did not meet the acceptability criteria for previous cargoes (24). More recently, the CONTAM Panel evaluated additional genetic toxicity studies on technical grade calcium lignosulfonate (LMWF < 1000 Daltons), which showed a lack of genotoxic potential of the test substance evaluated (25). However, a review of the data on the molecular weight distribution of the test substance indicated that it was not sufficiently representative of the LMWF in products intended to be shipped as previous cargo. Therefore, the CONTAM Panel stated that the existing toxicological database did not account for all grades of calcium lignosulfonate shipped as previous cargoes.

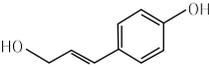
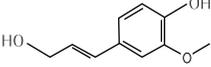
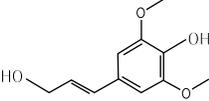
For the present assessment, the Committee identified and reviewed its previous evaluations of calcium lignosulfonate, and those of EFSA, and located additional references from these evaluations. This was followed by comprehensive searches for data on calcium lignosulfonate on PubMed and PubChem. The cut-off date for all searches was 20 August 2020. The retrieved references with relevant toxicological information were on the 90-day oral subchronic toxicity study of calcium lignosulfonate (40-65) conducted in rats that is discussed in the present assessment.

Chemical and technical considerations

Chemical and technical considerations for calcium lignosulfonate liquid are summarized in [Table 20](#).

Table 20

Chemical and technical considerations for calcium lignosulfonate liquid

Name: Calcium lignosulfonate liquid	
CAS number	Alternative CAS numbers
8061-52-7	None
Chemical details	Lignin liquor, sulphite lye, lignosulfonic acid, calcium salt Light brown to brown powder or a brown to black liquid
	Structure: Random polymer with an inconsistent degree of polymerization and cross-linking; structures of the three monomers are shown below.
	<div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;">  <p>A. <i>p</i>-Coumaryl alcohol</p> </div> <div style="text-align: center;">  <p>B. Coniferyl alcohol</p> </div> </div> <div style="text-align: center; margin-top: 20px;">  <p>C. Sinapyl alcohol</p> </div>
	Molar mass: polydisperse, random polymer with wide molecular mass distribution ranging from approximately 1000–250 000 Da
Route(s) of synthesis	Readily soluble in water, insoluble in most organic solvents Manufactured as a by-product from the sulfite pulping of wood. Wood chips are digested in an acidic calcium bisulfite solution. Cellulose is filtered out of solution, leaving the spent sulfite liquor containing calcium lignosulfonate and other breakdown components of wood. The crude spent liquor is steam-stripped to remove excess sulfur dioxide and volatile substances. Sugars from hemicellulose may be removed by fermentation followed by distillation of ethanol. Evaporation removes excess water.
Composition	Variable commercial formulations exist. Composition is dependent on the wood used in the pulping process, specific processing conditions, clean-up processes and additional chemical treatments carried out to create materials with specific functionalities. Commercial products are likely to contain various sugars and sulfur (sometimes present as sulfates) as impurities. Calcium lignosulfonate Liquid is reported to contain approximately 50% calcium lignosulfonate. One food-grade product, calcium lignosulfonate (40-65) (a powdered product), is specified as follows: weight-average molecular weight between 40 000 and 65 000 Da; molecular weight of > 90% is between 1000 and 250 000 Da; ≤ 5.0% calcium; degree of sulfonation 0.3–0.7; ≤ 5.0% reducing sugars; ≤ 0.5% sulfite; ≤ 14.0% total ash; ≤ 8.0% moisture; pH 2.7–3.3 (10% solution).
Uses	Used as a plasticizer/dispersant in concrete (about 45% usage; weight-average molecular weight of the typical product shipped as a previous cargo is reported in the range of 30 000–40 000 Da); also used in the production of cement and plasterboard, in petroleum drilling, as a dispersant for the application of pesticides, an emulsifier in asphalt, a defloculant in processing feedstuffs, and minor use as a food additive (as a carrier for fat-soluble vitamins, carotenoids and other functional ingredients).
Analytical methods	None found for previous cargoes. Possible means of determination in fats and oils using inductively coupled plasma (ICP) analysis for Ca residues
Potential reaction(s) with a subsequent cargo of fat or oil	Lignosulfonates are unlikely to react with free fatty acids and triglycerides present in cargoes of fats and oils under the conditions of transport.

Assessment

Biochemical aspects

To assess the toxicokinetic profile of calcium lignosulfonate (40-65), the Committee considered its previous evaluation of *in vitro* (27) and *in vivo* (28) studies conducted with calcium lignosulfonate (40-65), which concluded that it is poorly absorbed following oral exposure, and, therefore, has a low oral bioavailability. No data on biotransformation of calcium lignosulfonate (40-65) by the gut flora or via other mechanisms have been reported. However, the Committee expected the potential of calcium lignosulfonate (40-65) to undergo biotransformation to be very low considering its low systemic exposure following oral administration.

No toxicokinetic data on molecular weight fractions different from the molecular weight fractions of the food-grade calcium lignosulfonate were available. Therefore, the Committee could not evaluate the biochemical aspects of the non-food-grade calcium lignosulfonate that is shipped as a previous cargo.

Toxicity

The Committee considered the potential for acute toxicity of calcium lignosulfonate (molecular weight not specified) to be low based on oral LD₅₀ values of 31.6 g/kg bw in young albino Sprague-Dawley rats (sex not specified) and between 10 and 20 g/kg bw in male rats (strain not identified), reported in two independent studies (cited in (23) and (29)).

The Committee considered its own previous evaluation of calcium lignosulfonate (40-65) ([Annex 1](#), reference 190) and the data reviewed therein to conduct its toxicological evaluation. At that time, the Committee concluded that calcium lignosulfonate (40-65) was not genotoxic based on negative responses reported in a bacterial reverse mutation assay and an *in vitro* chromosome aberration assay (30, 31) ([Annex 1](#), reference 190). The Committee also concluded that calcium lignosulfonate (40-65) did not exhibit a potential for reproductive and developmental toxicity because no treatment-related or toxicologically relevant effects were observed at any dose in a maternal and developmental toxicity study in female Wistar rats (32) ([Annex 1](#), reference 190). The Committee noted a dose-related increase in the incidence of histiocytosis in the mesenteric lymph nodes in a 90-day feeding study of male and female Wistar rats administered calcium lignosulfonate (40-65) at doses of 0, 500, 1000 or 2000 mg/kg bw per day (21). However, the Committee did not consider this observation to be adverse as this finding has been reported with other substances of high molecular weights, such as polypentosan sulfate, copovidone (a copolymer of vinylpyrrolidone and vinyl acetate) and mineral oils (33, 34). Furthermore, the Committee considered that long-term rat studies with such high molecular weight substances did not

demonstrate any progression of histiocytosis to an adverse effect or carcinogenesis (33, 35, 36). The Committee identified the highest dose tested of 2000 mg/kg bw per day as the NOAEL and established an ADI of 0–20 mg/kg bw for calcium lignosulfonate (40-65) by application of an uncertainty factor of 100 ([Annex 1](#), reference 190) (20).

More recently, a report detailing additional clinical pathological examinations and a reassessment of the results of the 90-day rat feeding study of calcium lignosulfonate (40-65) was published, which supported the Committee's earlier evaluation of this study ([Annex 1](#), reference 190) (21, 26).

The Committee determined that calcium lignosulfonate (40-65) did not cause skin sensitization based on the absence of treatment-related effects in a lymph node assay in CBA mice (17) ([Annex 1](#), reference 190).

More recently, the CONTAM Panel reviewed additional genetic toxicity data (not available to the present Committee) provided for a LMWF (< 1000 Daltons) isolated from a technical product that was described as a representative of grades that were intended to be shipped as previous cargo (25). The two new genetic toxicity studies included a bacterial reverse mutation assay in *Salmonella* Typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of metabolic activation, and a micronucleus assay conducted with human lymphocytes in the presence and absence of metabolic activation (cited in EFSA, 2019 (26)). The CONTAM Panel concluded that the test substance showed negative responses in the genetic toxicity studies, but stated that the molecular weight distribution data on the test substance indicated an apparent loss of constituents of lower molecular masses (below 200 Daltons) (cited in (25)). Therefore, the CONTAM Panel concluded that the test substance was not sufficiently representative of the different molecular weight fractions of calcium lignosulfonate shipped as a previous cargo (25).

The Committee noted that there are no other toxicity data or data in humans available on different molecular weight fractions constituting the non-food-grade calcium lignosulfonate that is shipped as a previous cargo. Therefore, the Committee could not conduct a toxicological evaluation of the non-food-grade calcium lignosulfonate that is shipped as a previous cargo.

Allergenicity

There are no reports of allergenicity upon oral exposure to calcium lignosulfonate that would indicate that the substance that is shipped as a previous cargo is, or contains, a known food allergen.

Assessment of dietary exposure

A dietary exposure assessment conducted at a previous meeting of the Committee estimated that the maximum potential dietary exposure to calcium lignosulfonate (40-65) could reach 7 mg/kg bw per day (Annex 1, reference 190). The present Committee conducted a dietary exposure assessment based on data from Australia and New Zealand. The mean estimated exposure to calcium lignosulfonate (40-65) as a permitted food additive ranged from 1 to 4 mg/kg bw per day. The estimated exposure for high consumers at the 90th percentile of exposure ranged from 2 to 6 mg/kg bw per day. There were no data on dietary exposure to calcium lignosulfonate added to animal feed or used as a dispersion agent and stabilizer in pesticides for preharvest or postharvest applications. The generic human dietary exposure value for previous cargoes of 0.3 mg/kg bw per day indicates that any potential dietary exposure to calcium lignosulfonate (40-65) from previous cargoes in food oils would be a minor contributor to overall dietary exposure.

The Committee could not perform a dietary exposure assessment for the non-food-grade calcium lignosulfonate due to unavailability of the relevant data.

Evaluation

The Committee previously established an ADI of 0–20 mg/kg bw for the food-grade calcium lignosulfonate (40-65) (Annex 1, reference 190) (1), the upper bound of which is above the estimated exposure for calcium lignosulfonate as a previous cargo for edible fats and oils of 0.3 mg/kg bw per day. There are no data on allergenicity resulting from oral exposure to calcium lignosulfonate (40-65) that would indicate that it is, or it contains, a known food allergen. Therefore, food-grade calcium lignosulfonate (40-65) meets the criteria for acceptability as a previous cargo for edible fats and oils.

Lignosulfonates are unlikely to react with free fatty acids and triglycerides present in cargoes of fats and oils under the conditions of transport.

The Committee could not determine the specific chemical composition or molecular weight distribution of the non-food-grade calcium lignosulfonate that is shipped as a previous cargo but recognized that it has a wide molecular weight distribution. The Committee acknowledged that no toxicokinetic data to determine oral bioavailability of or systemic exposure to the non-food-grade calcium lignosulfonate shipped as a previous cargo are available. Therefore, the ADI for calcium lignosulfonate (40-65) does not apply to the material that is shipped as a previous cargo unless it is food-grade calcium lignosulfonate. In the absence of adequate data on chemical specifications and toxicokinetics, the Committee concluded that the systemic effects of oral exposure to the non-food-grade calcium lignosulfonate cannot be evaluated as no oral toxicity, genotoxicity

or allergenicity data are available on this substance. Therefore, in the absence of relevant toxicological data on test substances that are sufficiently representative of different molecular weight fractions constituting the non-food-grade calcium lignosulfonate that is shipped as a previous cargo, the Committee concluded that the non-food-grade calcium lignosulfonate does not meet the criteria for acceptability as a previous cargo for edible fats and oils.

A toxicological monograph on the solutions including dietary exposure and chemical and technical considerations was prepared.

Recommendations

The Committee recommended that sufficient chemical and toxicological information that allows the evaluation of non-food-grade calcium lignosulfonate liquid as shipped are made available prior to the next evaluation. At a minimum, this information should address the following:

- molecular weight range(s), chemical component identification and relative composition;
- toxicological data on representative products.

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4. Trichothecenes, T-2 and HT-2

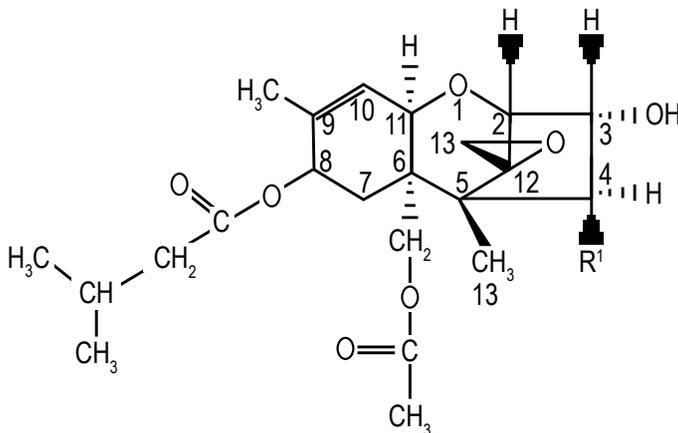
4.1 Explanation

T-2 toxin (T-2) and HT-2 toxin (HT-2) are type A trichothecene mycotoxins, which are closely related epoxy sesquiterpenoids. Surveys have revealed the presence of T-2 and HT-2 in a wide range of foodstuffs but they are primarily contaminants of cereals and cereal-based products. T-2 and HT-2 have been reported to be produced by *Fusarium acuminatum*, *F. equiseti*, *F. langsethiae*, *F. poae*, *F. sibiricum* and *F. sporotrichioides*.

T-2 is the trivial name for 4 β ,15-diacetoxy-3 α ,dihydroxy-8 α -[3-methylbutyryl-oxy]-12,13-epoxytrichothec-9-ene (CAS number 26934-87-2). HT-2 is the trivial name for 15-acetoxy-3 α ,4 β -dihydroxy-8 α -[3-methylbutyryloxy]-12,13-epoxytrichothec-9-ene (CAS number 21259-20-1). The structures of T-2 and HT-2 differ only in the functional group at the C-4 position (Fig. 1). HT-2 is formed from the deacetylation of T-2, which can occur as a result of metabolism of the fungus, the infected plant or animals after ingestion. These toxins co-occur with several other type A trichothecenes (for example, 4,15-diacetoxyscirpenol and neosolaniol) and modified mycotoxins – phase I and II metabolites formed in the fungus or the infected plant (for example, T-2 triol and T-2-3-glucoside).

Figure 1

Structure of type A trichothecenes HT-2 (R¹=OH) and T-2 (R¹=OAc)



T-2 and HT-2 were previously evaluated by the Committee at its fifty-sixth meeting ([Annex 1](#), reference 152). The Committee concluded at that meeting that there was substantial evidence for the immunotoxicity and haematotoxicity of T-2 in several species, and that these are critical effects after short-term intake. The Committee further concluded that the safety of food contaminated with T-2 could be evaluated from the LOAEL of 0.03 mg/kg bw per day for changes in white and red blood cell counts identified in the 3-week dietary study in pigs. The Committee used this LOAEL and a safety factor of 500 to derive a provisional maximum tolerable daily intake (PMTDI) for T-2 of 60 ng/kg bw per day. The Committee further concluded that the toxic effects of T-2 and its metabolite HT-2 could not be differentiated, and hence HT-2 was included in the PMTDI, resulting in a group PMTDI of 60 ng/kg bw per day for combined concentration of T-2 and HT-2. At its eighty-third meeting in 2016, the Committee included 4,15-diacetoxyscirpenol (DAS) in the group PMTDI of 60 ng/kg bw per day for T-2 and HT-2 ([Annex 1](#), reference 233).

In response to a request from the Codex Committee on Contaminants in Foods (CCCF) for an updated risk assessment including an exposure assessment on T-2 and HT-2, these compounds were evaluated by the present Committee. The evaluation included analytical methods, sampling protocols, effects of processing, prevention and control, levels and patterns of contaminants in food commodities, and dietary exposure assessment data for T-2 and HT-2 that had become available since the last evaluation in 2001. The toxicological evaluation and overall risk assessment will follow at a future meeting.

4.2 Analytical methods

The Committee reviewed the analytical methods for the determination of T-2 and HT-2 developed since the fifty-sixth meeting and noted considerable advances in methodology, particularly with respect to the development of multi-mycotoxin analytical methods based on high-performance liquid chromatography–mass spectrometry (HPLC-MS).

While thin-layer chromatography has largely been superseded by more modern methods, reports of its use for T-2 toxin and other trichothecenes can still be found. Screening methods, such as enzyme-linked immunosorbent assay (ELISA), lateral flow immunoassays, fluorescence polarization, and various biosensors and chemosensors continue to be developed and commercialized based mainly on monoclonal antibodies. These assays can be tailored for detection of T-2 toxin alone or the sum of T-2 and HT-2 combined.

Whereas the Committee noted at its fifty-sixth meeting that gas chromatography (GC) with derivatization and detection by electron capture or MS was the primary technique for quantification, there has been a strong shift

away from GC towards the extensive use of HPLC. Depending on the extract clean-up technique, these toxins, either alone or together with other type A and B trichothecenes, can be determined by HPLC with UV or fluorescence detection. For this purpose, several derivatizing agents have been described.

The major advance in routine analysis since the previous Committee meeting has been the development of HPLC-MS methods, which enable simultaneous quantification and confirmation. Although capable of targeted single analyte determination, these methods can be used for multi-mycotoxin determination in which T-2 and HT-2 can be determined as part of a suite of toxins and/or secondary metabolites. Modern methods achieve limits of detection (LODs) in the low or sub $\mu\text{g}/\text{kg}$ range, but require consideration of optimum conditions of extraction and extract purification to accommodate the differing chemistries of the target analytes. Two approaches for treating the extract are the “dilute-and-shoot” method in which the extract is injected into the HPLC after solvent dilution or the use of a generic clean-up (QuEChERS – quick, easy, cheap, effective, rugged and safe) to remove impurities such as lipids. A feature of MS detection, particularly with multi-mycotoxin determination using limited extract purification, is the occurrence of matrix effects. To overcome these problems, stable isotope-labelled internal standards or matrix-matched standards are used. Quantification can also be performed by the standard addition method. A T-2 and HT-2 certified reference material of ground oat flakes is available to aid method development and quality assurance. Modified forms of T-2 and HT-2, including numerous plant metabolites, can be identified by HPLC-MS/MS; however, validation and quantification is limited by the availability of analytical standards.

4.3 Sampling protocols

Currently, sampling methods for the analysis of T-2 and HT-2 in cereal grains use protocols for other mycotoxins. Many countries have their own sampling guidelines. For example, China uses GB/T 30642-2014, countries in Europe use EC 401/2006, and Canada and the USA have designated sampling guidelines (1, 2). Additionally, sampling guidance is available from Codex Alimentarius (CAC/GL 50-2004). In recent years, the drive towards safer food has highlighted the need to determine levels of T-2 and HT-2 contamination in different food commodities. Therefore, it is important to simplify, harmonize and validate sampling plans for T-2 and HT-2.

4.4 Effects of processing

In general, T-2 and HT-2 levels can be reduced by various processes commonly used in the food and feed industry. Cleaning and sorting are useful first steps in the reduction of T-2 and HT-2 contamination. T-2 and HT-2 are mostly located in the outer layers of cereal grains, and are recovered in higher concentrations in husk, bran and germ relative to other milling fractions. Therefore, the by-products from sorting and milling should be strictly managed. T-2 and HT-2 concentrations decrease during cooking at about 150 °C. Higher temperatures increase the extent of degradation of the toxins. Fermentation can reduce levels of contamination by T-2 and HT-2, although pH, moisture, temperature and the fermentation organisms impact concentrations.

4.5 Prevention and control

Information on the prevention and control of T-2 and HT-2 is limited to a small number of studies in a few commodities (primarily oats) and these often agree with the greater volume of information available for the related trichothecene, deoxynivalenol (DON). For preharvest mitigation, decreased concentrations of T-2 and HT-2 are associated with having fewer cereals in rotation and growing resistant cultivars. Ploughing may also be beneficial, depending on the rotational position of the host crops. Unlike with DON, growing maize as a previous crop is not a risk factor and limited studies indicate fungicides do not reduce T-2 and HT-2 contamination. For postharvest mitigation, prevention of further T-2 and HT-2 production by *Fusarium* species is achieved by storing commodities at low moisture content. Various microbes, enzymes and chemicals have demonstrated ability to metabolize or degrade T-2 and/or HT-2, but these have been mainly tested in liquids and may not be technically feasible for most foodstuffs.

4.6 Levels and patterns of contamination in food commodities

When T-2 and HT-2 were assessed previously at the fifty-sixth meeting of the Committee, the percentages of analyses from 1990–2000 ($n = 999$) that exceeded 100 µg/kg were 0.4% and 0.9% for T-2 and HT-2, respectively. The value of 100 µg/kg was used by the Committee at that meeting to allow comparison to a previous study due to the wide range of LODs, which decreased over time (3). In the current assessment of data from the GEMS/Food contaminants database, there were 49 912 samples analysed for T-2 and HT-2 from 2001 to 2020. Within this dataset 0.8% and 1.5% of samples exceeded 100 µg/kg T-2 and HT-2, respectively. It cannot be determined if these increases in reported frequency of high concentrations of T-2 and HT-2 are due to increases in the mycotoxin

concentrations over time or to a greater focus on sampling in regions and/or commodities with higher levels of T-2 and HT-2.

Based on data from the GEMS/Food contaminants database, comparison of analyses for T-2 and HT-2 across global regions has identified stark differences in the number of tests reported, the distribution of foodstuffs analysed and the analytical results. Most of the analytical records were submitted by the European Region, with limited numbers submitted by a few countries within the other regions. Some of these countries only submitted results for a single foodstuff (sorghum from four African countries and cassava from the USA). Three countries in the Western Pacific Region submitted analytical results for a wide variety of foodstuffs, but they were mostly negative. Canada also submitted results for a wide variety of foodstuffs, with 1.5% positive samples, a lower bound (LB) mean concentration of 0.6 µg/kg, and a few samples with greater than 100 µg/kg combined T-2 and HT-2. In contrast, T-2 and HT-2 levels reported in Europe were much higher in cereals and any food category that does or may contain cereals. More detailed analysis of the European dataset showed that the highest levels were detected in oat, maize, barley and wheat grain (LB mean concentrations of 241, 24, 17 and 5.2 µg/kg, respectively) with significantly lower concentrations occurring in milled products, excluding bran and by-products.

Although limited in quantity, the literature generally supported the conclusion that T-2 and HT-2 levels are low in all regions of the world outside Europe. For example, a total diet study in sub-Saharan Africa analysed composite food samples (n = 194) representing food intake at eight locations across four countries (Benin, Cameroon, Mali and Nigeria) for numerous mycotoxins (4). No samples had detectable T-2 or HT-2 (LOD = 0.4 and 0.8 µg/kg, respectively).

As with other *Fusarium* mycotoxins that are produced within the growing crop, their concentrations will fluctuate between growing seasons and regions, depending on climatic conditions. Most studies reporting T-2 and HT-2 concentrations are based on single-year surveys and the effect of seasonal variability cannot be assessed. A 7-year (2002–2008) investigation of *Fusarium* mycotoxins in harvested oats in the United Kingdom showed the annual combined mean concentration of T-2 and HT-2 ranged from 121 to 727 µg/kg (5).

Recent studies have identified numerous modified mycotoxins that are the result of metabolism in planta; some have also been found to exist in naturally contaminated material. T-2 tetraol and HT2-3-glucoside can occur at high concentrations compared to the parent mycotoxins. There are also several other metabolites that occur individually at low concentrations compared to the parent molecules, but may collectively contribute significantly to the overall type A trichothecene occurrence in cereals and cereal products. In recent studies using host plants inoculated with isotope-labelled mycotoxins, 70–85% of the inoculated T-2 or HT-2 were metabolized (6–8).

4.7 Food consumption and dietary exposure assessment

4.7.1 Chronic dietary exposure

Since the previous evaluation, several national or regional estimates of chronic dietary exposure have been published. The Committee considered evaluations from Belgium, China, the Czech Republic, Ecuador, Europe, France, Ireland, Malawi, Morocco, the Netherlands, New Zealand, Nigeria, Pakistan, Romania, Serbia, Spain, Sweden, sub-Saharan Africa, Tunisia and the United Republic of Tanzania. These reports include dietary exposure assessments for T-2 (12 studies), HT-2 (14 studies) and the sum of T-2 and HT-2 (12 studies). In several studies, these toxins were not detected or were detected so infrequently that dietary exposure could not be estimated. Estimates of dietary exposure reviewed mainly related to European and north African countries. [Table 21](#) provides a summary of the range of exposure estimates derived from the scientific literature. Exposure estimates have been further separated into those pertaining to children, including infants and toddlers, and those pertaining to adults or the general population. Dietary exposure estimates have mostly been presented as ranges from an LB to an upper bound (UB). LB estimates are generally based on mean toxin concentrations calculated with results below the LOD or limit of quantitation (LOQ) being assigned a value of zero. UB estimates are generally based on mean toxin concentrations calculated with results below the LOD or LOQ being assigned a value equal to the LOD or LOQ. Across studies, the foods providing the major contributions to chronic dietary exposure are cereals and cereal-based, particularly wheat and wheat-based, products.

Based on the observed geographical distribution of T-2 and HT-2 contamination of foods (mainly Europe and North America) and available food consumption information, the Committee, at its current meeting, decided it was unnecessary to derive additional national estimates of chronic dietary exposure to T-2 and HT-2.

At the current meeting, the Committee did not present international estimates of dietary exposure to either toxin or the sum of the toxins using the GEMS/Food cluster diets. It was concluded that dietary exposure to T-2 and HT-2 for clusters covering the known geographical distribution of T-2 and HT-2 was suitably covered by existing European estimates of chronic dietary exposure and no international estimates of chronic dietary exposure were derived by the Committee.

4.7.2 Acute dietary exposure

Three studies reported in the scientific literature estimated acute dietary exposure to T-2, HT-2 or the sum of T-2 and HT-2. Two of the studies were duplicate diet studies carried out in the Netherlands, while the third study, by EFSA, estimated

Table 21

Summary of the range of estimates of chronic dietary exposure to T-2, HT-2 and the sum of T-2 and HT-2, derived from the literature

Toxin/population group ^a	Estimated dietary exposure, range ^b (ng/kg bw per day)			
	Mean		High percentile ^c	
	LB	UB	LB	UB
T-2				
Children	0.4–26	13–79	5.7 ^d –150	27–200
Adults	0.1–6.4	9.1–24	1.6–29	16–66
HT-2				
Children	0.0–27	4.1–91	3.6–64	15–240
Adults	0.0–14	0.4–33	2.4–23	14–59
Sum of T-2 and HT-2				
Children	0.8–53	8.2–169	6.5–210	31–400
Adults	0.3–27	2.7–60	1.9–87	11–120

LB: lower bound, UB: upper bound.

^a For the purpose of this summary table, “children” were taken to be any population group described as infants, toddlers or children. The maximum age for children varies from study to study, but in all cases “children” will refer to individuals aged 15 years or younger. “Adults” were taken to be any population group described as adults, adolescents, elderly or very elderly. The minimum age for adults varies from study to study, but in all cases “adults” will refer to individuals older than 10 years.

^b Ranges are presented separately for lower and upper bound estimates of mean and high percentile estimates of dietary exposure.

^c 95th percentile, unless otherwise indicated.

^d 90th percentile.

acute dietary exposure for a range of European countries. The EFSA study estimated maximum UB 95th percentile acute dietary exposures to T-2, HT-2 and the sum of T-2 and HT-2 of 137, 165 and 170 ng/kg bw, respectively (9). These estimates were for infant cohorts, with acute dietary exposure decreasing with increasing age. The duplicate diet studies estimated mean acute dietary exposure to the sum of T-2 and HT-2 for young children (8–12 months) of 40 ng/kg bw (range 10–160 ng/kg bw). For 128 adults, acute dietary exposure to the sum of T-2 and HT-2 was in the range not detected to 18.6 ng/kg bw.

The Committee did not present additional national estimates of acute dietary exposure.

4.7.3 Combined chronic dietary exposure to T-2, HT-2 and DAS

At its eighty-third meeting, the Committee assessed 4,15-diacetoxyscirpenol (DAS) and concluded that DAS was similar in structure and toxic effects to T-2 and HT-2. At that time, DAS was included in the group PMTDI for T-2 and HT-2. A combined LB mean dietary exposure estimate for the three toxins for the European Region can be derived. Depending on the cohort, the median LB dietary exposures to the sum of T-2 and HT-2 are in the range of 3.0 to 15 ng/kg bw per day. The estimated LB mean dietary exposure to DAS determined at the

eighty-third meeting was 3 ng/kg bw per day, giving combined group (T-2, HT-2 and DAS) dietary exposure estimates of 6.0 to 18 ng/kg bw per day.

4.8 Evaluation

The Committee reviewed the information regarding analytical methods, sampling, effect of processing, prevention and control, occurrence in food commodities and dietary exposure made available since the last evaluation of T-2 and HT-2 at its fifty-sixth meeting in 2001 ([Annex 1](#), reference 152). Analytical methods have been improved in the past two decades with multi-mycotoxin HPLC-MS methods allowing the quantification of T-2 and HT-2 below or close to 1 µg/kg. A large body of occurrence data for T-2 and HT-2 had been submitted to the GEMS/Food contaminants database in the past two decades, but these were largely from Europe with a paucity of data from other regions. This may reflect the generally low incidence and low concentrations of T-2 and HT-2 found outside Europe. In Europe T-2 and HT-2 occur frequently in cereal crops, particularly in oats. There is also evidence of co-occurrence of several other type A trichothecenes and their metabolites in cereals. It was concluded that dietary exposure to T-2 and HT-2 covering the known geographical distribution of T-2 and HT-2 was suitably covered by existing European estimates of chronic and acute dietary exposure. No additional international or national estimates of chronic or acute dietary exposure were derived by the Committee. The Committee derived chronic dietary exposure estimates of 6.0 to 18 ng/kg bw per day for T-2, HT-2 and DAS combined. The toxicological evaluation and overall risk assessment will follow at a future meeting.

4.9 Recommendations

The Committee recommended the following:

- 1) development of multi-mycotoxin methods and standards for the quantification of type A trichothecenes and their various metabolites that occur in plants;
- 2) research to investigate the spatial distribution of T-2 and HT-2 in agricultural commodities to ensure standard sampling methods for mycotoxins are appropriate;
- 3) that occurrence data from a wider range of countries be generated using analytical methods with suitably low LODs, to decrease the uncertainty in dietary exposure estimates and confirm the geographical distribution of these toxins.

A monograph addendum was prepared.

References

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5. Recommendations

- 1) The Committee recommended that the Codex Committee on Fats and Oils (CCFO) consider revising criterion no. 2 in RCP-36-1987 as adopted by CAC 34 (2011).
 - Based on the consumption of fats and oils by infants and young children, there is no health concern for the general population from dietary exposure to previous cargo chemical substances if the ADI or TDI is sufficiently protective, for example, the ADI or TDI is greater than, or equal to 0.3 mg/kg bw per day. Substances for which there is no numerical ADI or TDI should be evaluated on a case-by-case basis (e.g. MOE approach).
 - Where there are additional sources of dietary exposure to the previous cargo chemical substances, they should be considered in the exposure assessment.
- 2) To conduct an evaluation of montan wax for acceptability as a previous cargo, data from toxicological testing of appropriate test substances that are sufficiently representative of the forms of montan wax that are shipped as a previous cargo are needed, taking into account variability due to source, region and degree of refinement.

The Committee recommended that sufficient chemical and toxicological information that allows the evaluation of montan wax as shipped are made available prior to the next evaluation. At a minimum this information should address the following:

- degree of refinement and chemical constituents;
 - repeat dose toxicological data on representative products in a relevant animal model.
- 3) The Committee recommended that sufficient chemical and toxicological information that allows the evaluation of calcium lignosulfonate liquid as shipped are made available prior to the next evaluation. At a minimum this information should address the following:
 - molecular weight range(s), chemical component identification and relative composition;
 - toxicological data on representative products.

- 4) The Committee recommended the following:
- development of multi-mycotoxin methods and standards for the quantification of type A trichothecenes and their various metabolites that occur in plants;
 - research to investigate the spatial distribution of T-2 and HT-2 in agricultural commodities to ensure standard sampling methods for mycotoxins are appropriate;
 - that occurrence data from a wider range of countries be generated using analytical methods with suitably low LODs, to decrease the uncertainty in dietary exposure estimates and confirm the geographical distribution of these toxins.

Annex 1

Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

1. General principles governing the use of food additives (First report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).
2. Procedures for the testing of intentional food additives to establish their safety for use (Second report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).
3. Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants) (Third report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. I. Antimicrobial preservatives and antioxidants, Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
4. Specifications for identity and purity of food additives (food colours) (Fourth report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. II. Food colours, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).
5. Evaluation of the carcinogenic hazards of food additives (Fifth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).
6. Evaluation of the toxicity of a number of antimicrobials and antioxidants (Sixth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962 (out of print).
7. Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents (Seventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).
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10. Specifications for identity and purity and toxicological evaluation of food colours. FAO Nutrition Meetings Report Series, No. 38B, 1966; WHO/Food Add/66.25.
11. Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases (Ninth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).

12. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases. FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29.
13. Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances (Tenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.
14. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents (Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.
15. Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.
16. Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.
17. Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics (Twelfth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.
18. Specifications for the identity and purity of some antibiotics. FAO Nutrition Meetings Series, No. 45A, 1969; WHO/Food Add/69.34.
19. Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances (Thirteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.
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 29. A review of the technological efficacy of some antioxidants and synergists. FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.
 30. Evaluation of certain food additives and the contaminants mercury, lead, and cadmium (Sixteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.
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Annex 2

Summary of toxicological and dietary exposure information



Food and Agriculture
Organization of the
United Nations



World Health
Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Ninetieth meeting
Virtual meeting, 26 October – 6 November 2020

SUMMARY AND CONCLUSIONS
Issued December 2020

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held on a virtual online platform from 26 October – 6 November 2020, with an additional day for approval of the report on 24 November 2020. The purpose of the meeting was to evaluate the acceptability of certain substances as previous cargoes and the safety of certain food contaminants. The present meeting was the 90th in a series of similar meetings.

The 90th meeting of JECFA was originally scheduled for 27 October – 5 November 2020 at WHO headquarters in Geneva, Switzerland. Because of the travel restrictions and lockdowns due to the COVID-19 pandemic in many countries, it was not possible for the joint FAO/WHO JECFA secretariat to convene the meeting as scheduled. Therefore, the meeting was held as a video-conference.

In view of the time differences in the countries of origin of the invited experts, the only possible time for a video-conference was restricted to a 4-hour time slot (12:00–16:00 CEST) a day. This allowed only 40% of the usual daily length (8–10 hours) of a JECFA meeting, precluding complete evaluation of all the 23 scheduled compounds. In an effort to regain some additional meeting time, the ninetieth JECFA meeting was extended by 3 days, adding Monday 26 October, Friday 6 November and Tuesday 24 November 2020. As these circumstances meant that less meeting time had been available, compared to a normal JECFA meeting, some of the previous cargoes and contaminants that were originally scheduled for discussion could not be considered, namely: previous cargoes (solvents and reactants) and the ergot alkaloids. All items that were deleted from the agenda of the 90th JECFA meeting will be re-scheduled for evaluation at future JECFA meetings.

Dr D. Benford served as Chairperson and Dr R. Cantrill as Vice-Chairperson.

Dr M. Feeley, Ottawa, Canada and Ms K.B. Laurvick, FAO, served as joint rapporteurs.

The Committee evaluated 18 substances that may occur as previous cargoes and the trichothecenes T-2 and HT-2. The tasks before the Committee were a) to elaborate principles governing the evaluation of the acceptability of previous cargoes; (b) to undertake toxicological evaluations and dietary exposure assessments, and (c) to undertake toxicological evaluations and dietary exposure assessments in relation to contaminants in food. It became apparent during the meeting that the time limitations precluded the toxicological evaluation of the trichothecenes T-2 and HT-2. The toxicological evaluation and overall risk assessment will therefore follow at a future meeting.

The report of the meeting will be published in the WHO Technical Report Series. The report will summarize the main conclusions of the Committee in terms of acceptability of substances proposed as previous cargoes. Its presentation will be similar to that of previous reports – namely, general consideration, comments on specific previous cargoes or groups of previous cargoes, and on trichothecene contaminants in food, followed by recommendations. An annex will include a summary (similar to the summary in this report) of the main conclusions of the Committee in terms of acceptability of previous cargoes and other toxicological and safety recommendations.

Toxicological and dietary exposure monographs on the previous cargoes or groups of previous cargoes considered will be published in WHO Food Additives Series No. 81.

More information on the work of JECFA is available at:
<http://www.fao.org/food-safety/resources/publications/en/>
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Toxicological and dietary exposure information and conclusions

Previous cargoes evaluated

Previous cargo	Evaluations
Alcohols (Group 2)	
Tridecyl alcohol, myristyl alcohol and unfractionated fatty alcohols	<p>The Committee noted the limitations of the current dataset of toxicological evaluations, and the need to use a read-across approach where appropriate.</p> <p>Based on the weight of evidence across long-chain fatty alcohols, tridecyl and myristyl alcohol and unfractionated fatty alcohols can be considered not to raise concerns for genotoxicity.</p> <p>For tridecyl alcohol, the Committee used the dose level of 184 mg/kg bw per day, at which mild histopathological changes were reported in the liver following a 14-day study of oral gavage exposure in rats, as a reference point. This was supported by the data on other long chain alcohols, for which the NOAELs recorded in the rat upon subchronic administration via the diet range from approximately 200 to 1000 mg/kg per day. The Committee noted limitations in the study design, but concluded that it could be used to establish a margin of exposure in the absence of longer-term studies. Considering the estimated human dietary exposure of 0.3 mg/kg bw per day, the margin of exposure is 610, which is adequate to address the uncertainties in the database.</p> <p>For myristyl alcohol, the Committee identified a NOEL of 167 mg/kg bw per day as the reference point from a 90-day dietary study with a C14-16 branched and linear alcohol in rats, based on decreased body weight gain at 702 mg/kg bw per day, possibly attributable to reduced palatability of the diet. Considering the estimated human dietary exposure of 0.3 mg/kg bw per day, the margin of exposure is 560, which is adequate to address the uncertainties in the database.</p> <p>For unfractionated fatty alcohols, the Committee adopted a read-across approach, using data on two representative fatty alcohols, tridecyl alcohol and myristyl alcohol, and long chain alcohols. NOAEL values of between 200 mg/kg bw per day and 1000 mg/kg bw per day have been reported for fatty alcohols with chain lengths in the C6-C22 range, based upon subchronic dietary studies in the rat. Based upon read-across, plus the fact that unfractionated fatty alcohols are present in natural food sources, the Committee concluded that the unfractionated fatty alcohols with components in the C6-C22 range are not of toxicological concern at the estimated dietary exposure level of 0.3 mg/kg bw per day.</p> <p>There are no reports of allergenicity following oral exposure to tridecyl and myristyl alcohols and to unfractionated fatty alcohols that would indicate that they are or contain a known food allergen.</p> <p>Tridecyl alcohol, myristyl alcohol and unfractionated fatty alcohols may react with a previous cargo in transesterification reactions with glycerides or esterification reactions with free fatty acids present, but the rates of reaction are likely to be slow at ambient temperature and any products would be naturally occurring waxes.</p> <p>Therefore, the Committee concluded that tridecyl alcohol, myristyl alcohol and unfractionated fatty alcohols meet the criteria for acceptability as previous cargoes.</p>
Isodecyl alcohol, isononyl alcohol and isoocetyl alcohol	<p>The Committee noted the limitations of the current dataset of toxicological evaluations, and the need to use a read-across approach where appropriate.</p> <p>The Committee noted the negative data for mutagenic activity for isoocetyl alcohol and isononyl alcohol, lack of clastogenic activity of isodecyl alcohol, and the weight of evidence across long-chain fatty alcohols for a lack of mutagenic potential. The Committee considered that isodecyl alcohol, isononyl alcohol and isoocetyl alcohol can be considered non-genotoxic. The Committee noted that no carcinogenicity studies have been identified for isodecyl alcohol, isononyl alcohol and isoocetyl alcohol. Based upon the weight of evidence across several aliphatic alcohols, including the linear alcohol 1-dodecanol, the Committee concluded that isodecyl alcohol, isononyl alcohol and isoocetyl alcohol are unlikely to possess carcinogenic potential.</p>

For **isodecyl alcohol**, the Committee concluded that a NOEL of 158 mg/kg bw per day for maternal toxicity from a comparative developmental toxicity study on rats was a suitable reference point. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the margin of exposure is approximately 520, which the Committee concluded is sufficient to address the uncertainties in the database.

For **isononyl alcohol**, the Committee considered that a NOEL of 158 mg/kg bw per day for maternal toxicity from a comparative developmental toxicity study on rats was a suitable reference point. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the margin of exposure is approximately 520, which the Committee concluded is sufficient to address the uncertainties in the database.

For **isooctyl alcohol**, no reproductive or developmental toxicity studies were identified. Using read-across from isodecyl alcohol and isononyl alcohol, the Committee concluded that it is highly unlikely that isooctyl alcohol possesses significant reproductive or developmental toxicity. The Committee considered that the dose of 130 mg/kg bw per day, which resulted in mild histopathological changes in the liver following a 14-day oral gavage exposure in rats, was a suitable reference point. The Committee noted limitations in the study design but concluded that it could be used to establish a margin of exposure in the absence of longer-term studies. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the margin of exposure is approximately 430, which the Committee concluded is sufficient to address the uncertainties in the database.

There are no reports of allergenicity upon oral exposure to isodecyl alcohol, isononyl alcohol and isooctyl alcohol that would indicate that they are or contain a known food allergen.

Isodecyl alcohol, isononyl alcohol and isooctanol may react with a previous cargo in transesterification reactions with glycerides or esterification reactions with free fatty acids present, but the rates of reaction are likely to be slow at ambient temperature and any products would be naturally occurring waxes.

Therefore, the Committee concluded that isodecyl alcohol, isononyl alcohol and isodecyl alcohol meet the criteria for acceptability as previous cargoes.

1,3-Propanediol (1,3-PD)

1,3-PD is not genotoxic.

The Committee considered that the LOEL of 250 mg/kg bw per day, based on marginal fetal effects in rats should be used as the reference point. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the margin of exposure is 830, which is adequate to address the uncertainties in the database.

There are no reports of allergenicity upon oral exposure to 1,3-PD that would indicate that it is or contains a known food allergen.

1,3-PD is a very stable liquid at room temperature and it is unlikely to polymerize or participate in hydrogenation or dehydrogenation reactions without the presence of a catalyst or microorganism.

Therefore, the Committee concluded that 1,3-propanediol meets the criteria for acceptability as a previous cargo.

1,4-Butanediol (1,4-BD)

The Committee noted that both 1,4-BD and γ -butyrolactone are rapidly metabolized to γ -hydroxybutyric acid, whereupon they share metabolic fates. The Committee concluded that data on γ -butyrolactone could be used for read-across to fill data gaps with 1,4-BD.

The Committee concluded that 1,4-BD is not genotoxic, and that the data for γ -butyrolactone are consistent with 1,4-BD being unlikely to possess carcinogenic potential.

The Committee noted that a range of toxic end-points have been reported for 1,4-BD and γ -butyrolactone from various studies. The Committee concluded that acute and transient central nervous system effects, most notably hyperactivity, provided the most relevant end-point. A NOEL of 100 mg/kg bw was identified by the NTP, and the Committee considered that this was appropriate as a reference point in the current evaluation. Considering the estimated dietary exposure of 0.3 mg/kg bw per day, the margin of exposure is approximately 330, which the Committee concluded is sufficient to address the uncertainties in the data.

There are no reports of allergenicity upon oral exposure to 1,4-BD that would indicate that it is or contains a known food allergen.

1,4-BD is unlikely to polymerize or participate in hydrogenation or dehydrogenation reactions without the presence of a catalyst or microorganism. There is a low possibility of ester formation with free fatty acids.

Therefore, **the Committee concluded that 1,4-butanediol meets the criteria for acceptability as a previous cargo.**

Butyl ethers (Group 5)

Methyl tertiary butyl ether (MTBE)

Upon evaluating the available toxicity studies and examining the toxicological relevance of effects reported therein, the Committee considered that the NOAEL of 300 mg/kg bw per day identified from the 90-day oral subchronic study of MTBE in rats was the most appropriate RP. The Committee concluded that the estimated exposure to MTBE from drinking-water is a minor contributor (0.008 mg/kg bw per day) as compared with the estimated exposure to MTBE in food oil commodities from previous cargoes (0.3 mg/kg bw per day), and that there are no other known potential sources of dietary exposure to MTBE. A comparison of the RP of 300 mg/kg bw per day with the estimated exposure of 0.3 mg/kg bw per day for MTBE as a previous cargo yields a margin of exposure of 1000, which is sufficient to address the uncertainties in the databases.

There are no data on allergenicity upon oral exposure to MTBE that indicate that it is or it contains a known food allergen.

MTBE as a previous cargo is not expected to react with edible fats and oils to form any reaction products.

Therefore, **the Committee concluded that MTBE meets the criteria for acceptability as a previous cargo for edible fats and oils.**

Ethyl tertiary butyl ether (ETBE)

Upon evaluating the available toxicity studies and examining the toxicological relevance of effects reported therein, the Committee concluded that the NOAEL of 100 mg/kg bw per day identified from the 180-day oral subchronic study of ETBE in rats was the most appropriate RP. The Committee concluded that the estimated exposure to ETBE from drinking-water is a minor contributor (0.01 mg/kg bw per day) compared with the estimated exposure to ETBE in food oil commodities from previous cargoes (0.3 mg/kg bw per day), and that there are no other known potential sources of dietary exposure to ETBE. A comparison of the RP of 100 mg/kg bw per day with the estimated exposure of 0.3 mg/kg bw per day for ETBE as a previous cargo yields a margin of exposure of 330, which is sufficient to address the uncertainties in the databases.

There are no data on allergenicity upon oral exposure to ETBE that indicate that it is or it contains a known food allergen.

ETBE as a previous cargo is not expected to react with edible fats and oils to form any reaction products.

Therefore, **the Committee concluded that ETBE meets the criteria for acceptability as a previous cargo for edible fats and oils.**

Oils and waxes (Group 3)

Mineral oil, medium and low viscosity, class II and class III

The critical toxicological end-point for evaluation of mineral oil saturated hydrocarbons (MOSH) is liver granuloma formation and increase in liver weight in F344 rats. The Committee acknowledged that F344 rats represent the only strain and species that have shown liver granulomas accompanied by an inflammatory response due to MOSH exposure. In humans, lipogranulomas in the liver associated with exposure to MOSH have been observed, but these have not been associated with inflammatory reactions or other adverse consequences with clinical relevance. Given the lack of sufficient information on the mechanism of liver granuloma formation in F344 rats, the Committee concluded that it could not dismiss the human relevance of these liver granulomas and used them and the increase in liver weight in its assessment of mineral oil hydrocarbons (MOH) as previous cargoes.

The Committee decided to use the NOAEL of 22 mg/kg bw per day of a MOSH mixture (C14-C50, including class II and class III mineral oil, medium and low viscosity) as a RP. The Committee applied an MOE approach to assess the acceptability of MOSH as a previous cargo. Considering the estimated dietary exposure of 0.4 mg/kg bw per day (0.3 mg/kg bw per day from previous cargoes, plus 0.1 mg/kg per day from other sources), the MOE is 55. In its judgement of this MOE, the Committee took into account that the end-point of granuloma formation is determined in the most sensitive species, sex and strain, that the RP used is one tenth of the dose

showing the effect and the uncertainty of the human health significance of the end-point. Furthermore, the exposure estimate is conservative. Based on these considerations the Committee concluded that the MOE of 55 was sufficient to address the uncertainties in the databases.

There are no data on allergenicity upon oral exposure to the mineral oil, medium and low viscosity, class II and class III, or MOSH that would indicate that they are or contain a known food allergen.

No potential information has been identified with respect to the reaction of mineral oil with edible fats and oils, although migration studies have confirmed that mineral oil migrates into fats and oils.

The Committee concluded that mineral oil, medium and low viscosity, class II and class III meet the criteria for acceptability as previous cargoes provided the MOH is food grade.

Commercial MOH products range from being free of mineral oil aromatic hydrocarbons (MOAH) (food grade mineral oil) to containing 30% MOAH (crude mineral oil). **The Committee noted that crude mineral oil is banned as a previous cargo and MOAH, which contain mutagenic and carcinogenic substances, would be unacceptable as previous cargoes.** The current evaluation is based on the assumption that MOH products shipped as previous cargoes are highly refined food-grade products free of MOAH.

Montan wax

While oral bioavailability of montan wax is expected to be limited and the material appears to be of low acute toxicity, in the only repeat dose study available montan wax produced toxicity at all doses tested. The Committee noted that montan wax is a highly variable and poorly defined material. Given the high degree of variability in composition, the extent to which the particular test article in the subchronic study is representative of the diversity of the various forms of crude, desinated or refined montan wax currently in commerce is unknown. Therefore, the Committee could not characterize the hazard of montan wax shipped as a previous cargo.

No specific information was found on the reactions of montan wax with edible fats and oils.

The Committee determined that the available evidence was not sufficient to characterize the risk of montan wax; as a result, it was concluded that montan wax does not meet the criteria for acceptability as a previous cargo for edible fats and oils.

Propylene tetramer

Although no chronic or carcinogenic studies were identified, the Committee concluded that propylene tetramer does not have genotoxic potential in vitro nor any structural alerts for carcinogenicity. These findings are consistent with other individual olefins present in propylene tetramer or mixtures thereof. The Committee noted the availability of a recent guideline-compliant subchronic study in rats and decided to use the NOAEL from this study of 40 mg/kg bw per day based on increased liver weights as an RP in a margin of exposure approach to evaluate the acceptability of propylene tetramer as a previous cargo for edible fats and oils. Comparison of the generic maximum anticipated oral exposure to propylene tetramer from previous cargoes of 0.3 mg/kg bw per day with the RP of 40 mg/kg bw per day yields a margin of exposure of approximately 130. This margin is considered adequate to address uncertainties in the health effects database.

Therefore, and in consideration of the fact that this substance is not known or anticipated to be a food allergen, **the Committee concluded that propylene tetramer meets the criteria for acceptability as a previous cargo for edible fats and oils.**

Soybean oil epoxidized (ESBO)

The overall toxicity database for ESBO is relatively complete, including acute, subchronic and chronic toxicity studies. ESBO is not genotoxic or carcinogenic and is not a reproductive or developmental toxicant. The overall systemic toxicity of ESBO is considered to be low and no toxicologically relevant impurities or reaction products with edible fats or oils are anticipated. The Committee decided to use the NOAEL of 125 mg/kg bw per day based on organ weight changes at the next highest dose in a 2-year rat oral bioassay as a reference point (RP) to evaluate the acceptability of ESBO as a previous cargo for edible fats and oils. It should be noted that ESBO is also used in a variety of food packaging applications, which may contribute significantly to exposure. A recent study estimated the cumulative daily intake of ESBO from its use in PVC-based food-contact articles to be 0.13 mg/kg bw per day for the general US population. A worst-case exposure estimate of 0.43 mg/kg bw per day can therefore be derived by combining the maximum estimated exposure from ESBO as a previous cargo (0.3 mg/kg bw per day) with other sources associated with food packaging. Comparison of the RP with this estimate yields a margin of exposure of approximately 290. The Committee considered this margin adequate to account for uncertainties in the health effects and exposure databases.

ESBO is not known or anticipated to be a food allergen.

No specific information has been identified on the reaction of ESBO with edible fats and oils, although migration studies have confirmed that ESBO migrates into oily foods and oil-based food simulants (e.g. olive oil).

Therefore, the Committee concluded that ESBO meets the criteria for acceptability as a previous cargo for edible fats and oils.

Solutions (Group 4)

Calcium nitrate and calcium ammonium nitrate

Considering that toxicological datasets on calcium nitrate and calcium ammonium nitrate are sparse, the Committee evaluated available toxicological data on calcium, ammonium and nitrate to conduct their toxicological evaluation. The Committee also reviewed available toxicological data on magnesium and phosphates, as dolomite and phosphate rock could be used in the manufacture of calcium ammonium nitrate and calcium nitrate, respectively.

The Committee estimated exposure to calcium nitrate and calcium ammonium nitrate from previous cargoes for edible fats and oil as 0.3 mg/kg bw per day each, which is much less than the exposures to calcium, nitrate, ammonium, magnesium and phosphates expected from dietary sources. The Committee considered health-based guidance values for calcium, nitrate, ammonium, magnesium and phosphates, established under previous evaluations, to conduct the toxicological evaluation of calcium nitrate and calcium ammonium nitrate at the anticipated exposure level from previous cargoes for edible oils and fats. The estimated exposure value for calcium nitrate and calcium ammonium nitrate as previous cargoes for edible fats and oils is 0.3 mg/kg bw each, which does not exceed the ADI for nitrate of 0–3.7 mg/kg bw, expressed as nitrate ion, and the MTDI of 70 mg/kg bw for phosphates, diphosphates and polyphosphates. The previous Committees did not assign a numerical ADI and allocated an ADI “not specified” for most calcium, ammonium and magnesium salts based on their low oral toxicity profiles. Furthermore, the Committee considered that human exposure to these substances resulting from their use as previous cargoes would be a minor contributor to the total dietary exposure.

There are no data on allergenicity upon oral exposure to calcium nitrate and calcium ammonium nitrate that would indicate that these substances are, or contain, known food allergens.

The Committee concluded that the formation of calcium, ammonium or magnesium salts of free fatty acids is possible. However, due to the anticipated absence of alkaline conditions and an insufficient concentration of counter ions and free fatty acids (necessary for the reactions to occur), these reaction products are not expected to be formed in detectable amounts in a cargo of edible fats and oils.

Therefore, the Committee concluded that calcium nitrate and calcium ammonium nitrate meet the criteria for acceptability as previous cargoes for edible fats and oils.

Calcium ligno-sulfonate

The Committee previously established an ADI of 0–20 mg/kg bw for the food-grade calcium lignosulfonate (40-65), the upper bound of which is above the estimated exposure for calcium lignosulfonate as a previous cargo for edible fats and oils of 0.3 mg/kg bw per day. There are no data on allergenicity of oral exposure to calcium lignosulfonate (40-65) that would indicate that it is or it contains a known food allergen. Therefore, food-grade calcium lignosulfonate (40-65) meets the criteria for acceptability as a previous cargo for edible fats and oils.

Lignosulfonates are unlikely to react with free fatty acids and triglycerides present in cargoes of fats and oils under the conditions of transport.

The Committee could not determine the specific chemical composition or molecular weight distribution of the non-food grade calcium lignosulfonate that is shipped as a previous cargo but recognized that it has a wide molecular weight distribution. The Committee acknowledges that no toxicokinetic data to determine oral bioavailability of or systemic exposure to the non-food grade calcium lignosulfonate shipped as a previous cargo are available. Therefore, the ADI for calcium lignosulfonate (40-65) does not apply to the material that is shipped as a previous cargo unless it is food-grade calcium lignosulfonate. In the absence of adequate data on chemical specifications and toxicokinetics, the Committee concluded that the systemic effects of oral exposure to the non-food grade calcium lignosulfonate cannot be evaluated as no oral toxicity, genotoxicity or allergenicity data are available on this substance.

In the absence of relevant toxicological data on test substances that are sufficiently representative of different molecular weight fractions constituting the non-food grade calcium lignosulfonate that is shipped as a previous cargo, the Committee concluded that the non-food-grade calcium lignosulfonate does not meet the criteria for acceptability as a previous cargo for edible fats and oils.

Food contaminants

Conclusions on the chemical characterization and dietary exposure assessment

Trichothecenes, T-2 and HT-2

The Committee reviewed the information regarding analytical methods, sampling, effect of processing, prevention and control, occurrence in food commodities and dietary exposure since the last evaluation of T-2 and HT-2 at the fifty-sixth meeting in 2001. Analytical methods have been improved in the last two decades with multi-mycotoxin HPLC-MS methods allowing the quantification of T-2 and HT-2 below or close to 1 µg/kg. There were a large number of occurrence data for T-2 and HT-2 submitted to the GEMS/Food contaminants database in the last two decades, but these were largely from Europe with a paucity of data from other regions. This may be due to the generally low incidence and low concentrations of T-2 and HT-2 found outside Europe. In Europe T-2 and HT-2 occur frequently in cereal crops, particularly in oats. There is also evidence of co-occurrence of several other type A trichothecenes and their metabolites in cereals. It was concluded that dietary exposure to T-2 and HT-2 covering the known geographical distribution of T-2 and HT-2 was suitably covered by existing European estimates of chronic and acute dietary exposure. No additional international or national estimates of chronic or acute dietary exposure were derived by the Committee.

The Committee derived chronic dietary exposure estimates of 6.0 to 18 ng/kg bw per day for T-2, HT-2 and diacetoxyscirpenol (DAS) combined. The toxicological evaluation and overall risk assessment will follow at a future meeting.

Annex 3

Meeting agenda



Food and Agriculture
Organization of the
United Nations



World Health
Organization

**90th JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)
26 October – 6 November 2020**

Virtual meeting: 12:00–16:00 (Geneva time)

1. Opening
2. Declarations of Interests (information by the Secretariat on any declared interests and discussion, update by experts)
3. Election of Chairperson and Vice-Chairperson, appointment of Rapporteurs
4. Adoption of the agenda
5. Matters of interest arising from previous Sessions of the Codex Committee on Contaminants in Food (CCCCF) and Codex Committee on Fats and Oils (CCFO)
6. Critical issues and questions from Working Papers (first brief round of discussion on all subjects to inform the full Committee)
7. Evaluations
 - 7.1. TPrevious cargoes
 - 7.1.1. Alcohols
 - 7.1.2. Butyl ethers
 - 7.1.3. Oils and waxes
 - 7.1.4. Solutions
 - 7.1.5. Solvents, reactants
 - 7.2. Trichothecenes (T2 and HT2)
8. Other matters to be considered (general considerations).
9. Other matters brought forth by the Committee during discussions at the meeting.
10. Adoption of the report.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

Evaluation of certain food additives

Eighty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1027, 2020 (106 pages)

Evaluation of certain veterinary drug residues in food

Eighty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1023, 2020 (116 pages)

Evaluation of certain food additives

Eighty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1020, 2019 (109 pages)

Evaluation of certain food additives

Eighty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1014, 2019 (156 pages)

Evaluation of certain veterinary drug residues in food

Eighty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1008, 2017 (150 pages)

Safety evaluation of certain food additives

Eighty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives
WHO Food Additives Series, No. 75, 2018 (244 pages)

Evaluation of certain food additives

Eighty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1007, 2017 (92 pages)

Safety evaluation of certain contaminants in food

Eighty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives
WHO Food Additives Series, No. 74, 2018 (897 pages)

Evaluation of certain contaminants in food

Eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1002, 2017 (166 pages)

Evaluation of certain contaminants in food

This report presents the conclusions of a Joint FAO/WHO Expert Committee convened to evaluate the safety of various contaminants from the transport of previous cargoes, and the trichothecenes, T-2 and HT-2. The first part of the report contains a brief description of the general consideration addressed at the meeting. A summary follows of the Committee's evaluations of technical, toxicological and/or dietary exposure data for four groups of previous cargoes: alcohols (Group 2), butyl ethers (Group 5), oils and waxes (Group 3) and solutions (Group 4). It also summarizes the chemical characterization and dietary exposure assessment of the trichothecenes, T-2 and HT-2. Annexed to the report is a summary of the toxicological and dietary exposure information for the previous cargoes and tricothecenes considered at this meeting.

