Committee on Toxicity

Committee on Carcinogenicity

Committee on Mutagenicity

Annual Report

2023

Committee on Toxicity of Chemicals in Food, Consumer, Products and the Environment Annual Report 2023

Contents

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment Annual Report 2023 ……...

About the Committees……...

Preface……

COT Evaluations……

Oral nicotine pouches……..

Interim position on per- and polyfluoroalkyl substances……

Statement paper on the guidance levels for the fortificants in the bread and flour regulations……..

COT Assurance……..

Assessment of the risk of allergic reaction from fortification of non-wholemeal wheat flour with folic acid……

Committee Procedures……

Public consultation on draft EFSA opinion on polybrominated diphenyl ethers (PBDEs)…….....

Public consultation on draft EFSA opinion on polychlorinated naphthalenes (PCNs) in food and feed ……..

Discussion paper on existing health-based guidance values (HBGVs) for T2 & HT2 mycotoxins……

Draft EFSA opinion on the Tolerable Upper Level for vitamin B6……..

Public consultation on EFSA'S 2023 re-evaluation of the risk to public health from inorganic arsenic in food……

EFSA public consultation on Update of the risk assessment of mineral oil hydrocarbons (MOH) in food……

On going work……

Position paper on chitosan in bio-based food contact materials……..
Hepatotoxicity of green tea catechins……..
Review of titanium dioxide as a food additive……
Discussion paper on the effects of pica during pregnancy……..
Lead in the maternal diet……..
Arsenic in the maternal diet……
Ginger in the maternal diet……
The potential risks from ergot alkaloids in the maternal diet……
Statement on the risk assessment of cow's milk in children aged 1 to 5 years, in the context of plant-based drinks evaluations……
Draft dioxin report……
Advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins……
Scoping paper on the advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins……
Pinnatoxin group……
Pectenotoxin group……
Assessment and draft interim position statement on bisphenol A (BPA)……
Aircraft cabin air……
Sub-statement on the potential risk(s) from exposure to microplastics: Inhalation route……
Novel formulations of supplement compounds designed to increase oral bioavailability……
UK COT FSA New Approach Methodologies Roadmap (2023) Draft Version 3..
Assessment of ocean bound plastic (OBP)……

Other Committee Activities: Joint Expert Groups, Presentations and Workshop

Presentation from the PhD Student……
Evolving Our Assessment & Future Guiding Principles Workshop……..
Opportunities and outlook for United Kingdom Food and Chemicals regulation post European Union Exit-COT Workshop Report……
Horizon Scanning……

Joint Expert Groups……

Assurance of Joint Expert Group opinions……

AEJEG assessments……..

FCMJEG assessments……..

Working Groups……

Joint ACNFP/COT Working Group on Cannabidiol (CBD)……

Plant-based drinks……

PFAS……..

Codex report on food allergen thresholds……

2023 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment……..

Chairman……..….

Members……..…

Secretariat……

Associate Members…….

Declaration of members' interests during the period of this report……..

About the Committees

This is the 33rd joint annual report of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) and the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC).

The aim of these reports is to provide a brief background to the Committees' decisions. Those seeking further information on a particular subject can obtain details from the Committee's statements and minutes, available from the websites listed below or from the Committee's administrative Secretary.

In common with other independent advisory committees, Committee members are required to follow a Code of Conduct which also gives guidance on how commercial interests should be declared. Members are required to declare any commercial interests on appointment and, again during meetings if a topic arises in which they have an interest. If a member declares a specific interest in a topic under discussion, and it is considered to be a conflict of interest, he or she may, at the Chairman's discretion be allowed to take part in the discussion but is excluded from decision-making. Annex 1 contains the terms of reference under which the Committees were set up. The Code of Conduct is at Annex 2 and Annex 3 describes the Committees' policy on openness.

Annex 4 is the Good Practice Agreement for Scientific Advisory Committees. Annex 5 contains a glossary of technical terms used in the text. Previous publications of the Committees are listed at Annex 6. An alphabetical index to subjects and substances considered in previous reports is available on the COT website.

These three Committees also provide expert advice to other advisory committees, such as the Scientific Advisory Committee on Nutrition, and there are links with the FSA Science Council, Veterinary Products Committee and the Expert Committee on Pesticides (formerly the Advisory Committee on Pesticides).

The Committees' procedures for openness include the publication of agendas, finalised minutes, agreed conclusions and statements. These are published on the internet at the following links:

Committee on Toxicity

Committee on Carcinogenicity

Committee on Mutagenicity

This report contains summaries of the discussions and links to the Committees' published statements. Paper copies are available upon request to the Secretariats.

Preface

Professor Alan Boobis (Chair)

OBE PhD CBiol FRSB FBTS FBPhS

COT evaluations

Oral nicotine pouches

1.1 The COT was requested by the Office of Health Improvement and Disparities (OHID) Tobacco team to consider the toxicological risks from the use of oral nicotine pouches that do not contain tobacco, including ones that may contain up to approximately 120 mg nicotine per pouch.

1.2 Oral nicotine pouches contain tobacco-derived nicotine and food grade ingredients and are placed between the lip and gum to release the nicotine into the saliva so it can be absorbed within the mouth before entering the blood stream.

1.3 The Committee considered the available information on ingredients present in the products and reviewed the oral bioavailability of nicotine to assess any potential risks associated with use of oral nicotine pouches.

1.4 COT noted that oral nicotine pouches provide a pharmacologically active dose of nicotine in both CC smokers and nicotine-naïve users and, as such, they are not ‘harmless’ products. However, use of oral nicotine pouches could be considered as part of a harm-reduction strategy if their use is of lower risk than that of CC smoking and if concurrent use of other nicotine-containing products is avoided.

1.5 It was anticipated that nicotine-related ill-effects on health could occur with long-term use of oral nicotine pouches. Risks include effects on a range of endpoints in users and their offspring.

1.6 Experienced users may self-titrate nicotine intake. Systemic exposure levels of nicotine equivalent to those from CC smoking can be achieved from use of oral nicotine pouches. Factors influencing the level of nicotine exposure and retention include the type of pouch used, user profile, usage parameters, nicotine concentration, and the overall formulation of the pouch contents. However, there is potential for the use of oral nicotine pouches by adults in excess of that

recommended by the manufacturers, which could be of concern due to the potential for increased and prolonged nicotine exposure.

1.7 The health risks from other constituents of CC smoke or oral nicotine pouches have not been fully assessed. However, it is plausible that use of oral nicotine pouches, produced according to appropriate manufacturing standards and used as recommended, as a replacement for CC smoking, would be associated with a reduction in overall risk of adverse health effects, although the magnitude of the decrease will depend on the effect in question.

1.8 Individuals who have never been exposed to nicotine and who take up the use of oral nicotine pouches would be at risk from effects of nicotine to which they would not otherwise be exposed. This includes the risk of addiction.

1.9 Use of oral nicotine pouches in parallel with other nicotine-containing products (e.g., CC, ENDS) could potentially lead to increased nicotine exposure compared with that from use of a single product-type and may increase the overall risk of nicotine-related toxicity.

1.10 While there are limited data on which exposure estimates can be made, the estimated exposure to nicotine from 10 mg pouches as outlined by Azzopardi et al (2021) exceeds the COT reference value. It is very likely that exposures from pouches containing higher levels of nicotine as reported to the Committee by DHSC would be significantly higher, and as such the potential risks would be greater, both for people using these pouches and from accidental ingestion.

1.11 The Committee considered that accidental exposure of children to oral nicotine pouches is possible, and that appropriate (i.e., childproof) packaging and labelling is a key safety issue. The appeal and ease of availability of oral nicotine pouches to individuals under 18 years of age was also highlighted as of potential concern for uptake in this age group.

1.12 There is an absence of data on the potential influence of co-exposure to food and drink (hot and cold) or the effects of mechanical manipulation (e.g., sucking or chewing) on absorption of nicotine from oral nicotine pouches. Additionally, it was

considered that prolonged buccal membrane exposure to food-grade ingredients within the pouches would result in a high local exposure which has not been addressed from a food safety perspective.

1.13 The Committee expressed concerns over the current regulatory framework for oral nicotine pouch products as they did not fall under specific regulations. It was noted that the different regulatory frameworks for different potential harm-reduction products also made it difficult to compare such products, as the data requirements varied.

1.14 The Committee commented on the variation in how manufacturers present nicotine content and strength across different products, which may be confusing for the consumer. In addition, use of the description ‘tobacco-free’ may be misleading as the nicotine may be derived from tobacco, which raises concerns regarding carry over of toxicologically relevant contaminants (e.g., metals and nitrosamines).

1.15 An absence of independent data on use/exposure to oral nicotine pouches was identified, with currently available data being largely industry sponsored.

1.16 Overall, the COT considered that the use of oral nicotine pouches, as recommended by the manufacturer, as a replacement for CC smoking was likely to be associated with a reduction in overall risk of adverse health effects, although the magnitude of the decrease will depend on the effect in question. Use of oral nicotine pouches by nicotine-naïve users was likely to be associated with some adverse health effects to which the user would not otherwise have been subject, as a pharmacologically active dose of nicotine is delivered. Concurrent use of oral nicotine pouches with CC smoking or other nicotine-containing products could increase and prolong nicotine exposure compared to a single source.

1.17 The use of oral nicotine pouches could result in prolonged exposure of the buccal membrane to the flavouring products and other constituents used in the pouches. The effect of this had not been investigated and is an important data gap. There are large gaps in nicotine exposure data for the use of oral nicotine pouches in humans, which prevent detailed comparison with CC smoking or the use of other smokeless products. It is not currently possible to predict the adverse health effects

that could be associated with use of oral nicotine pouches in the long term, particularly at higher nicotine content levels. As the information and science relating to oral nicotine pouches is changing rapidly, the COT will keep this area under review.

1.18 The full COT statement can be found at: Statement on the bioavailability of nicotine from the use of oral nicotine pouches and assessment of the potential toxicological risk to users.

Interim position on per- and polyfluoroalkyl substances

1.19 The COT had considered per- and poly-fluoroalkyl substances (PFAS) on a number of previous occasions and published a statement in 2022 on the European Food Safety Authority (EFSA) opinion in which the scientific basis of the new EFSA tolerable weekly intake (TWI) for the sum of four PFAS was reviewed. The Committee was subsequently asked to consider what further guidance can be provided to support human health risk assessments undertaken by UK Government Departments and Agencies.

1.20 The Committee considered there were a number of uncertainties with regards to the critical endpoint of decreased vaccine response in children, used as a basis for the EFSA TWI and draft US EPA RfDs for PFOA and PFOS, with respect to the biological significance of the response and reservations concerning the critical studies (Abraham et al. (2020) and Grandjean et al. (2012)). In the statement on the EFSA TWI the COT expressed a number of reservations with respect to some of the modelling undertaken to determine the TWI.

1.21 In considering the wider evidence base, the Committee noted that a number of different approaches had been adopted by other authoritative bodies in deriving their HBGVs due to differences in the critical study and endpoint selected, resulting in a range of available HBGVs for a number of different PFAS.

1.22 The Committee noted other challenges regarding the risk assessment of PFAS including the lack of data for most PFAS and consequently HBGVs only being

derived for a small number and the uncertainty over how best to assess all detected PFAS, such as by summing all PFAS present or grouping similar substances.

1.23 Due to the uncertainties noted and the need for more guidance to support UK Government Departments and Agencies undertaking risk assessments for PFAS, the COT would undertake its own consideration of the evidence base and risk assessment.

1.24 Future COT work to be undertaken by a subgroup of Members would include:

- An independent review of toxicological and epidemiological data, focusing on a number of critical endpoints, and considering the biological relevance of the endpoints assessed.
- Consideration of the toxicokinetics of PFAS.
- Whether and how different PFAS can be grouped for assessment.
- Deriving a HBGV or a number of HBGVs as the data allow.

1.25 The Committee acknowledged that a further review of PFAS would be an extensive and lengthy undertaking. In the meantime, where risk assessments would be undertaken for the potential risks associated with exposure to PFAS, consideration should be made of the available HBGVs for the specific compounds identified, recognising the uncertainties with respect to the critical effects and modelling approaches adopted.

1.26 The full COT position paper can be found at: Interim Position Paper on Per- and Polyfluoroalkyl Substances.

Statement paper on the guidance levels for the fortificants in the bread and flour regulations

1.27 The Bread and Flour regulation (BFR) stipulates the levels of calcium carbonate, iron, thiamin (also known as vitamin B1) and nicotinic acid that must be present in flour. In 2022, the Department for Environment, Food and Rural Affairs (Defra) held a consultation on the BFR 1998 review and asked whether the consultees agreed with the proposal to raise the minimum levels of calcium

carbonate, iron and niacin added in non-wholemeal wheat flour to 15% of the nutrient reference values (NRV) supplied by 100g of flour as stated in point 1 of Part A of Annex XIII of regulation EC No. 1169/2011. NRVs are established guidelines for the recommended daily energy and nutrient consumption. The minimum amount of thiamin required to be present in non-wholemeal wheat flour will remain the same at 19% of the NRV.

1.28 The COT were asked by DHSC to provide a risk assessment on the dietary exposure of calcium carbonate, iron, nicotinic acid and thiamin at the current and proposed fortification levels to identify if there were any potential adverse health effects.

1.29 High calcium intakes (around 4 g per day) can cause milk-alkali syndrome in people with peptic ulcers. Milk-alkali syndrome is characterised by hypercalcemia (a condition where calcium blood levels are above normal), alkalosis (a condition where the blood becomes too alkaline, i.e., has a PH >7) and impaired kidney function, symptoms of high blood pressure, problems affecting the brain, abdominal pain and a build-up of calcium in tissues of the body. In individuals at risk of colonic polyps, calcium at levels of 1.6 g or 2 g per day can lead to ill-health effects that include problems in the gastrointestinal system (i.e., mouth, throat, oesophagus, stomach, small intestine, large intestine, rectum and anus). Hight calcium diets can also affect how other minerals such as iron, zinc, magnesium and phosphorus can be absorbed by the body (via the intestine).

1.30 High intakes of iron in infants of around 20 mg per kg of body weight can result in irritation to the gastrointestinal system. Lethal doses in children are between 200 and 300 mg per kg bodyweight. High intakes of iron in adults between 50 and 220 mg per day can cause constipation, nausea, and vomiting. It can also cause inflammation and perforation (formation of holes) of the gastrointestinal tract, has effects on the metabolism of cells, central nervous system, liver, and heart. For adults the lethal dose is 1.4g per kg bodyweight. Excessive levels of iron can also result in increased levels of bilirubin in the blood and enzymes (alkaline phosphates and aminotransferase). Other side effects may include anorexia, ophthalmological effects (effects on the eye), darkening of the skin and incipient psychosis.

1.31 High intakes of niacin can cause flushing (redness of the skin), itchy skin, nausea, vomiting, diarrhoea, and constipation. Long term intakes of 3 g per kg of body weight can cause jaundice, hyperglycaemia (high blood sugar levels) and abdominal pain.

1.32 Thiamin can cause effects such as muscle tremors, rapid pulse and nerve hyperirritability that can occur from daily doses of 17 mg, headache, nausea, irritability, insomnia, rapid pulse and weakness have been reported at high intakes >7 g) headache, nausea, irritability, insomnia, rapid pulse and weakness. Other effects that can occur from daily doses of 17 mg per day include muscle tremors, rapid pulse, and nerve hyperirritability.

1.33 A tolerable upper level (TUL) or safe upper level have not been established for calcium, iron, nicotinic acid and thamin by the UK Expert Group on Vitamins and Minerals (EVM, 2003). Although, the EVM reported that intakes of 1,5000 mg per day of calcium in supplemental form was not to be expected to result in any adverse effects. For iron, intakes of 17 mg per day would not be expected to produce any adverse effects. However, this level does not apply to individuals which increased susceptibility to iron overload. For nicotinic acid in supplemental form, the EVM reported intakes of 17 mg per day would not be expected to produce any adverse effects. This level does not apply to sustained release preparations of nicotinic acid. Whilst the EVM did not set an UL for nicotinic acid, the Scientific Committee on Food (SCF, 2003) did set an UL of 10 mg per day. For thamin, the EVM proposed a guidance level of 100 mg per day.

1.34 Exposure assessments were performed using data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) and National Diet and Nutrition Survey (NDNS) to estimate intakes of these minerals to the UK population from food sources. In the absence of any published data, various online sources were used to estimate the intakes of these minerals from supplements. The assessment determined how much exposure there was to the above minerals from:

a) non-wholemeal flour (i.e., wheat flour without grain wheat)
b) all food groups in the entire diet

c) supplements

1.35 Acute (short-term) intakes for all minerals (calcium, iron niacin and thamin) at the current and proposed fortification level in food did not exceed levels considered to be acutely toxic and are therefore not a health concern.

1.36 Chronic (long term) intakes of calcium, iron, niacin, and thiamin at the current and proposed fortification levels in food did not exceed their guidance levels. Therefore, chronic intakes of calcium, iron, niacin, and thiamin from fortified non-wholemeal flour are not of concern to health.

1.37 Intakes of calcium from supplements alone did not exceed the guidance level. However, daily intakes of iron, niacin and thamin from supplements alone may result in exceedance of their guidance levels when higher dosage supplements are consumed. However, it is important to note that not all of the population consume supplements. Therefore, health risk may only occur in members of the population who consume high dosage iron, niacin, and thiamin supplements.

1.38 Intakes of calcium from both food and supplements will not result in exceedance of the guidance level of calcium. However, intakes of iron, niacin and thamin from food and supplements combined can lead to exceedances of their guidance levels. Given, that the exceedance of the guidance levels is evident from supplement consumption alone, the exceedances of iron, niacin and thiamin here would only be of toxicological concern to individuals that consume high dosage of iron, niacin, and thiamin through supplements.

1.39 The COT concluded that the proposed increase in the fortification level of calcium, iron and niacin in non-wholemeal flour would not result in any excess risk. However, there would be a possible exceedance in individuals that consume supplemental iron, niacin and thiamin alongside food containing and/or fortified with these minerals.

1.40 The full statement can be accessed using this link Blank style sheet for COT Papers 2014 (food.gov.uk).

COT Assurance

Assessment of the risk of allergic reaction from fortification of non-wholemeal wheat flour with folic acid

1.41 The FSA and Food Standards Scotland undertook a risk assessment to consider the risk in terms of hypersensitivity to UK consumers if folic acid was used to fortify non-wholewheat flour at a level of 250 µg per 100 g without its presence being labelled on the packaging or not conveyed by other means during a 3-month derogation period. The Committee were asked to review and assure the draft risk assessment.

1.42 The UK prevalence of hypersensitivity to folic acid is not known. Leading UK allergy specialists and the UK wide charity operating for people at risk from severe allergic reactions and anaphylaxis were contacted to inform the risk assessment and were not aware of evidence of hypersensitivity to folic acid in the UK. A small number of cases have been reported in the literature although these were linked to the use of food supplements rather than the consumption of food.

1.43 An allergen reference dose for folic acid has not been established and so the usual approach for assessing hypersensitivity risk could not be followed. Instead, the 75th and 97.5th percentile amount of folic acid that would be consumed if non-wholemeal flour is fortified at the proposed level was estimated and found to be lower than the amount reported to have caused adverse reactions from supplements described in the published literature, with the exception of two cases.

1.44 This suggests that while it may be possible for the proposed amount of folic acid in fortified non-wholemeal wheat flour to trigger reactions, this is only likely to occur very rarely in highly sensitive individuals and is not significant on a population basis.

1.45 Symptoms of the reported adverse reactions to folic acid supplements range from mild to severe (including anaphylaxis) although no deaths have been reported in the literature. There are currently no reports of hypersensitivity to folic acid in food.

1.46 Overall, if non-wholemeal flour is fortified with folic acid at 250 µg per 100 g without its presence being labelled on the packaging of the final food or, in the case of food sold loose, not conveyed by other means during a 3-month derogation period, then the risk of hypersensitivity to folic acid in UK consumers is estimated to be as follows:

- The **frequency of adverse reactions to folic acid in food** to be **very low** (i.e., very rare but cannot be excluded).
- The **severity of illness in relation to adverse reactions to folic acid in food** to be **medium** (i.e., moderate illness: not usually life-threatening, sequelae rare, moderate duration).
- The **level of uncertainty** to be **medium** (i.e., there are some but no complete data available; evidence is provided in small number of references)

1.47 This risk assessment was published in 2023 and can be found using this link: Standard Reporting Framework for Risk Assessments (food.gov.uk).

Committee Procedures

Public consultation on draft EFSA opinion on polybrominated diphenyl ethers (PBDEs)

1.48 In June 2023, The European Food Safety Authority (EFSA) released for public consultation a draft update of its risk assessment of polybrominated diphenyl ethers (PBDEs) in food; PBDEs were previously used as flame retardants in construction materials, furniture, and electric and electronic equipment and are widespread environmental contaminants.

1.49 EFSA had previously published a risk assessment of PBDEs in 2011. In the new assessment, two additional congeners were considered, and a total margin of exposure approach was used. The draft updated assessment concluded that the dietary exposures estimated raised a potential health concern for toddlers, with >70% certainty at mean exposure and >95% certainty at 95th percentile exposure.

The Committee were asked to provide comments on the draft opinion to be submitted to EFSA as part of their consultation process.

1.50 The Committee considered the animal data to be generally robust but noted that some significant assumptions had been made. They agreed that neurodevelopmental effects and reproductive toxicity were the critical endpoints. The available epidemiological studies, though robust, were difficult to assess, and the epidemiological evidence was considered to provide less of a signal than the toxicological data.

1.51 The Committee considered that some of the evidence from animal studies for a substance-related effect was questionable, and this should have been considered in the uncertainty analysis. Some of the neurobehavioral changes were very minor and there were major inconsistencies in the neurobehavioral changes reported, which lacked biological plausibility. In a developmental neurotoxicity study conducted according to OECD test guideline 426, a technical PBDE product showed no adverse effects at any dose level, which contrasted greatly with the point of departure identified for its major constituent congener, but there did not appear to be any discussion of this. The Committee considered that considered that findings in single studies, in particular those without clear dose-response relationships, should be treated with caution, especially when an adequate OECD guideline study identifies no adverse effects.

1.52 Animal studies showed effects on the thyroid and the draft opinion appeared to be trying to link this to thyroid disease in humans, but the Committee considered this a step too far. The effects observed in studies in rats were typical of a liver-thyroid effect seen in rats, with microsomal enzyme induction causing increased clearance of thyroid hormones. The draft opinion did not appear to discuss direct versus indirect effects on the thyroid.

1.53 The Committee found the uncertainty analysis difficult to interpret. It was not considered useful without a rationale being provided and without further information on how the numbers for percent certainty were generated and what they mean. Risks may be overestimated by the body burden approach used when considering

the endpoints and susceptible populations and the very long half-lives in humans, which were up to 8 years, and it was unclear how this had been taken into account in the uncertainty analysis.

1.54 The recommendations made in the draft appeared largely pertinent. However, the Committee questioned the objective of some of the recommendations for those PBDEs that are no longer used, e.g., the development of Adverse Outcome Pathways (AOPs), when there was already a significant amount of toxicology and exposure data available, and a risk had been identified.

1.55 The comments agreed by the Committee were submitted to EFSA as part of their public consultation process. The final EFSA opinion is expected to be published in early 2024.

Public consultation on draft EFSA opinion on polychlorinated naphthalenes (PCNs) in food and feed

1.56 EFSA released for public consultation a draft opinion on polychlorinated naphthalenes (PCNs) in food and feed in November 2023. PCN mixtures were used in the past in dielectrics, lubricants, electric cable insulation, preservatives of wood, paper and fabric, cutting and grinding fluids, and plasticisers and can also be formed as unintentional biproducts in the production of other industrial chemicals. They are formed by combustion processes including incineration, forest fires and burning of coal. They are lipophilic, bioaccumulative and occur widely in food and feed. They are considered persistent organic pollutants (POPs) under the Stockholm Convention.

1.57 EFSA's evaluation focused on hexaCNs due to very limited data on other PCN congeners. No suitable epidemiological data were identified. The toxicological data were considered insufficient to establish an HBGV and a margin of exposure (MOE) approach was taken, based on a $BMDL_{20}$ for decreased platelet count in a subchronic toxicity study in rats which tested a hexaCN mixture. MOEs for the exposure to hexaCNs were all much larger than 2000, and the draft opinion concluded that these did not raise a health concern. No risk characterisation was performed for animals exposed via feed because suitable points of departure could

not be identified for each species. The Committee were asked to provide comments on the draft opinion to be submitted to EFSA as part of their consultation process.

1.58 The Committee largely agreed with the opinion and with the recommendations made and agreed that dietary exposures to hexaCNs are not a concern. Any information on production, environmental persistence, and trends in occurrence levels over the last 10-20 years would be useful. One of the recommendations, in recommending non-animal methods in order to assess risks from feed, was open ended, and clarity would be welcome.

1.59 While the Committee agreed that dietary exposures to hexaCNs are not a concern, it was not clear how the conclusion of 99% certainty of no health concern had been arrived at from the uncertainty analysis conducted. The Committee considered that some clarity and explanation would be useful.

1.60 The Committee could not see why the toxicology data in laboratory animals could not also be used to characterise the risks to animals exposed via feed, allowing for uncertainties as had been done for the human health risk characterisation.

1.61 The comments agreed by the Committee were submitted to EFSA as part of their public consultation process. The final EFSA opinion is expected to be published in mid-2024.

Draft EFSA opinion on the Tolerable Upper Level for vitamin B6

1.62 The EFSA Food and Nutrition Innovation Unit held a public consultation on their draft opinion on a proposed tolerable upper intake level (TUL) for vitamin B6. The COT were asked to provide comments on the draft opinion to be fed back to EFSA.

The TUL was based on the observation of peripheral neuropathy in a study in women being treated for premenstrual syndrome. The Committee agreed that this

was the most relevant toxicological endpoint noting that it had been observed in both humans and animals. However, the Lowest Observed Adverse Effect Level (LOAEL) used to derive the TUL and the rationale for the accompanying uncertainty factors needed additional clarification as they might not reflect the full variability of the human pharmacokinetics; additional discussion of the suitability of the TUL for pregnant women would be useful.

1.63 The Committee considered that further clarification of the section on Absorption, Distribution, Metabolism and Excretion (ADME) was needed, as this suggested binding was to the lysine residues of albumin in some parts of the section but noted binding to lysine residues in other proteins in addition to albumin elsewhere in the section.

1.64 The Committee discussed biomarkers of vitamin B6 intake and status, stating it would provide greater context if commentary on the implications of genetic variability, for example in alkaline phosphatase activity, were provided. A recently published paper by Jarett et al (Am J Clin Nutr, 116, 1767-1778, 2022) was cited which showed an interaction between vitamin B6 status and genotype which affected the dose-response. It was agreed that this study should be brought to the attention of EFSA.

1.65 Members commented on the case reports reviewed by EFSA. In particular, the accuracy of the summary for the Dalton and Dalton (1987) study was questioned; the participant was not positively re-challenged but rather symptoms recurred when consumption of the vitamin was resumed.

1.66 It was noted that the recommended range of the health-based guidance value (HBGV) for vitamin B6 was wide; 10-100 mg for adults. This reflected variability, but also choices made in the selection of LOAELs and UFs. A paragraph introducing or providing an explanation of the broad range of HBGVs would be beneficial for context setting and transparency.

1.67 The Committee expressed concern regarding the interpretation of the LOAEL identified in the dog studies which was outlined in the animal data section of the opinion. Members stated that while pathological changes had been observed, there

was uncertainty around the measurement of the neurological endpoints, and it was questioned how sensitive these clinical signs would be.

1.68 It was also highlighted that there seemed to be a mismatch between human and animal data and the comparability of the reproductive toxicity endpoints since the available human data related to effects on women rather than their offspring.

1.69 Members supported the proposed recommendations for further research made by EFSA, in particular those for further studies on toxicogenetics.

1.70 The Committee were of the opinion that further detail on the reason behind EFSA's selection of 50 mg/day Vitamin B6 as the threshold at which peripheral neuropathy occurs was needed, given that the available nutrivigilance data indicted effects at lower doses.

1.71 The Committee made a number of minor editorial comments and suggestions which were also submitted to the consultation.

1.72 The final EFSA opinion is expected to be published later in 2023.

Public consultation on EFSA'S 2023 re-evaluation of the risk to public health from inorganic arsenic in food

1.73 In July 2023, the EFSA Panel on Contaminants in the Food Chain (CONTAM) published a draft opinion re-evaluating the health risks arising from the presence of inorganic arsenic (IAs) in food. EFSA had considered it appropriate to update their assessment as new studies had become available on the toxic effects of iAs, as well as new information on occurrence and exposures. The COT were asked to comment on the draft opinion as part of the EFSA public consultation process.

1.74 The draft opinion was also circulated to Members of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) who provided comments which were combined with those of COT.

1.75 Members agreed that the draft opinion was comprehensive and clearly laid out.

1.76 The Committee noted that the relationship between arsenic and skin lesions is well established, though the mechanism is unclear, and further information was needed in this area. It was noted that the paper by Diamond-Gilbert (Environ Health Perspectives, 121, 1154-60, 2013) which was discussed by EFSA in this context referred specifically to invasive squamous cell carcinoma. A lot of the data came from human studies in Bangladesh where there were high levels of arsenic in drinking water. It was possible that UV radiation was a co-carcinogen.

1.77 EFSA used a margin of exposure (MOE) approach in their assessment as iAs is considered a genotoxic carcinogen with additional epigenetic effects. While the calculated MOEs raised potential health concerns with respect to skin cancer, supported by the uncertainty analysis, EFSA concluded that they were unable to derive a level of low concern for IAs as the endpoint used was human cancer and there was no EFSA guidance on the use of such an endpoint. The Committee did not accept this view, noting that human data had been used in this way by EFSA for other compounds with a presumed linear dose-response relationship, such as lead.

1.78 The final EFSA opinion is expected to be published later in 2023.

EFSA public consultation on "Update of the risk assessment of mineral oil hydrocarbons (MOH) in food

1.79 The European Food Safety Authority (EFSA) were asked by the European Commission (EC) to assess any toxicity studies on mineral oil hydrocarbons (MOH), that had become available since the 2012 EFSA evaluation and to update their scientific opinion, if necessary. EFSA were also asked to update their exposure assessment and to update the risk characterisation, if necessary. The COT were asked to comment on the draft opinion.

1.80 The Committee noted that the datasets for mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH) differed significantly and hence the current opinion should really be considered as two different assessments, one for MOSH and one for MOAH.

1.81 Following the publication of the 2012 opinion, EFSA commissioned toxicology studies on MOSH, which were available for the current evaluation. The rat study provided additional data on the Fischer rat and hence allowed for a clear conclusion on strain sensitivity, which had previously been suggested but not confirmed. The study used to establish the Health Based Guidance Value (HBGV) proposed in the EFSA opinion was a well-defined study, with the No Observed Adverse Effect Level (NOAEL) being at the highest dose tested. Overall, the Committee agreed with EFSA's approach to the assessment of MOSH.

1.82 Members also agreed with the overall approach taken by EFSA for the assessment of MOAH, utilising the BMDL10 for PAH8 in the absence of studies to define a reference point (RP) for 3- or more ring MOAH.

1.83 However, Members would have liked to have seen additional detail on the derivation of the uncertainty factors, in particular the application of an additional uncertainty factor of 6. While the Committee did not disagree with the use of the additional factor, the discussion and underlying reasoning was complicated, and a clearer definition/explanation would have been useful.

1.84 Overall, the Committee agreed that the 2023 EFSA draft opinion was a good compilation and discussion of the available data and agreed with EFSA's approach and conclusions.

1.85 Members noted that setting standards for MOH was difficult, especially as MOH was a mixture of compounds, often not well defined. Hence it was difficult to conclude on a representative chemical, and the assessment was further complicated by the fact that there was incidental exposure to other MOHs.

1.86 The Committee would have liked to have seen further details covered within EFSA's recommendations, especially with regard to the specifications of food grade MOH, and other sources of MOAH in food.

1.87 The comments agreed by the Committee were submitted to EFSA as part of their public consultation process.

1.88 The final EFSA opinion is expected to be published later in 2023.

On going work

Existing health-based guidance values (HBGVs) for T2 & HT2 mycotoxins

1.89 T2 and HT2 are mycotoxins which are produced by Fusarium fungi and found in cereal grains and their products. The COT last assessed T2 and HT2 mycotoxins in 2018 when reviewing the diet of infants aged 0 to 12 months and young children aged 1 to 5 years. At the time, the COT agreed with the group Acute Reference Dose (ARfD) and group Tolerable Daily Intake (TDI) for T2 and HT2 established by the European Food Safety Authority (EFSA) in 2017.

1.90 Commission Recommendation 2013/165/EU sets out indicative levels for T2/HT2 in a number of food commodities. However, the European Commission has now proposed replacing these current indicative values with legislative limits for T2/HT2 in the EU. These draft legislative limits are much lower that the pre-existing indicative values and may have an impact on UK industry, especially on cereals. Currently there is no retained EU law covering T2 and/or HT2. However, the FSA has had extensive dialogue with industry, and has previously been involved in EU working groups on the development of appropriate maximum levels.

1.91 The COT were asked to consider the existing HBGVs for T2/ HT2 published by EFSA and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and to confirm an appropriate HBGV for FSA risk assessments. The Committee reviewed the available data on the absorption, distribution, metabolism, and excretion of T2 and HT2 in animals and humans, as well as their toxic effects, such as haematotoxicity, immunotoxicity, emesis, and reduced body weight used in the establishment of the HBGVs along with the mode of action, species sensitivity, and dose-response relationships of T2 and HT2.

1.92 The Committee noted that it was unclear why JECFA did not include an uncertainty factor to account for interspecies differences; this could be because JECFA had considered emesis to be a direct effect rather than a central effect, and

therefore no variability would be expected in the kinetics. The COT did not necessarily disagree, but clarification on this would be helpful when the full toxicological monograph was available.

1.93 Overall, the Committee was content with the use of EFSA's HBGVs for future risk assessments.

1.94 The FSA intends to assess the level of risk arising from dietary exposure to T2/HT2 for UK consumers through a call for UK occurrence data, once completed, this will be presented to the Committee for their consideration.

Position paper on chitosan in bio-based food contact materials

1.95 As part of an ongoing programme of work on bio-based food contact materials (BBFCMs), the Committee discussed the potential allergenicity and environmental impacts of chitosan, a biodegradable polysaccharide derived from chitin.

1.96 Chitin is mainly obtained from crustacean shells but can also be derived from fungi and insects. Chitosan is produced by deacetylating chitin. Both chitin and chitosan have applications in food, medicine, and biotechnology. BBFCMs containing chitin or chitosan are used in applications such as films, coatings, and drinking straws.

1.97 The Committee considered information on the prevalence, causes, and symptoms of shellfish allergy, which is mainly triggered by tropomyosin, a muscle protein found in crustaceans and molluscs. The possibility of cross-reactivity between shellfish and other sources of chitin or chitosan, such as insects and fungi was also considered.

1.98 The Committee further considered the challenges and uncertainties regarding the migration, degradation, and allergenicity of these materials.

1.99 A position paper setting out the views of the Committee will be published in 2024.

Hepatotoxicity of green tea catechins

1.100 In 2017, following a series of reports of adverse effects on the liver following the consumption of green tea supplements, the European Commission requested the European Food Safety Authority (EFSA) to assess the available information on the safety of green tea catechins (principally - epigallocatechin-3-gallate (EGCG) from all dietary sources including preparations such as food supplements and traditional infusions, with a focus on liver toxicity. At that time, and at the request of the Department of Health and Social Care (DHSC), who have the policy lead for food supplements in England, the FSA Chemical Risk Assessment Unit team reviewed the EFSA opinion informally and agreed with its conclusions.

1.101 Following a request to the Food Standards Agency from the Nutrition Labelling Composition and Standards (NLCS) Common Framework on behalf of the UK, the COT have been asked to evaluate whether the conclusions of the 2018 EFSA opinion are still applicable (EFSA, 2018), in view of any new data that have become available since its adoption, to enable them to consider the next steps.

1.102 The 2018 EFSA opinion itself and its evaluation by the COT, focus on green tea catechins and the associated cases of probably idiosyncratic hepatotoxicity, rather than being a safety assessment of either green tea catechins or green tea infusions and extracts more generally.

1.103 A discussion paper was presented to the Committee in September 2021, since which drafts of the statement have been reviewed, with the final substantive discussion being held in May 2023.

1.104 The statement will be finalised by the COT in 2024.

Review of titanium dioxide as a food additive

1.105 Following the publication of the European Food Safety Authority (EFSA) opinion on titanium dioxide in 2021, which concluded that titanium dioxide could no

longer be considered ‘safe’ for use in food, the Food Standards Agency (FSA) initiated a review of the EFSA opinion. The EFSA opinion was presented to the COM in June 2021 (MUT/2021/03) and to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in July 2021 (TOX/2021/36). The COM had several concerns over the EFSA opinion on the genotoxicity of titanium dioxide. Due to this and following the advice of the COT the FSA initiated an independent evaluation of the safety of the use of titanium dioxide as a food additive.

1.106 In October 2021, paper MUT/2021/08 was presented to the COM, which summarised the available genotoxicity on titanium dioxide. Members considered that it was not possible to evaluate the genotoxicity of titanium dioxide at that stage. The COM suggested a sifting approach to the available genotoxicity should be adopted as a first step before evaluation. The Chair of the COM, a subgroup of the COM and the secretariat subsequently attended meetings to discuss and agree the criteria and methodology for sifting to identify suitable papers for the evaluation of titanium dioxide.

1.107 At the COM June 2022 meeting, paper MUT/2022/05 provided information and papers on approaches relating to the sifting and evaluation of the quality genotoxicity studies and evaluating data on nanomaterials. As an update since that meeting, members were informed that a sub-group of the COM had met to discuss the process to select relevant and appropriate studies to be reviewed by the committee. A proforma had been produced, which would be shared with members. This considered two levels, namely, whether the characteristics of the test material had been sufficiently described (e.g., micro or nano sized particles) and the quality and reliability of how the genotoxicity studies had been conducted.

1.108 In March, July, September and October 2023, papers TOX/2023/16, TOX/2023/32, TOX/2023/44 and TOX/2023/56 were presented to the COT, respectively. These papers summarised the following topics and endpoints: Absorption, Distribution, Metabolism, Excretion (ADME), Aberrant Crypt Foci, Reproductive and Developmental Toxicity, immunotoxicity, neurotoxicity and the derivation of a potential Health-Based Guidance Value for titanium dioxide, dependent on the outcome of the review by the COM.

1.109 In the October 2023 meeting, COT members were kept updated with the progress of the COM sub-group review. It was noted that a third draft statement along with the concluding statement on the genotoxic potential of titanium dioxide would be finalised by May 2024. The COM sub-group would be considering potential mechanisms and whether the effects were linked to the nanoparticle fraction.

Lead in the maternal diet

1.110 The Scientific Advisory Committee on Nutrition (SACN) is reviewing the scientific evidence that bears on the Government's dietary recommendations for women of childbearing age. The SACN have requested that the Committee on Toxicity (COT) review the risks of toxicity from chemicals in the maternal diet, including lead.

1.111 Lead is a heavy metal which is ubiquitous in the environment and is thus present in the diet of the general population, including women of childbearing age. However, dietary lead levels have fallen since the phasing out of lead in petrol, plumbing and paints.

1.112 Chronic lead poisoning from low level, repeated exposure gives clinical signs of persistent vomiting, encephalopathy, lethargy, delirium, convulsions, and coma. The central nervous system, erythropoietic system and the kidneys are most affected by lead exposure, but all bodily systems can be adversely affected. In pregnant women, lead can cause increased blood pressure and may be associated with preeclampsia and premature birth.

1.113 Potential risks from maternal exposures to lead were characterised by margins of exposure (MOEs), calculated as the ratio of the benchmark dose level (BMDL) to estimated exposures from diet, soil and air. A $BMDL_{01}$ has been set for the reduced development of intellectual function in offspring. Specifically, a dietary exposure of 0.5 µg/kg bw/day was associated with a 1% change in full scale IQ score (EFSA 2010). As the BMDL was for a small effect, derived from pooled analysis of multiple cohort studies of exposures in infants and children, it is likely to

be conservative and protective for all other adverse effects of lead in all populations. EFSA therefore concluded that a margin of exposure of 10 or greater should be sufficient to ensure that there was no appreciable risk of a clinically significant effect on IQ. At lower MOEs, but greater than 1.0, the risk is likely to be low, but not such that it could be dismissed as of no potential concern (EFSA, 2010).

1.114 In 2013, the COT added that an MOE of >1 can be taken to imply that at most, any risk is likely to be small. MOEs <1 do not necessarily indicate a concern, but scientific uncertainties mean that a material risk cannot be ruled out. This applies particularly when MOEs are substantially <1. The COT further concluded, in agreement with EFSA, determined that neurodevelopmental effects represent the most sensitive endpoint for effects in the developing foetus whilst also being protective of the other toxicological end points in the mother (COT, 2013).

1.115 The Committee assessed exposure to lead from various sources (food, drink, air, soil and dust). Overall, the committee concluded that lead toxicity will depend on total exposure from all sources, it therefore considered an aggregate exposure to determine an overall likely level of risk.

1.116 A combined exposure assessment, considering exposure to lead from all sources, relative to the BMDL01 of 0.5 µg/kg bw/day, gives an MOE range of 1-2 depending on the individual contribution to the total of each source (food, drinking water, soil/dust). A scenario in which there are high levels of exposure to lead from food, drinking water and soil/ dust would result in an MOE of 1, however, this assumes a worst-case for all sources for a prolonged period of time. In a scenario where there are average levels of exposure to each source, the MOE is 2. These MOE values indicate that an aggregate risk of toxicity from lead in relation to the maternal diet and other potential sources of maternal exposure is likely to be small.

1.117 A statement setting out the Committee's assessment of lead will be published in 2024.

Arsenic in the maternal diet

1.118 As part of the work on the maternal diet, the COT was asked to consider the potential effects of excess arsenic (As) intake. The COT most recently reviewed arsenic in 2016 as part of the programme of work with SACN on the diets of infants and young children and provided comments on the most recent Draft EFSA opinion (2023) for public consultation.

1.119 Arsenic is a metalloid that occurs in the environment in a variety of forms as a result of both natural and anthropogenic activity. Acute exposure to inorganic arsenic (iAs) results in clinical symptoms such as nausea, vomiting, colicky abdominal pain, and diarrhoea. Chronic iAs exposure results in non-specific symptoms including abdominal pain, diarrhoea, and sore throat and can result in multisystem disease and malignancy, including cancer, skin lesions, developmental effects, cardiovascular disease, neurotoxicity and diabetes. Health outcomes resulting from iAs toxicity varies between individuals and different geographical areas.

1.120 It is generally accepted that iAs compounds are more toxic than the organic As compounds that are commonly found in fish, seafood, and other marine organisms (arsenobetaine, arsenosugars, and arsenolipids).

1.121 The potential risks from maternal exposures to inorganic arsenic were characterised by margins of exposure (MOEs), calculated as the ratio of the benchmark dose level (BMDL) to estimated exposures from diet, soil and air (individually and aggregated). Previously in 2016, the COT concluded that the JECFA (2011) $BMDL_{0.5}$ of 3.0 µg/kg bw/day for lung cancer should be used in the characterisation of the potential risks from exposure to inorganic arsenic. The JECFA BMDL was based on exposure to iAs via drinking water from shallow wells. The majority of the epidemiological studies have focused on exposures to iAs via drinking water and have not measured or reported total dietary exposure to iAs. The COT also previously concluded that an MOE of 10 or above would be considered of a low concern.

1.122 The main contribution to As exposure in the UK is from dietary sources; non-dietary sources such as water, air, soil, and dust contributed negligible quantities.

1.123 The aggregate exposure for iAs from all sources for average consumers resulted in an MOE of 11, while the MOE for high consumers was 6. A risk to the health of women of childbearing age, specifically for high consumers, could not be excluded.

1.124 During the COT's evaluation of arsenic in the maternal diet EFSA published their draft opinion on arsenic in food. The Committee agreed that they would wait until EFSA formally publish their opinion, expected in early 2024, to finalise their discussions and subsequent COT statement, later in 2024.

Discussion paper on the effects of pica during pregnancy

1.125. As part of the discussions regarding the contribution of soil and dust to lead exposure in the maternal diet, the Committee requested further information on the practice of pica, the consumption of non-food substances, in pregnant women.

1.126 Members noted that the main concern with respect to pica was geophagia (the consumption of earth, soil, or clay), primarily of soil of ancestral origin, due to the presence of contaminants, notably heavy metals. Geophagia (and pica more generally), was not a practice uniformly distributed across the population and the cultural differences in consumption of soil would mean that there could be large differences in exposure. Furthermore, exposure would be difficult to determine, as the background levels of heavy metals in UK soils would not be appropriate to estimate exposure, as the soils consumed as part of geophagia are often imported from around the world.

1.127 The Committee concluded that the risks of pica behaviour could not be quantified, however, Members considered whether or not pica behaviour should be discouraged on health grounds. Although anecdotally, anaemia had been associated with pica, the relevance of this was difficult to interpret as anaemia was almost ubiquitous in pregnancy and that it may be necessary to stratify by socioeconomic

status before being able to understand the nature and the direction of the relationship between pica and anaemia.

1.128 The Committee agreed that the chemicals of concern from pica were predominantly heavy metals as these had largely been covered elsewhere in the review of the maternal diet. Therefore, it was concluded that, given the limited data set, it would be more appropriate to include a general consideration of pica in the overarching statement for the maternal diet, which would be published at the completion of this work.

Ginger in the maternal diet

1.129 As part of the current programme of work on the maternal diet, the Committee considered the use of herbal dietary supplements during pregnancy. These were supplements that were not officially recommended by the relevant authorities, but which were promoted by anecdotal evidence and unofficial sources as having various purported benefits. Ginger was identified as one of the supplements that should be considered in more detail.

1.130 Ginger (Zingiber officinale) is a flowering tropical plant originating in Southeast Asia and grown in warm climates including China, India, Africa and the Caribbean. The rhizome (underground stem) of the ginger plant is commonly used as a spice and flavouring in many countries around the world and is increasingly growing in popularity as a natural remedy due to its purported immune system-boosting properties and also for motion sickness and post-operative nausea and vomiting.

1.131 The COT have previously reviewed the potential effects of ginger and in particular, the use of ginger supplements during pregnancy and lactation, reviewing the available data on toxicity to the mother, effects on the development of the fetus or embryo, and possible interactions with medicines. A revised statement was reviewed by the Committee in 2023 and included additional studies which had previously been identified by the COT to further inform the database on the possible influence of ginger components on cyclooxygenase (COX) and prostaglandin activity.

1.132 A further draft of the statement will be brought back to the Committee in 2024 with a clearer distinction between the forms of ginger; in particular, those used as traditional culinary spice compared to the more concentrated forms of ginger such as ‘shots’. Further clarification on several points highlighted by the COT would also be provided.

1.133 The statement will be finalised by the COT in 2024.

The potential risks from ergot alkaloids in the maternal diet

1.134 As part of the ongoing programme of work on the maternal diet, the Committee were asked whether exposure to ergot alkaloids (EAs) would pose a risk to maternal health.

1.135 Ergot alkaloids (EA) are secondary metabolites produced by the fungi families Clavicipitaceae and Trichocomaceae, with Claviceps purpurea being the most widespread Claviceps species in Europe. Based on their occurrence and the available toxicological data the European Food Safety Authority (EFSA) considered six EAs in their risk assessment in 2005, namely: ergotamine, ergocornine, α-ergocryptine, ergosine, ergocristine (peptide ergot alkaloids) and ergometrine (a lysergic acid amide). EFSA further included both forms (-ine and inine) in their assessment, while the -inine forms are considered biologically inactive interconversion occurs under various conditions (EFSA, 2005, Tasker and Wipf, 2021). Bromocriptine is synthetic ergoline derivate and it is used in the treatment of Parkinson’s disease and pituitary tumours (Herdman et all., 2001).

1.136 Due to their structural similarities to neurotransmitters, EAs can act as agonists or antagonists of noradrenaline, dopamine and serotonin neurotransmitters (Arroyo-Manzanares et al., 2017, Fitzgerald and Dinan, 2008) and have been reported to produce direct peripheral effects such as uterotonic action or vasoconstriction, indirect peripheral effects such as serotonin antagonism or adrenergic blockade, and central nervous system (CNS) effects such as induction of hypothermia and emesis (EFSA, 2012).

1.137 The potential risk from EAs in the maternal diet was discussed by the Committee in 2022. It was concluded that EAs would not have adverse effects on maternal health at likely levels of exposure. A statement on ergot alkaloids will be published in 2024.

Statement on the risk assessment of cow's milk in children aged 1 to 5 years, in the context of plant-based drinks evaluations

1.138 The Department for Health and Social Care's (DHSC) is conducting an Equalities Analysis covering both the Nursery Milk Scheme and the Healthy Start Scheme, which considers equalities issues posed by the current legislation as it pertains both to plant-based drinks, and also to animal milks other than cow's milk. DHSC is keen to ensure that this Equalities Analysis reflects the most up-to-date advice on safety and toxicity issues from COT, and on nutritional issues from the Scientific Advisory Committee on Nutrition (SACN). Hence, this process is currently on hold whilst the SACN/COT Joint Working Group on Plant Based Drinks considers plant-based drinks.

1.139 The COT agreed in July 2021 that Cow's milk should act as the main comparator for plant-based drinks and therefore a statement on potential chemical risks from Cow's milk was formulated.

1.140 Within this statement, the COT reviewed an extensive range of chemical compounds that could be present incidentally or as contaminants in cow's milk to allow comparison with plant-based dairy alternatives. The COT concluded that the vast majority of potential contaminants assessed presented no risk of adverse health effects in children aged 6 months to 5 years of age at the levels observed within cow's milk. The exceptions are iodine, BaP and PAH4, AFM1 specifically and total aflatoxins due to the contribution of AFM1, for which any risk to health in children aged 6 months to 5 years of age is unlikely but cannot be completely excluded. The possible risks to health in these age groups from exposure to isoflavones in cow's milk is unknown, as no HBGVs have been established for these compounds in

young children and hence there is a lack of knowledge on the toxicological significance of the levels that might be found in cow's milk.

1.141 The full statement can be found using this link: Background - Statement on the risk assessment of cow's milk in children aged 1 to 5 years, in the context of plant-based drinks evaluations | Committee on Toxicity (food.gov.uk).

1.142 A lay summary will be published in 2024.

Review of dioxins – draft systematic review

1.143 Following the Committee's assessment of the scientific basis and implications for risk management of the 2021 EFSA tolerable weekly intake (TWI) for dioxins and dioxin-like polychlorinated biphenyls (PCBs), the COT decided to undertake their own review of the relevant endpoints.

1.144 The Committee acknowledged that the review of dioxins would be an extensive and lengthy undertaking. To assist with the work, a systematic literature review on dioxins was commissioned, focusing on the relevant endpoints; male reproductive toxicity, immunotoxicity, the mechanism of action of dioxins via the aryl hydrocarbon receptor (AhR), and covering a predefined time frame from 2017 to 2021. The review also included a non-systematic consideration of the data on the potential carcinogenicity of dioxins and dioxin-like PCBs and whether this involved a genotoxic mechanism.

1.145 The Committee considered the commissioned report detailed and to provide a large amount of data for review. However, information from lower scoring studies was excluded from the report. As these studies could potentially hold relevant information to the overall assessments, the Committee agreed that there currently was not sufficient evidence to identify a key study or studies on which to establish a health-based guidance value (HBGV) and further consideration would be required.

1.146 Additional work in this area will commence in 2024.

Advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins

1.147 The Food Standards Agency (FSA) is considering the current advice and monitoring programme for marine biotoxins and whether there is a need to update or change existing legislation in the UK. The main purpose of this work is to identify any emerging marine biotoxin threats in UK waters, including considerations on increasing occurrence with increasing temperatures due to climate change. The views of the COT were sought on whether any of these marine biotoxins would pose a risk to human health.

1.148 The FSA programme of work included a scoping paper on emerging marine biotoxins to be discussed by the Committee, the marine biotoxins reviewed were selected based on published assessments and reports on emerging marine biotoxins by other authorities, as well as a brief literature search. There was also specific consideration of pinnatoxin (PnTX) and pectenotoxin (PTX), due to the recent availability of additional analytical standards and the recent removal from the EU monitoring programme, respectively.

Scoping paper on the advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins

1.149 The Committee considered the emerging marine biotoxins of potential concern to human health, i.e., brevetoxins, cyclic imines, palytoxins, saxitoxins, tetrodotoxins, novel azaspiracid analogues, novel paralytic shellfish poisoning (PSP) analogues and domoic acid analogues, and cyanobacteria toxins. There was a substantial amount of data available on the toxicology and occurrence on a number of the toxins, most of which are known and have the potential to be of concern to human health. However, the potential risk of these toxins depends on their occurrence, and this data, especially for UK waters and shellfish is lacking. The lack of occurrence data however did not exclude the possibility that these toxins were present in UK waters.

1.150 The Committee considered that to reach a conclusion on which of the marine biotoxins discussed would be of potential risk to UK consumers, further work is required, identifying, and tabulating the toxicological endpoints, lethal doses and occurrence data. It would be also useful to include information on the marine biotoxins which are already monitored and regulated, to put the potential risk of these emerging toxins into perspective.

1.151 The Committee will continue its work in 2024, aiming to identify the criteria to be fulfilled for a marine toxin to raise concern and consider how the previously discussed emerging marine biotoxins align with these criteria.

Pinnatoxin group

1.152 Pinnatoxins (PnTXs) are a group of paralytic neurotoxins that can be found in filter-feeding bivalve shellfish such as scallops and mussels. Although no confirmed cases of PTX intoxication have been reported in humans, ingestion of PnTXs compounds by rodents under laboratory conditions can cause paralysis, respiratory depression, and death. PnTXs are not currently regulated in England or Wales, but with the availability of new analytical standards, future monitoring programs of PnTX could aim to include PnTX-G, -E and -F.

1.153 The COT was asked by the FSA to evaluate and consider the current toxicological evidence and the potential public health risk related to PnTXs. Considerations was also given to the likelihood of PnTXs becoming more prevalent due to climate change and rising sea water temperatures around the UK.

1.154 The Committee agreed that the toxicological data base for PnTx was limited. Although some acute toxicity studies existed in mice, there were substantial evidence gaps for both the toxicity of PnTX and the exposure in humans. Overall, the Committee concluded that due to the lack of toxicological and occurrence data on PnTX it was not possible to determine the extent of any public health risk relating to PnTXs. Although no human intoxications have been reported to date and there is no strong evidence to suggest PnTXs are a risk to humans, based on the limited data the Committee was unable to fully exclude a risk.

1.155 Members concluded that if the technology, i.e., chemical analysis, was already in place in the UK it would be reasonable to include PnTX in any monitoring programme.

Pectenotoxin group

1.156 PTXs are a group of toxins associated with diarrhetic shellfish poisoning (DSP) which are produced by dinoflagellate algae. They are accumulated by filter-feeding shellfish such as scallops and mussels. Although no confirmed cases of PTX intoxication have been reported in humans, ingestion of certain PTX compounds by rodents under laboratory conditions can cause gastrointestinal symptoms and liver toxicity. PTXs are a regulated biotoxin group in the UK and are included in the group of toxins which are monitored routinely in UK shellfish.

1.157 The COT was asked by the FSA to consider the evidence in the 2009 EFSA opinion on pectenotoxin which was the basis for recent amendments to the European Union (EU) legislation removing PTXs from the list of monitored biotoxins in EU shellfish. In their 2009 opinion, EFSA concluded that PTXs were less toxic than okadaic acid (OA) - the toxin they are currently jointly regulated with– but when administered via the oral route, they have a different toxicological mode of action (MoA) and that they do not induce diarrhoea.

1.158 The COT found there was limited scientific data regarding the toxicity of PTXs, and the data that exist were for acute/short term exposure, rather than exposure over a prolonged period. Most of the available data were from rodent studies where PTX was administered via injection, which was not directly relevant to assessing the risk of intoxication by shellfish consumption in humans. Considering only the studies where PTX was orally administered to rodents, the Committee found the evidence was sufficient that PTX has a lower oral toxicity than OA. They also agree with EFSA that PTXs has a different MoA to OA and agreed that PTX should therefore not be expressed in OA equivalents. However, the Committee considered

the evidence that PTX-group toxins do not cause diarrhoea inconclusive, with some studies in rodents reporting diarrhoea after PTX administration.

1.159 Overall, the Committee concluded that based on effects seen in animals a toxicological risk from exposure to PTX was plausible, albeit probably low. However due to the lack of toxicological and occurrence data on PTX it was currently not possible to determine the extent of any public health risk of PTXs.

Assessment and draft interim position statement on bisphenol A (BPA)

1.160 Following public consultation in 2022, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) established a new tolerable daily intake (TDI) of 0.2 ng Bisphenol A (BPA)/kg bw per day in April 2023.

1.161 The Committee discussed the final opinion published by EFSA and confirmed that they did not support EFSA's conclusion that the observed change in the number Th17 white blood cells would continuously result in an adverse immune effect/inflammatory response. 40hrs was an intermediate endpoint and was not appropriate to derive a point of departure (POD) and subsequently a TDI. Given the uncertainties over the endpoint a more robust and transparent weight of evidence (WoE) approach and evidence integration should have been applied to a wider dataset to derive a more reliable and relevant endpoint on which to base a health-based guidance value (HBGV).

1.162 Following their diverging view from EFSA, the Bundesinstitut fuer Risikobewertung (BfR) published a full assessment of BPA in 2023, deriving a TDI of 0.2 µg/kg bw per day (equivalent to 200 ng/kg bw per day) based on (male) reproductive effects.

1.163 While assessments of BPA by other authorities pre-dated the EFSA 2023 assessment, and were therefore not considered relevant, the Committee considered the BfR approach in more detail and concluded that the endpoint applied and approach taken was reasonable, albeit with a significant level of conservatism, and was in line with previous approaches taken by the Committee themselves.

1.164 Overall, the Committee considered it possible that the current UK TDI for BPA would need to be revised to account for new evidence and ensure it was sufficiently protective. However, on balance the weight of evidence did not support the conclusions drawn by EFSA, or a TDI set as low as that derived by EFSA. The Committee instead agreed that the BfR approach was reasonable and to apply the TDI of 0.2 µg/kg bw per day as an interim measure.

1.165 The Committee will undertake their own weight of evidence approach and assessment of BPA in due course.

1.166 The work on BPA is ongoing but an interim position statement highlighting the discussions and considerations of the Committee will be published in spring 2024.

Aircraft cabin air

1.167 In 2007, the COT published a statement on aircraft cabin air, having been asked by the Department for Transport (DfT) to undertake an independent scientific review of data submitted by the British Airline Pilots Association (BALPA) relating to organophosphate (OP) compounds, the cabin air environment, ill-health in aircraft crews and the possible relationship to smoke/fume events in aircraft, due to concerns about the possible effects on aircrew health of oil/hydraulic fluid smoke/fume contamination incidents in commercial aircraft (COT, 2007).

1.168 In 2013, DfT asked the COT to undertake an independent scientific review of the results of DfT-funded aircraft cabin environment research commissioned in response to recommendations made by COT in 2007, after which the COT issued a position statement on cabin air (COT, 2013).

1.169 The COT was recently asked by DfT to investigate whether any new data have been published and to re-evaluate their previous views, and in particular consider the question “Is there evidence of exposure to chemical contaminants in cabin air that could have long-term health impacts, either from acute exposures or due to long-term low level exposures including mixtures, e.g., of volatile organic compounds (VOCs)?”.

1.170 In 2023, the Committee continued this consideration and reviewed discussion papers on concentrations of VOCs in European aircraft and comparison with regulatory standards and health-based guidelines and a paper on the basis of the regulatory values for carbon dioxide. The COT also considered drafts of the statement on this topic, and it is anticipated that the statement will be finalised in 2024.

Sub-statement on the potential risk(s) from exposure to microplastics: Inhalation route

1.171 In 2019, as part of horizon scanning, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) identified the potential risks from microplastics as a topic it should consider to inform Food Standards Agency (FSA) discussions on this (TOX/2019/08). Since then, several discussion papers have been presented to the COT and in 2021, the COT published an overarching statement on the potential risks from exposure to microplastics (COT Statement 2021/02). This document provided a high-level overview of the current state of knowledge, data gaps and research requirements with regards to this topic.

1.172 There is evidence for the presence of plastic particles in the air (indoor and outdoor) and thus inhalation is a possible route of exposure.

1.173 The purpose of the sub-statement was to provide supplementary material to the overarching statement on microplastics (COT Statement 2021/02) and to consider in detail the potential toxicological risks of exposure from microplastics via the inhalation route (i.e., exposure resulting from the presence of microplastics in the air (indoor, outdoor and occupational settings)). It is based on currently available literature and data from internal tools at the UK FSA (these internal tools include: a literature search application and signal prioritising dashboards).

1.174 The final draft of this paper was presented at the end of 2023 and will be published in 2024, completing the current work on microplastics.

Novel formulations of supplement compounds designed to increase oral bioavailability

1.175 In the discussions on the safety of turmeric in 2022 the COT identified novel formulations, particularly those with the potential to increase oral bioavailability, as a key area of uncertainty in the risk assessment of dietary supplements. Such formulations include micellar, nano- and micro-formulations, including colloidal dispersions and liposomal systems. Therefore, the Committee proposed that novel formulations designed to increase the oral bioavailability of supplements should form the basis of a general discussion paper.

1.176 The Committee considered an overview of the structure and physicochemical properties of several novel supplement formulation types, including colloidal, liposomal, and micellar systems. The biological mechanisms through which such formulations may alter bioavailability were also reviewed. Pharmacokinetic studies in human subjects with novel formulations of three different supplements were reviewed as exemplars: vitamin C, curcumin, and cannabidiol (CBD).

1.177 In terms of establishing health-based guidance values (HBGVs) for novel supplement formulations, it was noted that this was important for consumer safety, as maximum dosage levels for certain compounds may not be applicable to novel formulations of the same compounds. The Committee concluded that the critical factor was understanding how external dose related to internal exposure for standard and novel formulations, and when/if these diverged. In the absence of specific kinetic data, it was stated that a worst-case approach would be to assume 100% bioavailability of the active compound. The Committee noted that these data are often unavailable, and that the pharmaceutical industry is likely to have more extensive datasets that might aid in these kinds of assessments.

1.178 The Committee agreed that they had reviewed sufficient information to reach general conclusions regarding novel formulations, and that no further and/or specific information was required. The Committee also agreed, given that supplements would vary on a case-by-case basis, it was not necessary to provide further case studies and/or exposure assessments to reach general conclusions.

1.179 As a next step, a position paper will be drafted in 2024 that summarises the Committees comments, which could potentially be included in future guidance documents.

UK COT FSA New Approach Methodologies Roadmap (2023) Draft Version 3

1.180 The UK FSA and the COT have been considering New Approach Methodologies (NAMs) to understand the best scientific methodologies available for use in the risk assessment of chemicals and to consider how these can be incorporated and accepted in a regulatory context.

1.181 In order to achieve this, the FSA and COT are developing a UK New Approach Methodologies (NAMs) roadmap towards acceptance and integration of NAMs including predictive toxicology methods using computer modelling into safety and risk assessments for regulatory decision making. This will not only require the historic 3Rs approach (replacement, reduction and refinement of animal experiments) but the expansion to the 6R principle which also includes reproducibility, relevance, and regulatory acceptance.

1.182 Following presentation of the roadmap at various international conferences, meetings and workshops, Members were asked to note and comment on the recent updated draft version of UK NAMs roadmap which incorporates the feedback received. This includes data integrity and capability, training and the integrated transition into acceptance.

1.183 Work on the roadmap will continue including incorporating any additional information gathered from conferences, meetings, and workshops as well as the outputs from the FSA literature review on New Approach Methodologies (NAMs) to Support Regulatory Decisions for Chemical Safety.

Draft joint statement on the request for an assessment of tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE) in canned food packaging materials

1.184 The Committee discussed the draft assessment on tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE), following previous discussions by the COT, the Joint Expert Group on Food Contact Materials (FCM JEG) and sister Committee on Mutagenicity (COM). The work is ongoing, but publication of the final assessment is expected in spring 2024. This item is reserved as the data are commercially confidential.

Assessment of ocean bound plastic (OBP)

1.185 The Food Standards Agency (FSA) and Food Standards Scottland (FSS) are currently undertaking work on the potential use of plastic materials from the open environment in food packaging applications, specifically plastic materials intercepted before entering the marine environment.

1.186 Following initial discussions by the Joint Expert Group on Food Contact Materials (FCM JEG) and COT, the FSA and FSS undertook a call for evidence between March and October 2022, this was followed by additional data collection from the companies that engaged with the call, upon enquiry by the FCM JEG. Additional companies were also identified as suppliers of these materials between November 2022 and January 2024, and were contacted for any information they may hold.

1.187 The FCM JEG has assessed all information provided to the FSA and FSS to date and is currently in the process of drafting the final assessment, publication is expected in spring 2024.

Other Committee Activities: Joint Expert Groups, Presentations and Workshop

Presentations

Presentation from the LIDo-TOX AI PhD Student

1.188 The FSA and COT have been considering New Approach Methodologies (NAMs) in order to understand the best scientific methodologies available for use in the risk assessment of chemicals, and to consider how these can be incorporated and accepted in a regulatory context.

1.189 In 2021, the FSA started funding a PhD Student at King's College London as part of their Interdisciplinary Doctoral Program (LIDo-TOX AI).

1.190 The PhD student has been working to understand how NAMs will improve indicative levels of safety in chemical risk assessment.

1.191 In addition, these new partnerships have helped with networking, research collaboration, training opportunities and other activities. The studentship also complements the work set out in the COT FSA UK Roadmap towards using new approach methodologies in chemical risk assessment.

1.192 The PhD student presented a yearly review to the Committee, updating them on his progress to date using Artificial Intelligence and in silico tools for the assessment of food safety.

1.193 The main work so far comprised three parts: (1) Exploration of dimensionality reduction algorithms, for powering Quantitative Structure Activity Relationship (QSAR) models of mutagenicity, constructed of simple feed-forward Deep Neural Networks (DNNs); (2) Development of Graph Convolutional Networks (GCNs) to improve mutagenicity predictions, via graph classification of molecules, while also allowing for mining of structural alerts (SAs); (3) Development of Graph Neural Networks (GNNs) for node classification of molecules, in order to predict toxicological properties of brominated flame retardants (BFRs), starting with acute toxicity and comparing to predictions from the Toxicity Estimation Software Tool (TEST) of the United States (US) Environmental Protection Agency (EPA).

1.194 The COT Members were impressed with the progress to date and gave feedback to the PhD student.

Opportunities and outlook for United Kingdom Food and Chemicals regulation post European Union Exit-COT Workshop Report

1.195 The COT, UKHSA and FSA organised a workshop in July 2022 on "Opportunities and outlook for UK food and Chemicals regulation post EU exit".

1.196 The participants were from industry, academia and regulatory agencies and the day was divided into three sessions:

- The landscape of regulation post EU exit: UK stakeholder perspectives, international perspectives, opportunities and challenges for UK divergence;
- Major drivers for change and potential impact on chemical regulation; and
- Indirect Effects: food prices, food security, supply chain, fraud (Food regulation/human health).

1.197 Each of the sessions consisted of presentations followed by a roundtable discussion and included interactive sessions.

1.198 The workshop report is now available online and PDF.
(DOI: https://doi.org/10.46756/sci.fsa.ebr546)

Evolving Our Assessment & Future Guiding Principles Workshop

1.199 The COT held a workshop in May 2023 to start work on updating their guidance on toxicity testing and its supporting principles. The starting point for the process was to use existing frameworks and guidance but with the aim of introducing innovative improvements where appropriate.

1.200 The workshop aimed to identify areas where guidance needed to evolve and included reviewing fundamental risk assessment principles, current guidance on risk assessment and what can be learned from it, integration of new approach methodologies, exploring hazard vs risk and weight of evidence. The overall objective of the workshop was to discuss how the Committee moves forward in a new era of risk assessment.

1.201 Members discussed the output of the workshop, considering “must, could and should” priorities to be taken forward. It was emphasised that the most important aim was to have applicable guidance to ensure public safety.

1.202 The assessment of benefits was not within the terms of reference of the COT, but thought should be given as to how COT advice can be best aligned for this to be undertaken when needed or appropriate.

1.203 Members noted that to take the guidance forward, establishing an initial framework would be important; this could then be expanded and linked to other guidance as necessary. There were two parts to the work, to codify what the Committee currently do and then to provide guidance on areas where the approach was not yet codified such as benchmark dose modelling.

1.204 A sub-group would be formed in 2024 to take forward the next steps in updating the guidance. It was agreed that it would be important to work with the policy colleagues from the relevant Government Departments and not to re-invent the risk analysis process. In particular, the required levels of protection needed for consumers should be considered.

1.205 The finalised report will be published next year.

Horizon Scanning

1.206 The COT undertake horizon scanning at their February meeting, where they review the work anticipated for the coming year; this includes ongoing topics, the annual workshop, current or planned working groups and the skills balance of the Committee. However, Members are also encouraged to suggest topics for discussion throughout the year.

1.207 In 2023, In addition to the items outlined above, Members considered the following:

General horizon scanning

1.208 The COT terms of reference include advising, at the request of many different government departments, on a wide variety of chemicals and routes of exposure, making them very broad, and potentially overlapping with those of a number of other Scientific Advisory Committees. Thus, while the Committee's work is mostly reactive, the terms of reference also include advising on important general principles and scientific discoveries in relation to toxic risks, which was more proactive. The Committee is constrained by a heavy workload, but it is important that it is proactive where it can be, taking a lead on advances in the application of novel science in the risk assessment of chemicals. The work on new approach methodologies and evidence integration are examples of this.

1.209 It is important that the Committee is aware of emerging topics and a databank of potential areas of interest could be created as it would be useful to know whether there were topics being discussed elsewhere, such as by EFSA and ECHA, that may be relevant to topics that should be addressed by the Committee.

Phosphate based flame retardants

1.210 In 2019, the COT published a statement on phosphate-based flame retardants (PFRs) and the potential for neurodevelopmental toxicity. The Committee concluded that PFRs were very unlikely to share the neurodevelopmental effects of other organophosphate compounds, but they could not exclude the possibility that PFRs could produce neurodevelopmental toxicity by some other mechanism.

1.211 In 2021, the COT became aware of new data relating to PFRs and developmental neurotoxicity and a literature search was carried out to capture any additional data published between 2019 and 2021. The Committee also requested such searches be carried out in subsequent years to capture any new published data.

1.212 The Committee reviewed the most recent update and considered that unless the Department of Health and Social Care (DHSC) requested another review, there

was insufficient new information to justify taking this topic further at this time. However, the literature should continue to be monitored, though there was no need for an update every year, unless significant (in terms of toxicology or amount) new information became available.

The microbiome

1.213 It was agreed that the microbiome should remain under consideration by the Committee, with a view to re-examining the topic when new data become available.

Joint Expert Groups

Assurance of Joint Expert Group opinions

1.214 The Joint Expert Groups (JEGs) were established by the FSA to assess applications for the authorisations of regulated products that were previously authorised by the European Food Safety Authority (EFSA). The two JEGS are the FCM JEG which covers food contact materials and the AEJEG which has responsibility for food additives, enzymes and other regulated products. In 2023 the COT provided support, challenge and assurance to the work of the two JEGS for assessments as set out below.

AEJEG assessments

1.215 The COT considered Risk Assessments prepared by the Joint Expert Group on Additives, Enzymes and other Regulated Products (AEJEG) regarding the following regulated product applications:

- For the modification of specifications to include fermentation by Yarrowia lipolytica as a production method for steviol glycosides.
- For the modification of specifications to include fermentation by *Saccharomyces cerevisiae* as a production method for steviol glycosides.

- For the modification of specifications to include production from stevia leaf extract by enzymatic conversion as a production method for steviol glycosides.
- The authorisation of a new flavouring 2-Hydroxy-4-methoxybenzaldehyde.

1.216 All items are currently reserved as they cover draft AEJEG Committee Advice Papers not currently published.
1.217 AEJEG Committee Advice Papers will be published in 2024.

FCMJEG assessments

1.218 The COT considered Risk Assessments prepared by the Joint Expert Group on Food Contact Materials (FCMJEG) regarding the following regulated product application:

- On the safety of the use of 2-hydroxyethyl methacrylate (HEMAP) as a component in the manufacture of kitchen countertops and sinks. This assessment is for HEMAP only, and not the final reaction mixture used in the manufacture. This item is currently reserved as the Committee Advice Paper is not currently published. Publication of the final assessment is expected in 2024.
- On the safety assessment on the evaluation of the recycled poly(ethylene terephthalate) decontamination process operated by PETUK Ltd. for use in manufacture of articles in contact with food. The COT endorsed the assessment made by the FCM JEG. This item is currently reserved as the Committee Advice Paper is not currently published. Publication of the final assessment is expected in 2024.

Working Groups

Joint ACNFP/COT Working Group on Cannabidiol (CBD)

Cannabidiol (CBD)

1.219 A joint Subgroup of the ACNFP and COT was formed to address a series of questions in relation to the safety of CBD-containing and hemp-derived ingredients. The overarching aim of the Subgroup is to enable the FSA to perform risk assessments for CBD in food. The group established an ADI for pure form CBD (>98% purity) of 0.15 mg/k bw/day (10 mg/day for a 70 kg adult) as set out in a joint statement. Work continues on the assessment of novel products containing a lower proportion of CBD.

1.220 The joint position paper from the Advisory Committee on Novel Foods and Processes (ACNFP) & Committee on Toxicity (COT) on establishing a provisional acceptable daily intake (ADI) for pure form (≥98%) cannabidiol (CBD) in foods, based on new evidence can be found using this link: Joint position paper from ACNFP & COT on establishing provisional ADI for pure form CBD in foods | Advisory Committee on Novel Foods and Processes.

Plant-based drinks

1.221 Plant-based drinks have become increasingly popular in the United Kingdom (UK) both for individuals with an allergy to cows' milk or lactose intolerance and those who wish to avoid dairy products for other ethical or cultural reasons. Three such drinks were reviewed by the Committee, with a statement being published in 2022.

1.222 The Scientific Advisory Committee on Nutrition (SACN) have also considered these drinks from a nutritional perspective. To bring these two strands together, a joint Working Group was established to undertake a benefit risk-assessment of soya, oat and almond drinks as replacements for cows' milk. To support this work, a risk assessment of the components and contaminants, potentially present in cows' milk was conducted (see paragraph?). The Working Group started work in December 2021 and it is hoped that a draft report will be published for consultation in 2024.

PFAS

1.223 Following publication of the COT Interim position on per- and polyfluoroalkyl substances, a COT subgroup on PFAS has been formed.

1.224 The terms of reference for this subgroup are:

1.225 To provide guidance to UK Government Departments and Agencies to support human health risk assessments of per- and poly-fluoroalkyl substances (PFAS) where exposures to existing and legacy PFAS is occurring through food, drinking water and other environmental media. This will include:

- Undertaking an independent review of toxicological and epidemiological data, focusing on a number of critical endpoints, and considering the biological relevance of the endpoints assessed.
- Considering the toxicokinetics of PFAS.
- Determining whether different PFAS can be grouped for assessment and how this can be done.
- Deriving a HBGV or a number of HBGVs as the data allow

1.226 The subgroup will endeavour to follow the guidance from the Joint COT and COC Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE) subgroup in undertaking this assessment.

1.227 The subgroup held two meeting in 2023, which considered papers on animal and in vitro data on thyroid effects of PFAS and animal data on liver effects of PFAS. Further papers on these endpoints as well as papers on other endpoints will be considered in the future.

Codex report on food allergen thresholds

1.228 The Committee were asked to carry out an assessment of the Codex Expert Committee's report on establishing threshold levels for allergen of global importance (Part 2: review and establish threshold levels in foods for the priority allergens) to inform decisions by the FSA on whether it would be appropriate for the Eliciting Dose

(ED) reference doses recommended in the Codex report to be applied to regulated allergens in the UK.

1.229 The assessment was carried out by a subgroup comprising of several COT members along with other external experts, under the chairmanship of Prof Ian Kimber. The COT subgroup met virtually on four separate occasions. The Chair of the Codex Expert Committee on allergen thresholds (2nd Joint FAO/WHO Expert Consultation meeting) was invited to attend one of these meetings to clarify and answer some questions about the Codex Expert Committee's report.

1.230 In addressing questions posed in the Terms of Reference, the COT subgroup reached the following conclusions:

- There is no reason to suggest that the data are not sufficiently representative of the UK population.

- There are uncertainties regarding the way in which ED values have been derived – and, as a consequence, the accuracy of these values. Given the available data upon which derived ED values are based this is a limitation that must – at present – be acknowledged. However, there are no key gaps that can be filled using the published literature.

- There is insufficient evidence to demonstrate that using reference doses based on ED_{05}, as opposed to ED_{01} values would not significantly impact on public health.

1.231 The report of the subgroup was then presented to the Committee. The following comments were made:

1.232 It was noted that the underpinning data used to derive the EDs (both ED_{01} and ED_{05} values) in the Codex Expert Committee report were not made available with the report and were not otherwise available. This made it difficult to confirm the conclusions and access to the raw data would have been beneficial.

1.233 The report contained few graphs showing the modelling used and those that were included did not give confidence that the proposed eliciting doses were of appropriate values. The benchmark approach used was not the same as that normally used in toxicology. It was further noted that no safety factors were included.

1.234 However, the Committee acknowledged that while the dataset for some of the allergens was based upon very small numbers, there probably were no other data available in the literature to refine the dataset.

1.235 It was also noted that the reference to “mild anaphylaxis” in the report did not seem appropriate as NICE have a very clear definition that anaphylaxis is always a severe reaction.

1.236 The Committee agreed with the way the assessment of the report had been undertaken by the COT subgroup and with the contents and key conclusions reached by them.

1.237 The Committee also emphasised that since both ED_{01} and ED_{05} values represented effect levels, more people would be affected if the ED_{05} were used rather than the ED_{01} but the decision on which value to use will need to take into account additional considerations and was for risk managers to make rather than the COT.

1.238 The COT subgroup’s report can be viewed at: COT Codex Subgroup Report on Codex Allergen Thresholds Report FINAL SO ACC V_0.pdf (food.gov.uk).

2023 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Chair

Professor Alan Boobis OBE, PhD, FBTS, FBPhS
Emeritus Professor of Toxicology in the Faculty of Medicine at Imperial College London.

Members

Dr Phil Botham BSc, PhD
Principal Science Advisor at Syngenta (part time).

Ms Jane Case
Lay Member.

Dr Stella Cochrane BSc PhD
Science Leader for Allergy and Immunology in Unilever's Safety and Environmental Assurance Centre.

Dr James Coulson BSc MBBCh Dip Med Tox Dip Therapeutics LLM MD FRCP FRCPE ERT
Clinical Reader at Cardiff University, Honorary Professor in Clinical Pharmacology and Toxicology, Cardiff Metropolitan University, Honorary Consultant Physician, Clinical Pharmacologist and Toxicologist, Cardiff & Vale University Health Board.

Dr Silvia Gratz
Senior Research Fellow at the Rowett Institute, University of Aberdeen.

Professor Thorhallur I. Halldorsson

Professor at the Faculty of Food Science and Nutrition at the University of Iceland.

Professor Gary Hutchison

Dean of Applied Sciences at Edinburgh Napier University, with responsibility for Life Sciences, Social Sciences, Psychology, Teacher Education and Sports Exercise and Health Sciences.

Dr Sarah Judge BSc, PhD.

Lecturer in Pharmacology in the School of Biomedical, Nutritional and Sport Sciences at Newcastle University.

Professor Gunter Kuhnle

Professor of Nutrition and Food Science, University of Reading.

Dr David Lovell

Emeritus Reader in Medical Statistics at St George's Medical School, University of London.

Professor Shirley Price

Emerita Professor of Toxicology at the University of Surrey.

Dr Mac Provan

Director of Regulatory Science Ltd.

Ms Juliet Rix

Lay Member.

Dr Michael Routledge

Associate Professor of Environmental Toxicology in the School of Medicine at Leeds.

Dr Cheryl Scudamore

RCVS Specialist in Veterinary Pathology (laboratory animals) working as independent consultant in experimental and toxicological pathology.

Dr Natalie Thatcher

Mondelēz International.

Professor Mireille Toledano

Chair in Perinatal and Paediatric Environmental Epidemiology, Faculty of Medicine, School of Public Health, Imperial College London.

Dr Simon Wilkinson

Senior Lecturer in Pharmacology in the School of Biomedical, Nutritional and Sports Sciences at Newcastle University.

Professor Philippe Wilson

Professor of Animal Science and Bioinformatics, Nottingham Trent University, and Head of Conservation at the Rare Breeds Survival Trust.

Professor Matthew Wright BSc, PhD

Professor of Toxicology, Institute of Cellular Medicine, Newcastle University.

Professor Maged Younes

Independent expert on toxicology and biochemical pharmacology.

Associate Members

An associate member of the Science Advisory Committees (SACs) is a membership designed to allow early or mid-career researchers to become involved in the work of the FSA SACs. Creating this role allows the FSA to engage with a more diverse range of individuals, as well as encouraging interest in future SAC and FSA work.

Professor Jeanette Rotchell

University of Lincoln

Dr Samantha Donnellan

Lecturer of Biomedical Sciences at Edinburgh Napier University

Ms Eimear O'Rourke

Queens University Belfast

Dr Ben Amies-Cull

Public health researcher at the University of Oxford.

Dr Charlotte Mills

Hugh Sinclair Lecturer in Nutritional Sciences within the Department of Food and Nutritional Sciences at University of Reading

Dr Tarek Abdelghany

Lecturer of Pharmacology and Physiology at the Institute of Education in Healthcare and Medical Sciences, School of Medicine, Medical Sciences and Nutrition, the University of Aberdeen.

Secretariat

Ms Catherine Mulholland BSc (Hons), ERT Scientific Secretary

Ms Britta Gadeberg BSc (Hons) MSc, Scientific Secretary – PHE

Dr David Gott BSc (Hons) PhD

Dr Alexander Cooper BSc (Hons) MSc PhD

Dr Barbara Doerr BSc (Hons) MSc PhD

Ms Jocelyn Frimpong Manso BSc (Hons) MSc

Ms Cleanncy Hoppie BSc (Hons) MSc

Mr Barry Maycock BSc (Hons) MSc

Dr Olivia Osborne BSc (Hons) (Exon) PhD ERT MIFST

Ms Claire Potter BSc (Hons) MSc ERT

Dr Joseph Shavila BSc (Hons) MSc PhD

Ms Sabrina Thomas BSc (Hons) MSc

Ms Chara Tsoulli BSc (Hons) MSc Ms

Ms Frederique Uy BSc (Hons) MSc

Miss Sophy Wells

Dr Gaetana Spedalieri

Mr Thomas Hornsby BSc (Hons) MSc

Ms Gail Drummond BSc (Hons) MSc, LLB, PG Dip (law)

Dr Emily Hudson BSc (Hons) Mres

Dr David Kovacic

Declaration of members' interests during the period of this report

Professor Alan Boobis OBE, PhD, FBTS, FBPhS

Personal Interest	**Employee:** Imperial College London, Department of Medicine (retired June 2017, part-time appointment from Aug 2017-May 2019). Full retiral June 2019. Emeritus Professor of Imperial College London, National Heart & Lung Institute.
Personal Interest	**Membership:** ILSI & ILSI, HESI Board of Trustees ILSI Europe. Board of Directors Science Advisory Board of Swiss Centre for Applied Human Toxicology. Dept. of Health Committee on the Medical Effects of Air Pollutants WHO/FAO JMPR. WHO/FAO JECFA (vet). WHO TobReg. WG10 TC126 (Intense Machine- smoking Regime for Testing Cigarettes). EUROTOX. British Pharmacological Society, British Toxicology Society, Society of Toxicology (USA). Royal Society of Biology (until 2017). Michigan State University MSU Center for Research on Ingredient Safety (CRIS) (External Advisory Committee). Agency for Innovations in Food and Chemical Safety Programme. Science, Technology and Research,

	Singapore (A*STAR) (Scientific Advisory Board).
Non Personal Interest	None.

Dr Phil Botham

Personal Interest	**Employee:** Syngenta - Principal Science Advisor (part time).
Personal Interest	**Shareholder:** AstraZeneca, Regulatory Science Associates (Part, Time Consultant).
Personal Interest	**Membership:** British Toxicology Society, Society of Toxicology (USA), European Centre for Ecotoxicology and Toxicology of Chemicals Scientific Committee, European Crop Protection Association Toxicology Expert Group, Crop Life International Human Health Steering Team.
Non-Personal Interest	None.

Ms Jane Case

Personal Interest	**Employee:** Company Secretary of Muse Interiors, Stevens & Bolton LLP (as Jane Hughes).
Personal Interest	**Membership:** None.
Personal Interest	**Shareholder:** Standard Life Santander
Non-Personal Interest	None.

Dr Stella Cochrane

Personal Interest	**Employee:** Unilever.
Personal Interest	**Membership / Affiliation:** Unilever representative on the UK FDF Allergen Steering Group (Deputy Chair), FDE Allergen Group and University of Nebraska Food Allergy Research & Resources Board.
Personal Interest	**Shareholder:** Unilever.
Non-Personal Interest	None.

Dr James Coulson

Personal Interest	**Employee:** Cardiff University, Director of Medical, Scientific and Toxicology Consultancy Ltd.
Personal Interest	**Membership:** British Medical Association, British Pharmacology Society, British Toxicology Society National Trust, Royal College of Physicians of London.
Non-Personal Interest	None.

Professor Thorhallur Ingi Halldorsson

Personal Interest	**Employee:** Faculty of Food Science and Nutrition, University of Iceland.
Personal Interest	**Membership:** European Food Safety Authority - Scientific committee and various working groups.

	Nordic Council of Ministers - revision of the 2022 Nordic Nutrition Recommendation). Icelandic Risk Assessment Committee for Food, Feed, Fertilizers and Seeds (IRAC) – occasional expert work. The Nutricia Research Foundation – review of applications once a year. The Icelandic Research Found (RANNIS) – occasional member of different expert panels.
Non-Personal Interest	None.

Professor Gary Hutchison

Personal Interest	**Employee:** Dean of Applied Sciences at Edinburgh Napier University.
Personal Interest	**Membership:** Hazardous Substances Advisory Committee DEFRA, British Toxicology Society.
Non-Personal Interest	None.

Dr SarahJudge

Personal Interest	**Employee:** Newcastle University, Lowcock Properties Ltd.
Personal Interest	**Membership:** British Pharmacology Society, British Toxicology Society International Association for Neurotoxicology.
Non-Personal Interest	Research Funding.

Professor Gunter Kuhnle

Personal Interest	**Employee:**

	Professor of Nutrition and FoodScience, University of Reading.
Non-Personal Interest	Research Funding.

Dr David Lovell

Personal Interest	**Employee:** Reader in Medical Statistics, St Georges Medical School, University of London.
Personal Interest	**Membership:** HESI GTTC – Biometrics Society, British Toxicology SocietyGenetics Society, Royal Society of Biology Laboratory Animal Science Association, Royal Statistical Society Statisticians in the Pharmaceutical Industry, United Kingdom Environment Mutagen Society (UKEMS), UK National Centre of Replacement, Refinement and Reduction of Animals in Research(NC3Rs), MRC EMINENT Scientific ReviewBoard. **Also, private member of:** British Trust of Ornithologists (BTO) English Heritage, Liberty, Campaign of the Protection of RuralEngland (CPRE), Kew Gardens, Sandwich Bay Bird Observatory Trust(SBBOT), Chelsea Physic Garden, National Trust.
Personal Interest	**Shareholder:** National Grid, Pfizer,

	AstraZeneca (spouse shareholder), National Grid plc (spouse shareholder).
Non-Personal Interest	None.

Professor Shirley Price

Personal Interest	**Employee:** None.
Personal Interest	**Membership:** None.
Non-Personal Interest	**Trusteeships:** Gas Safety Trust
Non-Personal Interest	**Other:** I can confirm that as the President of the British Toxicology Society (BTS) I hold a non-personal and non-specific interest in both GSK and AstraZeneca on the Society's behalf. These non-personal and non-specific interests relate to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training.

Dr Mac Provan

Personal Interest	**Employee:** Director of Regulatory Science Ltd.
Personal Interest	**Membership:** None.
Non-Personal Interest	None.

Ms Juliet Rix

Personal Interest	**Employee:** None.
Personal Interest	**Membership:**

	None.
Non-Personal Interest	None.

Dr Michael Routledge

Personal Interest	**Employee:** Lecturer/Senior Lecturer/Associate Professor University of Leicester.
Personal Interest	**Membership:** Member of working group, European Food Safety Authority, 2018-2019. Vice-President of UKEMS (UK Environmental Muta-Genesis Society).
Non-Personal Interest	None.

Dr Cheryl Scudamore

Personal Interest	**Employee:** Independent consultant in experimental and toxicological pathology.
Personal Interest	**Membership:** None.
Non-Personal Interest	None.

Dr NatalieThatcher

Personal Interest	**Employee:** Mondelēz International.
Personal Interest	**Membership:** None.
Non-Personal Interest	None.

ProfessorMireilleToledano

Personal Interest	**Employee:**

	Marit Mohn Chair in Perinatal & Paediatric Environmental Epidemiology,Imperial College London.
Personal Interest	**Membership:** None.
Non-Personal Interest	None.

Dr Simon Wilkinson

Personal Interest	**Consultancies and other fee-paid work:** Consultancy for L'Oreal, Paris.
Personal Interest	**Membership:** None.
Non-Personal Interest	None.

Professor Phillipe Wilson

Personal Interest	**Employee:** Nottingham Trent University, Rare Breeds Survival Trust.
Personal Interest	**Membership:** None.
Non-Personal Interest	None.

Professor Matthew Wright

Personal Interest	**Consultancies and Direct Employment:** Newcastle University.
Personal Interest	**Membership:** British Toxicology Society, Society of Toxicology (US), EFSA FAF Panel.
Personal Interest	**Miscellaneous:** Toxicology – Associate Editor.
Non-Personal Interest	**Support by Industry:**

	GSK, Lubrizol.

Professor Maged Younes

Personal Interest	**Employee:** Independent expert in toxicology and biochemical pharmacology.
Personal Interest	**Membership:** Chair of EFSA ANS panel, Chair Commission on evidence-based methods in risk assessment, Federal Institute for Risk Assessment (BfR), Germany. Society of Toxicology, USA German Society of Experimental and Clinical Pharmacology and Toxicology. Society for Risk Analysis.
Non-Personal Interest	None.

Dr Silvia Gratz

Personal Interest	**Employee:** Rowett Institute, University of Aberdeen
Personal Interest	**Membership:** The Nutrition Society (UK) The British Toxicology Society FSA Register of Specialists
Non-Personal Interest	None

[Note- Associate Members' interests to be added]