Committee on Toxicity of Chemicals in Food, Consumer, Products and the Environment Draft Annual Report 2024

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COT Evaluations 2024

In this guide

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This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Safety of Titanium dioxide (E171) as a Food Additive

1.1 Food grade titanium dioxide (TiO_2) was an authorised Food Additive (E171) in the EU, but from the 7th of August 2022, its use in food has been banned in light of the European Food Safety Authority's (EFSA's) conclusion that such use could no longer be considered as safe. It currently remains authorised in Great Britain. Food grade TiO_2 comprises a mixture of micro- and nanosized (<100 nm) particles and is used in food as a colour (white pigment). Titanium dioxide is also widely used in cosmetics and medicines.

1.2 Titanium dioxide has been the subject of multiple safety evaluations including three recent evaluations by EFSA in 2016, 2019 and 2021.

1.3 In their most recent Opinion (2021), the EFSA Panel concluded that E171 could no longer be considered as safe for use as a food additive, due to uncertainties in some of the data, such as on genotoxicity (DNA damaging effects). Following this, in 2021 the COT published an interim position on titanium dioxide in which the Committee expressed its scientific concern about the basis of the EFSA conclusions. A detailed review has now been undertaken by the COT, which includes the conclusions on genotoxicity (DNA damaging effects) from the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM), to assess the safety of TiO_2 as a food additive.

1.4 The COT has reviewed toxicological studies that have been conducted using any form of TiO_2, including nanoparticles, but its conclusions are based primarily on those which used food grade TiO_2 (E171), which predominantly consists of aggregates, of smaller primary particles, with a median particle size of 200 – 300 nm.

1.5 The following endpoints were reviewed by the COT: the development of aberrant crypt foci (ACF) in the intestine (as a potential indicator of carcinogenicity), inflammation and immunotoxicity, reproductive and developmental toxicity and neurotoxicity. The COM reviewed the data on genotoxicity (damage to DNA which could ultimately lead to cancer) and reported their findings to the COT in May 2024.

1.6 The COT considered that the data from the relevant studies available indicated that TiO_2 did not induce ACF, nor were there significant effects in studies that assessed inflammation and immunotoxicity, reproductive and developmental toxicity, and neurotoxicity. On balance, the Committee considered that a no observed adverse effect level (NOAEL) of 1,000 mg/kg bw per day, was robust.

1.6 Overall, the COM concluded that there was little evidence in the literature to suggest that food grade TiO2 (E171) caused induction of genotoxicity (DNA damaging effects), and that there was unlikely to be any health concern related to genotoxicity induction from use of TiO2 (E171) as a food additive. Following discussions of the COM report at their meeting in March 2024, the COT included the COM conclusions in their overall review of the evidence.

1.7 The COT concluded that 1,000 mg/kg bw per day was a robust Point of Departure (POD) on which to base a health-based guidance value (HBGV). This was the highest dose tested, so it is not known how much more TiO2 would have to be administered before effects were seen.

1.8 A standard uncertainty factor of 100 (10 for inter-species differences and 10 for inter-individual variability) was agreed by Members and applied to the POD which resulted in a HBGV (acceptable daily intake) of 10 mg/kg bw per day.

1.9 Titanium dioxide (E171) can be found in a number of food categories, and the exposures calculated and considered by the COT for infants, toddlers, children, adolescents, adults, and the elderly used food consumption data from UK surveys and maximum occurrence levels of titanium dioxide reported by EFSA (2021).

1.10 Estimated exposures for adults (18+) and the elderly are below the established HBGV. Although exposures for infants, toddlers, children and adolescents consuming a lot of TiO2-containing food are estimated to be 1.3 - to 2.6- fold higher than the HBGV, actual exposures are likely to be lower and in addition, the HBGV is likely to be conservative. Therefore, adverse health effects would not be expected.

1.11 The COT concludes that it is unlikely that there would be a risk to health from current UK dietary exposures of E171 TiO2.

1.12 The full COT statement: Safety of Titanium dioxide (E171) as a Food Additive .

Statement on the potential health effects of raspberry leaf tea in the maternal diet

1.13 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. To help SACN in this, the COT was asked to review

the risks of toxicity from certain chemicals and products in the maternal diet. This statement focuses on the possible risks from taking raspberry leaf tea, or extracts of raspberry leaf, in tablets or tinctures, during pregnancy.

1.14 Raspberry leaf, as tea, tablet or tincture, is most commonly taken during pregnancy as a dietary supplement in the belief that it stimulates and facilitates labour and shortens its duration. A recent study in Australia reported use by 38% of pregnant women, while a UK study in 2007-2008 reported use by approximately 24% of pregnant women. In addition to such preparations, several raspberry leaf products are registered as traditional herbal medicines in the UK. However, these are directed at non-pregnant women for the symptomatic relief of menstrual cramps. Some clinics offer enemas containing raspberry leaf, though it is not clear whether any are aimed at pregnant women.

1.15 A number of studies, starting in the 1940s, have investigated the effects of extracts of raspberry leaf on the uterus (womb) or other smooth muscle, either in intact animals or isolated from animals. The results of these studies were highly variable, with some showing smooth muscle contraction and others relaxation. This variability was likely due to factors such as differences in the components in the extracts and doses of the extracts tested, the type of smooth muscle tissue tested, pregnancy status of the animal, and whether the study was in an intact animal or on isolated uterus or other smooth muscle. The mechanism by which raspberry leaf could have the claimed effects on labour is also poorly understood, and it is unclear what the active components might be. A number of mechanisms have been suggested, but the evidence for these is limited and contradictory.

1.16 Limited data were available on the reproductive toxicity of raspberry leaf in laboratory animals, and only one study was identified that had evaluated it for short- term repeat-dose toxicity, conducted in mice. Another source of uncertainty was a lack of specific information on the absorption, distribution, metabolism and excretion of the constituents of raspberry leaf by the body following their consumption. However, some evidence indicated that raspberry leaf extracts are less toxic when given to mice orally than when injected intravenously. This suggests that they have poor oral bioavailability; that is, that only small amounts of the toxic constituents reach the systemic circulation following ingestion.

1.17 Limited data were found on levels of contaminants, such as heavy metals, in raspberry leaf, and on levels of pesticide residues. However, the data available did not indicate any safety concerns.

1.18 The COT also took into account the available human data. These included two studies conducted in Australia. The first identified women who had given birth in hospital and who had taken raspberry leaf tea, tablets and/or tinctures during pregnancy, and compared them to matched women who had not taken raspberry leaf during pregnancy. No adverse effects were identified in the mothers or infants, or on the delivery, from consuming raspberry leaf. The second study, by the same group, was a double-blind, placebo-controlled trial, in which women were randomly assigned to receive raspberry leaf tablets or placebo tablets during pregnancy. No adverse effects were identified, with the possible exception of constipation, which was reported exclusively by 4 of the 96 women receiving raspberry leaf. However, the COT noted that estimates of UK consumption of raspberry leaf tea, or of raspberry leaf from tea, tinctures and capsules combined, which were based on data collected from online sources, were up to four or more times higher than the raspberry leaf dose tested in this trial.

1.19 In addition, the COT took into account data collected by the UK Teratology Information Service (UKTIS), a national service that collects pregnancy outcome data from women exposed to medicines and chemicals in pregnancy. There have been very few reports of adverse effects in pregnant women taking raspberry leaf or their children received by the UKTIS since its inception in 1983 to the present date, despite the reported high prevalence of use of raspberry leaf.

1.20 Overall, the COT concluded that the risk associated with raspberry leaf use during pregnancy was low but with high uncertainty due to the data limitations. The COT considered that poor oral bioavailability of the toxic constituents of raspberry leaf (based on indirect information) might also contribute to why it appears to have little adverse effect on human health. However, if raspberry leaf products that are modified to increase their bioavailability become available in the future, these may require a separate safety evaluation.

1.21 The full COT Statement can be found at: Statement on raspberry leaf tea.

Hepatotoxicity of green tea catechins

1.22 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.

1.23 Following a request to the Food Standards Agency from DHSC under the Nutrition, Labelling, Composition and Standards (NLCS) Common Framework, 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. Conclusions made by the Committee will help inform the next steps for risk management. 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.

1.24 The technical statement and lay summary have been published and are available on the COT website and through the following DOI link: https://doi.org/10.46756/sci.fsa.wii944.

Assessment of Bisphenol A (BPA)

1.25 Following extensive reviews and discussions of the scientific evidence of the new European Food Safety Authority (EFSA) tolerable daily intake (TDI) for bisphenol A (BPA), and the subsequent assessment by the German Federal Institute for Risk Assessment (BfR) in 2023, the COT adopted the tolerable daily intake (TDI) of 0.2 µg/kg bw per day set by the BfR.

1.26 The Committee noted that the scientific issues raised by the BfR aligned with the concerns and comments highlighted by the COT during their discussions and the public consultation held by EFSA.

1.27 The use of a male reproductive endpoint, i.e. sperm count and mobility, by the BfR was consistent with the critical endpoint used in previous COT assessments. While the COT agreed that the BfR had added a significant degree of conservatism to their derivation of the TDI, they could not identify any endpoint that would be more suitable and concluded that the overall assessment by the BfR and endpoint applied, and approach taken was reasonable.

1.28 In line with EFSA and the BfR, the Committee highlighted that the most recent exposure data available predates the 2015 EFSA opinion. To be able to undertake a full risk assessment, the COT will require up to date exposure data, which will enable the Committee to fully assess realistic exposures in, and

potential risks to, the UK population.

1.29 The position paper on bisphenol A was published in May 2024.

1.30 The Committee will be publishing a supplementary statement in 2025, providing more detail on their discussions of the EFSA opinion and BfR assessment, their evaluation of the evidence base, and deliberations to adopt the TDI derived by the BfR.

Updated position paper on Bamboo Bio-Composites in Food Contact Materials

1.31 Risk assessment advice on biobased food contact materials (BBFCMs) has been increasingly requested from the Food Standards Agency (FSA), hence it was considered timely for the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to review the available toxicological information on BBFCMs (COT, 2021).

1.32 In 2019, the European Commission (EC) asked the European Food Safety Authority (EFSA) to assess whether the authorisation of untreated wood flour and fibres (FCM no. 96) as an additive in plastic food contact materials was still in accordance with EC Regulation 1935/2004, and also to consider whether bamboo could be considered under the scope of this authorisation. Following EFSA conclusion that wood and bamboo should be considered distinct and each material regarded on a case-by case basis, the EC recommended that Member States should take stringent action on bamboo composite FCMs and set out a coordinated control plan. In addition, the food safety authorities of Belgium, Luxembourg and the Netherlands (Benelux) published a joint letter calling for the market withdrawal of bamboo-melamine plastics. The FSA is aware of the stance by the EC and of the individual Member States and is considering an appropriate course of action based on scientific evidence.

1.33 In December 2020, reports to the FSA in relation to bamboo composite FCMs were predominantly related to misleading labelling on packaging and/or their advertisement, as well as incidences of formaldehyde/melamine migration levels exceeding legal limits. In 2021, and due to the EU’s conclusion, that bamboo is an unauthorised additive within plastic FCMs, reports received by the FSA had predominantly been of non-compliance of plastic-bamboo FCMs in the European market. This included the advertisement of products from UK businesses on EU facing markets. Hence, the COT undertook a more detailed review of the potential

health risks of bamboo composites in Food Contact Materials (FCMs).

1.34 The COT assessed the reports by the German Federal Institute for Risk Assessment (BfR) and the Netherlands Food and Consumer Product Safety Authority (NVWA) and noted that the BfR applied their own tolerable daily intake (TDI) of 0.6 mg/kg/day for formaldehyde whereas the NVWA and EFSA used a lower TDI of 0.15 mg/kg/day.

1.35 Overall, the COT concluded that the exposure assessments were conservative but not necessarily worst-case. It was agreed that although the NVWA and BfR opinions took slightly different approaches, in general the same conclusions were reached. Based on the assessment of the BfR and NVWA reports the Committee concluded that the migration of formaldehyde and melamine from bamboo composite cups was a potential concern to human health.

1.36 To assist the COT with their assessment the FSA launched a call for evidence in 2023 to obtain further information from industry, consumers, or interested parties on the safety and stability of plastic contact materials and articles containing bamboo and other plant-based material. In March 2024, the COT assessed the information submitted to the FSA in response to the call for evidence as well as an additional report (EU-ChinaSafe, 2022).

1.37 Based on the considerations of the new evidence submitted to the FSA and the currently available data, the COT agreed that there was still insufficient exposure data on which to perform a complete risk assessment. Concerns remained regarding the migration of formaldehyde and melamine from these FCMs, while the actual composition of these products remained uncertain.

1.38 Updated position paper on Bamboo Bio-Composites in Food Contact Materials

Joint statement on the safety assessment of Tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE)

1.39 Towards the end of 2021 the UK Food Standards Agency (FSA) policy team received a request by the food contact can coating sector to assess the suitability of tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE) for use in coatings in canned food packaging materials.

1.40 As the European Food Safety Authority (EFSA) had not carried out an assessment this necessitated national authorities to consider the safety and use of TMBPF-DGE as an epoxy in can coatings. In 2022, the Dutch Authorities included TMBPF-DGE in their revision of the Dutch Commodities Act (Warenwet), allowing it to be used as a coating in canned food packaging subject to specific restrictions. In accordance with mutual recognition principles, goods lawfully placed on the market within an EU member state can be freely placed on the market within Northern Ireland (NI). This does not apply to Great Britain (GB).

1.41 TMBPF-DGE is being suggested as a possible replacement for bisphenol A (BPA) in can coatings, with several global brands already marketing cans coated with TMBPF-DGE-based polymers in the European Union (EU). Manufacturers are now intending to apply the coating to cans destined for the GB market.

1.42 All information provided to the FSA on TMBPF-DGE has been considered by the Joint Expert Group on Food Contact Materials (FCMJEG), the Committee on Toxicity of Chemicals, Consumer Products and the Environment (COT) and the Committee on Mutagenicity (COM), for their specific expertise.

1.43 TMBPF-DGE is a mixture derived from the reaction of tetramethyl bisphenol F (TMBPF) with epichlorohydrin. TMBPF-DGE is then further processed to form an epoxy resin and polymer dispersion, which is then used as a component in coatings in canned food packaging materials, in contact with all food types (beverages included). It should be noted, that while testing was performed on TMBPF-DGE, as well as the epoxy resin, the assessment is on the safety of TMBPF-DGE only and does not include evaluation of any of the other chemicals included in the manufacture of the epoxy resin or final product.

1.44 TMBPF-DGE contains epoxy (glycidyl) groups and as such is intended to be reactive. However, reactivity is negligible in the finished (cured) coating where it is incorporated into the polymer backbone. While TMBPF-DGE derived epoxy groups remaining in the resin may react with food constituents, no interactions with food substances after polymerisation are anticipated.

1.45 The migration of TMBPF-DGE and its derivatives was based on extraction in acetonitrile, which the Committees agreed was the worst-case extraction and hence would be the worst-case migration of TMBPF-DGE. The anticipated migration was within the specific migration limit and also below the restriction to bisphenol A diglycidyl ether (BADGE) and BFDGE, its closest comparators.

1.46 The Committees considered TMBPF-DGE to be genotoxic *in vitro*. However, while some uncertainties remain, specifically around the potential of TMBPF-DGE to induce polyploidy, the *in vivo* genotoxicity data were negative and provided a sufficient margin of safety. Overall, the Committees agreed that it is unlikely that there would be a risk to human health from any mutagenic effect of TMBPF-DGE.

1.47 Members concluded that the available, albeit screening-level, data on non-genotoxic endpoints did not indicate any reproductive or developmental effects at a concentration of 300 mg/kg or raise any other toxicological concerns at exposures of ≤ 100 mg/kg.

1.48 While not a requirement for the assessment, the endocrine data available for TMBPF-DGE epoxy resin were of good quality with the Committees concluding that there was no concern over endocrine effects of TMBPF-DGE at the expected exposure levels.

1.49 Members did not consider it appropriate to establish a HBGV due to the lack of a long term/chronic toxicity study and other database deficiencies.

1.50 When considering all available information, including a comparison of TMBPF-DGE with BADGE, its closest comparator, the available data did not identify any safety concerns for the usage of TMBPF-DGE in can coatings. The MOE was at least 67,000, well above the value of 1000 considered to indicate a lack of any safety concern. In addition, the TTC approach provided re-assurance, given its in-built conservatism and supported the conclusion that the estimated exposure to TMBPF- DGE would be below any level of potential concern. Hence, the FCMJEG and COT did not see any scientific reason to apply restrictions to the proposed usage of TMBPF-DGE.

1.51 Given that there is no legislative framework in place for the assessment of substances in can coatings nor the ability to create or amend a positive list at present, the FSA policy team therefore does not anticipate formal authorisation of TMBPF-DGE but would take into account the finalised risk assessment in their risk management considerations. The objective will be to ensure that it appropriately sets out operator requirements and expectations.

1.52 Safety assessment of tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE) for use in coating in canned food packaging materials

Aircraft cabin air

1.53 The COT was asked to 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?”. This follows a COT statement in 2007 addressing aircraft cabin air, relating to organophosphate compounds, the cabin air environment, ill-health in aircraft crews and the possible relationship to smoke or fume events (COT, 2007) and subsequently a position statement following research on aircraft cabin environment (COT, 2013).

1.54 The objective of the present review was to investigate whether specific chemicals commonly identified in aircraft cabin air could potentially cause ill-health in aircrew. This review did not look for other potential causes of aircrew ill-health (which the 2007 review did).

1.55 For the present review the COT considered a number of papers on organophosphates, volatile organic compounds, carbon monoxide and carbon dioxide.

1.56 Most of the published information on these chemicals in aircraft cabin air related to background levels during normal flight operation. There continued to be only very limited information on levels following smoke or fume events, with little additional data since COT’s previous work in 2007 and 2013. Smoke or fume events are when abnormal odours, smoke, haze or fumes occur in the aircraft cabin, which may come from various internal or external sources.

1.57 The COT considered the potential risk to health from organophosphate exposure in aircraft cabin air (TOX/2022/40). Two studies investigated health effects in aircrew. The COT considered there were shortcomings with both studies, in particular neither study reported the levels of organophosphate exposure the crew had experienced. However, the COT agreed with the authors’ conclusions that the data did not indicate any association between impact on mental ability and organophosphate exposures.

1.58 One paper carried out a risk assessment for a specific organophosphate, tri-ortho-cresyl phosphate, commonly used in aviation lubricants. Levels of exposure to this organophosphate were substantially below those at which a risk of adverse effects on health might arise.

1.59 The Committee concluded that it was unlikely that exposure to organophosphates at the low levels identified in aircraft cabin air would have adverse effects on aircrew.

1.60 For volatile organic compounds, levels in aircraft were compared with levels in other modes of transport (TOX/2022/46) or other work environments (TOX/2022/55) in the UK and EU. If the highest average levels of an individual compound in aircraft were above all the highest average levels in other environments in which that individual compound was measured, the COT carried out a specific risk assessment for that chemical.

1.61 The reported levels of six volatile organic compounds in aircraft were above the levels in other UK and EU modes of transport or work environments (TOX/2023/15). However, the concentrations were all lower than relevant guidelines and standards, indicating that no risk to health is anticipated at these levels. Mixtures of volatile organic compounds were considered using a hazard index approach. This compares the level of each chemical with the level below which there would not be a risk to health and adds these ratios together. In considering the volatile organic compounds in aircraft cabin air, the result of this hazard index approach indicated that no effects, including mixture effects, are anticipated.

1.62 Levels of carbon monoxide and carbon dioxide in UK and EU-operated aircraft were collated and compared with various standards as well as levels that cause discernible symptoms (TOX/2022/65 and TOX/2023/14). The Committee considered these data and concluded that levels of carbon monoxide and carbon dioxide reported in aircraft are unlikely to be associated with any short- or long-term adverse health effects.

1.63 Overall, the COT concluded that the levels of the chemical contaminants reviewed (organophosphates, volatile organic compounds including as mixtures, carbon monoxide and carbon dioxide) in aircraft cabin air, at the concentrations reported, are unlikely to cause adverse health effects in aircrew after being exposed for long or short time periods. However, there is still limited information about the levels of chemicals in cabin air following smoke or fume events.

1.64 The full COT statement can be found at: Statement on Aircraft Cabin Air Quality | Committee on Toxicity

COT Procedures 2024

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Benchmark dose modelling in a UK chemical risk assessment framework

1.65 In 2021, as part of a horizon scanning exercise, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) identified the UK in future may need benchmark dose (BMD) modelling guidance. As part of its ongoing evaluation of New Approach Methodologies (NAMs) in chemical risk assessment, the Food Standards Agency (FSA) and the COT were considering the use and practice of BMD modelling within a UK food safety context.

1.66 The discussion paper set out the theory and practice of BMD modelling. The paper drew on previous evaluations by regulatory bodies and authorities. It also included a discussion of the areas of consensus and divergence between organisations and expert groups. The paper included a case study from the FSA Computational Fellow.

1.67 BMD modelling represents a useful tool in toxicology, but the No-observed-adverse-effect level (NOAEL) approach remains valid and, in many cases, is the only option (e.g. where effects are observed only at the highest dose). The requirement for deeper knowledge of the statistical and computational basis of the BMD approach may represent a barrier for further adoption in traditional

toxicology. Applying the BMD approach to toxicology data is a more complex undertaking than the traditional NOAEL approach. Some areas where BMD modelling may provide advantages over the traditional NOAEL approach include potency comparison, establishing toxicological equivalency factors (TEFs) and for situations where a reference point needs to be identified in the absence of a NOAEL.

1.68 With respect to the development of new BMD software these pieces of software have their own capabilities, which allow them to be tailored for specific scenarios and tasks. However, there is concern that this might lead to further divergence rather than convergence of BMD approaches. For example, the recent development of Bayesian BMD software as part of European Food Safety Authority (EFSA's) modelling suite there are concerns around how the Bayesian BMD modelling is used in practice, specifically with the selection of priors and whether this would introduce subjectivity into the analysis. Uncertainties have been expressed in the literature with respect to the Environmental Protection Agency (EPA) Bayesian modelling software.

1.69 There is debate about the role of benchmark dose modelling in other areas, such as genotoxicity testing, and the COT is aware of the views on BMD modelling by other UK Scientific Advisory Committees notably the COC and COM. BMD modelling is already being used by some expert groups, such as the UK Expert Committee on Pesticides and it would be useful to capture their experience.

1.70 The Committee acknowledged the rapidly developing nature of the BMD guidance, the development of new approaches, such as Bayesian approaches; and the recent proliferation of new BMD software but noted that it was still uncertain if, or what, important divergences existed between these developments.

1.71 BMD modelling should be viewed as a step towards a larger goal of more realistic, toxicodynamic systems approaches to risk assessment. This may become more feasible with the further development of models based on *in silico* and *in vitro* approaches.

1.72 The Committee noted that BMD modelling should be taken into consideration when updating COT guidelines.

COT ways of working

1.73 The workload of the Committee and in particular the Chair has increased over recent years, partly, though not solely, as a result of the UK’s exit from the EU, including the additional activities associated with the authorisation of regulated products. It was therefore timely to review the current working practices of the Committee to ensure that it remains sustainable. In addition, due to the increase in hybrid and virtual meetings, it was important to ensure the Committee could work in an effective manner, with Members being able to fully contribute and be engaged. Committee Chairs are appointed through an open recruitment process so it would not be appropriate to train current Members for the role or to have a formal succession planning process. However, it was agreed that, in addition to chairing the meeting when the Chair was unavailable or had a conflict of interest, it could be useful for the Deputy Chair to lead in a particular topic area to reduce the workload of the Chair. It was subsequently agreed that the COT Deputy Chair, Professor Shirly Proce, would focus on regulated products to strengthen links between the COT and the Joint Expert Groups.

1.74 The process by which small groups of Members were attached to particular papers to lead the Committee discussion was discussed. It was agreed that the small group work should start at an earlier stage for more complex topics and could also follow the process through to the preparation of first draft statements. Lay members and/or associate members could also be included in the small groups where appropriate.

1.75 Since final statements and position papers were the final output of the Committee, later drafts needed to be considered and agreed by the full Committee since they represented a collective view.

1.76 Since over half of the Committee’s meeting are fully online, Members discussed some potential changes to the current procedures; No changes were agreed but the topic remans under review.

1.77 The role of the lay Members was considered; while they may sometimes find it difficult to participate at meetings due to the very technical content, their contribution was much valued. It was agreed that lay Members from different Committees should meet to share their perspectives and consider best practice.

Ongoing Work 2024

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

1.79 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 legislative standards. The main purpose of this work is to identify any emerging marine biotoxins 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 emerging marine biotoxins would pose a risk to human health.

1.80 In December 2023 a scoping paper was presented to the Committee on whether a number of emerging marine biotoxins would pose a risk to human health. Following the discussions, and to aid the Committee in ranking the risk of each emerging marine biotoxin, the Secretariat produced a discussion paper in July 2024 providing a table with the main toxicological information. In addition, a table of the main toxicological information of currently regulated marine biotoxins was included, for comparison.

1.81 Limited estimates of potential adult exposures to the unregulated marine biotoxins, based on the European Food Safety Authority's (EFSA) shellfish portion size of 400 g, and a fish portion size of 140 g, as suggested by the Ministry of Agriculture, Fisheries and Food portion size book and assuming a body weight of 78.6 kg were also provided. The aim of the estimated exposures was to help Members establish whether occurrence at the levels reported in the literature would be of potential risk. However, this was not a detailed exposure assessment, and consumption data was not based on UK consumers, and hence may have overestimated actual exposures in the UK. Going forward it may be more appropriate, if required, to use data from the National Diet and Nutrition Survey (NDNS) to enable a more accurate and refined exposure assessment, although data for consumption of shellfish from this survey may still be limited.

1.82 There was limited data available, in general, but also on the impact of biotoxins on other animals living in (e.g. fish and shellfish) or frequenting (e.g. wild birds) freshwater. However, it is generally assumed that animals would avoid areas of high blooms, if they can. There was also very limited data on the overlap between algal blooms and exposure to toxins, made more difficult with some algae species having benthic stages.

1.83 Data on adverse effects of marine biotoxins were commonly from animal studies, and not from human data. Nonetheless, specifically for cyclic imines (CIs) monitoring was undertaken in some countries even though no human intoxications had been reported. The route of administration in animal studies differed widely, adding to the uncertainty in the available data, but intraperitoneal injection appeared to increase toxicity in a number of studies compared to oral administration.

1.84 The COT considered it useful for the UK to have a more formal strategy for the reporting of potential marine biotoxin intoxications, however they acknowledged that this may prove difficult for some marine toxins as standard testing may not be available.

1.85 There would however be benefits from enhanced UK surveillance programmes and looking at monitoring programmes in other countries, specifically e.g. in Scotland and Northern Ireland, and whether they could be adapted for England or rolled out UK wide. The Committee acknowledged the potential cost of such monitoring programmes but noted that this was outside the Committee's remit and would sit with the FSA.

1.86 Given the potential impact of climate change on the presence of marine biotoxins in UK waters, it could also prove useful to feed into the climate change impact strategy when considering the effects/impact of global warming on the ecosystem.

1.87 The Committee agreed that there were significant data gaps, especially the occurrence data for the UK therefore making it difficult to conclude on potential risk based on the currently available information.

1.88 However, the COT considered risk ranking the emerging marine biotoxins based on a scoring system, adapting a system that had previously been applied to mycotoxins. This would consist of assigning a numerical score to each emerging toxin for the following categories: toxicity, occurrence in UK waters, human health impact, and monitoring and/or regulation. Toxins exhibiting severe health effects and demonstratable occurrence in UK waters would score high and therefore should be prioritised for monitoring in UK fish and shellfish.

1.89 The Committee have asked the Secretariat to produce a discussion paper providing a risk ranking for each toxin, considering the different weighting of factors that would influence the final score.

1.90 The full 2024 discussion paper can be found at: Advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins | Committee on Toxicity.

1.91 A final discussion paper/statement is expected for 2025.

Deriving a health-based guidance value for antimony to support development of UK Drinking Water Standards

1.92 The UK Health Security Agency (UKHSA) advises the Drinking Water Inspectorate (DWI) on potential health risks from chemicals in drinking water. Post EU exit, the DWI is reviewing the regulatory standards for some chemicals in drinking water, including antimony. UKHSA is seeking advice from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) with respect to an appropriate health-based guidance value (HBGV) for antimony.

1.93 In 2024, the COT considered an initial discussion paper on the study underpinning evaluations by the World Health Organization (WHO, 2003), the US

Agency for Toxic Substances and Disease Registry (ATSDR, 2019) and Health Canada (Health Canada, 2024). The COT will consider further papers in 2025.

Citrinin in the maternal diet

1.94 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 citrinin.

1.95 Citrinin is a mycotoxin produced by several species of fungi of the genera *Aspergillus*, *Penicillium* and *Monascus* and is generally formed after harvest under storage conditions. It occurs mainly in grains but can also occur in other products of plant origin e.g. beans, fruits, fruit and vegetable juices, herbs and spices as well as in spoiled dairy products.

1.96 Citrinin is acutely nephrotoxic in mice and rats, rabbits, pigs and poultry, causing swelling and eventual necrosis of the kidneys. Citrinin also affects liver function but to a lesser extent. Both *in vitro* and *in vivo* studies have provided evidence for reproductive and developmental toxicity of citrinin.

1.97 The potential risk from citrinin in the maternal diet was discussed by the Committee in October 2024. It was concluded that citrinin would not have adverse effects on maternal health at likely levels of exposure. A statement on citrinin will be presented to the COT in 2025.

The potential risks from ergot alkaloids in the maternal diet

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

1.99 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. Bromocriptine is a synthetic ergoline derivate and is used in the treatment of Parkinson’s disease and pituitary tumours.

1.100 Due to their structural similarities to neurotransmitters, EAs have been suggested as agonists or antagonists of noradrenaline, dopamine and serotonin neurotransmitters (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.

1.101 In 2022 the Committee discussed the potential risk from EAs in the maternal diet and concluded that EAs would not have adverse effects on maternal health at the estimated levels of exposure in the UK.

1.102 A second draft statement was presented to the Committee in February 2024. Following the discussions, the Committee requested for additional paragraphs to be added regarding the effects of ergot alkaloids on the immune system and on the overall exposure.

1.103 The statement is expected to be published in 2025.

Ginger in the maternal diet

1.104 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.

1.105 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.

1.106 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 foetus or embryo, possible interactions with medicines and the possible influence on cyclooxygenase (COX) and prostaglandin activity.

1.107 The final statement on ginger in the maternal diet will be published in 2025.

Discussion paper on the effects of Calcidiol supplementation during pregnancy

1.108 As part of the current programme of work on the maternal diet, the Committee considered the exposure to excess calcidiol would pose a risk to maternal health, as part of this review. This follows the previous review of vitamin D published in 2023.

1.109 Calcidiol is a novel source of vitamin D3 which is formed via chemical synthesis from cholestatrienol. Calcidiol is also known as calcidiol monohydrate, 25- hydroxycholecalciferol monohydrate (25(OH)D3 monohydrate), calcifediol or 25- hydroxyvitamin D (25(OH)D), with the latter two being the forms used in supplementation. Calcidiol is a synthetic form of 25(OH)D, which is an inactive precursor to the biologically active form of vitamin D known as 1,25-dihydroxyvitamin D (1,25 (OH)2D).

1.110 In 2024 the ACNFP established a Tolerable Upper Level (TUL) of 40 µg/day for an application submitted for calcidiol monohydrate. A conversion factor of 2.5 was applied to the EFSA TUL of 100 µg/day for vitamin D to calculate the TUL for calcidiol. However, EFSA determined a safe level of intake of 10 µg/day for the same calcidiol monohydrate product; which may have reflected the request from the applicant.

1.111 Exposures to calcidiol from food sources did not exceed the ANCFP TUL of 40 µg/day or the EFSA safe level of intake of 10 µg/day. Combined exposures from food and supplements showed intakes were below the ACNFP TUL but exceeded the EFSA safe level of intake up to 2.1-fold.

1.112 The COT were unable to conclude on an appropriate Health Based Guidance Value (HGBV) for risk characterisation and requested the paper return to the COT with more clarification on how EFSA derived a safe level of intake of 10

µg/day.

1.113 A final COT statement is due to be published in 2025.

Assessment of ocean bound plastic (OBP)

1.114 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.

1.115 Following the FSA and FSS call for evidence between March and October 2022 and the identification of additional suppliers of these materials between November 2022 and January 2024, the Food Contact Materials Joint Expert Group (FCMJEG) have assessed all information provided to the FSA and FSS up until January 2024.

1.116 The final assessment by the FCMJEG on environmental plastic and ocean bound plastic, and confidential supplementary material from the call for evidence was discussed by the COT and overall, the COT was content with the position statement of the FCMJEG. Publication is expected in early 2025.

Risk assessment of T2 and HT2 mycotoxins in food

1.117 The assessment of T-2 and HT-2 mycotoxins in food was initiated following a proposal by the European Commission in 2020 to establish maximum levels for these mycotoxins, which are lower than the indicative levels set under EU Recommendation 2013/165/EU. The FSA requested the COT evaluate the potential risks these toxins pose to UK consumers. This review aimed to support the FSA’s reassessment of mycotoxin limits and inform potential risk management strategies, particularly as T-2 and HT-2 are known to contaminate cereal grains and products, posing possible health risks through dietary exposure.

1.118 At the July 2024 committee meeting, the discussion centred on a scoping paper that presented an initial exposure assessment based on UK dietary habits and occurrence data from both industry submissions and national surveys. This assessment employed data spanning 2008 to 2023, reflecting the inherent variability in mycotoxin levels due to weather conditions and agricultural practices. However, most data represented unprocessed food commodities,

adding uncertainty to the exposure estimates. For example, the lack of consideration of the effect of processing such as dehulling or scouring, would significantly reduce mycotoxin levels thus exposures are likely to be overestimated.

1.119 The approach also relied on consumption data from the National Diet and Nutrition Survey (NDNS), applying high-percentile consumption models across multiple food groups. This methodology assumes an unrealistically high exposure scenario, as it is improbable that a single individual would consistently consume foods at the 97.5th percentile across all categories. These factors, combined with variability in analytical methods over time, resulted in significant uncertainties in the risk assessment.

1.120 During the meeting, the Committee raised questions about the reliability of the data and analytical methods, highlighting the need for validation of industry-supplied occurrence data. The absence of robust data on processed food products and actual consumer consumption patterns further limited the assessment. More targeted surveys and studies, particularly focusing on processed foods, will be crucial for refining exposure estimates. The potential utility of biomonitoring data, such as urinary mycotoxin levels in specific populations, was also noted as a promising avenue for understanding actual exposures.

1.121The review considered health-based guidance values (HBGVs) established by EFSA and JECFA for both acute and chronic exposures. Preliminary findings indicated that while mean exposures were generally below the acute reference dose (ARfD), high-percentile chronic exposures exceeded the tolerable daily intake (TDI) in some population groups. However, these exceedances were uncertain due to the limitations of the exposure model. Consequently, the Committee concluded that it could not definitively characterise the health risks associated with these mycotoxins at this stage.

1.122 The Committee acknowledged the importance of addressing these uncertainties and refining the risk assessment process. Suggestions included improved occurrence data collection, accounting for processing factors, and trend analysis to better understand mycotoxin variability. A refined exposure assessment and risk characterisation, incorporating these elements, is planned for presentation in 2025. This will enable more informed regulatory decisions and public health guidance concerning the safety of T-2 and HT-2 mycotoxins in the UK food supply.

Application to authorise iron enriched yeast as a permitted form of iron which can be voluntarily added to foods for specific groups, food supplements and general foods (Reserved)

1.123 Following a request from the DHSC under the Nutritional Labelling Standards and Composition Group (NLCS) framework, the COT reviewed an Application from Danstar Ferment AG a subsidiary company of Lallemand Inc. to include iron enriched yeast (Saccharomyces cerevisiae) as an optional permitted form of iron which can be added to fortify foods, food supplements and categories in scope of foods for specific groups (FSG) in Great Britain.

1.124 DHSC received a request from Lallemand Bio-Ingredients in November 2022 for iron enriched yeast to be voluntarily permitted as a source of iron in the following Great Britain legislations: Annex II of assimilated Regulation (EC) No 1925/2006, assimilated Regulation (EU) No 609/2013 and Schedule 1 & 2 of The Nutrition (Amendment etc.) (EU Exit) Regulations 2019.

1.125 This item was reserved as the application contains confidential information and is still under review by the COT.

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Other Committee Activities: Joint Expert Groups, Presentations and Workshop 2024

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This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Postdoctoral Fellow presentation

1.126 The FSA and COT have been reviewing New Approach Methodologies (NAMs) to scope the best scientific methodologies available to be used in the risk assessment of chemicals in foods and the environment, and to understand how these can be incorporated and accepted in a regulatory context. NAMs include but are not limited to, high throughput screening and other in vitro assays, omics and in silico computer modelling strategies (e.g. Artificial Intelligence (AI) and machine learning) for the evaluation of hazard and exposure in risk assessment

1.127 In 2021, the FSA started funding a 4-year computational toxicology postdoctoral fellow at the University of Birmingham and a PhD Student (London Interdisciplinary Doctoral Program-LIDo) at King's College London on the use of artificial intelligence in chemical risk assessment.

1.128 The fellow and PhD student have been working alongside other government departments to understand how NAMs will improve indicative levels of safety in chemical risk assessment.

1.129 In addition, these new partnerships have helped with networking, research collaboration, training opportunities and other activities in this area. The Fellowship and studentship also compliment the work set out in the COT FSA UK Roadmap towards using NAMs in chemical risk assessment.

1.130 The Postdoctoral Fellow prepared a yearly review and gave a presentation to the Committee on progress of the two case studies that have been conducted, to date.

1.131 The first case study focused on the plasticiser di-2-ethylhexyl terephthalate (DEHTP) and the main objective was to derive a health-based guidance value HBGV. Concentration-response data obtained from ToxCast, via the Chemicals

Dashboard (US EPA), was used.

1.132 The second case study was to establish HBGV for a perfluorinated substance, perfluorooctanoic acid (PFOA) using a workflow utilising multiple NAM approaches. The NAMs used included: NAMs in relation to the type of testing platform using *in vitro* hepatic microtissues; NAMs in relation to the type of data/read-outs using transcriptomics data, which provide an untargeted measurement of extensive gene expression; NAMs in relation to data analysis using Physiologically Based Pharmacokinetic (PBPK) modelling.

1.133 The Fellow also presented some preliminary work on the third case study, which is on tropane alkaloids.

1.134 The COT Members were impressed with the progress to date and gave feedback to the Fellow.

Marine biotoxins – Presentation on occurrence and exposure to pinnatoxin (data reserved)

1.135 The FSA is considering the current advice and monitoring programme for marine biotoxins and whether there is a need to update or change existing legislative standards.

1.136 As pinnatoxins (PnTX) are not currently regulated in England or Wales, the views of the COT were sought on whether PnTX would pose a risk to UK consumers. Therefore, in July 2023, the information and data on the risks associated with PnTX in shellfish was discussed. At the meeting the Committee concluded that due to the lack of toxicological and occurrence data it was currently not possible to determine the extent of any public health risk Occurrence data on PnTX would be useful to help fill some data gaps, including whether the UK population would be exposed to PnTX from shellfish consumption.

1.137 The recent availability of new analytical standards has allowed PnTX to be monitored in UK shellfish. Liquid chromatography–mass spectrometry (LCMS) monitoring data for PnTX-G were available to the FSA by the Agri-Food and Biosciences Institute (AFBI) in Northern Ireland and by Food Standards Scotland (FSS) and these data were discussed by the Committee in May 2024. The data are currently confidential as they are awaiting publication by the respective institutes.

1.138 The available occurrence data also allowed for some preliminary PnTX exposure estimates to be carried out for UK consumers, using EFSA's estimated shellfish portion size of 400 g (excluding shells). The Committee noted that the exposures estimated by EFSA using this portion size assumed that a consumer would eat 400 g of a single shellfish type and questioned how likely this would be for some shellfish species. It was noted that cultural differences could also lead to variation in the amounts and types of shellfish consumed. Data from the National Diet and Nutrition Survey (NDNS) showed that in the UK shellfish is consumed in lower quantities than EFSA's estimated 400 g. Therefore, some of the exposure estimates presented may be overestimations of UK exposures.

1.139 The Committee questioned whether PnTX-G was known to co-occur with other marine biotoxins, however, there did not appear to be any reports of regular co- occurrence. It was noted that the different feeding habits of shellfish could potentially influence toxin levels.

1.140 With respect to reducing the levels of PnTXs in shellfish, there were no data available on the efficacy of depuration tanks and as PnTXs are lipophilic biotoxins this would make extraction into clean water less likely. The toxins are relatively heat stable but processes such as cooking or dehydration of the meat during steaming and canning could lead to different levels of PnTX in the final product compared to the raw shellfish.

1.141 Overall, the Committee thought the information presented was useful but reiterated that there were significant data gaps on PnTX, especially regarding its toxicity.

New Approach Methodologies (NAMs) in regulatory decisions for chemical safety presentation and review

1.142 Dr Letizia Carramusa from the Yordas Group presented the results of a FSA funded a literature review on New Approach Methodologies (NAMs) to Support Regulatory Decisions for Chemical Safety to the Committee.

1.143 It was explained that the he objectives of the project were: to collate, review and categorise the most up-to-date scientific literature for the UK's own evaluation of NAMs in the field of chemical risk assessment; to assess the regulatory readiness of NAMs and the degree to which these technologies have been successfully integrated into regulatory frameworks; to gather and

summarise expert opinions on the gaps that hinder the further adoption of New Approach Methodologies (NAMs) in the regulatory process.

1.144 The literature search and methodology were outlined. Publications were retrieved from 2014 onwards to prioritise the most recent literature and ensure the relevance of the studies. NAMs published more than a decade ago were excluded from the literature review as they were considered to be either well-established within the regulatory framework or have been superseded by improved methods, meaning that research into them had halted.

1.145 Global stakeholder interviews were then undertaken. Topics and key findings from the interviews included: views on the term “NAM”; research investment focus; how NAMs integrate with traditional hazard assessment and when they will become the primary approach, either to supplement existing approaches, or to completely replace animal testing; regulatory application, especially for food; how are NAMs best used for regulatory activities and how food regulations integrate NAMs; the barriers to integration of NAMs and how they can be overcome; and the types of substance or material where NAMs can play a role in the near future. It was concluded that no single NAM can replace animal studies entirely and the FSA should explore the adoption of concepts like "endorsement" or "qualification" used in the US for tier-one decisions.

1.146 Members complimented the Yordas Group for a comprehensive, interesting and thorough review.

1.147 The Committee noted that physiologically based pharmacokinetic (PBPK) modelling was more commonly used than described in the report. Specifically, JECFA reports on contaminants regularly utilized PBPK modelling, emphasizing its critical role in determining Tolerable Daily Intakes (TDIs).

1.148 The Committee discussed the report with respect to recommendations related to qualification and validation of NAMs. There is a need for mechanisms to qualify, validate, and generate confidence in the suitability of the novel approaches and there are challenges in securing funding for this purpose. This, and previous, reports have noted funding in the area of NAMs predominantly supports innovation rather than translation of research. The lack of funding avenues for translation through UK Research and Innovation (UKRI) was noted and the need for alternative funding solutions stressed. The distinction between scientific validation and qualification for regulatory application was noted, with more focus on the latter being noted. There is ongoing work in the USA and Asia on this area, and collaboration within the Organisation for Economic Co-operation

and Development (OECD) framework is recommended.

1.149 Members noted unavoidable bias in retrospective evaluations of the adequacy of conventional animal toxicity studies, particularly in pharmaceuticals since the drugs evaluated in human studies were a selective subset as many did not make it through the pre-clinical development process, and NAMs were likely used as part of that process. As an example of this, pre-clinical testing was very effective in identifying direct hepatotoxins before market release, and those drugs that were withdrawn for liver toxicity post-marketing almost always involved idiosyncratic reactions, which were not detectable in animal studies or even clinical trials.

1.150 It was noted that genetic toxicology, methods such as the Ames test had been deemed “Out of Scope” prior to the report being written, as they were already well established.

1.151 The importance of understanding adverse outcome pathways (AOPs) in making more informed safety assessments was noted, despite their inherent uncertainties. It was important to strengthen AOPs to allow meaningful risk assessment, and there should be focus on working within the OECD framework.

1.152 The Committee suggested that they along with other advisory groups should highlight gaps in evidence, particularly where additional data from the use of NAMs could improve confidence in decision-making. Furthermore, the Committee highlighted the need to champion the use of the best science in regulatory risk assessment, including the use of NAMs as appropriate, which would require stimulating engagement from developers, especially in the context of limited funding.

FSA Research Programme Presentation

1.153 A presentation was given to Members to update them on the updated structure of the FSA research programme and provide a brief overview on the roles and responsibilities of individuals and groups involved in the commissioning and delivery of the research programme.

1.154 The Research Evidence Programme (REP) most closely aligned to the work of the COT is the Chemical, Radiological and Food Hypersensitivity REP. The external research projects currently being delivered within this programme and of interest to the Committee are:

- Advancing in silico Methods of Assessing Toxicological Risk (Fellowship).
- TOX-AI: Digitalising Toxicological Databases using artificial intelligence and in silico tools for food safety (Studentship).
- Multi-allergen analysis using multiplex PCR, include case study for mustard allergen detection (L&S).
- Projects due to be commissioned in early 2025 are: Determination of the bioavailability of cyanogenic glycosides on consumption.
- Literature review of nitrates and nitrites as food additives.

1.155 Updates on the status of the Chemical, Radiological and Hypersensitivity REP will be provided to the Committee periodically and the outputs from some projects may be brought to the Committee for peer review.

Evolving Our Assessment & Future Guiding Principles Workshop Report

1.156 The COT held a workshop in May 2023 to start work on updating their guidance on toxicity testing and its supporting principles. The overall objective of the workshop was to discuss how the Committee moves forward in a new era of risk assessment.

1.157 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 (NAMs), exploring hazard vs risk and weight of evidence. The four sessions were: Where are we at; What we need to improve; How to achieve; and Looking to the future - moving forward.

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

1.159 The workshop report is now available: (DOI: https://doi.org/10.46756/sci.fsa.qpo647)

Gut reactions: xenobiotics and the microbiome workshop

1.160 The COT held a workshop in October 2024 in London, United Kingdom on xenobiotics and the microbiome. The workshop included themed sessions

consisting of short flash presentations followed by roundtable discussions. There was attendance from multiple stakeholders including academia, government and industry.

1.161 The workshop set out to explore the complex current state of the science of the microbiome pathophysiology and the possible impact of xenobiotics on host-microbiome interactions and vice versa, including possible mechanisms and health implications, with a particular emphasis on the gut microbiome and dietary exposure.

1.162 In addition, the aim was to enable new insights, review the science, initiate discussions to determine where the data gaps are in research, what effects are of concern, and how might xenobiotics be evaluated practically for such effects in the future.

1.163 The four sessions were: Interactions of the host microbiome system; Gut microbiome and xenobiotics; Assessing the impact on the microbiome; Possible ways to evaluate in the short to medium term and microbiome interventions for maintaining health and treating disease and Future Directions.

1.164 The finalised report will be published in due course.

Hazardous Substances Advisory Committee (HSAC) discussion on the effects of flame retardants on human health: developing a work programme

1.165 The COT was invited by Defra to comment, along with the Hazardous Substances Advisory Committee (HSAC), on developing a work programme on flame retardants and using information on human risk to aid prioritising the compounds or groups of compounds for review.

1.166 The COT provided a number of comments with respect to availability of evidence on effectiveness, toxicity and exposure data to allow comparisons across different flame retardants. Grouping and read-across were suggested as a means to aid prioritisation. A number of aspects related to sources and routes of chemical exposure were noted for consider.

1.167 Defra thanked the COT for its input which it would take forward with the Secretariat and other partners.

Horizon Scanning

1.168 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.

1.169 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 continuing work on new approach methodologies is an example of this.

1.170 A number of topics were suggested for potential consideration as either individual papers or as a future COT workshop; these included potential regulatory changes to chemicals in the environment, the microbiome (including the effects of chemicals other than antimicrobials), the presence of novel contaminants in the oceans that could enter the food chain, vegan/vegetarian foods and their ultra- processed replacements (where these were in the COT remit), non-EATS (estrogen, androgen, thyroid and steroidogenesis) mechanisms for endocrine disruption, and obesogens.

1.71 Horizon scanning techniques were discussed more generally, with a view to considering what would be the most useful approach for the Committee to take and it was agreed to review this at a future date.

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Joint Expert Groups 2024

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FCMJEG

1.172 The COT considered risk assessments prepared by the Joint Expert Group on Food Contact Materials (FCMJEG) regarding the following regulated product applications:

- on the safety of the use of phosphoric acid, mixed esters with 2-hydroxyethyl methacrylate (HEMAP) as a component in the manufacture of kitchen countertops and sinks. This assessment was for HEMAP only, and not the final reaction mixture used in the manufacture. The final assessment was published in July 2024.
- On the safety of the use of Calcium tert-butylphosphonate as an additive used in the manufacture of plastic materials and articles intended to come into contact with food. The final assessment is expected to be published early 2025.

On the safety of the recycling processes:

- Document on the evaluation of the recycled poly(ethylene terephthalate) decontamination process operated by LINPAC for use in the manufacture of articles in contact with food.
- on the recycled poly(ethylene terephthalate) decontamination process operated by Wellman Neufchâteau Recyclage (subsidiary of Indorama Ventures) for use in the manufacture of materials and articles in contact with food.

- on the evaluation of the safety of the process for the recycling of post-consumer poly(ethylene terephthalate) into food contact materials.

1.173 These items are currently reserved as the Committee Advice Papers are not currently published.

Committee Advice Document on the safety of 2-hydroxyethyl methacrylate phosphate as a monomer for use in the manufacture of plastic food contact materials and articles

1.174 The COT considered a Committee Advice Document (CAD) prepared by the Joint Expert Group on Food Contact Materials (FCMJEG) regarding an application for 2-hydroxyethyl methacrylate phosphate (HEMA) as a monomer in a commercial product for use in the manufacture of kitchen countertops and sinks that are intended for contact with all types of food (RP1190).

1.175 All components of the commercial product are listed in assimilated Regulation EU No. 10/2011 on plastic materials and articles intended to come into contact with food. The application and the following assessment are for HEMA only, not the commercial product.

1.176 Satisfactory information regarding the identity of substance, physical and chemical properties, intended application of substance, data on migration of substance and toxicological data were submitted.

1.177 The toxicological information that formed the basis of the risk assessment was a bacterial reverse mutation test (Ames test), which was conducted in accordance with OECD No. 471, and an *in vitro* mammalian micronucleus test, in accordance with OECD No.487, on the commercial product. Results of the Ames test and *in vitro* micronucleus (MN) test showed no mutagenic, clastogenic or aneugenic potential for the commercial product under the experimental conditions described.

1.178 The specific migration of the sum of HEMAP plus its phosphate and diphosphate esters under the worst foreseeable conditions of use was 24.8 µg/6 dm2 (assumed that this is equivalent to contact with 1 kg food).Taking into account that the specific migration of the sum of HEMA plus its phosphate and diphosphate esters is not expected to exceed 50 µg/kg food and the negative

results in the Ames and *in vitro* micronucleus tests, the FCMJEG proposed a specific migration limit (SML) of 0.05 mg/kg food for HEMA.

1.179 Overall, the COT considered the information and data provided in the FCMJEG CAD sufficient to conclude that there was no concern for a risk to human health from the use of HEMA in the specific final commercial mixture in the manufacture of kitchen countertops and sinks up to a maximum percentage in formulation of 0.35%.

1.180 The full FCM JEG CAD: FCMJEG Applications | Committee on Toxicity

Committee Advice Document on Calcium *tert*-butylphosphonate as an additive for use in the manufacture of plastic food contact materials and articles

1.181 The COT considered a Committee Advice Document (CAD) prepared by the Joint Expert Group on Food Contact Materials (FCMJEG) regarding an application for calcium *tert*- butylphosphonate as an additive used in the manufacture of plastic materials and articles intended to come into contact with food (RP1702).

1.182 The information on the identity of the substance, the physical and chemical properties and intended application were considered satisfactory.

1.183 Results from the overall and specific migration tests demonstrated the migration of calcium *tert*-butylphosphonate to be close to or below the limit of detection (up to 10 µg/kg).

1.184 Owing to the low migration of calcium tert-butylphosphonate as an additive under the conditions of use specified in the application, limited toxicology testing was required. Results of the Ames test and *in vitro* micronucleus (MN) test showed no mutagenic, clastogenic or aneugenic potential for the commercial product under the experimental conditions described.

1.185 The available toxicology data showed calcium *tert*-butylphosphonate to be negative in the *in vitro* Ames test and *in vitro* micronucleus (MN) assay and therefore unlikely to be of concern for potential genotoxicity, especially based on low exposure to humans.

1.186 Overall, there is unlikely to be a genotoxicity risk to health from the use of calcium *tert*-butylphosphonate as an additive in the manufacture of plastic materials and articles intended to be in food contact with food. However, a potential health risk to infants <16 weeks via feeding bottles could not be assessed because infants <16 weeks are expected to be exclusively fed on breast milk and/or infant formula. There is a lack of data including exposure data for these circumstances having regard to the sensitive nature of the age group.

1.187 Calcium *tert*-butylphosphonate was therefore recommended for approval for use as an additive as outlined in the application and specified above.

1.188 The full FCM JEG CAD is due to be published shortly: FCMJEG Applications | Committee on Toxicity.

AEJEG assessments

1.189 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:

- Committee Advice on the safety of the Application to modify the conditions of use of E401 (sodium alginate) for use as a surface treatment in entire fruits and vegetables.
- Extension of use of nisin (E 234) to a new food category “egg analogues”
- Application for a change in the steviol glycoside specification in the United Kingdom to include a new manufacturing method for Steviol Glycosides including Rebaudioside D.
- Authorisation of new food additive substance Glycolipids.

1.190 All items are currently reserved as they cover draft AEJEG Committee Advice Papers not currently published.

1.191 AEJEG Committee Advice Papers will be published in 2025.

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Working Groups 2024

In this guide

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Joint ACNFP/COT Working Group on Cannabidiol (CBD)

1.192 A joint Subgroup of the Advisory Committee on Novel Foods and Processes (ACNFP) and COT was formed to address a series of questions in relation to the safety of Cannabidiol (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.

1.193 The group has now reviewed the group A ‘pure’ compounds and established an provisional 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.

1.194 The group is continuing to review the different purity groups of CBD products including considering the less pure group of B compounds and a lower proportion of CBD including “Group C products” which are products that contain between 2.5 and 67% CBD.

Plant-based drinks

1.195 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.

1.196 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. The Working Group started work in December 2021 with a draft report being published for peer review in 2024. It is hoped that the final report will be published in 2025.

PFAS Subgroup

1.197 The COT subgroup on per- and poly-fluoroalkyl substances (PFAS) was set up 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.

1.198 The subgroup held one meeting in 2024, which considered the evidence on thyroid effects and liver effects of PFAS. Further papers on other endpoints will be considered in 2025 and beyond.

Titanium dioxide (TiO2) subgroup

1.199 The TiO2 subgroup had been set up to develop and simultaneously sign off on the text of the statement. The group had three meetings at the start of 2024 and due to the work of the subgroup the statement was signed off by the Committee at the May meeting. An executive summary and the full statement were published in 2024 along with a lay summary of the statement.

Smoke Flavourings Working Group

1.200 Smoke Flavourings Working Group (SFWG) continue their assessment and started phase 3 assessment of these flavourings (conclusions on genotoxicity, assessment of general toxicity and Extended One Generation Reproductive Toxicity (EOGRT)).

1.201 The SFWG have also discussed a weight of evidence update paper to be used in their assessments.

ORO and ABB decisions

1.202 FSA Scientific Advisory Committees (SACs) and Joint Expert Groups (JEGs) that support the regulated products service, a ways-of-working paper (as TOX-2024- 10 for COT) was presented to Members. This explained two additional ways in which the FSA would be assessing regulated products. These updated ways of working were 1) the use of other regulator's opinions by the FSA (ORO) and 2) the use of an 'abbreviated process' (ABB) for safety assessments. These processes involve internal assurance via an FSA decision panel that is chaired by a senior leader from the Risk Assessment Unit with regular oversight from the FSA Chief Scientific Advisor. Applications progressing through these assessment routes would not routinely be considered by SACs, but a summary of the applications would be periodically presented to the COT for information.

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2024 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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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 (Up until May 2024)

Principal Science Advisor at Syngenta (part time).

Ms Jane Case (Up until May 2024)

Lay Member. Trowers & Hamlins LLP

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

Professor of Toxicology and Dean of Applied Sciences at Edinburgh Napier University.

Dr Sarah Judge BSc, PhD (Up until May 2024)

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 (Up until May 2024)

Lay Member.

Dr Michael Routledge

Associate Professor of Medical Education at University of Leicester.

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 (Up until May 2024)

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

Professor Maged Younes

Independent expert on toxicology and biochemical pharmacology.

Professor Peter Barlow

Chair of Immunology & Infection, and Head of the Centre for Biomedicine & Global Health within the School of Applied Sciences at Edinburgh Napier University.

Dr Steven Enoch

Reader in Computational Toxicology, Liverpool John Moores University.

Dr Chris Morris (from March 2024 onwards)

Senior Lecturer at Newcastle University

Dr Meera Cush (from March 2024 onwards)

Senior Managing Consultant in Regulatory Toxicology at Ramboll UK Limited

Mr Gordon Burton (from March 2024 onwards)

Public Interest Representative (Lay Member)

Mr Nick Richardson (from March 2024 onwards)

Public Interest Representative (Lay Member) Defence Science and Technology Laboratory (Dstl)

Dr Alison Yeates (from March 2024 onwards)

Lecturer in Biomedical Science within the School of Biomedical Sciences at Ulster University.

Dr Andreas Kolb (from March 2024 onwards)

Senior Research Fellow

Secretariat

Ms Catherine Mulholland BSc (Hons), ERT - **Scientific Secretary**

Ms Britta Gadeberg BSc (Hons) MSc ERT **Scientific Secretary – UK HSA**

Dr David Gott BSc (Hons) PhD (until May 2024)

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 (until October 2024)

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 Orphanos

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 Rachel Kerr BSc PhD

Ms Polly Bevan BSc MSc

Mr James Metcalfe BSc

Ms Alba Ureña Rusillo BSc MSc

Sub-groups active in 2024

Sub-groups active in 2024	Current COT Members serving
Joint SACN-COT Working Group on plant-based drinks.	Professor Alan Boobis Professor Gunter Kuhnle
Joint COT- ACNFP Working Group on Cannabidiol (CBD)	Professor Alan Boobis Dr Stella Cochrane Dr James Coulson Professor Gary Hutchison Professor Gunter Kuhnle Professor Shirley Price Dr Mac Provan Dr Simon Wilkinson

PFAS Working Group	Professor Shirley Price (Chair) Dr Phil Botham Dr James Coulson Dr Steve Enoch Professor Thorhallur Ingi Halldórsson Professor Gunter Kuhnle Professor Matthew Wright Dr Peter Barlow (ad hoc) Dr Stella Cochrane (ad hoc) Professor Gary Hutchison (ad hoc) Dr Sarah Judge (ad hoc)
Titanium Dioxide Working Group	Dr Peter Barlow Dr Phil Botham Professor Gary Hutchison Dr David Lovell Dr Cheryl Scudamore