Committee on
Toxicity

Committee on
Carcinogenicity

Committee on
Mutagenicity

Annual Report 2021

Committee on Toxicity of Chemicals in Food, Consumer, Products and the Environment Annual Report 2021

Contents

About the Committees

This is the 30th 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. Annex 6 is an alphabetical index to subjects and substances considered in previous reports. Previous publications of the Committees are listed at Annex 7.

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:

COT

COC

COM

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

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

Preface

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COT evaluations

The potential risk(s) of combined exposure to mycotoxins

1.1 The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has identified the potential risk(s) from combined exposure to mycotoxins as a possible concern during their review of mycotoxins in the diet of infants and young children.

1.2 Mycotoxins are secondary metabolites produced by plant fungi under particular climate and biological conditions, and can cause adverse health effects in both humans and animals. Those of greatest concern to human health are produced by several groups of filamentous fungi, namely *Aspergillus*, *Fusarium* and *Penicillium* species.

1.3 Mycotoxins are stable, low-molecular weight chemicals and are often not affected by food processing (*e.g.* cooking).

1.4 Cereals (*e.g.* wheat, oats, rice, corn (maize), barley, sorghum, rye, and millet) are often the crops most severely affected; however, some nuts, fruits and spices can also be affected.

1.5 Advances in analytical techniques have allowed the simultaneous detection and quantification of multiple mycotoxins in both food and animal feed.

1.6 Climate change could have a significant impact on mycotoxin production. Changes in the climate are expected to affect levels of rainfall, humidity, temperature *etc.,* which in turn, influence mycotoxin production, which varies for each individual pathogen species and/or strain.

1.7 Current government and industry regulations are usually based on assessing the risks from individual mycotoxins and, at most, group metabolites with the parent compound, but take no account of the varied dynamics and potential interactions between co-occurring groups of mycotoxins.

1.8 In light of this, new combinations of factors (mycotoxins/host plants and geographical location) will need to be considered when assessing the potential risk(s) from dietary exposure to mycotoxins.

1.9 Based on the available information, the COT was unable to complete a risk assessment on the potential risk(s) from combined exposure to mycotoxins for several reasons. These include:

- A lack of harmonisation of approaches/methodologies and data analysis/modelling for toxicological investigations.

- The underlying mechanisms of interactions between individual mycotoxins in different combination(s) have yet to be fully understood.

- There is little information on the potential toxic effect(s) of mycotoxin mixtures on the gut microbiota.

1.10 Considerations for possible co-exposures from breastmilk and weaning foods also need to be considered for infants and young children.

1.11 Co-occurrence data in food is scarce, and the available methods for multi-mycotoxin detection in food samples are still not harmonised for use in a regulatory setting. In addition to this the following need further consideration for a robust exposure assessment:

- The management data for which the true values are below the limit of detection and could not be accurately determined.

- The consistent and well-defined use of probabilistic models and methodologies for multi-biomarker studies that estimate levels of exposure to multiple mycotoxins in biological samples (*e.g.* urine).

1.12 The COT noted that there was a lack of UK specific data, particularly in biomonitoring; however, there were a number of studies ongoing and additional information will be available in the future. The Public Health England Secretariat informed COT Members that the UK will not be collecting new data for mycotoxins under the Human Biomonitoring for the European Union Initiative; however, in the future, more data could be obtained through Health Protection Research Units. The results of such research would be of potential value in the risk assessment of co-exposures to mycotoxins.

1.13 COT Members recommended that as a pragmatic first step, a review should be carried out of the mycotoxins that appeared to show a common effect on protein synthesis (*i.e.,* DNA or RNA synthesis), assuming dose additivity, and that frequently co-occur in food commodities – an exposure estimate could be performed and the estimates compared with the recommended health-based guidance values to calculate the Margin of Exposure or the Hazard Index utilised, to determine whether there is any potential concern from co-exposure to these mycotoxins in UK consumers.

1.14 Depending on the outcome of this screening risk assessment, research may be needed on those mycotoxins affecting ribosomal protein synthesis, to determine whether they do in fact exhibit dose additivity in their effects, to help develop a reliable basis for their cumulative risk assessment.

The full COT statement, including references, can be found on the COT website: Statement on the potential risk(s) of combined exposure to mycotoxins 2021.

Overarching statement on the potential risks from exposure to microplastics

1.15 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. Upon review of the literature, it was decided that nanoplastics should also be included. An initial scoping paper was presented to the COT in October 2019 (TOX/2019/62). Since then, the topic and additional information has been discussed several times by COT with the final substantive discussion in December 2020.

1.15 The purpose of this overarching statement is to bring together these discussions, summarise the COT conclusions reached to date and provide a high-level overview of the current state of knowledge, data gaps and research needs with regards to this topic.

1.16 Future sub-statements, which will consider in detail the potential toxicological risks of exposure to microplastics *via* the oral and inhalation routes, are intended to provide supplementary material for this overarching statement. The Committee will review the potential risks from oral exposure of microplastics (resulting from their presence in food and bottled drinks). A review of the potential risks of microplastics *via* the inhalation route will be produced jointly with the Committee of Medical Effects of Air Pollutants (COMEAP) Secretariat at Public Health England. The need for additional reviews of other significant routes of exposure will also be considered.

1.17 Micro- and nanoplastics are widespread. They are either intentionally added to products or occur as a result of plastics being fragmented down into smaller sizes by natural processes such as wear, weathering and corrosion. There is no internationally agreed definition of what a microplastic is, however, the most widely used size range is 0.1 to 5,000 µm. Plastic particles that are smaller than the lower range are considered nanoplastics (*i.e.* 1 nm to 0.1 µm).

1.18 The COT noted that there is little data on the effects of microplastics on mammals (including humans) whether taken in orally or *via* inhalation. Some microplastics are excreted from the body (~>90%) but small amounts of others may remain in the gut (gastrointestinal tract; GIT) or move from the GIT into organs or tissues (*via* endocytosis by M cells and paracellular persorption). No epidemiological or controlled dose studies that evaluated the effects of orally ingested microplastics in humans were identified. There is a similar lack of information on inhaled microplastics.

1.15 As such, the COT concludes that based on the available data, it is not yet possible to perform a complete assessment for the potential risks from exposure to micro and nanoplastics *via* the oral and inhalation routes. However, the Committee concurs with the conclusions reached by other authoritative bodies (EFSA, 2016; WHO, 2019; SAPEA, 2019; SAM, 2020; ECCC and HC, 2020) that further research

is required to better identify target tissues, threshold doses, and the toxic mode(s) of action for any toxicity observed.

1.17 The COT concluded that the literature data on exposure to particles from tyre wear would need separate consideration from microplastic exposure from food, since the particles were chemically quite different (in their polymeric nature). Risk assessment of such material was considered potentially outside the scope of the current exercise.

1.18 The most significant data gaps are the lack of appropriate and harmonised analytical methods for the detection of micro- and nanoplastics (together with suitable reference standards), as well as information on their toxicokinetic and toxicity profiles in/relevant to humans.

1.19 The COT highlighted that additional information will be needed from all exposure sources, which include indoor and outdoor air, dust and soil, before a risk assessment can be completed. The presence of MPs in food and water needs to be put into perspective with other sources of MPs such as atmospheric fallout.

1.20 Comprehensive assessment of microplastics and contaminant concentrations in different foods and the impact of cooking (on the release of and subsequent bioavailability of contaminants/leachates) need to be further investigated to better understand the implications for human health.

1.21 Current studies typically focus only on one type of particle/tissue interaction. As such, further research is necessary to explore the effects of the range of particle types in different tissues *in silico, in vitro* and *in vivo*. The range of particle types studied should also take account of emerging/novel plastic-based materials such as bioplastics.

The full COT statement, including references, can be found on the COT website: Microplastics Overarching Statement 2021.Page Break

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

1.22 The purpose of this sub-statement is to provide supplementary material to the overarching statement (COT Statement 2021/02) and to consider in detail the potential toxicological risks of exposure from microplastics ingested *via* the oral route (*i.e.* resulting from the presence of microplastics in food, drinking water and bottled drinks).

1.23 The COT noted that there are limited data regarding the toxicokinetic fate of orally ingested microplastics in mammalian species, and that microplastic particles can either translocate from the gastrointestinal tract (GIT) into organs or tissues (*via* endocytosis by M cells and paracellular persorption), and/or be excreted. The extent to which retention in the mammalian GIT tract is of concern, if at all, is not yet clear.

No epidemiological or controlled dose studies in which the effects of orally ingested microplastics in humans have been evaluated were identified.

1.24 As such, the COT concludes that based on the available data, it is not yet possible to perform a complete assessment for the potential risks from exposure to micro and nanoplastics to humans *via* the oral route. It should be noted that the COT's conclusions are consistent with those reached by other authoritative bodies, as described in the COT overarching statement on the potential risks from exposure to microplastics; COT Statement 2021/02; please refer to paragraphs 101-129).

1.25 The COT previously considered the extent to which exposure to tyre wear (a source of synthetic polymeric material) might contribute to the total burden of adverse effects of nano- and microplastics (NMPs) in humans (Annex B of TOX/2020/15). The COT concluded, however, that the literature data on exposure to particles from tyre wear would need separate consideration from microplastic exposure from food, since the particles were chemically quite different in their polymeric nature. Risk assessment of such material was considered to be outside the scope of the current exercise.

1.26 The most significant data gaps are the lack of appropriate and harmonised analytical methods for the detection and characterisation of micro- and nanoplastics (together with suitable reference standards), as well as information on their toxicokinetic and toxicity profiles in/relevant for humans.

1.27 The COT highlighted that additional information will be needed on all exposure sources, which include indoor and outdoor air, dust and soil before a holistic risk assessment can be completed. The presence of MPs in (sea)food and water needs to be put into perspective with other sources of MPs such as atmospheric fallout.

1.28 Comprehensive assessment of microplastics and contaminant concentrations in different foods and the impact of cooking on the desorption and subsequent bioavailability of contaminants/leachates, need to be further investigated to better understand the implications for human health.

1.29 Current studies typically focus on only one type of particle/tissue interaction, as such, further research is necessary to explore the effects of the range of particle types in different tissues *in vitro* and/or *in vivo*. These range of particle types should also take account of emerging/novel plastic-based materials such as bioplastics.

The full COT sub-statement can be found on the COT website: Sub-statement on the potential risk(s) from exposure to microplastics: Oral route 2021.

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Consumption of plant-based drinks in children aged 6 months to 5 years of age.

Introduction

1.30 The Department of Health and Social Care (DHSC), Public Health England (PHE) and the Food Standards Agency (FSA) are receiving an increasing number of enquiries regarding the use of plant-based drinks in the diets of infants and young children. Therefore, the COT was asked to consider the potential risks posed by soya, almond and oat drinks consumed in the diets of these age groups.

1.31 The UK government advises that first infant formula (which is usually based on cows' milk) is the only suitable alternative to breast milk in the first 12 months of a baby's life. Whole cows' milk can be given as a main drink from the age of 1 year. From this age, unsweetened calcium-fortified plant-based drinks, such as soya, almond and oat drinks can also be given to children, as part of a healthy, balanced diet.

1.32 The main challenge in the assessment of the safety of these drinks is the lack of information regarding dietary intakes for infants and young children following dairy-free or plant-based diets.

1.33 Organisations providing recommendations for ensuring a balanced diet for vegan children under 5 were used to identify appropriate portion sizes and consumption frequency to develop representative intake scenarios for children following dairy-free or plant-based diets. These were then used to calculate daily intake figures for different age groups in order to calculate exposure to the chemicals of concern in the different drinks.

1.34 Although the exposure estimates made the best use of the available data, there was a high degree of uncertainty with regards to actual intakes. This was because these figures were based on recommendations to ensure that dietary requirements for infants and children of these ages were met. Actual intakes may be different.

1.35 The Committee agreed to use the previously-adopted approach of assuming that a child's consumption was exclusively of a single plant-based drink as it is possible that young children may develop a preference for one drink. This was regarded as the most cautious approach because it assumes the highest intakes.

1.36 The need for real-world consumption information for people following plant-based diets in all age groups was highlighted by the Committee, as the popularity of these diets is increasing and information on realistic dietary intakes would help inform future risk assessments.

Soya

1.37 Soya drinks are a popular alternative to dairy products and their use is becoming more widespread. Soya products contain phytoestrogens (in the form of isoflavones). Concerns about adverse effects from isoflavones in the diet of infants and young children relate principally to their ability to mimic the female hormone, oestrogen, and therefore their potential impact on development and reproduction.

1.38 The safety of phytoestrogens was considered by the COT in 2003 and 2013. In 2003, the Scientific Advisory Committee on Nutrition (SACN) considered the COT outputs and concluded that there was no scientific basis for changing the current government advice – namely, that there is no substantive medical need for, nor health benefit arising from the use of soya-based infant formula, and that it should be used only in exceptional circumstances to ensure adequate nutrition, such as for babies who have cows' milk allergy. In 2013 this was reconfirmed by the COT. Currently, soya formula should be used only if it has been recommended or prescribed by a health visitor or GP.

1.39 For this evaluation, the Committee reviewed data published since the 2013 evaluation. The Committee concluded that new animal studies did not add significantly to the overall database.

1.40 As with previous evaluations, although there was some indication of possible adverse effects in human studies, it was not possible to determine from the available data, whether sensitivity to phytoestrogens varies among different age groups.

1.41 The Committee concluded that the intakes of phytoestrogens from consumption of soya drinks in children aged 6 months to five years was no greater than the estimated maximum intake by infants aged 0 – 6 months consuming soya formula where medically necessary (see paragraph 9 above). This maximum level of phytoestrogen intake was estimated to be 9.5 mg/kg bw per day.

1.42 The Committee agreed that, based on the available information, exposure to phytoestrogens from other soya-based products in the diets of children aged 6 months to 5 years of age was lower than that from soya drinks, and therefore of less concern. It was, however, noted that when exposure to phytoestrogens from all sources of soya in the diet was considered, the exposure came much closer to the maximum level of 9.5 mg/kg bw per day.

1.43 Members agreed that, in addition to potential toxicological concerns, consideration of nutritional issues would also be required to assess whether it was necessary to issue additional advice on the consumption of soya-based drinks in children aged 6 months to 5 years of age.

Oats

1.44 Oat drinks can be given to children following plant based or dairy- free diets, as an alternative to cows' milk. Oats can be contaminated with mycotoxins, notably the trichothecene mycotoxins T-2 and HT-2, deoxynivalenol (DON), and Ochratoxin

A (OTA). Mycotoxins are naturally occurring toxins produced by certain moulds. As such, they are unavoidable contaminants in certain foods, like oats. International standards are in place to limit exposures to mycotoxins to the lowest possible levels. The COT evaluated the available data and considered the estimated exposures to the above contaminants.

T2 and HT-2

1.45 The European Food Safety Authority (EFSA) considered the safety of T-2 and HT-2 in 2017. Health-based guidance values were established for emetic effects (causing vomiting) following acute (short term or single) exposure, and for immune- and hepatotoxicity effects (toxic effects on the liver) following long-term exposure. After reviewing UK intake data, COT concluded that in terms of acute exposure to the sum of HT-2 and T-2, consumption of a large quantity of oat drink (minimum of 5.4L/ day) was required to exceed the Acute Reference Doses (ARfD). Thus, acute exposure to HT-2 & T-2 from the consumption of oat drink was considered to be of low risk.

1.46 Generally, all long term exposures for T-2, HT-2 were below the respective TDI, with the exception of minor exceedances observed in children aged 1-2 years old for T-2 and HT-2. The assessment of total exposure from oat drinks combined with the general diet was considered conservative (i.e. high compared with likely reality) and as the exceedances were minor and transient in nature, it was concluded that there would be no chronic health effects in respect to T-2 and HT-2.

DON

1.47 For DON, a group Tolerable Daily Intake (TDI) was established for the sum of DON, and its related compounds, 3-Ac-DON, 15-Ac-DON and DON-3-glucoside based on animal studies in which body weight gain was reduced. Vomiting was identified as the critical effect following acute exposure in humans.

1.48 COT concluded that in terms of acute exposure to DON, consumption of a large quantity of oat drink (minimum 28L/d) was required to exceed the Acute Reference Dose (ARfD). Thus, acute exposure to DON was considered to be of low risk.

1.49 Generally, all long term exposures for T-2 and HT-2 were below the TDI, with the exception of minor exceedances observed in children aged 1-5 years old. The assessment of total exposure from oat drinks combined with that from the general diet was considered conservative and as the exceedances were minor and transient in nature, it was concluded that there would be no chronic health effects in respect to DON.

OTA

1.50 For OTA, EFSA in 2020 established a Margin of Exposure (MOE) approach for neoplastic and non- neoplastic effects (kidney tumours and microscopic kidney lesions, respectively) to assess the risk posed by OTA. The MOE is a measure that is used to determine the level of exposure at which there starts to be a safety concern. For genotoxic carcinogens, MOEs ≥10, 000 indicate low concern. For other effects, an MOE ≥100 indicates low concern. It is not clear whether OTA can cause kidney tumours by directly interacting with the DNA (genotoxic carcinogen), or via a different mechanism.

1.51 It was noted that there were many uncertainties in the cancer endpoint used for risk characterisation, and furthermore, it was unclear whether or not OTA was a genotoxic carcinogen and thus which MOE threshold value would be applicable. The Committee noted that the MOE of ≥10,000 for substances that are directly genotoxic and carcinogenic may not be appropriate in this case because there is some evidence that OTA does not interact directly with DNA. Some age groups had MOEs lower than desirable for non-neoplastic changes while all age groups had MOEs lower than 10,000 for cancer effects. The uncertainty in the assessment was considered to be high, especially considering the lack of analytical information on the presence of these contaminants in oat drinks and the assumptions used in the exposure assessment. It was noted that it is likely that the risk was being overestimated.

1.52 In respect of OTA, the Committee was unable to conclude whether the exposure estimates indicated a potential health concern. It was agreed that assessments of actual exposure are needed for adults as well as young children, to establish whether there were potential health concerns for the general population.

1.53 Overall it was concluded that for the sum of DON and T-2 and HT-2, based on the available data there was no risk to health. However due to the uncertainties in the available dataset, the risk from exposure to OTA could not be determined.

Almonds

1.55 Almond drinks have a lower nutritional value than soya or oat drinks, however they can be given to children as an alternative to cows' milk. The mycotoxin, aflatoxin B1 was identified as a possible chemical contaminant in almonds, which could be potentially transferred to almond drinks. Aflatoxin B1 is a genotoxic carcinogen, so the EU sets a legal limit for the amount of aflatoxin which can be present; this is called the maximum level and uses the 'as low as reasonably achievable' (ALARA) principle. This is to ensure that exposure to such compounds is at the lowest possible level. As no more reliable data on aflatoxin levels were available, it was assumed that the almonds contained aflatoxin at the legal maximum level.

1.56 The lack of analytical information on the effect that processing of almonds during almond drink manufacture has on the levels of aflatoxins, as well as the lack of information on the levels in almond drinks themselves, was considered the main limitation in assessing the risk to health. Considering the above limitations, it was concluded that undertaking a risk assessment based on the Maximum Levels set by EFSA was highly uncertain and was likely to lead to an overestimation of risk and therefore was not appropriate. The risk to health from exposure to AFB1 could not be determined.

1.57 Almonds also contain cyanogenic glycosides, which can be released when the almond is physically broken down by chewing or processing. When this happens, they may interact with the enzyme ß-glucosidase, also present in almonds. This enzyme breaks down the cyanogenic glycosides and can yield hydrogen cyanide. Exposure to large amounts of hydrogen cyanide can lead to convulsions, loss of consciousness, dizziness, weakness, mental confusion and heart failure.

1.58 High levels of glycosides are present in bitter almond varieties, whereas there is very little present in sweet varieties. The quantity of cyanogenic glycosides present in almond drinks is uncertain, but only low levels of cyanide have been detected on analysis. Available information indicates that bitter almond varieties are not grown in commercial almond orchards and although the inadvertent use of bitter almonds in almond milk drinks cannot be completely ruled out, bitter almonds would not be deliberately used as they would be unpalatable, imparting a strong ‘marzipan’ flavour to the drink. Overall, Members agreed that there were no specific concerns for acute toxicity from cyanogenic compounds in almond drinks.

Position paper on the alternatives to conventional plastics for food & drinks packaging

1.59 In conjunction with pressure from environmentally aware consumers and the strategy to reach net zero to mitigate the effects of climate change recent years have seen a major global increase in the development and use of alternative biobased materials to conventional plastics for food and drinks packaging.

1.60 These alternatives are a diverse, complex set of materials and blends. The materials are usually derived from living matter (animal, plant or fungal biomass) and are partially or wholly made of substances that are naturally available or are synthesised from biomass, such as sugarcane, corn, and algae. Some examples include, but are not limited to, wheat straws; beeswax wraps to replace clingfilm; and bamboo/rice husk for paper coffee cups.

1.61 The alternative materials are usually classified into three main groups: bio-based plastics, biodegradable plastics and compostable materials.
Advice on biobased food contact materials (BBFCMs) has been increasingly requested from the Food Standards Agency (FSA) so it was therefore 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.

1.62 Several papers have been presented to the COT, which included discussion of the following topics: the limited research that has been undertaken into the development of BBFCMs and the associated potential risks to the consumer; relevant market data and reports; a table of enquiries received from the FSA Food Contact Material (FCM) Policy Team - these included Non-intentionally added substances (NIAS) such as the presence of formaldehyde in bamboo cups and the allergic potential of material such as chitin and wheat; as well as a detailed discussion paper focussing on the immunogenicity and allergenicity of chitin and chitosan-based BBFCMs.

1.63 The COT acknowledged the challenges and complexities associated with BBFCMs as well as highlighting several limitations and knowledge gaps on BBFCMs research and regulation. These included labelling, composition (including biodegradability), contaminants and standardisation. Members noted that quantitative information was needed on contamination, degradation, migration of chemicals and allergens during the manufacture and use of commercial BBFCMs, as well as environmental impacts after disposal, such as the formation of micro/nanoparticles upon entering landfill or from energy-from-waste processes. It was noted that only limited evidence exists to demonstrate BBCFMs in direct food-contact applications meet similar standards of safety as conventional plastics.

1.64 Members agreed that there was a general lack of information on the presence of nanomaterials in BBFCMs. Therefore, overall, information on specific migration of all the possible migrating substances (nanofillers, plasticizers, antimicrobial additives, micron and nano sized plastic particles *etc*.) under different testing conditions would improve identification of potential hazards and enable an estimation of possible exposure. This would allow better demonstration that these novel biodegradable packaging materials meet comparable requirements. Additional toxicity studies or approaches to enable assessment of long term risk may be needed for a more comprehensive risk assessment.

1.65 The COT agreed a priority list of BBFCMs for health risk assessment based on their potential health hazards, extent of usage, and UK policy interest. The prioritised materials to be reviewed are: polylactic acid (PLA), starches, bamboo biocomposites and polyhydroxyalkanoates (PHA). This was not a closed list, other priority BBFCMs could be added as necessary based on the same criteria.
Health risk assessments of the prioritised BBFCMs should be considered within the context of life cycle assessment studies, which include environmental hazards to address indirect impacts on human health. However, this was not all within the remit of the COT. It was noted that the Department for Environment, Food and Rural Affairs (DEFRA) (and its expert scientific committee, the Hazardous Substances Advisory Committee, HSAC), the Organisation for Economic Cooperation and Development (OECD), and the Environment Agency were assessing the wider environmental impacts. These impacts should be monitored to identify additional potential hazards to human health.

1.66 Further assessments of intelligent packaging (also known as smart packaging) and nanomaterials used within food packaging will be undertaken as policy priorities and resources permit as part of the Committee's work and would include bio sensors as well as nano coatings.

The full COT statement can be found Here.

Review of the EFSA opinion on dioxins

1.67 The COT reviewed the scientific basis and implications for risk management of the new EFSA tolerable weekly intake (TWI) for dioxins and considered that there were substantial uncertainties over the derivation of the TWI and possible inconsistencies between the animal and human data. Given the implications for risk management, the Committee felt that the rationales for the choices of key studies were not sufficiently clear in the published opinion, which made it difficult to evaluate the strength of the evidence. These concerns meant that the COT was unable to endorse the opinion and considered it necessary to reconsider the evidence base and set its own tolerable intake.

1.68 EFSA established a new TWI of 2 pg/TEQ/kg bw, which is 7-fold lower than its previous tolerable intake, based on data from a Russian Children's study, identifying semen quality, following pre- and postnatal exposure, as the critical effect. The COT noted this study appeared inconsistent with the findings in a second study and considered the Russian study to provide only a weak data set. The studies on experimental animals (rodents) included in the EFSA evaluation confirmed that developmental effects occurred at body burdens similar to those used as the basis for the previous risk assessment. However, the COT considered there were inconsistencies in the animal data presented in the EFSA opinion and was unclear, in particular, regarding the rationale for the selection of the study to evaluate the critical body burdens. The COT had raised specific concerns about their reliability in 2001 and later FSA commissioned studies to address these concerns, which failed to replicate the specific findings but found other reproductive effects at similar body burdens. Overall, the data presented in EFSA's opinion implied that humans were more sensitive to dioxins than rats. However, this would be inconsistent with the existing body of data on dioxins and knowledge on the relative sensitivity of the human and rat aryl hydrocarbon receptor (AHR). Due to these uncertainties, the COT did not agree with the newly established TWI and the 7-fold reduction in the TWI appeared too conservative for the database overall. The Committee was unable to comment on the dietary exposures and whether they should be compared to the new TWI.

1.69 The European Commission (EC) has not yet adopted EFSA's new TWI due to ongoing work at the international level to review the basis and values of the WHO toxic equivalent factors (TEFs). The review of the TEFs and a finalised assessment by the EC are not expected until 2022, at the earliest. The COT noted that this also presupposes that the effects of concern are mediated via the AHR.

1.70 The Committee acknowledged that a further review of dioxins would be an extensive and lengthy undertaking. However, even if the current HBGV were immediately reduced, it would take decades to reduce body burden in the population, due to the nature of dioxins, especially their long half-life in humans. The current COT TDI was based on the most sensitive endpoint in the animal studies and is intended to protect the most sensitive population group, hence it would also be protective for all population groups and for other less sensitive effects.

1.71 Thus, while the re-assessment of dioxins is a necessary and important piece of work going forward, the COT did not consider it necessary in the meantime to alter its existing advice on dioxins. The COT considered that their current TDI of 2 pg/kg bw per day is protective for effects on the developing male fetus, that this was supported by later studies on this endpoint and was consistent with their consideration of the WHO-TEF concept.

COT principles for assessing risks from less than lifetime exposure or variable exposure over a lifetime

1.73 Dietary exposures to chemicals are typically compared to a health-based guidance value (HBGV), for example a tolerable daily intake (TDI), that has been established to be safe for long term exposure. Such values set a level of exposure that is considered acceptable if continued throughout a normal lifetime, i.e. it is an upper amount to which an individual can be exposed daily over a lifetime without a significant risk to health.

1.74 Sometimes people may be exposed to chemicals at a higher level for a shorter period of time. The COT produced a statement containing COT recommendations on possible ways of refining the risk assessment for such less-than-lifetime exposures. The statement includes a flowchart to illustrate the process, which is reproduced in Figure 1, below.

The full COT statement can be found on the COT website: Statement on COT principles for assessing risks from less than lifetime exposure or variable exposure over a lifetime.

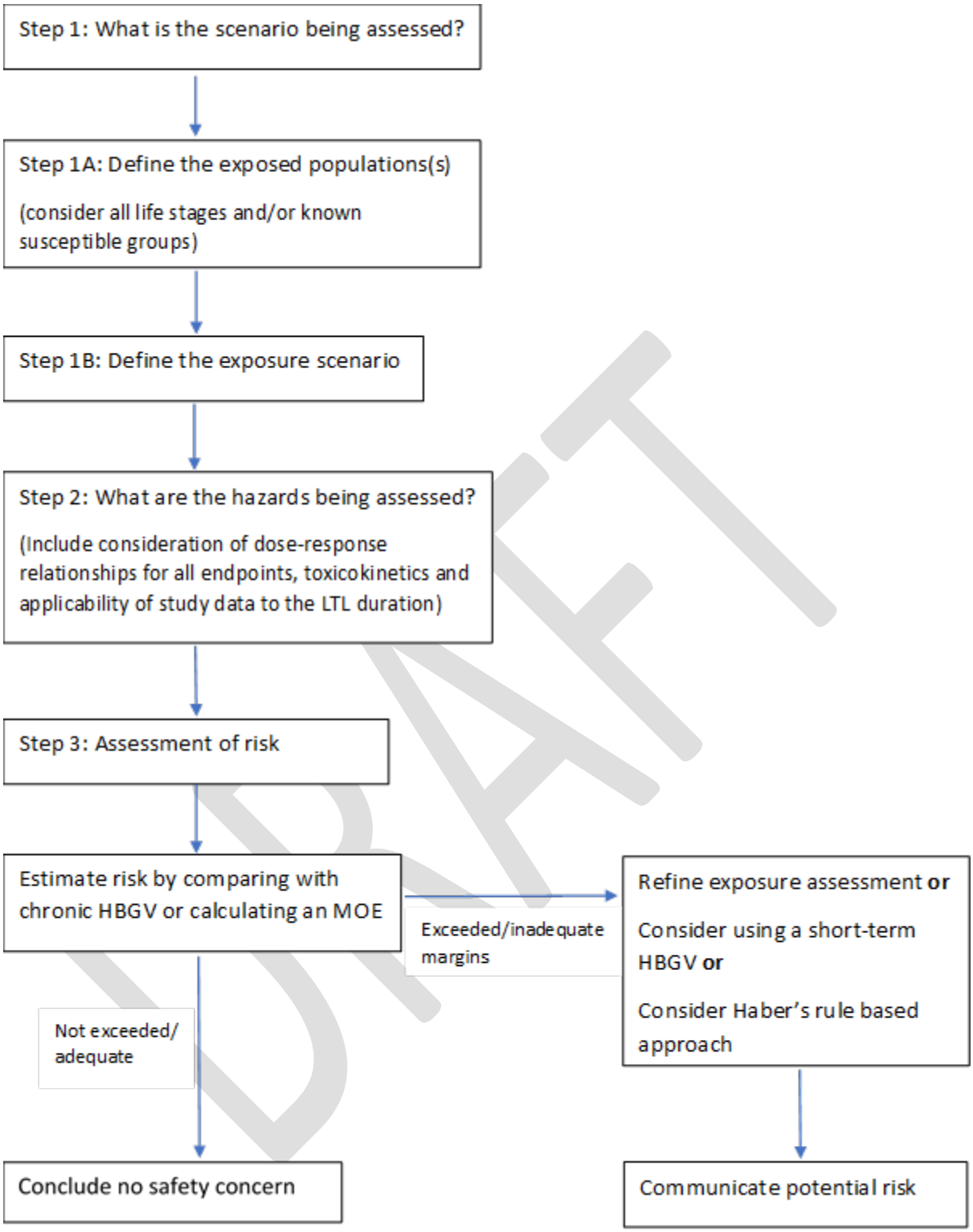

Figure 1: Flowchart to illustrate the process of assessing risks from less than lifetime or variable (LTLV) exposures. Where appropriate, toxicokinetic or toxicodynamic modelling could be applied to refine any of the steps.

Development of Human Biomonitoring Guidance Values in the HBM4EU project

1.75 The Committee were asked to comment on the methodology for the derivation of human biomonitoring guidance values by the European Human Biomonitoring Initiative, referred to as HBM4EU, which is a project designed to develop a harmonised and systematic strategy for the derivation of human biomonitoring guidance values (HBM-GVs).

1.76 Members considered other types of human biomonitoring guidance values to allow comparison with established methods, and discussed the potential application of the HBM4EU strategy and values, as well as their relevance to the UK.

1.77 There were two aspects that needed to be considered: the generation of the human biomonitoring guidance values and the application of these values to the population. It was also noted that, similar to determining any guidance value, the derivation of the human biomonitoring guidance values would depend on the type of data available and on establishing the relationship between the exposure and the effect. UK specific biomonitoring data would be useful for risk assessment and more information (such as appropriate auxiliary data) would be required before being able to use these values for this purpose.

1.78 In terms of the methodology for deriving the human biomonitoring guidance values, the values would need to be validated from a toxicological perspective. Ideally, exposure could be correlated to environmental levels in combination with human biomonitoring data, for example by collaborating with the agencies such as the Environment Agency or Defra to collect environmental biomonitoring exposure data. Correlation of National Diet and Nutrition Survey (NDNS) data with environmental biomonitoring data would be useful to refine exposures.

1.79 There may be insufficient toxicological data to establish human biomonitoring guidance values and a continuation project with targeted studies to allow for the generation of suitable data may be necessary.

1.80 On occasion, both external and internal guidance values will be needed - for example in cases where there is variability in the exposure depending on the product, and therefore monitoring of both product levels and internal levels in humans would be needed; this would need to be done on a case by case basis. Human biomonitoring guidance values are not often used stand alone, but they add value when they can be used in combination with other approaches

1.81 Further information would be useful on the pharmacokinetic requirements needed to establish a biomonitoring equivalent and it was noted that the sampling and exposure scenarios needed to fit sampling time. Requirements for marker substances were not included in the paper. Appropriate data on dermal exposure would also be important in ensuring the assumptions made were correct.

1.81 The Committee agreed that the strategy developed by HBM4EU was robust and scientifically valid; depending on kinetics information and data availability. In principle, the use of HBM-GVs derived by the HBM4EU in the UK would be possible. In practice, and in line with any other guidance value, detailed evaluation of the human biomonitoring value would be needed to determine whether the critical endpoint was appropriate for the UK population.

1.82 Going forward, the use of human biomonitoring guidance values in risk assessment could be helpful to the FSA and the Committee was content to review future case studies and offer their perspective. However, if endorsement of these values was needed, the Committee would have to perform a detailed evaluation to offer their perspective.

1.83 This topic has also been discussed by the COC (see paragraph ??)

First draft non-technical statement on how the Committees evaluate the relevance and reliability of data when assessing a chemical of concern.

1.84 This topic was brought to the COT by the COC Secretariat.

1.84 Guidance aimed at a Lay audience had been prepared, providing clarity on how the expert committees evaluate data with respect to consideration of biological relevance and statistical significance.

1.85 The topic arose during COC horizon scanning activities and the draft guidance for a number of years. the draft guidance been revised following review by lay members of the COC, COT and COM.

1.86 The COT considered the guidance was largely appropriate for the purpose of describing the mechanisms of ascribing biological and statistical significance to the assessment of the risk posed to the consumer by a chemical, but acknowledged that the statistical methods described were potentially overly complex for a lay readership. However, any simplification of the definition of concepts, such as the null hypothesis and p-value, should ensure that their meaning was lost.

1.87 The Committee noted that information on the workings of the sister committees should be included on the Committee website. However, further information was needed on some aspects, for example, how a particular chemical or issue was added to the agenda, how the risks to the consumer from it were assessed, and the basis of the conclusions reached. However, some of these aspects are covered in the Committee Code of Practice, albeit briefly

1.88 The Committee made a number of additional minor suggestions for amendments

Review of EFSA Scientific opinion on the safety assessment of titanium dioxide as a food additive (E171).

1.89 The COT was asked to comment on the "Scientific opinion on the safety assessment of titanium dioxide as a food additive (E171) " published by EFSA in May of 2021. In this opinion, the EFSA panel concluded that on the basis of the currently available evidence along with all the uncertainties, in particular the fact that the concern regarding genotoxicity could not be resolved, that E171 can no longer be considered as safe when used as a food additive.

1.90 The EFSA Opinion had also been presented to the COM for comments (see paragraph ??)

1.91 The Committee note the COM's preliminary comments, regarding the quality of the data and the difficulties in evaluating it adequately from the description given in the opinion. The lack of a good dataset and a well-defined test compound (due to the poorly defined specifications) are also considered as severe limitations. The COM consider the mechanism of genotoxicity appears to be indirect and probably has a threshold and, that the positive effects observed in the genotoxicity studies could be attributed to the nano-fraction of titanium dioxide.

1.92 The COT agree with the COM view and note the large discrepancy between the underlying dataset and the conclusions drawn by EFSA. On the genotoxicity of nanoparticles, it was noted that this could either be a concentration effect leading to oxidative damage or a stress effect, however, it was unclear as the results in different cell lines were equivocal and inconsistent. It was also noted that in some tests titanium dioxide had shown less reactivity.

1.93 In several parts of the Opinion, published papers are presented at face value, and there is no discussion of the results nor the Weight of Evidence to support the conclusions being made. There are also discrepancies and conflicts between the results of the studies reported and the overall conclusions.

1.94 On balance, the Committee considers that the weight of evidence does not support the conclusions drawn by EFSA. The Committee also agree with the comments of the COM with regards to risk communication that "As it stands the conclusion is highly risk adverse based on the weak evidence available, and it might create unnecessary concern to the public." Care should be taken when expressing such conclusions in a binary manner given the extensive uncertainties in the dataset.

1.95 The COT suggested that the COM should independently review the database on genotoxicity and apply the COM's Guidance on determining thresholds.

1.96 EFSA's concluded that no differentiation could be made with regards to size/form of titanium dioxide and different aspects of toxicity, however, it seems likely that nanoparticles may be driving the toxicity.

1.97 It was decided that an interim position paper, capturing the COT's view and the proposed next steps should be published (see paragraph ??).

Updated COT Evaluations

Cannabidiol (CBD)

Updated CBD position paper- Position paper on the potential risk of CBD in CBD food products: additional text summarising Committee discussions relating to dermal and inhalation exposure

1.98 The COT 'Position paper on the potential risk of CBD in CBD food products' published in July 2020 summarised the discussions and conclusions of the COT and COM from July 2019 to May 2020 on the available toxicological information of relevance to cannabidiol (CBD) in non-medicinal food products.

Dermal exposure to CBD

1.99 The Committee discussed data of relevance to dermal exposure to CBD from CBD-containing cosmetics products. Such products include serums, creams, washes/rinse-off products, bath products, deodorants, balms, and toothpastes.

1.100 Dermal exposure to CBD may contribute to systemic exposure and/or local effects. Although absorption levels would probably be low because the compound is lipophilic, repeat application could lead to accumulation in the stratum corneum and subsequent slow diffusion into the systemic circulation. Overall, the Committee considered that dermal absorption of CBD was unlikely to be greater than from oral exposure and may be lower. Dermal absorption of CBD was likely to be less than 10% compared with oral absorption. The Committee noted that absorption of CBD from cosmetic products may also occur via inhalation of sprays and mists generated during product use. Dermal pharmaceutical CBD products may differ from cosmetic CBD products, as these may have formulations designed to maximise dermal absorption.

1.101 There was insufficient information on the pharmacokinetics and toxicity of dermal CBD to conduct a risk assessment of the safety of CBD in cosmetic products.

1.102 No conclusions could be drawn on whether dermally applied CBD poses a safety concern, nor on the potential for drug interactions. The risk from aggregate exposure to multiple CBD products, including cosmetics, could not be determined due to lack of information. No good quality *in vivo* or *in vitro* data were available to allow estimation of systemic doses.

1.103 Overall, the Committee noted that additional exposure through topically applied CBD could potentially occur and this would increase overall systemic exposure of CBD. However, there are data gaps that need to be addressed to be able to evaluate the potential for adverse effects related to dermal exposure to CBD.

Exposure to CBD by inhalation

1.104 Inhalation exposure to CBD may occur via various sources, for example smoking CBD-containing plant material, use of electronic nicotine (and non-nicotine) delivery systems (E(N)NDS) containing e-liquids to which CBD has been added, or from aerosolised therapeutic applications.

1.105 The nature of the source material will affect the risk assessment, for example in terms of the presence or absence of thermal degradation products, and because different delivery methods may affect the bioavailability of CBD.

1.106 The available evidence base relating to potential adverse effects of inhaled CBD is small. However, some conclusions on the likelihood of toxicity from the inhalation of CBD can be inferred based on oral data. Inhalation exposures pose a potential safety concern and adverse effects could be greater than those from an equivalent oral dose as the bioavailability of inhaled CBD is often higher compared with oral exposure. Following absorption across the lung, the type of adverse effects occurring would be independent of route of exposure. Inhibitory drug interactions would be expected at levels comparable to those following oral exposure, given the apparent higher bioavailability across the lung compared with the gut. Effects on the central nervous system would be expected following inhalation, thus a health warning might be necessary relating to driving or using heavy machinery.

1.107 Some experimental data suggest a possible interaction of CBD with steroids could be a cause for concern, however this is an area of research that is currently not well understood.

1.108 Overall, there was insufficient information to generate a risk assessment regarding the safety of use of CBD in products intended for inhalation, but the available data indicated caution. The Committee agreed that the recommended upper limit of 1 mg/kg body weight per day established for dietary exposure to CBD should be applied to total combined exposure, including that from inhalation.

1.109 As a result of the COT discussions, some additional text was added to the existing position paper which summarises the discussions around dermal and inhalation exposure for inclusion in an updated position paper.

The full updated COT position paper can be found Here.

Statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e cigarettes): presence and pharmacokinetics of nicotine salts

1.110 At the end of 2020 and in 2021, the Committee considered data on the presence and pharmacokinetics of nicotine salts in electronic nicotine delivery system (ENDS) products.

1.111 It was agreed that this should be included as an addendum to the COT statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes).

1.112 The addendum to the statement will be published in due course.

Committee Procedures

Draft EFSA Scientific Committee Opinion on scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals.

1.113 In May 2021, EFSA released draft guidance, prepared by its Scientific Committee, on the grouping of chemicals for risk assessments of combined exposure to multiple chemicals. The Committee were asked to comment on the draft opinion as part of EFSA's public consultation process.

1.114 Overall, the Committee agreed that the proposed guidance provides a pragmatic and scientifically sound approach for grouping chemicals for a combined risk assessment.

1.115 The main comments of the Committee were as follows:

- Sorting different chemicals into assessment groups on the basis of common key events is appropriate but for data-poor chemicals, this may result in the formation of very large chemical assessment groups (CAGs), particularly if grouping is done on the basis of adverse effects, such as potential liver effects.

- Although the scientific criteria for dose addition were provided in the draft EFSA guidance, the underlying assumption of dose addition is not clearly stated.

- With regards to the prioritisation methods for grouping chemicals into assessment groups, the default threshold values appeared to be rather

arbitrary, and not entirely supported by scientific data; thus, the threshold values should be tested, and re-evaluated after some time.

- Appendix C ('statistical methods to study the probability of combined risk or combined exposure') was not directly referred to in the draft guidance document. It would be useful to have some examples where these statistical methods were used, such as use of correlation matrices for multivariate pattern analysis. Furthermore, it may be possible to obtain a high probability of co-exposure ('r' value) from assessment of a low number of chemicals.

Draft EFSA Scientific Committee Opinion on biological plausibility of non-monotonic dose responses and their impact on the risk assessment

1.116 In 2016, the European Food Safety Authority (EFSA) published the results of a contracted-out report on a systematic review of the existing literature where signs of non-monotonic dose responses (NMDRs) had been observed (Beausoleil et al., 2016). In the report, the scientific evidence for such NMDRs was assessed with a systematic review being performed in line with the EFSA guidance. The report extracted dose-response datasets from studies having at least 5 dose groups, which were then analysed by the PROAST software package. The strength of the evidence was characterised using visual/statistics-based checkpoints.

1.117 The EFSA Scientific Committee (SC) was asked to prepare a scientific opinion on the biological relevance, if any, of the apparent non-monotonic dose responses identified in the commissioned report and to address the possible consequences for the human health risk assessments conducted by EFSA. The COT was asked to comment on the opinion as part of the public consultation process. The opinion is a review of the previous methods used for assessing the presence of non-monotonic dose responses, not of the responses.

1.118 The COT made a number of specific comments which are presented below:

- A critical review of the key studies claiming NMDR is needed to compare against, for example, OECD guidelines, and to more fully address randomisation.
- Some of the evidence supporting the study showing a biphasic effect on heart rate was not included, suggesting that the conclusion regarding NMDR, or otherwise, could be seen as biased.
- Consideration was not given as to whether NMDR might affect the upper and lower confidence limits of the Benchmark dose (BMD), even if the curve was fitted only to those data points before the sign of the dose-response changed.
- The implications of NDMR of key events at low doses in the context of homeostatic control needs greater consideration.
- The opinion concludes that if an effect for which NMDR is observed is an apical effect and NMDR is supported by further experimental work, no further

investigations are needed. The corollary of this is that when such an observation was not supported by further experimental investigations, more work was needed. This meant that the opinion only provides for two possibilities 1) a conclusion of NMDR or 2) that more work was needed.

- Ethical justification is needed for the increased animal use that would be necessary in order to have sufficient data points to fully explore non-monotonicity. Moreover, possible confounders should be taken into account, and study design reviewed carefully before committing further resources to investigating possible nonmonotonicity.
- It was unclear whether the Scientific Committee's view is that there are additional data on apical effects suggesting that relevant NDMR do occur; and, if this is the case, then it is unclear why these were not considered in the earlier reports. Conversely, if the data suggested these effects do not occur, then it appears to be unclear why there is emphasis later on the need to consider the possible implications of NMDR at low doses, which should be investigated on a case by case basis (e.g. "in cases where biological considerations or previous results suggest that NMDR may be present"). Hence, the overall message of this opinion could be clearer

EFSA draft opinion on "Identification and prioritisation for risk assessments of phthalates, structurally similar substances potentially used as plasticisers in materials and articles intended to come into contact with food" and "draft protocol for the exposure assessment as part of the safety assessment of phthalates, structurally similar substances potentially used as plasticisers in materials and articles intended to come into contact with food"

1.119 EFSA published a "draft opinion on identification and prioritisation for risk assessments of phthalates, structurally similar substances potentially used as plasticisers in materials and articles intended to come into contact with food" and a "draft protocol for the exposure assessment as part of the safety assessment of phthalates, structurally similar substances potentially used as plasticisers in materials and articles intended to come into contact with food" for public consultation on the 5th of November 2021.

1.120 The new assessment follows on from EFSA's previous update on the risk assessment of five phthalic acid esters (ortho-phthalates), namely di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2- ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP) for use in FCMs, in December 2019.

1.121 The Committee was asked to comment on the draft opinion as part of the public consultation process. [Note – to be revised once December minutes have been cleared].

1.122 The main toxicological concern for phthalates are adverse effects on reproduction, with a mode of action involving fetal testosterone reduction. It is difficult

to group phthalates for hazard assessment purposes, given that reproductive toxicity is not the main toxicological outcome for all substances (i.e. DIMP and DIPP). Oher compounds with different toxicities have yet to be assessed, including some higher molecular weight phthalates. The current EFSA prioritisation list is bases on the previous assessment date of phthalates. However, the COT some of these compounds were currently undergoing further assessment by ECHA, and hence additional data with a focus on genotoxicity and reproductive effects may be forthcoming.

1.123 Overall, the approaches proposed by EFSA to prioritise phthalates and the corresponding assessment of their exposure are logical and pragmatic. However, until a complete list and toxicological profile for these substances is available, further comment on the (hazard) assessment would prove difficult.

1.124 Clearer information on exposure assessment would be helpful. A deterministic approach can result in an overestimation of exposure while a probabilistic approach could be potentially more realistic, especially if human biomonitoring is used to validate the findings. It is a positive step that the EFSA approach appears to be integrating human biomonitoring data. However, Members further information should be provided on how PBPK modelling would be used to interpret the human biomonitoring data.

1.125 It may prove difficult to exclude and/or separate occupational exposure within biomonitoring data. Occupational data may contribute significantly to overall exposure, potentially more so than the diet. A questionnaire on occupational exposure may be beneficial to gather additional information on this.

1.126 The exposure protocol Is sensible and it is useful to include exposure in EFSA's prioritisation process. However, until data are available and estimation of combined exposures is possible, the current approach is mostly theoretical.

1.127 EFSA will not be considering the UK population as part of their exposure assessment, hence the FSA may need to consider how to follow up on EFSA's evaluation from a UK perspective.

Public Consultation on Code of Practice for Scientific Advisory Committees and Councils

1.120 The Code of Practice for Scientific Advisory Committees and Councils' (CoPSAC) applies to science advisory committees and councils affiliated to the UK government that provide independent expert advice to facilitate decision making. CoPSAC has been revised based on feedback received from Committee and Council stakeholders, and a wider consultation was now taking place. The consultation was aimed at academics and other experts who provide science advice to the UK government and sought views on the independence, transparency, diversity, and inclusion aspects of the CoPSAC in particular.

1.121 The Committee made a number of comments.

- In the recruitment section, there needed to be a mention of how to increase diversity through different channels of advertisement.
- Further clarification was needed to distinguish declarations of interest and conflicts of interest.
- More clarity is required on how SAC Members are appointed.
- More information was needed on lay membership. The document implies that the appointment of lay Members is not mandatory, and there is also a need to clarify the expectations of lay Members.
- Section 5.5 concerning liability might be perceived as unintentionally negative. The penalty section needs to be revised and details on conduct need to be made clearer.
- The Committee noted section 7.1 on the environmental impact, including attendees' travel. Whilst the environmental impacts are considered to have been lower for virtual meetings, the quality of discussions in virtual versus in-person meetings may differ. Confidentiality may need to be reviewed, as this may be harder to control in a virtual meeting. However, virtual meetings may allow for greater diversity, as they may permit access for individuals who might otherwise be unable to attend in person. For future meetings, hybrid options could be useful.
- Guidance on the retention of both digital and physical documents by Members would be helpful.

Ongoing work

The COT risk assessment of substances in the diet of women in preconception, pregnancy and up to 24 months post-partum.

Background

1.128 The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its 2011 reports 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' and the 2018 report 'Feeding in the first year of life". In the latter report, the impact of breastfeeding on maternal health was also considered. In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments, e.g. in the area of food safety advice. Accordingly, the COT were asked to contribute to this project.

Prioritisation of xenobiotics

1.121 Following discussion of the prioritisation papers on substances to be considered for risk assessment, the Committee agreed that some substances were

of sufficient concern to be allotted individual papers and others could be grouped together into an overarching Statement.

1.122 The substances for which individual papers were requested are:

- vitamin D, iodine, caffeine, vitamin A, ginger, ochratoxin a, fumonisins, zearalenone, citrinin, ergot alkaloids, phytoestrogens, lead, mercury. cadmium, arsenic, selenium, acrylamide, oily fish, raspberry leaf and echinacea.

1.105 Substances to be included in an overarching statement are:

- Aflatoxins, nivalenol, deoxynivalenol, T2 & HT2, patulin, vitamin E, vitamin C, camomile, peppermint, evening primrose oil, dandelion, camomile, resveratrol, heterocyclic amines, legacy pesticides, non-dioxin-like PCBs and alcohol.

1.106 Other substances that may be reviewed include dioxins, bisphenol A and fusarenon-X, some of which are awaiting the opinions of other advisory bodies. The Committee may choose to add additional substances to the list, or change the approach to substances on the list as the work progresses.

Alcohol and the maternal diet: The 2016 Chief Medical Officers report

1.107 The Committee considered whether alcohol should be considered as one of the xenobiotics being considered in the review of the maternal diet. Although alcohol *per se* was not within the SACN remit it could be considered as a wider health issue.

As the database for the potential effects of alcohol in pregnancy was extensive, Members considered the most recent UK Government recommendations and the data on which they had been based in order to establish whether further work in this area would be of value.

1.108 The UK Government suggests that women who are pregnant or trying to become pregnant should avoid alcohol altogether. This advice, which is given on, for example, the NHS website, is based on recommendations from the “Low Risk Drinking Guidelines produced by the UK Chief Medical Officers (CMO) in 2016”. These recommendations were based on the findings of a number of systematic reviews and meta-analyses. The results of these studies were largely inconclusive with respect to the effects of low levels of alcohol exposure and methodological flaws in the studies were noted. A number of additional systematic reviews and meta-analyses have been published covering the same end points considered in the CMO report, but as previously, the results for low levels of exposure were inconclusive and methodological failings were noted.

1.109 The COM reviewed alcohol in 2005 and concluded that there was no clear evidence for a risk from (low) alcohol consumption during pregnancy but they were not able to fully exclude a risk. The COM further concluded that alcohol itself was probably not genotoxic, however the breakdown product acetaldehyde most likely

was. Overall, the COM was unclear what other chemicals may be present in alcoholic beverages that might cause an effect.

1.110 Alcohol is produced endogenously and metabolic enzymes have been proven to be extremely effective at preventing cellular damage in the body and aiding the elimination of alcohol. Hence, the biological mechanism would need to be taken into account when considering the available epidemiology and it is possible there is a threshold for the effects of alcohol.

1.111 The CMO report is thorough and the approach and conclusions on alcohol in pregnancy are reasonable, given the data considered in the report. The evidence is not strong enough to completely rule out some risk from low levels of alcohol exposure in pregnancy. As the data published since 2011 do not greatly add to the CMO report on the clarity of the issue and given the work and resources involved, a further review would be unlikely to change the current advice to women. Members therefore agreed not to take this review further.

Ongoing topics in maternal diet

Vitamin D

1.112 The Committee assessed if exposure to excess intake of vitamin D from various sources (including UV radiation, dietary sources, and supplements) would pose a risk to maternal health.

1.113 The relationship between oral vitamin D intake and serum levels is unclear due to many uncertainties such as season, time of day, amount of skin exposed, skin pigmentation and use of SPF sunscreen. However, exposure from UV radiation is considered unlikely to result in vitamin D toxicity due to inbuilt mechanisms in the skin where pre-vitamin D3 reaches a maximum concentration in the skin within a few hours after UVB radiation exposure. Other uncertainties in the assessment is the use of data from non-pregnant women of child-bearing age (i.e., 16-49 years) to construct the exposure assessment in pregnant women, since the diet of the latter may vary.

1.114 Higher strength vitamin D supplements are likely to be the biggest contributor to vitamin D exposure, and consumption of these supplements alone is sufficient to result in exceedance of the TUL of 100 µg/day. The diet alone without consumption of vitamin D containing supplements is unlikely to be a cause of concern, and consumption of both dietary sources of vitamin D and higher strength vitamin D supplements are likely to result in exposure levels greater than the TUL of 100 µg/day.

1.115 A statement setting out the Committee's assessment of vitamin D will be published in 2022.

Cadmium

1.116 The COT discussed a review of the literature on cadmium in the maternal diet and requested additional information, with particular regard to maternal dietary intake and the implications for subpopulations where consumption of certain food groups might be higher.

1.117 As smoking is a significant source of cadmium, information on cigarette smoke and vaping should be included also considering bystander/passive smokers. Further information on metallothionein and the role it plays in the body and the placenta was also requested.

1.118 The Committee will continue to work on cadmium during 2022.

Vitamin A

1.119 Vitamin A (retinol) is essential for the health of adults, children and developing fetuses, although both deficiency and excess lead to toxicity, particularly developmental malformation in the fetus.

1.120 Dietary retinol comes pre-formed from animal derived foods such as liver or liver products, or is converted from carotenoids such as β-carotene which form the colouring matter in vegetables such as carrots and peppers. Retinol is absorbed with dietary fats, bound to plasma proteins and stored in the liver. Retinol is oxidised in the tissues to retinal, which is essential for vision, and then to retinoic acid, which is essential for fetal development and other functions.

1.121 In many countries, the issue for maternal health is deficiency but in richer nations adequate dietary levels are normally met. A tolerable upper limit (UL) of 3000 µg retinol/day has been set by EFSA as a level unlikely to cause developmental malformations but there is uncertainty about the actual level that may be associated with toxicity. However, pregnant women are advised not to consume foods such as liver or supplements such as cod liver oil which may cause them to exceed the UL.

1.122 Oral and topical retinoid-based products are used to treat severe acne, often in young women who may become pregnant and although the risks are disputed, their use is not recommended in pregnancy. Recent evidence suggests that an association between retinoid acne treatment and depression may be ill-founded, but uncertainties still exist.

1.123 Few if any ill effects have been ascribed to taking supplements containing β-carotene.

1.124 A statement setting out the Committee's assessment of vitamin A will be published in 2022.

Ginger and ginger supplements

1.119 As part of the current programme of work on the maternal diet, the Committee considered the use of dietary supplements during pregnancy to identify those that might need reviewing. These are supplements that are not officially recommended but which are promoted by anecdotal evidence and unofficial sources as having various purported benefits. It was agreed that ginger should be considered in further detail.

1.120 The Committee considered the potential effects of ginger and 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 drugs as well as data on potential exposure.

1.121 As it is commonly believed that ginger suppresses morning sickness, pregnant women may be using the supplements for this purpose. Whilst ginger consumption in the diet is not considered to be of concern due to the long history of safe use for culinary purposes, however, problems could arise from consumption of more concentrated products such as the various forms of supplements.

1.122 There are limited human data and these are not strongly indicative of any toxicological concern but there are some indications of possible adverse effects and numerous uncertainties. Ginger did not appear to be systemically toxic but did appear to have reprotoxic effects at high doses in animal studies. Ginger is thought to affect prostaglandin function which may be relevant to this.

1.123 It is not possible to determine a point of departure to use in the risk assessment of ginger. While there is some equivocal evidence for the possible effect of ginger on reproduction, it is not possible to characterise it based on the data available. There is no clear indication that ginger is detrimental to consumers.

1.124 The potential for contamination of ginger with heavy metals and/or mycotoxins cannot be excluded.

1.125 A statement setting out the views of the Committee on will be published in 2022.

Iodine

1.126 As part of the work on the maternal diet, the COT was asked to consider the potential effects that excess iodine intake may have during preconception, pregnancy and lactation.

1.127 Iodine is an essential component of thyroid hormones which are important in growth and development. It is found in foods such as fish and seafoods as well as fortified products and food supplements. Seaweed is a very rich source of iodine and may lead to high levels of consumption in some consumers.

1.128 Iodine was initially discussed in 2020 and the Committee considered issues such as exposure, biomarkers and individual susceptibility to the effects of excess iodine.

1.129 Overall, members agreed that while there were no concerns in the general population, exposure to excess iodine in high seaweed consumers could pose a potential risk to maternal health. It was concluded that the currently available data was not sufficient to enable a risk benefit assessment to be performed.

1.130 The final statement setting out the Committee's views on iodine will be published in 2022.

NAMs Roadmap

1.131 Advances in biology, computer science and other related fields are paving the way for major improvements in how environmental and public health risks posed by potentially toxic chemicals can be evaluated. The combined advances in discovery and clinical sciences, data science and technology have resulted in toxicity testing which has reached a pivotal transformation point known as the 4th industrial revolution (4IR). One of the major recent scientific advancements is the development of New Approach Methodologies (NAMs) including high throughput screening, omics and in silico computer modelling strategies such as Artificial Intelligence and machine learning for the evaluation of hazard and exposure. This also supports the Replacement, Reduction and Refinement (3Rs) approach.

1.132 The future of the safety assessment of chemicals in food depends on adaptability and flexibility in utilising the best scientific methodologies and strategies available to respond to the accelerating developments in science and technology.

1.133 NAMs are gaining traction as a systematic approach to support informed decision making in chemical risk assessment. Integration of these technologies as part of the FSA chemical risk assessment process will be fundamental in the future in the future of human safety assessments to protect consumers.

1.134 The Food Standards Agency (FSA) responds to food incidents and it is important that robust risk assessments on the safety of a chemical can be provided. However, sometimes there is very little, or no, toxicological information for a given chemical. For such chemicals, the use of NAMs could provide a more indicative level of risk and therefore greater confidence can be provided for them as well as less uncertainty that individual compounds can be assessed.

1.135 In order to achieve this, the FSA and COT are developing a UK roadmap towards acceptance and integration of NAMs, including predictive toxicology methods using computer modelling, into safety and risk assessments for regulatory decision making.

1.136 During 2020, Members discussed the latest draft version of roadmap The Committee endorse the roadmap and a supporting workshop, and congratulate the

FSA for taking the lead in this area. Developing the roadmap will involve engaging with other government departments and regulatory bodies.

The potential health risks of bamboo bio-composite food contact materials

1.137 Advice on biobased food contact materials (BBFCMs) has been increasingly requested from the Food Standards Agency (FSA) so it was therefore considered timely for the Committee to review the available toxicological information on BBFCMs (see paragraph??).

1.138 It was agreed that a health risk assessment should be conducted for bamboo composites based on its potential hazards.

1.139 The migration of formaldehyde and melamine from bamboo composite cups is a potential concern to human health and it would therefore be appropriate to conduct a full risk assessment once UK data are available.

1.140 As obtaining the data and providing a full risk assessment will require time, the COT agreed to publish an interim position paper to set out their concerns and allow for risk management action.

1.141 The interim position paper will be finalised and published in 2022.

Chitin and chitosan in food packaging materials

1.142 The FSA is currently assessing whether there are any risks to health posed by bio-based food contact materials (BBFCMs). One of the first materials to be reviewed was including that containing chitin or chitosan.

1.143 Chitin and chitosan can be derived from fungi or from shellfish. Therefore there are potential concerns for individuals who are allergic to shellfish, but only limited data are available.

1.144 The risk of allergenicity from these BBFCMs appears to be low. However, before the potential risks to human health can be fully assessed, it would be useful to have an indication or estimation of total exposures to allergenic proteins from BBFCMs, for example the upper bound levels of ingestion, or range of amounts of BBFCMs in contact with different foods.

1.145 Further information on chitin or chitosan derived from fungi is also needed.

1.146 Due to a scarcity of relevant data in the scientific literature, it is not currently possible to undertake a reliable exposure assessment due to the uncertainties involved.

1.147 A second draft statement on this work will be presented to the COT in 2022.

PBPK Workshop

1.148 The FSA and the COT held a “PBPK for Regulators” workshop in December 2020 in a multidisciplinary setting with delegates from regulatory agencies, government bodies, academia and industry. The workshop provided a platform to enable expert discussions on the application of PBPK to human health risk assessment in a regulatory context.

1.141 The presentations covered current applications of PBPK modelling: in the agrochemical industry for *in vitro* to *in vivo* extrapolation (IVIVE); pharmaceutical industry for drug absorption related issues (e.g. the effect of food on drug absorption) and drug-drug interaction studies, as well as dose extrapolations to special populations (*e.g.* those with a specific disease state, paediatric/geriatric age groups, and different ethnicities); environmental chemical risk assessment fields; an overview of the current regulatory guidance; and a PBPK model demonstration. This enabled attendees to consider the wide potential and fit for purpose of application of PBPK modelling in these fields. Attendees further considered the applicability of PBPK models in the context of future food safety assessment, for refining exposure assessments of chemicals with narrow margins of exposure and/or to fill data gaps from more traditional approaches (*i.e.* data from animal testing).

1.142 The overall conclusions from the workshop proceedings were as follows:

- PBPK modelling tools are applicable in the explored areas of use, and there is some expertise available for their utilisation;
- PBPK modelling offers opportunities from which to address questions for compounds that are otherwise not solvable;
- Widespread acceptance amongst regulatory bodies appears to be limited by lack of available in-house expertise;
- Familiarisation using real world case studies would help in developing more experts in the field and increasing acceptance;
- In a regulatory context, establishing fitness for purpose for the use of PBPK models requires multi-partite discussion and harmonised guidance;
- PBPK modelling is part of the wider “new approach methodologies” for risk assessment.

1.143 A summary of proceedings from this workshop will be published in due course.

Risk assessment of potential constituents and contaminants in cow’s milk

1.144 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 (see paragraph ??).

1.145 As noted elsewhere, following on from the assessment of plant based drinks a joint SACN/COT Working Group has been established to bring together the nutritional and toxicological aspects of plant based drinks.

1.146 The main comparator for plant-based drinks should be cow's milk and to enable comparison, the potential chemical constituents and contaminants within cows' milk should be reviewed. These included veterinary medicine residues, pesticide residues, nitrate and nitrite, bisphenol A, phthalates, dioxins and dioxin-like biphenyls, non-dioxin-like polychlorinated biphenyls, polycyclic aromatic hydrocarbons, selected isoflavones, heavy metals, iodine, chlorate and perchlorate, mycotoxins, naturally occurring oestrogens in cows' milk, insulin like growth factor, per- and polyfluoroalkyl substances, brominated flame retardants and microplastics.

1.147 The Committee concluded that there were no health concerns arising from the consumption of cow's milk associated with the compounds noted above.

1.148 A statement covering the Committee's views on the safety of milk will be published in due course.

Interim Position paper on Titanium Dioxide

1.149 Following the discussions by both COT and COM a draft interim position paper on titanium dioxide, capturing the outcomes of the discussions from the two Committees and outlining the next steps was prepared.

1.150 The Interim Position Paper will be published in due course.

Working Groups

SETE

Report and Guidance of the Synthesis and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) of the Committee on Toxicity and the Committee on Carcinogenicity

1.149 The UK Committees on Toxicity (COT) and on Carcinogenicity (COC) regularly review epidemiological and toxicological evidence in their risk assessments. There is, therefore, a need for guidance on the approaches used by the Committees to integrate these evidence streams, both for scientific consistency and to ensure public transparency. To that end, the Committees established the Synthesising and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) to review and document current practice and provide applicable guidance.

1.150 SETE recognised that issues on which advice from the Committees is sought varies considerably and hence the guidance proposed should be sufficiently flexible to address this.

1.151 Scoping and problem formulation were identified as the crucial first step in the process. This ensures the right questions are asked, helps make the most efficient use of resources and identifies the most appropriate approaches to use in the assessment. An established system or guidance to assess the separate/different evidence streams should be followed where feasible.

1.152 For both epidemiological and toxicological evidence, a prescriptive checklist or scoring approach is not recommended. However, identifying the strengths and weaknesses of studies is important. The decision-making process should be robust, transparent, evidence-based, defensible and documented but equally importantly, it should be easy to use. Collaboration and ongoing dialogue between epidemiologists, exposure experts and toxicologists are strongly advised. Information on mode of action (MOA) can be invaluable for evidence integration as it underpins weight of evidence considerations by providing the mechanistic link between empirical observation and biological plausibility.

1.153 All lines of evidence should be considered, with no specific hierarchy a priori. One way to clearly depict the influence of the different lines of evidence on causality is via visual representation. Decisions on whether there is sufficient information to reach a conclusion or whether a causal relationship in humans is more likely or unlikely can be reached based on where the causal interference appears on a graph. It is important to begin with the initial estimate of causal interference at the centre of the graph. Depending on whether the toxicological, mechanistic or epidemiological evidence assessed supports or discounts (or has no clear influence on) a conclusion of causality, placement on the graph is then moved accordingly, either in a positive or negative direction. The movement is influenced by several factors, including the strength or weakness of the evidence, any relative weighing given to epidemiological and toxicological studies and the uncertainties associated with the data. As more information is included in the process and/or becomes available, the placement of the toxicological and/or epidemiological evidence can be easily adjusted and the impact on any possible conclusion easily seen.

1.154 In contrast to other approaches, the above visualisation aims to provide a pictorial representation of the consensus views of a Committee on the influence of the different lines of evidence on causation, assessed by debate and agreement of scientific experts. In this way, it provides a more objective means of collating the views of the Committee and communicating the agreed conclusion of a Committee on the likelihood of causation.

1.155 The conclusion should be stated, with an estimate of the overall uncertainty and, where appropriate, guidance on how data gaps could be filled.

1.156 The full SETE report and guidance document (Annex 1) can be found Here. Please note, the guidance will be trialled by the COT for 2 years and then reviewed.

Plant based drinks

1.157 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 have been reviewed by the Committee.

1.158 SACN have also considered these drinks from a nutrition perspective. To bring these two strand together, a joint Working Group had been established. The Working Group started work In December 2021 and it is hoped that it will report in 2022.

2021 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Chairman

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 (from April 2019)
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Ms Juliet Rix
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Dr Natalie Thatcher
Mondelēz International

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Emeritus Professor of Toxicology, Medical Toxicology Centre and Institute of Cellular Medicine, Newcastle University

Professor Philippe Wilson
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Professor Matthew Wright BSc, PhD
Professor of Toxicology, Institute of Cellular Medicine, Newcastle University

Professor Maged Younes
Independent expert on toxicology and biochemical pharmacology

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

Dr Simon Wilkinson

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Lawrence Finn
Shaddad Saleh
Emily Hudson
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Declaration of members interests during the period of this report

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Personal Interest	**Employee**	**Membership**

	Imperial College London, Department of Medicine (retired June 2017, part-time appointment from Aug 2017-May2019) Full retiral June 2019. Emeritus Professor of Imperial College London, National Heart & LungInstitute **Shareholder** Bank Santander Barclays Bank BG Group (until 2016)BT Group Centrica Iberdrola SA National GridLloyds	ILSI & ILSI HESI Board of TrusteesILSI Europe Board of Directors Science Advisory Board of Swiss Centre for Applied Human Toxicology Dept. of Health Committee on theMedical 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) Owlstone Medical (Owlstone Medical) (Scientific Advisory Board) Evidence-Based Toxicology Collaboration, Bloomberg School of Public Health, Johns Hopkins, USA (Scientific Advisory Board)
Non Personal Interest	**Grants** Horizon 2020 EUROMIX (until May 2019) Department of Health & Social	**Membership** None
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Non-Personal Interest	None	None
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Non-Personal Interest	None	None
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Non-Personal Interest	None	None
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Non-Personal Interest	None	None
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Professor Philippe Wilson		
Personal Interest	**Employee** Nottingham Trent University Rare Breeds Survival Trust	**Membership** None
Non-Personal Interest	None	None
Professor Matthew Wright		

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Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

Preface

Insert Text:

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PhD BSc (Hons) FBS CStat CBiol CSci

Ongoing Work

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COM evaluations

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Horizon scanning

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OECD

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2021 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Declaration of members interests during the period of this report

Awaiting Table from COM and a decision on formatting

Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Preface

Insert Text:

Professor David Harrison

MD DSc FRCPath FRCPEd FRCSEd

COC Evaluations

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Ongoing topics

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Joint meetings

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Horizon scanning

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Working Groups

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Guidance statements

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2021 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

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Declaration of members interests during the period of this report

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