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:

Committee on Toxicity

Committee on Carcinogenicity

Committee on Mutagenicity

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

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

Preface

It is 30 years since the COT issued its first report, also joint with COC and COM. In that time a lot has changed, but not the core function of the Committee, which remains to provide advice on the safety-in-use and on the potential adverse effects of chemicals in food, whether added intentionally or present incidentally.

At the beginning of year, Dr Sarah Judge, Newcastle University, became vice-chair of the Committee, for which I would like to thank her very much.

The Committee met on seven occasions during 2021, undertaking a busy and varied programme of work. The continuing COVID pandemic meant that the COT again held its meetings virtually but was able to successfully adapt to this new way of working to function effectively over the year. However, we look forward to being able to meet in person again as soon as that becomes possible.

The Committee has commenced a review of contaminants and other chemicals in support of the risk assessment of the maternal diet now being undertaken by the Scientific Advisory Committee on Nutrition (SACN). A number of topic areas were considered including environmental contaminants, excess nutrients and food supplements and the priority compounds identified; reviews of vitamin D, iodine and ginger were then started. The Committee also continued to work on another ongoing programme of work, on biologically based food contact materials - considering chitosan and bamboo composites as part of this.

Other topics discussed by the Committee this year have covered a wide range including variable lifetime exposure to chemicals, the combined effects of mycotoxins, , biomonitoring, oral exposure to microplastics, and the final EFSA opinion on titanium dioxide. Several previously reviews, including electronic nicotine delivery systems (e-cigarettes) and novel heat-not-burn tobacco products, have been updated along with cannabidiol where information on non-oral exposure was added to the position paper on CBD.

The Committee also discussed a roadmap setting out the way towards achieving the regulatory acceptance of New Approach Methodologies. These new techniques, including *in silico* modelling and *in vitro* assays, provide an important opportunity to not only reduce the use of laboratory animals but also have the potential to provide approaches that are faster, cheaper and more tailored in risk assessment. This was followed up in a virtual workshop which took place in October 2021. The FSA and COT are taking a UK lead on this important area.

The Committee also contributed comments to a number of public consultations from EFSA including on non-monotonic dose response and a draft protocol for the assessment of phthalates.

COT and COC Members along with other experts have been collaborating in a Working Group examining the Synthesis of Epidemiological and Toxicological Evidence (SETE). The resulting report was published in the Spring of 2021 and is an excellent example of the really valuable work that can be done by collaboration between the different Scientific Advisory Committees.

A joint Working Group has been set up between the COT and SACN colleagues to undertake a benefit- risk assessment of plant-based drinks consumed as an alternative to cows' milk. It is hoped this will report in 2022.

This year, the Committee said goodbye to Professor Faith Williams. On behalf of all Members, I would like to express the COT's sincere thanks to her for all her invaluable contributions to the work of the Committee over the years.

We welcomed new Members Professor Shirley Price from the University of Surrey, Professor Thorhallur Ingi Halldorsson from the University of Iceland and Dr Simon Wilkinson from Newcastle University to the Committee and look forward to working with them.

Next year it is expected that the work of the Committee will begin to change as it starts to oversee and assure the risk assessment of regulated products, which were previously assessed in Europe. To that end, three Joint Expert Groups (JEGs) have been established as part of the FSA Scientific Advisory Committee (SAC) structure and these JEGs will advise the FSA on regulated products; along with other SACs, the COT will oversee the work of these Groups and the Committee looks forward to working with them.

I would like to thank my fellow Committee Members for their commitment and invaluable contributions to the work of the Committee in very challenging circumstances. I would also like to express my sincere appreciation to the Secretariat who, despite the many difficulties they faced with the virtual meeting format and an evolving regulatory environment, continued to provide first class support for the Committee.

Professor
Alan Boobis (Chair)
OBE PhD CBiol FRSB FBTS FBPhS

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.

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 on the COT website: Position paper on the alternatives to conventional plastics for food & drinks packaging.

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.

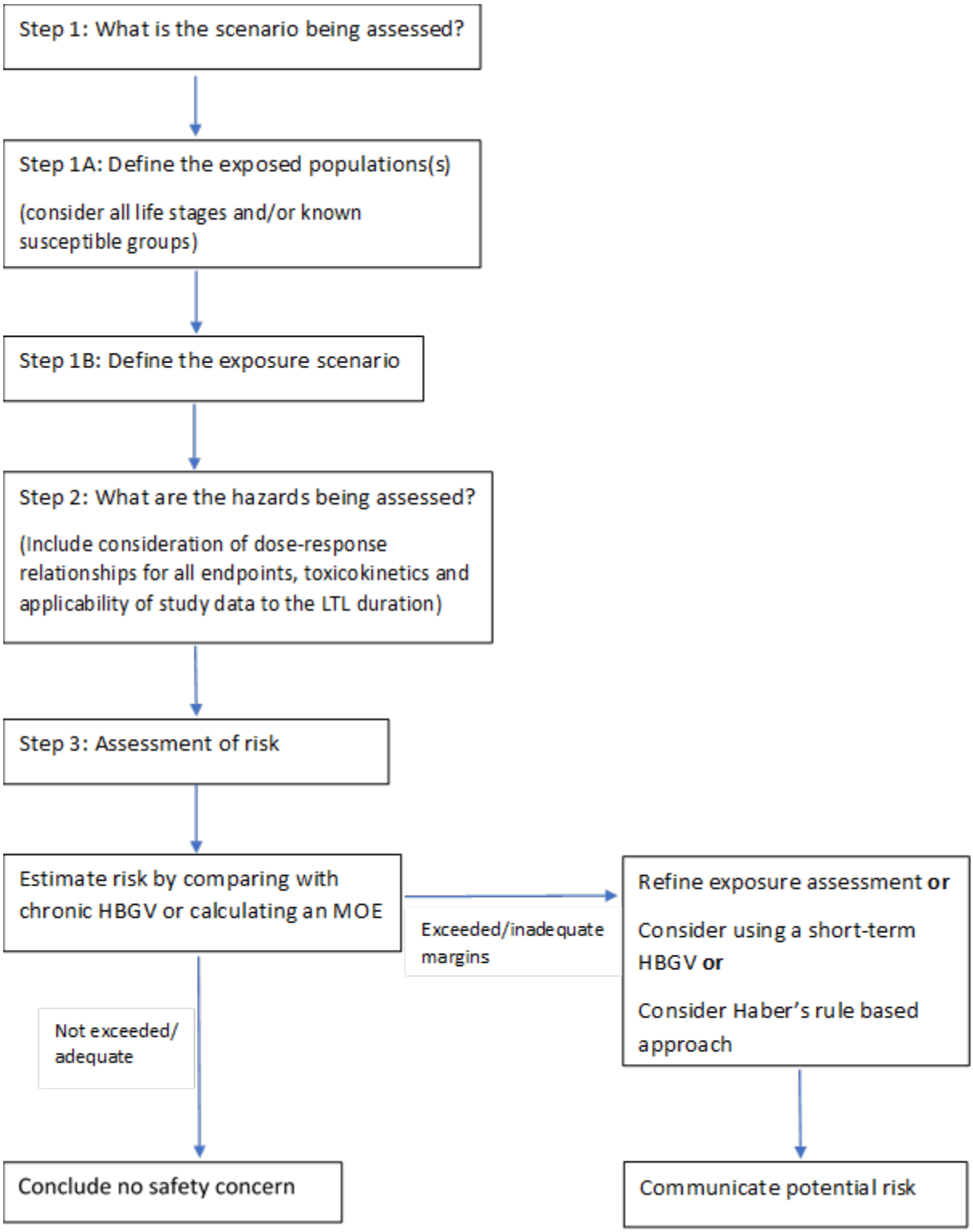

Figure 1: Flowchart to illustrate the process of assessing risks from less than lifetime or variable (LTLV) exposures. Where appropriate, toxicokinetic or toxicodynamic modelling could be applied to refine any of the steps.

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 3.1 below)

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.

1.85 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.

1.86 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.

1.87 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.

1.88 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.

1.89 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)

1.90 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.

1.91 The EFSA Opinion had also been presented to the COM for comments (see paragraph 2.33).

1.92 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.

1.93 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.

1.94 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.

1.95 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.

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

1.97 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.

1.98 It was decided that an interim position paper, capturing the COT's view and the proposed next steps should be published. This can be found at: COT position paper on titanium dioxide

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

1.99 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

1.100 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.

1.101 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.

1.102 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.

1.103 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.

1.104 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

1.105 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.

1.106 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.

1.107 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.

1.108 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.

1.109 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.

1.110 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 on the COT website: Updated position paper on the potential risk of CBD in CBD food .

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

1.111 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.

1.112 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).

1.113 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

1.114 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.

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

1.116 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

1.117 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.

1.118 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.

1.119 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"

1.120 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.

1.121 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.

1.122 The Committee was asked to comment on the draft opinion as part of the public consultation process.

1.123 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.

1.124 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.

1.125 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.

1.126 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.

1.127 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.

1.128 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

1.128 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.

1.129 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

1.130 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

1.131 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.

1.132 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.

1.133 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.

1.134 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

1.134 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.

1.135 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.

1.136 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.

1.137 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.

1.138 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

1.139 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.

1.140 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.

1.141 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.

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

Cadmium

1.143 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.

1.144 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.

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

Vitamin A

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

1.147 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.

1.148 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.

1.149 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.

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

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

Ginger and ginger supplements

1.152 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.

1.153 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.

1.154 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.

1.155 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.

1.156 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.

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

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

Iodine

1.159 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.

1.160 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.

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

1.162 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.

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

NAMs Roadmap

1.164 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.

1.165 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.

1.166 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.

1.167 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.

1.168 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.

1.169 During 2020, Members discussed the latest draft version of the 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

1.170 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.

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

1.172 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.

1.173 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.

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

Chitin and chitosan in food packaging materials

1.175 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.

1.176 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.

1.177 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.

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

1.179 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.

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

PBPK Workshop

1.181 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.

1.182 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).

1.183 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 1.30).

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. 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

1.150 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.

1.151 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.

1.152 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.

1.153 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.

1.154 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.

1.155 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.

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

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

Plant based drinks

1.158 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 – see paragraph 1.130.

1.159 SACN have also considered these drinks from a nutritional 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
Science Leader for Allergy and Immunology in Unilever's Safety and Environmental Assurance Centre.

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

Dr René Crevel
Director, René Crevel Consulting Limited.

Dr Caroline Harris PhD, CChem, FRSC
Practice Director and Principal Scientist, Exponent International Ltd.

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

Dr Sarah Judge BSc, PhD.
Lecturer in Pharmacology in the School of Biomedical, Nutritional and Sport Sciences at Newcastle University.

Dr Gunter Kuhnle
Professor of Nutrition and Food Science.

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

Dr Mac Provan
Director of Regulatory Science Ltd.

Ms Juliet Rix
Lay Member.

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

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

Dr Natalie Thatcher
Mondelēz International.

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

Professor Faith M Williams MA PhD hon FBTS (until March 2021).
Emeritus Professor of Toxicology, Medical Toxicology Centre and Institute of Cellular Medicine, Newcastle University.

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

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

Professor Maged Younes
Independent expert on toxicology and biochemical pharmacology.

Professor Thorhallur I. Halldorsson (from April 2021).
Professor at the Faculty of Food Science and Nutrition at the University of Iceland.

Dr Simon Wilkinson (from April 2021).
Senior Lecturer in Pharmacology in the School of Biomedical, Nutritional and Sports Sciences at Newcastle University.

Professor Shirley Price (from April 2021).
Emerita Professor of Toxicology at the University of Surrey.

Secretariat

Ms Catherine Mulholland BSc (Hons), ERT **Scientific Secretary**
Ms Britta Gadeberg BSc (Hons) MSc **Scientific Secretary – PHE**
Dr David Gott BSc (Hons) PhD
Dr Alexander Cooper BSc (Hons) MSc PhD
Dr Barbara Doerr BSc (Hons) MSc PhD
Dr Douglas Hedley BSc (Hons) MSc PhD
Ms Frances Hill BSc (Hons) MSc (until May 2021)
Ms Jocelyn Frimpong Manso BSc (Hons) MSc
Ms Cleanncy Hoppie BSc (Hons) MSc
Mr Barry Maycock BSc (Hons) MSc
Dr Olivia Osborne BSc (Hons) (Exon) PhD
Ms Claire Potter BSc (Hons) MSc ERT
Dr Joseph Shavila BSc (Hons) MSc PhD
Ms Chloe Thomas BSc (Hons) (until April 2021)
Ms Sabrina Thomas BSc (Hons) MSc
Ms Chara Tsoulli BSc (Hons) MSc
Ms **Frederique Uy** BSc (Hons) MSc
Miss Sophy Wells
Dr Gaetana Spedalieri (from September 2021)
Mr Thomas Hornsby BSc (Hons) MSc (from July 2021)
Mr Lawrence Finn BSc (Hons) MSc (from October 2021)
Ms Gail Drummond BSc (Hons) MSc, LLB, PG Dip (law) (from June 2021)
Dr Emily Hudson BSc (Hons) Mres (from November 2021)
Dr David Kovacic (from October 2021)

Declaration of members interests during the period of this report

Professor Alan Boobis OBE, PhD, FBTS, FBPhS

Personal Interest	**Employee:** Imperial College London, Department of Medicine (retired June 2017, part-time appointment from Aug 2017-May 2019). Full retiral June 2019. Emeritus Professor of Imperial College London, National Heart & Lung Institute.
Personal Interest	**Membership:** ILSI & ILSI,HESI Board of Trustees ILSI Europe. Board of Directors Science Advisory Board of Swiss Centre for Applied Human Toxicology. Dept. of Health Committee on the Medical Effects of Air Pollutants WHO/FAO JMPR. WHO/FAO JECFA (vet). WHO TobReg. WG10 TC126 (Intense Machine- smoking Regime for Testing Cigarettes). EUROTOX. British Pharmacological Society, British Toxicology Society, Society of Toxicology (USA). Royal Society of Biology (until 2017). Michigan State University MSU Center for Research on Ingredient Safety (CRIS) (External Advisory Committee). Agency for Innovations in Food and Chemical Safety Programme. Science, Technology and Research, Singapore (A*STAR) (Scientific Advisory Board).
Non Personal Interest	None.

Dr Phil Botham

Personal Interest	**Employee:** Syngenta - Principal Science Advisor (part time).
Personal Interest	**Shareholder:** AstraZeneca, Regulatory Science Associates(Part, Time

	Consultant).
Personal Interest	**Membership:** British Toxicology Society, Society of Toxicology (USA), European Centre for Ecotoxicology and Toxicology of Chemicals Scientific Committee, European Crop Protection Association Toxicology Expert Group, Crop Life International Human Health Steering Team.
Non-Personal Interest	None.

Ms Jane Case

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

Dr Stella Cochrane

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

Dr James Coulson

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

Dr René Crevel

Personal Interest	**Consultant:** Réne Crevel consulting.
Personal Interest	**Membership/affiliation:** ILSI Food Allergy Task Force: Chair.
Personal Interest	**Shareholder:** Unilever, Centrica, BG Group, National Grid, Lloyds.
Non-Personal Interest	None.

Professor Thorhallur Ingi Halldorsson COT Member from June 2021.

Personal Interest	**Employee:** Faculty of Food Science and Nutrition, University of Iceland.
Personal Interest	**Membership:** European Food Safety Authority - Scientific committee and various working groups. Nordic Council of Ministers - revision of the 2022 Nordic Nutrition Recommendation). Icelandic Risk Assessment Committee for Food, Feed, Fertilizers and Seeds (IRAC) – occasional expert work. The Nutricia Research Foundation – review of applications once a year. The Icelandic Research Found (RANNIS) – occasional member of different expert panels.
Non-Personal Interest	None.

Dr Caroline Harris

Personal Interest	**Employee:** Exponent International Ltd.
Personal Interest	**Membership:** International Union of Pure and AppliedChemistry.
Personal Interest	**Shareholder:** Exponent Inc.
Personal Interest	**Fellowships:** Royal Society of Chemistry.
Non-Personal Interest	**Membership:** Expert Committee on Pesticides.

Professor Gary Hutchison

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

Dr SarahJudge

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

Professor Gunter Kuhnle

Personal Interest	**Employee:** Professor of Nutrition and FoodScience, University of Reading.
Non-Personal Interest	None.

Dr David Lovell

Personal Interest	**Employee:** Reader in Medical Statistics, St Georges Medical SchoolUniversity of London.
Personal Interest	**Membership:** HESI GTTC – Biometrics Society, British Toxicology SocietyGenetics Society, Royal Society of Biology Laboratory Animal Science Association, Royal Statistical Society Statisticians in the PharmaceuticalIndustry, United Kingdom Environment Mutagen Society (UKEMS), UK National Centre of Replacement, Refinement and Reduction of Animals in Research(NC3Rs), MRC EMINENT Scientific ReviewBoard. **Also, private member of:** British Trust of Ornithologists (BTO) English Heritage, Liberty, Campaign of the Protection of RuralEngland (CPRE),

	Kew Gardens, Sandwich Bay Bird Observatory Trust(SBBOT), Chelsea Physic Garden, National Trust.
Personal Interest	**Shareholder:** National Grid, Pfizer, AstraZeneca (spouse shareholder), National Grid plc (spouse shareholder).
Non-Personal Interest	None.

Professor Shirley Price COT Member since June 2021.

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

Dr Mac Provan

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

Ms Juliet Rix

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

Dr Cheryl Scudamore

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

Dr NatalieThatcher

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

ProfessorMireille Toledano

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

Dr Simon Wilkinson COT Member since June 2021.

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

ProfessorPhilippe Wilson

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

Professor Matthew Wright

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

Professor Maged Younes

Personal Interest	**Employee:** Independent expert in toxicology and biochemical pharmacology.

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

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

Preface

I am pleased to present this report on the work of the Committee on Mutagenicity (COM) during 2021. I was honoured to be asked to take over the role of Chair of COM in May 2021 and I would like to begin by paying tribute to my predecessor (Dr David Lovell) for his stewardship of COM during the preceding years and Chairing the February 2021 meeting.

The Committee on Mutagenicity (COM) provides advice on potential mutagenic activity of specific chemicals at the request of UK Government Departments and Agencies. Such requests generally relate to chemicals for which there are incomplete, non-standard or controversial data sets for which independent authoritative advice on potential mutagenic hazards and risks is required. Recommendations for further studies are, on occasions, made.

The Committee also advises on important general principles and on new scientific work related to the assessment of mutagenic risk and makes recommendations on wider aspects of mutagenicity testing. The membership of the Committee, declarations of their interests, agendas and minutes of meetings, and statements are all published on the internet. Latest from the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

In 2021, the updated COM guidance on genotoxicity testing strategy was published (MUT/2021/01). This update, begun in 2020, sets out the suggested strategy for genotoxicity testing of chemicals and updates our position to consider advances in the field of safety testing. COM also updated guidance on testing of germ cell mutagens (MUT/2021/02) and the use of 3D tissue models as alternative approaches to animals in testing (MUT/2021/03). The documents will be published on the COM website. The 3D tissue strategy responds to the growing focus on animal alternatives driven by the production of novel sophisticated tissue models which can recapitulate aspects of human biology.

In 2021, COM discussed the safety testing of impurities (MUT/2021/04) and the use of QSAR and toxicogenomics in testing (MUT/2021/05 and MUT/2021/06).

In 2021, COM started a discussion of the genotoxicity of titanium dioxide (MUT/2021/07 and MUT/2021/12), following the updated opinion published by EFSA in 2021. This review of titanium dioxide will be continued in 2022.

In 2021, COM further discussed the use of toxicogenomics in safety testing (MUT/2021/08), separating out the transcriptomics aspect from the next generation sequencing (NGS) approaches. Given the advances in NGS in general, it is likely that over the coming years, NGS approaches may replace some traditional mutation testing platforms. COM also published guidance on a testing approach for nanomaterials, with a focus on considerations of the fact that key physico-chemical aspects of nanomaterials render some traditional genotoxicity tests not suitable (MUT/2021/09).

COM also discussed the potential genotoxicity of specific compounds as requested by Government departments and agencies. For example, COM reviewed the genotoxicity of Hydroxyanthracene Derivatives (MUT/2021/12) and associated human health risks.

The Committee carried out its annual Horizon scanning exercise, identifying potential topics for future work. The COM continues to be interested in hearing from Government Departments and Agencies on how its advice is acted upon.

The COM maintained its awareness of the implications of EU EXIT on its work and remained alert to the continuing uncertainty as to how the UK's regulatory environment and its relationships with international organisations will develop in 2022 and onwards.

I would specifically like to thank the COM secretariat for their exceptional support to the COM and to the WRc/IEH team for the excellent work they delivered in 2021. As always, I am grateful for the support of the individual members of the committee for their expert advice, the effort and time they put in and their support throughout the year.

Professor Gareth Jenkins

Ongoing Work

COM Guidance Series Update

2.1 The updating of the overarching COM Guidance document on a strategy for the genotoxicity testing of chemicals was finalised in 2021. Amendments to the overarching COM Guidance document had previously been considered at Committee meetings in July 2018 (paper MUT/2018/09), October 2018 (paper MUT/2018/13), February 2019 (MUT/2019/01), October 2019 (MUT/2019/12), February 2020 (MUT/2020/03), June 2020 (MUT/2020/09) and November 2020 (MUT/2020/16). An additional sub-group meeting was held in January 2021 to complete review of comments left outstanding following the November 2020 meeting.

2.2 Following consideration of paper MUT/2021/01 the update of the overarching COM Guidance document on a strategy for the genotoxicity testing of chemicals was agreed by members, signed off by Chair action and published on the COM website. It was intended that this would be updated in the future as part of a rolling revision.

Guidance Statement – Germ Cell Mutagens

2.3 Drafts of a stand-alone guidance statement on genotoxicity testing strategies for germ cell mutagens were considered at the Committee meeting in February 2019 (MUT/2019/05), in October 2019 (MUT/2019/12), in June 2020 (MUT/2020/11) and November (MUT/2020/17). In 2021, members considered paper MUT/2021/02, which presented changes suggested following the November 2020 meeting. Following agreed amendments, the finalised document was signed off by Chair's action and published on the COM website.

Guidance Statement – 3D Models

2.4 Drafts of a stand-alone guidance statement on the use of 3D models for genotoxicity testing were considered at the Committee meetings in February 2019 (MUT/2019/04), October 2019 (MUT/2019/12), June 2020 (MUT/2020/11) and November (MUT/2020/18). In 2021, members considered paper MUT/2021/03, which included suggested changes following the meeting in November 2020. Following agreed amendments, the finalised document was signed off by Chair's action and published on the COM website.

Guidance on Genotoxicity Testing Strategies for Nanomaterials

2.5 Genotoxicity testing of nanomaterials (NMs) was recognised by the Committee as a rapidly developing area. Paper MUT/2021/09 presented a draft COM Guidance on the genotoxicity testing strategy for NMs. This was prepared to a format previously agreed by COM at the meeting in November 2020 (MUT/2020/19). Members considered that it was important to add a note to clarify that 'Stage 0' of the COM recommended approach for genotoxicity testing would not apply to NMs. A question was raised regarding whether COM should recommend a positive control for NM testing. This was not considered feasible at present as this would probably need to be both assay and cell line specific, due to differing sensitivities. Members requested that this information be added to the document. It was also agreed that a note should be added to consider the most appropriate dispersion technique for a specific NM. Following these amendments, members agreed that a final version of the document could be signed off by Chair's Action and published on the COM website. It is recognised by the Committee that this is a rapidly developing area and updates will be carried out as new information becomes available.

Guidance Statement on Testing for Impurities – Update

2.6 The COM published a guidance statement in 2012 on a strategy for genotoxicity testing and mutagenic hazard assessment of impurities in chemical substances. Since 2012, there have been a number of initiatives in this area and as part of the ongoing update of the COM Guidance Statement series, members agreed that the Guidance document should be updated. A draft revised document was presented at the Committee meeting in November 2020 (MUT/2020/21) and following comments and suggestions from members a revised draft statement was produced (MUT/2021/04) and presented at the February 2021 meeting. During review it was suggested that the impurities guidance statement and QSAR guidance statement could be merged as there was overlap between the two areas.

COM Guidance Statement on the Use of QSAR Models

2.7 A range of Quantitative Structure-Activity Relationship (QSAR) models have been developed to predict genotoxicity. The COM has previously agreed that where no genotoxicity data are available, the intrinsic chemical and toxicological properties of a chemical must be considered prior to developing a genotoxicity testing programme, as reported in "Guidance On A Strategy For Genotoxicity Testing Of Chemical Substances" (COM, 2011) and as updated in 2021. This guidance describes a staged approach to testing consisting of stages 0 (preliminary considerations including physico-chemical properties), 1 (*in vitro* genotoxicity tests) and 2 (*in vivo* genotoxicity tests). QSARs are incorporated into Stage 0 of the COM guidance.

Alternatives to animal testing and the usefulness of computational methods in the prediction of genotoxicity are areas of increasing research. QSAR models and their predictions currently cannot replace the need to undertake the *in vitro* and *in vivo* genotoxicity tests required to derive conclusions on mutagenic hazard except in specific regulatory settings. As the development and use of QSAR is a rapidly developing field, it was agreed that the current text in the COM overarching guidance document should be reduced and a larger 'stand-alone' guidance statement be prepared which could be updated as needed.

2.8 A draft document - 'Guidance Statement on the use of QSAR models to predict genotoxicity' was prepared and discussed by COM in February 2019 (MUT/2019/03). Following amendments, a revised paper was discussed in February 2020 (MUT/2020/02) and November 2020 (MUT/2020/20). No agreement was reached as to whether the draft guidance statement was 'fit-for-purpose', and it was also suggested that QSARs could be incorporated into the COM guidance on impurities, as this is where it is likely to be used.

2.9 Following a further draft COM Guidance on QSARs (MUT/2021/05) considered at the February 2021 meeting, a sub-group discussion with some COM members was held in September 2021 to plan a way forward. It was suggested that, based on current acceptance and use of QSARs, incorporation of examples of use and reporting of data should be included in the updated impurities guidance document, with a link to the OECD portal provided to give the most current perspective/tools etc. A more general description (taken from the current draft document) would then be re-introduced into the COM overarching guidance document to support the Stage 0 testing text.

2.10 Members agreed that it was important for any COM guidance to highlight applications of QSAR, rather than providing a list of QSAR models and approaches.

Toxicogenomics and Risk Assessment: Application of Transcriptomics and Next Generation Sequencing to Genotoxicity and Carcinogenicity Assessment

2.11 At the COM meeting in February 2021, during discussions of some preliminary literature on 'toxicogenomics and risk assessment' (MUT/2021/06), members noted that this field could at present be considered to comprise two different major elements; the more highly established field of transcriptomics, and the newer area of next-generation sequencing technologies. It was felt that it would be useful for a document to be prepared providing a preliminary overview of these two areas and their potential applications to risk assessment in the fields of mutagenicity and carcinogenicity. Discussion paper MUT/2021/08 provided an overview of these two areas, summarising narrative from three recently published review articles.

2.12 Members noted that overall, this was a fast-developing area. For this reason, it may be difficult for the COM to establish a specific guidance document, as this would rapidly become out of date. However, members also considered that this is a

very important area in the development in genotoxicity assessment and should be kept under evaluation by the Committee.

2.13 Some major areas of work in this field were highlighted. These included: Current efforts to obtain mutational signatures and match these to environmental exposures, which was noted as an area that the COM would probably wish to focus on further; Progression of work on TGx-DDI (a transcriptomic biomarker for genotoxicity), noting that data is being passed to regulators with the aim to be able to provide guidance; Development of duplex sequencing at Health Canada, which is starting to be useful for investigations of germ-cell mutagenesis and for dose-response analysis; Use of cancer-driver mutations via the 'CarcSeq' method at FDA.

2.14 In terms of document progression, a more detailed paper could be envisaged, noting techniques and methodologies that are becoming available, and describing some examples of how these techniques may be becoming applicable to investigation of genotoxicity. It was agreed that further development of any paper from COM concerning the use of toxicogenomics for risk assessment purposes would be discussed by a small sub-group of interested members.

Presentation by Professor Michael K Skinner – Washington State University, USA – Environmental Toxicant Induced Epigenetic Transgenerational Inheritance of Disease. Generational Toxicology – Open to COC and COT Members

2.15 At the February 2021 meeting, Professor Skinner from Washington State University (Washington, USA) presented a talk entitled 'Environmental Toxicant Induced Epigenetic Transgenerational Inheritance of Disease: Generational Toxicology'. This was also open to COC and COT members.

2.16 As an introduction, Professor Mike Skinner highlighted that it is difficult to explain all disease based solely on the genome and that that environmental factors also play a role on the occurrence of disease. What is observed is not completely explained by the paradigm of the genome affecting gene expression, which in turn affects physiology and the development of disease. For example, the development of disease in identical twins is reported to vary when identical twins live in different regions. This indicates that other factors are involved in addition to individual DNA sequence.

2.17 Professor Mike Skinner summarised animal studies that showed adverse effects in future generations (i.e., F2 and later generations, where the germline was not directly exposed to the initial test chemical) arising from an initial chemical exposure in pregnant females. The observed adverse effects arose from epigenetic changes. Epigenetic effects could arise from chemical induced changes in DNA methylation, histone modifications and effects on RNA (i.e., not involving a change in

the DNA sequence). Such chemical induced epigenetic changes can result in modification of gene expression.

2.17 Professor Skinner noted that if a gestating F0 female animal is exposed to a particular chemical, then the F3 generation would be first generation that did not receive a direct test chemical germline exposure. Chemical induced effects seen in the F3 generation and subsequent generation could be due to epigenetic effects or inherited changes in gene expression arising from the initial gestating exposure of the F0 female. This would be an example of transgenerational inheritance. If a non-pregnant female or a male animal was exposed to the test chemical, then the F2 generation would be the first generation that did not receive direct germline chemical exposure. Chemical induced effects in this generation could arise from inherited epigenetic changes (this would be an example of transgenerational inheritance).

2.18 A number of examples of results of chemical exposure in animals were reported where 90% of treated animals showed adverse effects in the F3 generation resulting from an initial F0 gestating female exposure. For example, vinclozolin (agricultural fungicide), TCDD/Dioxin, DDT, bisphenol A and diethyl hexyl phthalate produced adverse effects in the F1 generation and in the F3 generation. Flutamide (anti-androgenic pharmaceutical) produced adverse effects in F1, but not in F3 generation. However, atrazine (agricultural herbicide) and glyphosate (herbicide) did not induce adverse effects in F1 but did in F3 (transgenerational effect). Examples of chemically induced transgenerational disease effects included spermatogenic defects, male infertility, prostate disease, premature ovarian failure, ovarian polycystic ovarian disease, birth defects, kidney disease, obesity, behavioural effects and immune effects.

2.19 Other types of exposures can also induce epigenetic and transgenerational effects, such as extreme temperature, drought, high fat diet or caloric restriction, smoking and alcohol. Studies were described where various transgenerational epimutations and clusters were detected in the sperm genome in the F3 generation following initial chemical exposure, such as with vinclozolin and DDT.

2.20 One of the most sensitive periods of exposure is during fetal gonadal sex determination when the germ line is undergoing epigenetic programming and DNA re-methylation occurs. The suggestion that environmental toxicants can re-programme the germ line to induce epigenetic transgenerational inheritance of disease, is a new paradigm in disease aetiology, and indicates the need to assess generational toxicology in the future.

2.21 Key take home messages from the presentation included: the germline (eggs and sperm) are where epigenetic changes are critical because they get passed on in a transgenerational manner; this epigenetic transgenerational inheritance does not involve an inherited change in the DNA sequence; and a recommendation that adverse transgenerational effects need to be investigated in chemical health risk assessment. It was suggested that animal studies would be required to do this because current *in vitro* studies would not be suitable.

2.22 In discussions following the presentation, clarification was sought by members around how assessment of intragenerational effects may be included in current testing regimes. At the present time this can only be achieved through laboratory animal studies where the third generation needs to be evaluated, with minimum study length of between 1 and 1.5 years. It is not feasible to assess the germ cells of affected individuals because the shifts in developmental programming need to be established before the effects of the exposure are seen. A large proportion of the changes seen in earlier generations are due to direct exposure.

2.23 At present, transgenerational effects have been shown for many toxic compounds and so such testing is likely to be needed on a routine basis. There are no *in vitro* approaches that are effective to replace *in vivo* assays. It was considered possible that thresholds existed for the level of DNA methylation sites, below which long-term disease was avoided.

2.24 Diet was discussed as a major factor that had previously been linked with epigenetic changes. For a generational impact to occur the dietary influences have to be quite severe (for example, calorific restriction or high fat diets), with small shifts in diet not having an impact. Timing of exposure was also found to be key, with exposure during the early fetal life period being critical. Environmental toxicants were considered to have an effect at similar levels to calorific restriction. The importance of epidemiology studies in supporting animal data and showing causality was also discussed. Epigenetic biomarkers are needed for use in epidemiological studies, and these have not been developed.

2.25 The Chair thanked the speaker on behalf of the Committee for an interesting and informative presentation. In conclusion, it was agreed that the COM would keep an active watching brief on developments in the area, particularly in relation to inclusion in toxicity testing regimes.

Presentation on Toxicogenomics in Toxicology Testing by Dr Scott Auerbach, Division of the National Toxicology Program, National Institute of Environmental Health Sciences, USA

2.26 At the June 2021 COM meeting, Dr Scott Auerbach provided a presentation on toxicogenomics in toxicology testing. Dr Auerbach noted that functional omics technologies are a powerful tool for the characterisation of chemical effects in biological systems. Historically the primary use of omics technologies, transcriptomics in particular, has been to characterise chemical mode of action to understand toxicological mechanisms and human relevance. More recently effort has been put into use of transcriptomics as a means to identify a biological effect point of departure that roughly approximates a point of departure derived from much more resource intensive studies such as the two-year cancer bioassay.

2.27 The presentation discussed how transcriptomics has been used for qualitative characterisation of chemical effects and how it is being modelled to derive a

genomic-based point of departure. In addition, some of the current scientific challenges that need to be addressed to facilitate more widespread use of genomic point of departure values for health-based guidance value determination were also discussed.

2.28 Following the presentation, the sensitivity of the methodology was queried as some genotoxic compounds may not have a strong genotoxicity signal over the shorter exposure time. This is addressed by the inclusion of doses of test substance up to the maximum tolerated dose during screening which should produce a signal if it is genotoxic. The limitation of precision of toxicogenomics in its ability to determine what proportion of cells are affected to produce the measured 'fold' change was highlighted. This was anticipated to be a chemical specific issue as those only affecting a small number of focal points (e.g., nitrosamines) would take longer to produce a signal than chemicals affecting multiple sites (e.g., 3,3',4,4'-Tetrachloroazobenzene) and should be taken into account to avoid inaccuracies. The use of gene-set dose response data (as a point of departure) with benchmark dose modelling was also discussed. There is no standard model to use with such data as the adverse effect size (BMR) for a particular gene is not known for many chemicals. It is also not possible at this time to take into account the effect of co-variables, which is an important consideration for human data, however this is being actively addressed by a number of groups.

Presentation on OECD development of the Mini-Ames
Dr Robert Smith, Covance

2.29 Dr Robert Smith, the UK representative on the OECD expert group developing the mini-Ames test, gave a presentation and summary of the activities of the OECD expert group on the miniaturised bacterial mutation assay.

2.30 New approaches to the or Ames test (OECD TG 471) are being explored, such as miniaturised assays, as they offer higher throughput with a significant reduction in the amount of test material required, resources and cost.

2.31 Several miniaturised versions have been developed and are already extensively used for screening purposes during product development/candidate selection or for impurity assessment/qualification. These have some differences when compared to the standard Ames assay and are not described in any existing OECD Test Guideline. Differences include the use of multi-well plates, use of liquid media rather than agar plates, the number of bacterial strains used, and the use of reduced numbers of bacterial cells (and volumes, etc.).

2.32 Following the presentation, members considered the possibility that data obtained from Ames II™ assays run by inexperienced laboratories may have influenced the findings of the Detailed Review Paper (DRP). However, there had been a requirement for laboratories to show proficiency prior to submitting data for

inclusion. Although there was good concordance between the 4 assays evaluated (6 and 24-well agar plates, micro-fluctuation and Ames II™ assays) there was some remaining discussion around comparison of top doses, as the microfluctuation assay expressed doses as µg/ml and the Ames assay as µg/plate. It was also considered that exposure might be enhanced for the fluctuation assay, as fewer cells are present. The effect of pre-incubation in the fluctuation assay was queried and had been associated with a small increase in sensitivity and specificity. The maximum limit on concentration per well/plate was considered by members to be a critical factor for take-up of the assays once finalised. The OECD had produced a DRP on the evaluation of various mini-Ames assays cited in the literature compared with the standard Ames test. The OECD DRP was circulated to COM members for comment.

COM evaluations

Review of the EFSA Opinion on Titanium Dioxide (E171) Presented by the Food Standards Agency

2.33 The Food Standards Agency requested advice from the COM on the genotoxicity of Titanium Dioxide, following a re-evaluation by the European Food Safety Authority (EFSA) published in 2021.
2.34 Titanium dioxide is an authorised Food Additive in the EU and under GB Food Law (retained EU law Regulation No 1333/2008 on food additives). It is used in food as a colour to make food more visually appealing, to give colour to food that would otherwise be colourless, or to restore the original appearance of food.
2.35 Titanium dioxide has been the subject of multiple safety evaluations. Following a review of Titanium dioxide specifications in 2019 and based on the fraction of nanoparticles present in E171, it was considered that the food additive fell under the scope of the EFSA guidance on nanotechnology and a recommendation for re-assessment of the safety of Titanium dioxide was proposed.
2.36 In the most recent evaluation published in 2021, data evaluated was for the food additive Titanium dioxide E171 as well as titanium dioxide other than E171 containing a fraction of nanoparticles <100nm or nano titanium dioxide. Concerning the genotoxicity studies, combining the available lines of evidence, the EFSA Panel on Food Additives and Flavourings (FAF) concluded that Titanium dioxide particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations. No clear correlation was observed between the physico-chemical properties of Titanium dioxide particles – such as crystalline form, size of constituent particles, shape and agglomeration state – and the outcome of in vitro or in vivo genotoxicity assays (i.e. a cut-off value for Titanium dioxide particle size with respect to genotoxicity could not be identified). The EFSA FAF Panel concluded that several modes of action (MOA) may operate in parallel and the relative contributions of the different molecular mechanisms resulting in the genotoxicity of Titanium dioxide particles are unknown. Based on the available data, no conclusion could be drawn as to whether the genotoxicity of Titanium dioxide particles is mediated by a mode (s) of

action with a threshold(s). Therefore, the EFSA FAF Panel concluded that a concern for genotoxicity of Titanium dioxide particles cannot be ruled out.

2.37 The COM were requested to consider paper MUT/2021/03, which summarised the EFSA 2021 evaluation and included a number of questions that the COM were requested to consider.
2.38 The COM had concerns over the quality and robustness of some of the studies considered by EFSA to draw its conclusions and noted that the overall data considered by EFSA was heterogenous (e.g. the range of particles evaluated was diverse; different types of approach and assays; different doses; different cell models; some studies were published in obscure or non-genotoxicity journals and the inclusion of non-GLP studies, which all contributed to the difficulty in making comparisons and an overall evaluation). Members were also concerned over the potential for publication bias in the studies evaluated by EFSA (i.e. where negative studies were less likely to be published). It was also noted that until relatively recently, the specification of E171 was poorly defined, which contributed to uncertainty and difficulty in evaluation.
2.39 Regarding mode of genotoxic action, the COM agreed that the evidence indicated an indirect interaction with DNA with a threshold for genotoxicity. Some positive results were found with a mixture of nano and micro particles. It was impossible to interpret which fraction was responsible, although pure micro sized particles generally were negative. The in vivo studies tended to be of better quality and negative. The nano-fraction in E171 is thought to be low but the fraction of nanoparticles (<100nm) can be over 50%. The percentage of the nano-fraction and its bioavailability are important factors when considering risk assessment.
2.40 Members considered that the lack of quality in the evidence (e.g. mixed particle sizes (micro and nanoparticles) and a wide variety of testing approaches) did not allow definitive conclusions to be drawn and therefore did not agree with the EFSA overall conclusions on the genotoxicity of E171 Titanium dioxide. A review of more reliable and robust dataset may be required before conclusion could be drawn on the mutagenicity of titanium dioxide particles. Members noted that EFSA made no clear distinction between the genotoxicity of nano-sized and micro-sized titanium dioxide
2.41 particles. EFSA seemed to have put a lot of emphasis on the evidence from nano-sized particle studies when nanoparticles made up only a small fraction of E171. The COM suggested that if practicable, restricting the amount of nanoparticles in the specification for E171 may reduce any potential genotoxicity risk. Additionally, the COM considered that the wording of EFSA's conclusion was not helpful from a risk communication perspective. Due to the heterogenous data and equivocality of the evidence further refinement of the data evaluated may be needed before definitive conclusions on the genotoxicity and safety of titanium oxide could be made. Currently, the EFSA conclusions were not justifiable based on the available evidence and this may create unnecessary concern for the public.
2.42 The COM agreed to develop an approach to evaluating all the available data (e.g., sifting for relevant and suitable studies) before continuing its review of the genotoxicity of titanium dioxide and before it could derive any firm conclusions or opinion.

Hydroxyanthracene derivatives

2.43 On the request of the UK-wide Nutrition Labelling Composition and Standards (NLCS) policy group, the UK Food Standards Agency (FSA) commissioned an independent view from the COM to advise on the genotoxicity of hydroxyanthracene derivatives (HADs) based on the 2018 EFSA opinion and any new data that have become available. Paper MUT/2021/11 provided a summary and discussion of the EFSA 2018 scientific opinion on the safety of HADs for use in food. Relevant literature studies published after 2018 were also described, including studies by Galli et al. (2021a,b) and Hu et al. (2021). Members were asked to consider whether they agreed with the EFSA 2018 conclusions and whether any of the EFSA conclusions would be affected by the results of the additional studies published since the EFSA 2018 opinion.

2.44 The Committee agreed that that overall, the available evidence indicated that emodin, aloe-emodin, and dantron are genotoxic in vitro, namely from Ames tests. Mixed results for in vitro genotoxicity had been reported in the literature. This was sometimes due to a lack of clarity on the preparation used for testing. Decolourised extracts (which were generally negative as they contain a far lower concentration of HADs), and whole extracts (which were positive as they contain greater concentrations of HADs). However, more information was needed to be confident that there was also genotoxicity in the mammalian cell assays, because i) the mouse lymphoma and micronucleus data summarised in the EFSA opinion were published in 1996 (since then, changes have been made to how genotoxicity is evaluated, for example to make sure excessive doses are not used), and ii) Müller et al. (1996) did not perform statistical evaluation of the data. Therefore, overall, it was not clear to the COM if the positive results in the mammalian cell assays were reflective of mutagenicity, or rather reflective of toxicity from the use of excessively high concentrations.

2.45 In terms of in vivo genotoxicity, one member questioned how much weight should be placed on negative mouse data published after 2018, as EFSA agreed that mice appear to be less sensitive than rats to the gastrointestinal effects caused by HADs. The Committee agreed that the studies published after 2018 are mostly negative in vivo data, which weaken the evidence that there is a genotoxic effect in vivo.

2.46 While EFSA concluded that results from the in vivo bone marrow micronucleus assay were irrelevant (due to insufficient bone marrow exposure), the COM noted that plasma analysis was conducted and the active compound was detected or quantified in plasma, indicating there was sufficient bone marrow exposure (albeit at a low level). COM further noted that a US National Toxicology Program (NTP) study included an assessment of plasma levels and micronucleus formation in rats and mice with acute intraperitoneal exposure (to ensure adequate systemic exposure) and these results were also negative. Therefore, the COM agreed that the negative results from the in vivo bone marrow micronucleus assay were valid and concluded that there is reasonable evidence that there is no genotoxic effect in vivo.

2.47 The COM considered that the carcinogenic effects of HADs, including those seen in the comet assay of colon cells, were caused by the high levels of irritation, inflammation, and diarrhoea. The 2-fold increase in tail moment (present at all dose levels) in colon cells under the comet assay was not caused by DNA reactivity, but

rather an indirect mechanism involving ROS generation and/or topoisomerase II inhibition (mechanisms that were indicated from in vitro data). Since the Committee concluded that HADs do not show a genotoxicity mechanism, a new in vivo genotoxicity study would not be helpful.

2.48 The COM agreed that it should in theory be possible to establish a daily intake of HADs that does not give rise to health concerns using carcinogenicity data. However, more in vivo carcinogenicity data were needed to carry out dose response modelling and to identify a point of departure. The COM agreed that a specification for supplements regarding HADS contents would be useful for comparison against a potential Acceptable Daily Intake (ADI).

2.49 The FSA Secretariat agreed to provide an update to the COM in due course.

Horizon Scanning

Forward look from the Chair

2.50 The Chair suggested two main areas of potential interest to the COM, which were genomics and next generation sequencing, and the use of genotoxicity markers in human biomonitoring. It was anticipated that in the next few years genomics and sequencing would be seen more in genotoxicity, including Duplex sequencing. There was a potential for this to support or even replace genotoxicity testing, particularly testing for gene mutation or point mutation. Developments in these areas may also provide an opportunity to gain more information from biomonitoring, occupational exposure or environmental exposure.

Presentation by Health and Safety Executive

2.51 Dr Lata Koshy gave a presentation on the work of the Health and Safety Executive (HSE) post the UK exit from the EU. HSE are involved in a number of activities within UK REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), which includes identifying hazards, such as mutagenicity, and identifying substances of Very High Concern (SVHC). Most of the HSE work on Classification, Labelling and Packaging regulation relates to hazard identification for industrial chemicals. The HSE is also involved in the regulation of biocides and pesticides. Additionally, the HSE produces summaries for ministers and HSE opinions on the mandatory classification of substances and whether to align with EU opinion. The future work programme of the HSE is still being worked out post EU Exit and will be limited by resource and recruitment. HSE anticipated that it would complete the evaluation of two to three active substances per year. Evaluation of mutagenicity is a key part in determining whether an active substance will be given approval. Mutagenicity is also a key factor in the UK review of new and existing substances and import tolerance for pesticides. Due to the short timeline, it may be difficult consulting with COM, which has three meetings per year.

2.52 Some key differences for HSE since the UK exit from the EU is that the HSE has to act in isolation from EFSA and ECHA and from that peer review process. Its independence meant that it had to improve its own individual peer review process and has set up various expert groups and developed links with various other expert advisory groups. HSE may consult the COM in the future in relation to complex genotoxicity data sets and for advice in reviewing GHS for germ cell mutation category 1 and 2. The COM guidance documents, and expert advice will be useful to the HSE and its advice on specific areas, for example, on mode of action/threshold mode of genotoxic action and the use of QSARs.

Government assessors

2.53 Assessors from other Government Departments and agencies were asked for any horizon scanning topics they wished to highlight. VMD had an interest in biopharmaceutical molecules and their potential for mutagenicity. VMD were not aware of any guidance on how to assess the mutagenic potential, for example, of modified stem cells or monoclonal antibodies, particularly those sourced from different species (e.g. xenogeneic stem cells). VMD may seek the view of the COM of this area in the future. BEIS noted that it had set up its own expert scientific advisory groups following UK exit from the EU and that it would be seeking to develop links with secretariats for other expert advisory groups, such as the COM.

2.54 Members of the COM were asked to send in any thoughts on horizon scanning topics to the COM secretariat.

OECD

2.55 The COM was sent a consultation on a new draft Test Guideline on the mammalian erythrocyte Pig-a gene mutation assay. Members were requested to send any comments to the secretariat so that these could be collated and sent to the OECD.

OECD Draft Detailed Review Paper on the Miniaturised Versions of the Bacterial Reverse Gene Mutation Test

2.56 Members were requested to provide comments on an OECD Draft Detailed Review Paper (DRP) on the miniaturised Ames test (bacterial reverse gene mutation test) for collation by the National Coordinator at UK HSA. Assessors were requested to also send any comments which would be submitted separately.

2.57 It was noted that the DRP will not lead to a revision of the TG (TG471), but the aim of the review was to provide recommendations on the use of each of the mini-Ames tests proposed. From a UK perspective it was considered important to highlight and record any controversial points that were not in line with UK practice.

2.58 There was general agreement with the recommendations of the DRP. It was felt that until a robust validation process of the mini-Ames assays had been carried out, no further progress could be made in implementing the assays for regulatory testing. Further justification was requested, including better definition of what the assay is for, e.g., increasing output and reducing costs, incorporation of information relating to how laboratories were chosen to take part and whether there is a clear benefit of using mini-Ames assays above TG471. It was intended that a short written summary of the text submitted to OECD would be provided to COM members at the meeting in March 2022.

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

Chairman:

Dr David Lovell PhD BSc (Hons) FRSB CStat CBiol (until 30/04/2021).

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

Professor Gareth Jenkins (from 01/05/2021).

Professor of Molecular Carcinogenesis, Faculty of Health, Medicine and Life Science, Swansea University.

Members:

Dr Carol Beevers

Broughton Nicotine Services.

Mr Amit Bhagwat

Lay Member.

Dr Stephen Dean (until 31/12/2021).

Imagen Therapeutics.

Professor Shareen Doak

Institute of Life Science, Swansea University Medical School.

Dr Paul Fowler

FSTox Consulting.

Professor David Harrison MD DSc FRCPath FRCPEd FRCSEd

Professor of Pathology, University of St Andrews.

Dr George Johnson

Associate Professor, Swansea University Medical School.

Ms Julia Kenny

GlaxoSmithKline.

Dr Ruth Morse (until 31/08/2021).

Senior Lecturer in Human & Clinical Genetics, University of the West of England, Bristol.

Dr Andrew Povey

Reader in Molecular Epidemiology, University of Manchester.

Mrs Madeleine Wang

Lay Member.

Secretariat

Dr Ovnair Sepai	PHE Scientific Secretary
Ms C Mulholland	FSA Scientific Secretary
Mrs N Blowfield	Administrative Secretary

Declaration of members interests during the period of this report

Professor Gareth Jenkins COM Chair from 01/05/202.

Personal Interest	**Employer:** Swansea University.
Personal Interest	**Honorary Contract:** Swansea Bay University Health Board.
Personal Interest	**Membership:** President of United Kingdom Environment Mutagen Society (UKEMS). Member: British Association for Cancer Research. Senior Editor Mutagenesis (OUP), Editorial Board (and former editor 2013-2015) Mutation Research (Elsevier). Health & Care Research Wales Grant panel (studentships) 2016 – present.
Non-Personal Interest	**Grants:** National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (2018-2022). Former NC3Rs grants (2012-2016 & 2010-2014) Former grants Health & Care Research Wales (2016-2020, 2014-2017. Unilever studentship 2014-2017. MRC/AstraZeneca PhD studentship (ITTP scheme) (2019-2023). Cancer Research Wales (2019-2023). BBSRC/Algae UK grant (2020-2022).

Dr David Lovell PhD BSc (Hons) FRSB CStat CBiol COM Chair until 30/04/2021.

Personal Interest	**Pension:** Pfizer.
Personal Interest	**Membership:** HESI GTTC (Committee member). Biometrics Society. British Toxicology Society (BTS). Genetics Society. Royal Society of Biology (RSB). Laboratory Animal Science Association (LASA). Royal Statistical Society {RSS). Statisticians in the Pharmaceutical Industry (PSI). United Kingdom Environment Mutagen Society, (UKEMS).

	UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs) – Board Member. MRC EMINENT Scientific Review Board. British Trust of Ornithologists (BTO). English Heritage. Liberty. Campaign of the Protection of Rural England (CPRE). Kew Gardens. Sandwich Bay Bird Observatory Trust (SBBOT). Chelsea Physic Garden. National Trust.
Personal Interest	**Shareholder:** National Grid plc. AstraZeneca (Spouse Shareholder). National Grid plc (Spouse Shareholder).
Non-Personal Interest	None.

Dr Carol Beevers

Personal Interest	**Employee:** Exponent International Ltd (up to 27 July 2021) Broughton Group (from 01 September 2021)
Personal Interest	**Membership:** HESI GTTC (workgroup member). OECD (workgroup member). IWGT (work group chair). United Kingdom Environmental Mutagen Society (UKEMS).
Personal Interest	**Pension:** Covance. Exponent. Broughton (from November 2021).
Personal Interest	**Shareholder:** ITM Power. NIO Inc. Blackberry.
Non-Personal Interest	None.

Mr Amit Bhagwat

Personal Interest	**Owner and Shareholder:** Research and Consulting Business.
Personal Interest	**Trustee** Myrovlytis Trust.

	Council on Nature Conservation and Countryside.
Non-Personal Interest	Bradford Teaching Hospitals NHS Foundation Trust - Public Governor (Rest of England & Wales). British Computer Society – the Chartered Institute for IT - Chair/Volunteer for Learned Events and Public Service Activities. NHS England subsidiary board on Mental Health Digital Programme – Public Member. Prescribed specialised services advisory group, DHSC – Public appointment.

Dr Stephen Dean COM Member until 31/12/2021.

Personal Interest	**Employee:** Imagen Therapeutics, From February 2020 (Equity Holder).
Personal Interest	**Shareholder:** Standard Life.
Non-Personal Interest	None.

Professor Shareen Doak

Personal Interest	**Employee:** Swansea University.
Personal Interest	**Membership:** United Kingdom Environmental Mutagen Society (UKEMS). Fellow of the Learned Society of Wales. British Association for Cancer Research (BACR).
Non-Personal Interest	**Trustee:** St David's Medical Foundation (medical research & education charity).
Non-Personal Interest	**PhD Studentship Grants:** Unilever (2017 – 2020). AstraZeneca (2009 – 20160. Unilever (2010 -2017).
Non-Personal Interest	**Research Grant:** 2008 – 2010 Hoffman-LaRoche, Unilever.

Dr Paul Fowler

Personal Interest	**Pension:** Unilever (UK). Covance.

	Miscellaneous: De Montfort University – External Examiner. FSTox Consulting – Director.
Personal Interest	**Membership:** IGG (Chair). UKEMS (committee member). Roundtable of Toxicology Consultants (RTC). British Toxicology Society (BTS). EEMGS (Secretary).
Non-Personal Interest	None.

Professor David Harrison

Personal Interest	**Employee:** University of St Andrews, UK. NuCana plc, UK.
Personal Interest	**Employee/Non-executive Director:** ILC Therapeutics Ltd. Benenox Ltd, UK – Non-executive Director (unpaid). PathAlba Ltd – Director (unpaid) – dormant.
Personal Interest	**Consultant:** NHS Lothian – Honorary Consultant.
Personal Interest	**Membership:** None.
Personal Interest	**Shareholder:** VBL Ltd, UK. Ryboquin Ltd, UK.
Personal Interest	**Miscellaneous:** Cunningham Trust – Scientific Adviser. University of Edinburgh, UK – Honorary Professor. University of Glasgow, UK – Honorary Professor. University of Florida, Adjunct Professor. Viewbank Leuchars Ltd – Director (no salary).
Non-Personal Interest	**Miscellaneous:** iCAIRD research consortium – Director (unpaid role). Families First St Andrews (children's charity) – Trustee (unpaid role). Visiopharm – Member, Scientific Advisory Board. Royal College of Pathologists – Fellow. Royal College of Physicians of Edinburgh – Fellow. Royal College of Surgeons of Edinburgh – Fellow. UK Committee on Mutagenicity – Member. Scottish Government A1 Leadership Circle – Member. EU Horizon 2020, Partner in KATY Award, grant support. Innovate UK/UKRI – Director of iCAIRD.

Dr George Johnson

Personal Interest	**Consultancy:** Fermenich, Cefic, American Chemistry Council, Teva, Greenberg Traurig llp, Osler, Hoskin & Harcourt llp, Janssen, Merck.
Personal Interest	**Pension:** USS (university superannuation scheme).
Personal Interest	**Director:** GTox ltd.
Personal Interest	**Membership:** United Kingdom Environmental Mutagen Society (UKEMS). HESI (committee member). President of the European Environmental Mutagenesis and Genomics Society (EEMGS) 2019-2021. EMA expert member. IWGT, expert member. ICEM, committee member.
Non-Personal Interest	**Relevant grant funding:** GSK, post-doctoral research funding – 2021-2022 nitrosamine research. SCIENSANO. MYCX-IT. 2020-ongoing. EMA. funding through Fraunhofer item. 2022-2023. HESI. fast fund. msc tuition fees 2022.

Ms Julia Kenny

Personal Interests	**Employee:** GlaxoSmithKline.
Personal Interests	**Pension:** GlaxoSmithKline.
Personal Interests	**Shareholder:** GlaxoSmithKline.
Personal Interests	**Membership:** UK Environmental Mutagen Society (UKEMS).
Non-Personal Interest	None.

Dr Ruth Morse COM Member until 31/04/2021.

Personal Interest	**Member:** United Kingdom Environmental Mutagen Society. British Society of Toxicology. Genetics Society.
Non-Personal Interest	**Miscellaneous:** Medical Research Council with AstraZeneca. (ITTP programme) - PhD studentship collaborative grant 2015-2020. Petroleum Technology Fund, Nigeria – PhD. Studentship 2016-2020.

Dr Andrew Povey

Personal Interest	**Shareholder:** Lloyds, Standard Life, Halifax, Santander (Partner Shareholder), Norwich Union (Partner Shareholder), Roadchef Topco Ltd (Partner Shareholder).
Personal Interest	**Miscellaneous:** European Crop Protection Agency – Part of consortium recently awarded grant on exposure assessment.
Personal Interest	**Membership:** UK Molecular Epidemiology Group (UK-MEG). UK Environmental Mutagen Society (UKEMS). American Association for Cancer Research (AACR) Molecular Epidemiology Group (MEG). British Association for Cancer Research (BACR).
Non-Personal Interest	**Miscellaneous:** RTZ – Departmental Research Grant. Manchester University – Research equipment bought using departmental funds from consultancies with industry and other bodies.

Ms Madeleine Wang

Personal Interest	None.
Non-Personal Interest	None.

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

Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their potential to cause cancer in humans at the request of UK Government Departments and Agencies.

The membership of the Committee, agendas and minutes of meetings, and statements are all published on the internet (Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment).

This year's meetings continued in virtual form, and I am grateful to Members, Secretariat and other contributors for ensuring that the work continues, despite the challenges this has brought.

The Committee have this year started considerations around relevance and reliability of evidence, a piece of work being jointly considered with COM and COT and this will continue into 2022, and aligned with work being undertaken by the FSA Science Council on third party evidence.

We have continued our review and update of the COC guidelines, undertook our annual horizon scanning, and continued the discussion on modification of risk of developing clinical cancer by chemicals as part of our efforts to review the conceptual framework we use for assessment and advice. This last topic will take time to come to fruition but crucially relies on Members being aware of, and integrating, new results from emerging technologies. We will continue to work on developing our work in this area in the coming years to ensure our guidance to Government Departments and Agencies is relevant to the challenges we face.

Professor David Harrison

MD DSc FRCPath FRCPEd FRCSEd

COC Evaluations

Human Biomonitoring for EU and Development of Human Biomonitoring Guidance Values in the HBM4EU project

3.1 A presentation was given by Dr Sepai, Public Health England (PHE), at the COC meeting on 11th March 2021 and the COT meeting on March 23rd, 2021, with a supporting paper 'Development of Human Biomonitoring Guidance Values in the HBM4EU biomonitoring project'.

3.2 Human biomonitoring (HBM) programmes can provide essential information for identifying population exposures to chemicals of concern that can be assessed with regards to potential health risks against derived guidance values (GVs) in specific population subgroups or areas. These can be important complements to the conventional sources of information for regulatory chemical risk assessments and for supporting public and occupational health protection policies.

3.3 There is currently a diversity in the derivation of health-based guidance values for both the general population and for occupational exposures. Dr Sepai outlined the methodology for the derivation of human biomonitoring guidance values (HBM-GVs) by the European Human Biomonitoring Initiative, referred to as HBM4EU. This is a project involving 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. The UK has been involved in the project with PHE leading the UK input. The initiative is designed to develop a harmonised and systematic strategy for the derivation of HBM-GVs.

3.4 Importantly, the HBM4EU strategy is based on current practices for deriving health-based assessment values based on internal exposure, which will supplement those already derived relating to external exposure measurements. The key schemes on which the HBM-GV derivation methodology is based are those already existing from the German Human Biomonitoring Commission, Summit Toxicology and the French Agency for Food, Environmental and Occupational Health & Safety. Members of the COC and COT were asked to consider whether the derived HBM-GVs could be used for risk assessment purposes and if the HBM-GVs would be accepted by the UK.

3.5 It was agreed, in principle, by members of both Committees that the framework was a robust and scientifically valid way to determine HBM-GVs but offered suggestions to make some components of the process more explicitly stated, including the impact of data availability (for example, toxicokinetic data) on the estimated level of confidence associated with each HBM-GV. It was accepted that the estimated level of confidence would vary on a case-by-case basis, depending on available data, which should be reflected in the use of the HBM-GV in different tiers for risk assessment purposes. As the values are able to be applied to any population, the absence of UK-specific population data was not considered an issue for derivation, with the caveat that the critical endpoint on which the HBM-GV was

derived is appropriate for the UK population. However, members considered that UK-specific data would be required before the HBM-GVs could be used for risk assessment purposes in the UK.

3.6 The COT commented that the HBM-GV's would need to be validated from a toxicological perspective (see paragraph 1.78). It was also suggested that refinements in exposure assessment could be achieved through the collection of environmental data (in collaboration with the Environment Agency or Defra) and through the inclusion of all routes of exposure, including dermal. Members agreed that going forward, the use of HBM-GVs in risk assessment could be particularly helpful to the FSA and that the Committee was happy to look at future case studies and offer their perspective. If endorsement of individual values was needed, the Committee would have to perform a detailed evaluation to offer their opinion.

Modification of Cancer Risk

3.7 COC had expressed its aspiration in the preceding years to move away from traditional risk assessment approaches for potential carcinogens, to a more holistic approach encompassing consideration of the modifying effects of chemicals on all stages of cancer development. This has been reinforced by increasing concern over the reliability and applicability of the rodent two-year bioassay in predicting chemical carcinogenicity relevant to humans. In addition, consideration had also been made of combining two guidance statements covering hazard identification and characterisation (G03), and alternatives to the two-year bioassay (G07) to a combined document on considering modification of cancer risk using a weight of evidence-based approach.

3.8 The COC discussed this further in 2021, in the main Committee and as a sub-group discussion. It was agreed that there was currently insufficient information available on all aspects of cancer development and the potential modification of these events by chemicals to facilitate its use by risk assessors. Therefore, distinct COC guidance could not be developed at this point, but two guidance statements G03 and G07 should be updated (see 3.26 below). A paper capturing these thoughts was published in Toxicology Research by two members, (Harrison & Doe (2021) The modification of cancer risk by chemicals. Toxicology Research, 10(4), 800-809). This covered many of the aspects discussed by the Committee and it was agreed the topic would not be progressed to a separate published COC document.

FSA Science Council Draft Principles and Guidelines on Third Party Evidence

3.9 The COC was presented the draft set of principles and guidelines on third party and uncommissioned evidence that had been prepared by the FSA Science Council to support consideration of such evidence and provide transparency on the ways in which evidence submitted in a non-standard way would be assessed.

3.10 The COC made some suggestions for clarity in terms of the audience for the principles and guidelines and to be clear on the meaning of the wording on data cleaning.

3.11 The document has subsequently been finalised by the FSA Science Council. See Rapid Evidence Review on the Critical Appraisal of Third-Party Evidence (food.gov.uk) for further details.

Terms of reference for the Office for Product Safety and Standards (OPSS) Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS)

3.12 The terms of reference for the Office for Product Safety and Standards (OPSS) Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS) was presented to the COC for awareness of this group. The COC fed back the suggestion of having lay representation on the group in the future.

Presentation by Dr Steve Dean "In vitro high content screening using patient-derived cell models"

3.13 The presentation by Dr Steve Dean, Imagen, described a personalised treatment for cancer that evaluates potential drug therapies using patient derived cell models. The PredictRx assay utilises a biopsy from patients to derive cells that are screened against 60 drugs to determine sensitivity of the tumour cells. They report a good prediction of clinical response with an 89% positive predictive value and 99% negative predictive value for those currently tested. Due to the low number and heterogeneous nature of the tumours, between 3 and 5 needle biopsies are usually taken which are pooled. The results therefore represent an average of the responses of the different tumour cells.

3.14 Since 2019, with informed consent, the patient-derived cells have been stored in a biobank and a searchable database has been established. The biobank has a range of solid tumour types and is being expanded to include haematological tumours. As with primary cell lines, patient-derived cell models generally have a limited life span, and to ensure that the cell models do not diverge from the original, a limited number of passages are allowed. The biobank and database are a key resource for the evaluation of new drug candidates at all stages of development, including the potential to enhance Phase I II and III clinical trials.

3.15 The biobank and database are also seen as a potentially interesting resource for cancer research to help gain an understanding of carcinogenicity and mutagenicity. Advantages include high throughput analysis of a range of endpoints

including cytotoxicity and apoptosis, cell cycle, DNA damage & repair, morphological and phenotypic changes, cell stress and inflammation, cell signalling and transcription factors and drug internalisation. Importantly, the cell models are reliable pre-clinical models with a traceable origin and are accompanied by patient histories.

3.16 Following the presentation, the COC noted that this was potentially a good example of how *in vitro* methodology may allow risk assessors to steer away from the use of traditional *in vivo* study data and allow better understanding of mechanisms in humans. The stability of the cell models was questioned as this was seen as crucial to ensure that the models continued to represent the patient. As this could be different for each model, whilst this is being evaluated, the models are currently limited to 15-20 passages. It was recognised that validation will be key to getting clinical acceptance as a diagnostic tool and acceptance of findings within regulatory submissions.

3.17 The translatability of the approach, particularly the data, to establish mechanistic rather than response data was also raised. This had been attempted successfully for a metabolic syndrome and was believed to be applicable more widely to non-cancer endpoints. Artificial Intelligence platforms may play a key role in interpreting mechanistic data. Benefits of the use of the approach to assess risk included the high throughput nature, availability of detailed genotypic and phenotypic parameters and a response pathway analysis.

Joint ongoing topics

Relevance and Reliability of Evidence

3.18 The topic of ‘biological relevance and statistical significance’ has been raised as an area of interest during Committee horizon scanning activities for a number of years. A scoping paper was presented at the Joint COC/COM meeting in November 2020 also attended by some COT members, which outlined some of the more relevant and significant work that has been published on this issue in recent years. It was agreed that the general public would benefit from guidance that provided clarity on how the expert Committees evaluate data with respect to consideration of biological relevance and statistical significance.

3.19 A document providing a brief outline of the Committee evaluation process focussing on the relevance and reliability of data was drafted and discussed by COC and COT in 2021. During the COC and COT discussions it was proposed that two documents be developed. One aimed at the lay audience about the process used by the Committees to evaluate evidence and reach conclusions, which could possibly be presented on the website rather than formally as a statement. A second document aimed at a more informed audience on statistical significance testing and consideration of biological relevance, for which the current draft would be the basis.

3.20 This topic will be discussed further, including by COM.

Horizon scanning

3.21 The COC undertakes horizon scanning exercises at regular intervals with the aim of identifying new and emerging issues which have potential to impact on public health.

3.22 At the end of discussion in 2021, it was agreed that the priority topics were:

- Maintain a watching brief on factors affecting cancer susceptibility including shift work, stress and other lifestyle factors and how that might affect assessment of chemicals and carcinogenicity.
- Consider an update to guidance on assessment of nanomaterials, possibly as a joint activity across COC, COM and COT.
- Gain awareness of the potential effects of antibiotics and antivirals on the microbiome.
- Consider a joint discussion with COM on thresholds for in vivo mutagens and whether there is new information subsequent to the 2010 COM opinion.
- Endocrine disruption and the link with carcinogenicity, acknowledging that endocrine disruption is also within the COT remit.
- Impact of chemicals on potential for metastasis or progression of cancer, in particular with respect to the tumour microenvironment.
- Communication of cancer risk and how COC should be involved with this, especially with the move away from a yes/no decision on whether a substance is a carcinogen, and ensuring consistency in describing risks, possibly starting with a landscape review of terminology across a number of Committees (FSA and UKHSA) and led by Lay Members..
- Ensuring appropriate considerations are made to acknowledging diversity in the population especially where there might be differences in risk between different groups.

3.23 The Committee continues to have a standing agenda item for each meeting on horizon scanning topics and to update the COC on upcoming topics for UK and international scientific advisory groups.

Working Groups

COT/COC subgroup on the synthesis and integration of epidemiological and toxicological evidence in risk assessment

3.24 The COT and COC set up a subgroup to review the approaches to synthesising epidemiological and toxicological evidence that are used in chemical risk assessments. More information is provided in the COT section 1.150-1.157

Guidance statements

3.25 The Committee continued to develop the guidance statement series during 2021. This included finalising revisions to the cancer risk characterisation methods (G06) statement.

3.26 Updates to the guidance on hazard identification and characterisation (G03), the use of biomarkers in carcinogenic risk assessment (G04) and alternatives to the two-year bioassay (G07) are ongoing and these are expected to be finalised in 2022.

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

Chairman:

Professor David Harrison MD DSc FRCPath FRCPEd FRCSEd

Professor of Pathology, University of St Andrews.

Members:

Mr Derek Bodey MA

Public Interest Representative.

Dr Gill Clare BSc PhD

Independent Consultant in Genetic Toxicology.

Dr Meera Cush

Managing Consultant (Toxicologist), Ramboll.

Dr Ruth Dempsey

Consultant: RD Science Speaks Consultancy, Sàrl.

Dr John Doe PhD

Research Fellow, Liverpool John Moore's University.

Dr Richard Haworth MA VetMB DPhil FRCPath DipECVP DABT

Head of Pathology UK, GlaxoSmithKline.

Dr Ray Kemp BA MSc PhD MRTPI SIRM

Public Interest Representative.

Dr David Lovell PhD BSc (Hons) FRSB CStat CBiol (until 30th April 2021).

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

Professor Gareth Jenkins (from 1st May 2021).

Professor of Molecular Carcinogenesis, Faculty of Health, Medicine and Life Science, Swansea University.

Professor Neil Pearce BSc DipSci DipORS PhD DSc FRSNZ FMedSci FFPH

Professor of Epidemiology and Biostatistics, London School of Hygiene and Tropical Medicine.

Dr Lesley Rushton OBE BA MSc PhD CStat HonFFOM

Emeritus Reader in Occupational Epidemiology, Imperial College London.

Dr Lesley Stanley

Consultant in Investigative Toxicology.

Professor Heather Wallace BSc(Hons) PhD FRCPath FBTS FRSC FRSB FBPS ERT

Professor in Biochemical Pharmacology and Toxicology, University of Aberdeen.

Secretariat

Miss B Gadeberg BSc(Hons) MSc PHE Scientific Secretary to 30 Sept 2021.

UKHSA Scientific Secretary from 1st October 2021.

Ms Catherine Mulholland BSc (Hons), ERT Scientific Secretary

Dr D Gott BSc(Hons) PhD FSA Scientific Secretary

Mrs N Blowfield Administrative Secretary

Declaration of members interests during the period of this report

Professor David Harrison

Personal Interest	**Employee:** University of St Andrews UK, NuCana plc UK.
Personal Interest	**Employee/Non-executive Director:** ILC Therapeutics Ltd. Benenox Ltd, UK – Non-executive Director (unpaid). PathAlba Ltd – Director (unpaid) – dormant.
Personal Interest	**Consultant:** NHS Lothian – Honorary Consultant.
Personal Interest	**Shareholder** VBL Ltd UK, Ryboquin Ltd UK.
Personal Interest	**Miscellaneous:** Cunningham Trust – Scientific Adviser. University of Edinburgh, UK – Honorary Professor. University of Glasgow, UK – Honorary Professor. University of Florida, Adjunct Professor. Viewbank Leuchars Ltd – Director (no salary).
Non Personal Interest	**Miscellaneous:** iCAIRD research consortium – Director (unpaid role). Families First St Andrews (children's charity) – Trustee. (unpaid role). Visiopharm – Member, Scientific Advisory Board. Royal College of Pathologists – Fellow. Royal College of Physicians of Edinburgh – Fellow. Royal College of Surgeons of Edinburgh – Fellow. UK Committee on Mutagenicity – Member. Scottish Government A1 Leadership Circle – Member. EU Horizon 2020, Partner in KATY Award, Grant Support. Innovate UK/UKRI – Director of iCAIRD.

Mr Derek Bodey

Personal Interest	None
Non Personal Interest	None

Dr Gill Clare

Personal Interest	**Pension:** Shell Research Ltd, AstraZeneca.
Personal Interest	**Shareholder:** AstraZeneca,

	Diageo, Marks and Spencer.
Personal Interest	**Consultant:** Covance.
Personal Interest	**Miscellaneous:** OPSS Register of Specialists from December 2020. OPSS Scientific Advisory Group from March 2021. Food Standards Agency (FSA) Joint Expert Group on Food Contact Materials (FCM-JEG) from May 2019. HSE REACH Independent Scientific Expert Pool from June 2021. Member of joint COT and COC Synthesis and Integration of Epidemiological and Toxicological Evidence sub-group, 2019 – 2021.
Non Personal Interest	**Membership:** United Kingdom Environmental Mutagen Society (UKEMS).
Non-Personal Interest	None.

Dr Meera Cush

Personal Interest	**Employee:** University of Surrey – Visiting Lecturer.
Personal Interest	**Membership:** Royal Society of Biology.
Non-Personal Interest	None.

Dr Ruth Dempsey

Personal Interest	**Shareholder:** RD Science Speaks Consultancy, Sarl (Shareholder and director).
Personal Interest	**Membership:** British Toxicology Society. Swiss society of Toxicology. Royal society of Biology.
Personal Interest	**Pension:** Philip Morris International.
Personal Interest	**Consultant:** Philip Morris International, doTERRA Europe.
Non-Personal Interest	None.

Dr John Doe PhD

Personal Interest	**Associate:**

	Regulatory Science Associates Ltd.
Personal Interest	**Membership:** British Toxicology Society (BTS).
Personal Interest	**Pension:** Syngenta
Personal Interest	**Consultant:** ECETOC, Syngenta, Covance.
Personal Interest	**Miscellaneous:** Liverpool John Moores University (Honorary Research Fellow).
Non-Personal Interest	None.

Dr Richard Haworth

Personal Interest	**Employee:** GlaxoSmithKline.
Personal Interest	**Membership:** British Society of Toxicological Pathology.
Personal Interest	**Shareholder:** GlaxoSmithKline. Royal Dutch Shell (Spouse Shareholder). United Utilities (Spouse Shareholder).
Non-Personal Interest	None.

Dr Ray Kemp

Personal Interest	**Director:** Rhodes-Kemp Law Ltd.
Personal Interest	**Member:** Royal Town Planning Institute Specialist. Committee on Medical Aspects of Radiation in the Environment (COMARE). Institute of Risk Management. Committee on Radioactive Waste Management (CoRWM).
Personal Interest	**Non-Executive Director:** Dept of Business, Energy and Industrial Strategy (BEIS).
Personal Interest	**Independent Expert:** International Atomic Energy Agency – Mission to Fukushima Prefecture.
Personal Interest	**Independent Expert:** Office for Rail and Road.
Non-Personal Interest	None.

Dr David Lovell PhD BSc (Hons) FRSB CStat CBiol COC Member until 30th April 2021.

Personal Interest	**Pension:** Pfizer.
Personal Interest	**Membership:** Biometrics Society. British Toxicology Society (BTS). Genetics Society. Royal Society of Biology (RSB). Laboratory Animal Science Association (LASA). Royal Statistical Society (RSS). Statisticians in the Pharmaceutical Industry (PSI). United Kingdom Environment Mutagen Society (UKEMS). UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs) – Board Member. MRC EMINENT Scientific Review Board. British Trust of Ornithologists (BTO). English Heritage. Liberty. Campaign of the Protection of Rural England (CPRE). Kew Gardens. Sandwich Bay Bird Observatory Trust (SBBOT). Chelsea Physic Garden. National Trust. HESI GTTC (Committee member).
Personal Interest	**Shareholder:** National Grid plc. AstraZeneca (Spouse Shareholder). National Grid plc (Spouse Shareholder**).**
Non-Personal Interest	None.

Professor Gareth Jenkins COC Member from1st May 2021.

Personal Interest	**Employer:** Swansea University.
Personal Interest	**Membership:** President: of United Kingdom Environment Mutagen Society (UKEMS). Member: British Association for Cancer Research.
Personal Interest	**Honorary Contract:** Swansea Bay University Health board.
Personal Interest	**Senior Editor:** Mutagenesis (OUP), Editorial Board (and former editor 2013-2015) Mutation Research (Elsevier). Health & Care Research Wales Grant panel (studentships) 2016-present.

Non-Personal Interest	**Grants:** National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (2018-2022). Former NC3Rs grants (2012-2016 & 2010-2014). Former grants Health & Care Research Wales (2016-2020, 2014-2017. Unilever studentship 2014-2017. MRC/AstraZeneca PhD studentship (ITTP scheme) (2019-2023). Cancer Research Wales (2019-2023). BBSRC/Algae UK grant (2020-2022)

Professor Neil Pearce

Personal Interest	None.
Non-Personal Interest	None.

Dr Lesley Rushton OBE BA MSc PhD Cstat HonFFOM

Personal Interest	**Member:** Industrial Injuries Advisory Council – Chair.
Non-Personal Interest	**Miscellaneous:** IEH Consultancy Ltd – Research Support.

Dr Lesley Stanley

Personal Interest	**Self-employed:** Dr Lesley Stanley, Consultant in Investigative Toxicology.
Personal Interest	**Membership:** European Registered Toxicologist (ERT.) Fellow of the British Toxicology Society (FBTS). Advisory Committee on Novel Foods and Processes (ACNFP).
Personal Interest	**Consultancy:** School of Medicine, University of Dundee (2020 to date). Details of previous consultancy contracts available upon request.
Personal Interest	**Expert Appointments:** REACH Independent Scientific Expert Pool. OPSS Register of Experts.
Personal Interest	**Honorary Appointment:** Associate, School of Life Sciences, Edinburgh Napier University (Non-Stipendiary).
Personal Interest	**Investments:**

	Investment Portfolio managed by Quilter Cheviot (joint with spouse). FundsNetwork Stocks and Shares ISA. Aviva Personal Pension Plan.
Personal Interest	**Ministry and Charities:** Ordained Local Minister, Church of Scotland (non-stipendiary). Honorary Chaplain, University of Stirling (non-stipendiary). Supporter, Christian Aid “In Their Lifetime” programme and International Justice Mission.
Non-Personal Interest	None.

Professor Heather Wallace BSc Hons PhD FRCPath FBTS FRSC FRSB ERT

Personal Interest	**Shareholder:** Bank Santander SA, BT Group, NovaBiotics, Aviva.
Personal Interest	**Membership:** EUROTOX – Past President. British Toxicological Society (BTS). Medical Research Scotland – Chair and Trustee. Paediatric Medicines Expert Advisory Group – MHRA. Herbal Medicines Advisory Committee – MHRA.
Personal Interest	**Miscellaneous:** EFSA – CONTAM Panel. Cell ProTx – Director.
Non-Personal Interest	None.