Committee on

# Toxicity

Committee on

# Carcinogenicity

Committee on

# Mutagenicity

# Annual Report 2020

# Committee on Toxicity of Chemicals in Food, Consumer, Products and the Environment Annual Report 2020

## Contents

## About the Committees

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

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

In common with other independent advisory committees, Committee members are required to follow a Code of Conduct which also gives guidance on how commercial interests should be declared. Members are required to declare any commercial interests on appointment and, again during meetings if a topic arises in which they have an interest. If a member declares a specific interest in a topic under discussion, and it is considered to be a conflict of interest, he or she may, at the Chairman's discretion be allowed to take part in the discussion but is excluded from decision-making. Annex 1 contains the terms of reference under which the Committees were set up. The Code of Conduct is at Annex 2 and Annex 3 describes the Committees' policy on openness. Annex 4 is the Good Practice Agreement for Scientific Advisory Committees. Annex 5 contains a glossary of technical terms used in the text. Annex 6 is an alphabetical index to subjects and substances considered in previous reports. Previous publications of the Committees are listed at Annex 7.

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

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

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

# Committee on the Toxicity of Chemicals in Food, Consumer Productsand the Environment

## Preface

I am pleased to present this report, which summarises the work of the Committee on Toxicity (COT) during 2020. The COT assesses chemicals for their potential to harm human health. Evaluations are carried out at the request of the Food Standards Agency, Department of Health and Social Care, Public Health England, and other Government Departments and Regulatory Authorities, and are published on the Internet as statements or shorter position papers. Details of membership, agendas and minutes are also published on the internet. The Committee met on seven occasions during the year undertaking a busy and varied programme of work.

The Committee met on eight occasions during the year, undertaking a busy and varied programme of work. The continuing COVID pandemic meant that from the end of March onwards, the COT held its meetings virtually. Despite the difficulties this caused, the Committee was able to function effectively over the year.

Two workshops were held during the year. The first, on “Exploring Dose Response”, took place in March, and was held in Manchester. This discussed the use of new approach methodologies in a regulatory setting. This was followed by “PBPK for regulators” which was held virtually in December. Both workshops provided interesting and informative presentations and I hope that the Committee will continue to take these opportunities to explore how new developments in the field might impact on its work.

The Committee has completed its programme of work reviewing the risks to infants and young children from a variety of contaminants and other chemicals in the diet, which was undertaken at the request of the Scientific Advisory Committee on Nutrition (SACN). This was a substantial and, I believe, important body of work. The Committee has now started a review of contaminants and other chemicals in support of the risk assessment of the maternal diet now being undertaken by SACN.

Building on the well-received work of the joint COT and COC Working Group on the Synthesis of Epidemiological Evidence (SEES), which was published in 2018, COT and COC Members and other experts have been collaborating in a Working Group examining the Synthesis of Epidemiological and Toxicological Evidence (SETE). Such activities use the complementary knowledge and skills of our SACs to great effect. It is hoped that the SETE report will be published in the Spring of 2021.

Another ongoing programme of COT work relates to evaluating the absolute and relative risks from the use of electronic nicotine delivery systems (e-cigarettes) and novel heat-not-burn tobacco products. Over the course of the year, the topics discussed as part of this

programme included risks to adolescents and young children, bystander and user exposure, inhalation of flavourings and their thermal decomposition products, and nicotine. This work has now been completed, with a final statement being published in September 2020.

Other topics discussed by the Committee this year have been very varied and have included cannabidiol, the potential health effects of contaminants in plant-based drinks, turmeric and curcumin, microplastics, combined mycotoxin exposure and Biologically Based Food Contact Materials. The Committee also contributed comments to a number of public consultations from EFSA and from the WHO.

Along with the other FSA Scientific Advisory Committees, the COT website has undergone a significant refresh, improving the layout and accessibility of the Committee's output.

This year, the Committee said goodbye to Dr John Thompson and Professor John Foster and on behalf of all Members, I would like to express the COT's sincere thanks to them for their invaluable contributions to the work of the Committee over the years.

We welcomed Professor Philippe Wilson from Nottingham Trent University to the Committee and look forward to working with him.

Next year will bring significant changes to the work of the Committee as it prepares to oversee and assure the risk assessment of regulated products that 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 all their hard work and valuable contributions to the work of the Committee through the year in particularly difficult circumstances. I would like to express my particular appreciation to the Secretariat for their continued and excellent support throughout a year in which they had to contend with both changes brought about by EU exit and the COVID-19 pandemic. Throughout, they managed the Committee admirably.

**Professor**

**Alan Boobis (Chair)**

**OBE PhD CBiol FRSB FBTS FBPhS**

## COT evaluations

### Statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes).

Background

1.1 The COT was requested by the Department of Health and Social Care (DHSC) and Public Health England (PHE) to assess the potential risk to human health from electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (collectively abbreviated to E(N)NDS), both from their use and incomparison with conventional cigarettes. These products are commonly known as 'e-cigarettes' and their use is termed 'vaping'.

What are E(N)NDS?

1.2 E(N)NDS are battery-powered devices in which a liquid ('e-liquid') is heated to produce aerosol ('vape') that is inhaled by the user ('puffing', 'vaping'). E(N)NDS devices are available in many different forms; they are sometimes referred to as either 'closed' systems, with a disposable or replaceable e-liquid container which cannot be refilled, or 'open' systems that can be refilled with e-liquid. Some products allow the user to modify the operating characteristics. This is a rapidly changing market and product characteristics can change quite quickly.

1.3 The way these devices are used varies between individuals including when and howoften they vape, the way they take a puff (for example, how deeply and for how longthey breathe in), and the strength of nicotine, if any, used in e-liquid.

1.4 'ENDS' (electronic **nicotine**-delivery system) products were developed to provide analternative means of nicotine delivery that more closely mirrored the experience of cigarette smoking than other nicotine-replacement therapies such as skin patches orchewing gums. In the UK, E(N)NDS are suggested as an aid to quitting smoking, as it is considered likely their use would be less harmful to health than continuing to smoke cigarettes.

1.5 Some devices are used with an e-liquid that does not contain any nicotine, and sothese products have been called 'ENNDS' (electronic **non-nicotine** delivery systems). These non-nicotine products may also help people to quit smoking by providing a substitute for the behavioural and physical characteristics of smoking.

1.6 In the UK, ENDS are regulated under the Tobacco and Related Products Legislation. The maximum strength of nicotine in e-liquid that is permitted for sales is 20 mg/mL, but some countries allow the sale of products containing higher levels, for example double this strength. This may affect how the different studies are interpreted in the context of likely UK use. ENNDS products are regulated under the General

Scope of the COT review

1.7 In compiling the information for review, the COT looked at the types of substancesthat users and bystanders may be exposed to, the level of exposure, and what is currently known about possible harm to human health from exposure to these substances. This was for both ENDS and ENNDS products. This information was also compared with that from the use of conventional cigarettes.

1.8 The COT review assessed the risks only from typical use of E(N)NDS products produced to good manufacturing standards and its conclusions do not apply to the use of the products in a non-standard manner, such as the addition of illicit drugs which may have additional risks.

1.9 The main aim of the COT review was to look at the possible impact on human health that might occur when E(N)NDS are used to help people to quit smoking. For this, the Committee looked at how any possible health risks from using E(N)NDS compare with harm to health that is known to be linked with smoking cigarettes. The Committee also considered the possible health risks of E(N)NDS use in its own right.

Committee discussion

1.10 Common contents of e-liquids were identified as the ‘carrier substances’ propylene glycol and glycerol, nicotine, a range of flavourings, and other flavour-related chemicals. In addition, non-standard substances, including impurities within the e- liquid constituents, and metal particles were also identified for consideration. Studies assessed whether any of the aerosol components produced during vaping can be detected in the surrounding air, leading to bystander exposure. In general, analyticalstudies of e-liquids, the aerosols produced from E(N)NDS and emissions into surrounding air were often inconsistent in how they had been carried out, so it was difficult to draw firm conclusions.

1.11 It was considered likely that current smokers would reduce the risk of harm to their health if they switched completely to using E(N)NDS. The reduction in risk would be different for different health effects. For example, the risk of developing lung cancer would be expected to decrease more than the likelihood of triggering asthma symptoms.

1.12 Some research showed that E(N)NDS are used to support the continued smoking of cigarettes (so called ‘dual use’), such that there is no or only limited reduction in overall cigarette use, and as such this might increase the risk of harm to health compared with cigarette smoking only. However, this was something on which only limited information was available.

1.13 Data indicated that E(N)NDS use might increase the likelihood of users experiencing symptoms of irritation, including a burning sensation in the

Throat, nose or eyes. In addition, it is possible that vaping may increase respiratory symptoms in people withrespiratory disease or conditions, and adverse cardiovascular symptoms in people with cardiovascular disease. Such effects can also occur in those who smoke conventional cigarettes.

1.14 The Committee was concerned about the possibility of harm to health from the flavouring ingredients, often approved for use as food flavouring agents, used in e-liquids whenheated and inhaled. This is because these substances may result in health effects after inhalation that do not occur when consumed in food. There was insufficient information to assess this risk. The Committee has therefore proposed the types of information that would be useful for assessment of the risk to the user from the addition of flavouring agents to E(N)NDS (see framework for the risk assessment of flavourings)

1.15 People who take up the use of nicotine-containing ENDS when they have not previously used nicotine-containing products were thought likely to experience immediate, short-lasting effects from nicotine exposure, such as increased heart- rate. This may also apply to some bystanders who are exposed to nicotine in levels of nicotine in air would mostly be relatively low. In the longer term, it was also considered that there would be additional risks to those taking up ENDS including becoming addicted to nicotine use. There is good evidence that exposure to nicotine during pregnancy, childhood, adolescence and young adulthood may adversely affect development. However, the Committee concluded that the information on this was not adequate to conclude on the level of risk from ENDS use.

1.16 During 2019 and early 2020, there was an outbreak in the US of a respiratory illness related to the use of E(N)NDS products. This has been linked to the presence of vitamin E acetate which is banned from UK-regulated nicotine vaping products. Although outside the scope of the present COT review, this topic remains under review by the Committee.

1.17 As E(N)NDS products were developed only recently, it was acknowledged that there is a lack of information on possible adverse health effects following long-term use. Itis currently not known what effects might occur, and whether these will be the same as the effects caused by cigarette smoking.

Overall conclusions

1.18 Overall, the COT concluded:

a) The use of E(N)NDS products, produced according to appropriate manufacturing standards and used as recommended, as a replacement for smoking cigarettes, is likely to lead to a reduction in harm to health. The amount by which the risk decreases will depend on the health effect in question.

b) People who do not already use tobacco products who take up using E(N)NDS risk some negative health effects to which they would not otherwise have been subject.

c) The use of flavouring products in e-liquids is an area of uncertainty, as very little information is available on whether these chemicals can damage human health when heated and inhaled. There is currently no information that this is happening, but this is an important data gap.

d) E(N)NDS use leads to some emissions into surrounding air. The risks to bystanders in rooms where vaping takes place appears to be low in most situations, but some effects from exposure to nicotine in the surrounding air may occur, such as increased heart-rate.

e) Much of the knowledge that is needed to assess the risks related to possible harm tohuman health from long term use of E(N)NDS is not currently available and can be obtained only from suitable epidemiology studies. This is reflected in the different policies on E(N)NDS across different countries.

f) Information and science relating to E(N)NDS is changing rapidly and the COT willkeep this area under review.

The full COT statement can be found Here

**Framework for risk assessment of flavouring compounds in electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)**

1.19 E(N)NDS are battery-powered devices containing a liquid (E(N)NDS liquid or 'e-liquid') that is heated during use to produce an aerosol, which is inhaled by the user ('puffing', 'vaping').

1.20 Constituents that have been identified in E(N)NDS liquids and/or aerosols include propyleneglycol (PG), glycerol (vegetable glycerine, VG), water, nicotine, ethanol, ethylene glycol, di-ethylene glycol, flavouring compounds, flavour enhancers and sweeteners. Other substances that have been detected, some at only trace levels include carbonyls, volatile organic compound (VOCs), tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), metals and phenolics.

1.21 Flavouring compounds are one of the five most commonly listed ingredients in E(N)NDSliquids, along with PG, VG, nicotine and water with over 7000 unique flavours being reportedly available; detailed information is not available on the dominant specific flavourings on the UK market.

1.22 The primary concern about the use of flavouring compounds is that whilst many have been evaluated and approved for use in food, few have undergone acute or chronic toxicity testingvia the inhalational route, directly or following thermal degradation.

1.23 Consequently, a framework for the risk assessment of flavouring compounds has been developed, this provides a number of steps

designed as a set of principles to guide the riskassessment process for a flavouring compound in
E(N)NDS.

The full COT statement can be found Here

**Statement on the potential risk from chemicals in the diet of infants aged 0 to 12 months and children aged 1 to 5 years**

1.24 The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked by the Scientific Advisory Committee on Nutrition (SACN) to review the risk of toxicity from chemicals in the diets of infants (aged 0 to12 months) and young children (age 1 to 5 years). The aim of the reviews was to identify and appraise new evidence that had emerged since the Government's recommendations on complementary and young child feeding were formulated andto determine whether the current advice should be revised.

1.25 Separate statements have been published on acrylamide, aluminium, arsenic, copper, cadmium, hexabromocyclododecane, iodine, lead, manganese, methylmercury, nickel, ochratoxin A, polybrominated biphenyls, polybrominateddiphenyl ethers and T-2 toxins, HT-2 toxins and neosolaniol.

1.26 The Overarching Statement summarising the conclusions of the COT on chlorate, chromium, furan, perchlorate, selenium, zinc and alcohol, caffeine, food additives, legacy pesticides, soya phytoestrogens, vitamin A and trans fatty acids was published in February 2019.

1.27 The Addendum to the Overarching Statement summarising the conclusions of the COT on contaminants and process contaminants (hexachlorocyclohexane, monochloropropane diol, polycyclic aromatic hydrocarbons, tetrabromobisphenol A),the most commonly used reduced calorie sweeteners in the UK (aspartame, acesulfame K, saccharine, sorbitol and xylitol, steviol glycosides, sucralose), a number of mycotoxins (aflatoxins, citrinin, cyclopiazonic acid, 4,15 diacetoxyscirpenol, deoxynivalenol and its acetylated/modified forms, ergot alkaloids, fumonisins, fusarenon-X, moniliformin, nivalenol, patulin, sterigmatocystin, zearalenone) and the natural plant toxins, tropane alkaloids was published in February 2020.

1.28 The COT has further evaluated the information provided by EFSA on perfluorooctanesulfonic acid and perfluorooctanoic acid in 2018 and perfluoroalkyl substances (PFASs) in 2020 and on dioxins and dioxin-like compounds in 2020. It isanticipated that a statement on PFASs will be published in 2021. Due to the uncertainties and inconsistencies in the description and evaluation of the key studiesin EFSAs assessment of dioxins the COT could not agree with the revised tolerable weekly intake (TWI) and recommended undertaking a review of the evidence base on dioxin to derive a health-based guidance value (HBGV). The COT is

awaiting the final publication by EFSA on bisphenol A and phthalates before deciding if a full re- evaluation of its current advice is required.

The overarching COT statement can be found Here.

The addendum to the overarching COT statement can be found Here

**Position paper on CBD in food products**

1.29 Cannabidiol (CBD) is a compound extracted from the *cannabis sativa* plant which has been investigated and researched for potential medical applications for several years, including in the treatment of epilepsy and seizures. However, CBD is now being used in non-medicinal products, which have become increasingly popular andhave entered the food sector. These products include beverages (beer, spirits, wine,coffee and soda style drinks), edible oils (tinctures, drops, syrup, olive oils), chewables (gum drops) and chocolate. These products were confirmed as novel foods in January 2019, which means there was no significant history of consumptionin the EU before May 1997 and that they now need to be evaluated and authorised before they can be placed on or continue to be on the market. This will be done by the Advisory Committee on Novel Foods and Processes (ACNFP).

1.30 Risk assessment advice on CBD had been increasingly requested from the Food Standards Agency (FSA) for products currently on the market so it was therefore considered timely for the available toxicological information on CBD to be reviewed.

1.31 As a result, discussions took place at COT and the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) meetings from July 2019-May 2020.

1.32 Preliminary discussions in July 2019 concluded that the COT could not reach a conclusion on the safety in use of CBD products based on the information available. It was noted that some CBD products would contain not only CBD but alsoa range of other related cannabinoids including tetrahydrocannabinol (THC). The precise composition of individual CBD products depends on the production and extraction methods used. The presence of THC above certain levels would mean that the product would not be authorised as a novel food and would become the responsibility of the Home Office under legislation on the misuse of drugs.

1.33 The Committee agreed that there was potential for interactions between the cannabinoids present in different CBD products and this, in turn, could affect theiradverse effects in a product specific way.

1.34 Further discussion took place in January 2020, when the Secretariat had been able to obtain, examine and discuss some of the recent clinical and

non-clinical data on the medicinal form of CBD, reviews and assessment reports of which were now publicly available online (with thanks to the cooperation of GW Pharmaceuticals (the manufacturers of Epidiolex®). This data was from pharmaceutical grade CBD in its purest form i.e., >98% CBD; however, other commercially available CBD products,as might be used in novel foods, may be less pure and might contain other cannabinoids, which would have their own toxicological effects, as well as potentiallyinteracting with CBD itself and hence might affect the adverse

effects of CBD. It is important to note that few data are available on these related substances.

1.35 Even with this new data, COT Members agreed that there was still insufficient data to undertake a provisional risk assessment as it was not possible to determine a reliable point of departure such as a NOAEL. However, some general conclusionscould be drawn that applied to CBD as a novel food.

1.36 Members concluded that there were observable adverse effects from CBD (Epidiolex® formulation) exposure of humans, most notably the following:

a) adverse effects on the liver (hepatic injury) at a CBD dose of ≤ 5 mg/kg bodyweight (bw)/day.
b) inhibitory interactions with some medications at a CBD dose of ≤ 1 mg/kg bw/day,but there was insufficient information to determine the overall range of drugs that might be affected.
c) somnolence effects were noted at ≤ 10 mg/kg bw/day. Members agreed that the British National Formulary warning regarding driving and operating machinery should be noted.
d) reproductive toxicity was observed in laboratory animals treated with CBD as well as developmental effects in the offspring. However, the mechanism was unclear. CBD was not teratogenic.
e) due to CBD's physiochemical properties, it is likely to transfer into breastmilk and could therefore pose a risk to nursing infants.

1.37 The Committee recognised that the balance between risks and benefits needs to be considered when assessing medicinal products. However, different considerations apply when assessing additives to food and novel foods.

1.38 Initial discussions with COM in October 2019 concluded that the scientific literature (in vitro and in vivo genotoxicity studies) identified and reviewed were inadequate as studies were not conducted to recognised test methods or Good Laboratory Practice (GLP) standards. Therefore, a conclusion on the genotoxic potential of CBD could not be reached.

1.39 In February 2020, the COM reviewed the *in vitro* and *in vivo* genotoxicity studies provided from the pre-clinical evaluation of CBD (Epidiolex® formulation) which suggested that, in its pure form (>98%), CBD did not have genotoxic potential. However, the COM requested the raw data from the studies be provided to finalise their conclusions

1.40 The FSA put out consumer guidance in February 2020 on the safety of

CBD in CBD food products which drew on the views of the COT.

1.41 For the safety of CBD in CBD food products, the FSA noted that signs of adverse effects on the liver were observed at a CBD dose of 5 mg/kg bw in patients and in healthy human volunteers. This is equivalent to 350 mg in a 70 kg adult. However, adverse effects on the liver might occur at doses of less than 5 mg/kg bw/day but there were fewer data, so it was not possible to draw definite conclusions. CBD has also been shown to cause inhibitory interactions with some medications at doses of 1 mg/kg bw/day (equivalent to 70 mg in a 70 kg adult – i.e., 1 mg per kg bw). The effect at lower doses is not known. Therefore, 1 mg/kg bw/day of CBD represents a pragmatic upper level of intake above which there would be clear concerns about safety, until further data are available.

1.42 The FSA advised consumers to think carefully before taking any CBD food products and recommends that healthy adults do not take more than 70 mg a day in total, unless a doctor advised otherwise. This applies to a person having an average bodyweight of 70 kg and those having lower body weights should reduce their dose accordingly (70 mg in a 70 kg adult – i.e., 1 mg per kg bw). Further, this advice does not mean that these levels are definitely safe, but that there is evidence adverse health effects could occur at intakes above this level.

1.43 As a precaution, FSA recommends that CBD should not be consumed by pregnant or breastfeeding women or by people taking medication.

1.44 It is important to note that the CBD intake deemed acceptable will ultimately be determined by an individual's weight and health status.

The full COT statement can be found Here

**Statement on the effect of xenobiotics on the gut microbiome and the effect the gut microbiome on xenobiotics with reference to chemical risk assessment**

1.45 In horizon scanning in the March 2019, the Committee agreed that since the importance of the microbiome in many areas of health and disease was becoming increasingly apparent, the effects of xenobiotics on the microbiota and of the microbiota on xenobiotics should be considered in a short discussion paper. Both the makeup of the microbiological population, i.e., the species of bacteria and other microorganisms present, and its functional makeup, i.e., the biochemical pathways contributed by the total mass of microorganisms, would be taken into account, along with other potential interactions, for example between air pollution, microorganisms in the respiratory tract and the development of asthma.

1.46 The discussion paper was presented to the Committee, who decided that a full Statement should follow. The statement was prepared and progressed throughCommittee meetings in 2019, being published early in 2020.

1.47 The human body hosts a wide range of microbes such as bacteria, fungi and viruses (sometimes collectively called the microbiota or the microbiome), the majority of which are present in the digestive system, largely in the appendix and large intestine.More scientific work has been carried out on the bacteria in the digestive tract than on the other types of organisms present, so this paper concentrates on these (and the term microbiota will sometimes be used). Most of the bacteria found in the digestive tract have evolved to live there and we co-exist with them from an early age.

1.48 Many of the bacteria are beneficial, digesting food and producing essential substances that humans cannot, but sometimes they can cause disease. The microbiota interact chemically with cells lining the gut to prevent inflammation and the absorption of toxins. The gut bacteria and the immune system work together to prevent invasion by pathogens. Food and the general environment contain chemicals(such as pesticides and heavy metals) that may kill some types of organisms and allowing others to grow more than usual. This effect is called dysbiosis. However, some changes can also occur in diseases such as Crohn's disease, naturally as animals and people age, and with diet, and they may not in all cases be directly associated with any harm to the host.

1.49 Drugs and other substances (xenobiotics) that are deliberately or unknowingly swallowed may affect the gut microbes or be affected by them. For example, antibiotics used to treat bacterial infections elsewhere in the body also kill or affectthe growth of the gut bacteria and other drugs may become less effective or more toxic as a result of changes to them caused by the bacteria.

1.50 Many studies on the effects of chemicals on the gut bacteria have been carried out using mice or rats because the experiments would not be possible or ethical to perform on humans. Experimental animals can be bred and housed in such a way that they are "germ free" and have no gut bacteria. Human bacteria can then be transplanted into their digestive tracts and experiments can be carried out to look at changes in bacteria in live animals ("in vivo") rather than just grown in the laboratory ("in vitro"). This is as close as animal experiments can get to simulating human gut bacteria, but it is still a "model" rather than a real situation. Differences exist betweenthe animals and humans that make it difficult to draw clear conclusions about the consequences to humans.

1.51 Experiments in animals have shown that heavy metals, pesticides, antibiotics and a variety of food additives and other substances (such as sweeteners, alcohol and environmental pollutants) when consumed at relatively high doses can alter the make-up of the bacterial community, but how many of these changes might be seen at human dietary levels of the chemicals is unclear.

1.52 Studies have been carried out to test the effects of chemicals on the bacteria foundin humans grown in vitro or have looked at the bacteria in

samples of faeces from people exposed to, or treated with, a particular chemical or drug.

1.53 Faecal samples from people suffering from diseases such as irritable bowel syndrome, diabetes or Crohn's disease have also been investigated. Changes in the bacterial communities have been noted, but several points need to be taken into account when accessing the significance of the findings:

- A "model" made up of known bacteria is not the same as a whole natural bacterial community, so not all possible effects would be seen and some ofthe effects may not occur in the whole community.
- Some bacteria cannot be cultured outside the body because they need precise conditions or are "fed" by other species
- Not all of the types of bacteria in the gut come out in the faeces
- It is difficult to decide whether changes seen in a disease are a cause or aneffect of the disease, or of any medication taken to treat that disease.
- It is also difficult to determine if a change seen after exposure to a drug or some other substance is an effect that would cause harm to the host of thebacteria or whether the bacteria have just adjusted to its presence.

1.54 Although the range of species and number of bacteria in the gut may be affected byexposure to chemicals, there is often sufficient overlap in the functions they performin an individual that the change in the population may have no ill effect on health.

Risk assessment.

1.55 The assessment of risk is further complicated by the fact that even in healthy animals and people the bacterial population present in the body varies widely between individuals. Using germ-free animals to study the effect of different chemicals on known bacteria allows for some risk assessment but is not easy and, as described above, has its own limitations.

1.56 New methods are available, such as the so-called "gut on a chip", which attempts to simulate the conditions found in the digestive system in the lab by growing human cells and bacteria together to create a "3-D" biological model. Here all of the cell types in the gut interact with each other in a similar way to that in a living animal or human. Chemicals can then be added, and their effects determined. However, these models are still at a relatively early stage.

1.57 There is a current trend towards personalised treatment in medicine but there is presently insufficient concrete information about what changes in the gut bacteria constitute a risk to health and which are compensation for chemically-induced stress to enable risk assessment of the effects of a given chemical on an individual via the gut bacteria.

1.58 The Committee recognised that research is constantly increasing the knowledge andunderstanding of the gut microbiota and how they relate to human health. It will keepthe subject under review, particularly where it applies to chemical risk assessment.

The full COT statement can be found Here

**The potential risks of exposure from microplastics**

1.59 The potential risks from microplastic exposure was identified as a topic that the Committee should consider following horizon scanning. Following review of the literature, it was decided that nanoplastics should also be

included. An initial scoping paper was presented tothe COT in October 2019 since when the topic and additional information have beendiscussed several times by the Committee with a view to producing an overarching statement.

1.60 The purpose of the overarching statement is to bring together the discussions, summarise the COT conclusions reached to date and provide a high-level overviewof the current state of knowledge on micro and nanoplastics, the data gaps and the research needs.

1.61 There are limited data regarding the toxicokinetic fate of orally ingested microplastics in mammalian species. They can either remain confined in the gastrointestinal tract (GIT), translocate from the GIT into organs or tissues and/or be excreted (~>90%). At the time of review, no epidemiological or controlled dose studies that evaluated the effects of orally ingested microplastics in humans were identified by the Committee.

1.62 As such, the COT concluded that based on the available data, it was not yet possibleto perform a complete risk assessment for the potential risks from exposure to micro-and nanoplastics *via* the oral and inhalation routes, however, they concurred with theconclusions reached by other authoritative bodes such as European Food Safety Authority (EFSA), Scientific Advice Mechanism (SAM), Science Advice for Policy by European Academies (SAPEA), World Health Organisation (WHO), Environment and Climate Change Canada (ECCC) and Health Canada (HC).

1.63 The Committee concluded that the literature data on exposure to particles from tyrewear would need to be considered separately from microplastics in food, since the polymeric nature of the particles was chemically different.

1.64 The most significant data gaps were the lack of appropriate and harmonisedanalytical methods for the detection of micro- and nanoplastics (together with suitable reference standards), as well as their toxicokinetic and toxicity profiles in/relevant for humans.

1.65 To conduct a full risk assessment, additional information will be needed from all exposure sources, including indoor and outdoor air, dust and soil. The presence of micro and nano-plastics in food and water will need to be considered along with other sources such as atmospheric fallout.

1.66 The COT recommends the following research priorities for the risk assessment of micro- and nanoplastics.

a) A comprehensive assessment of micro- and nanoplastics and contaminant concentrations in different food types (*e.g.*, seafood, edible meat tissue and offal, vegetables, fruit, drinks) and matrices (*e.g.,* air, soil, food and water) and the impact of the effect that cooking may have

on the desorption and subsequent bioavailability of contaminants/leachants, in order to better understand the implications for human health.

b) Consideration of the potential degradation of novel/emerging plastic-

based materials on the market such as biobased plastics (*e.g.*, bamboo ware, polylacticacid, chitin) and other advanced polymer matrix composite materials into micro- and nanoplastics during use and end-of-life should be taken into accountwhen considering the potential risks of exposure to such materials, as it is unclear how much they already contribute to microplastic exposure.

c) Current studies typically only deal with one type of particle/tissue interaction, as such, further research is necessary to explore the effect(s) of a particle on different tissues in situ, and on the combination of particle polymer types, sizes, and shapes in vitro and/or in vivo, in different tissue types.

d) Research is also required to identify the persistence and potential accumulation of micro and nano-plastic particles in the human body. Studies to elucidate whether they are digestible are also required.

1.67 Future sub-statements will consider in detail the potential toxicological risks of exposure from microplastics *via* the oral and inhalation routes to provide supplementary material in support of this overarching statement. This could include areview of the potential risks from oral exposure of microplastics, and a review of the potential risks of microplastics *via* the inhalation route to 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.

1.68 The overarching statement and lay summary will be prepared and made available on the COT website in due course.

**WRAP study on potatoes and acrylamide**

1.69 The Committee were asked to review and comment on a Waste and Resources Action Plan (WRAP) study on potatoes and acrylamide formation prior to

publication.

1.70 In line with requirements for potatoes used in food manufacturing, the FSA currently recommend that consumers store potatoes in a dark cool place at temperatures above 6 °C. Consumers are advised not to keep potatoes in the fridge because keeping potatoes at temperatures < 6 °C could lead to the process of “cold sweetening” and an increase in acrylamide formation, especially if the potatoes are then fried, roasted or baked. However, fresh potatoes are stored at <6°C in the retail supply chain for up to ten months. This suggested that home storage conditions would have a negligible effect on sugar content, which would render the current FSA guidance inappropriate. Storage of potatoes in the fridge could help reduce food waste by better preserving them.

1.71 Members agreed that the study had demonstrated adequately that home storage of potatoes in the fridge presented no material increase in acrylamide forming potentialof potatoes. Members noted the variability between potato types and suggested that it would be useful if there were a table in the final paper that showed the ‘headline’ statistical information on the key variables (temperature, type of potato etc).

1.72 Members discussed the conclusions of the study, and it was noted that there would be no potential health issues (relating to acrylamide formation) if a consumer decidednot to store potatoes in the fridge.

**Statement on the potential risks of combined exposure to mycotoxins**

1.73 The potential risks from combined exposure to mycotoxins was identified as a topicthat the COT should consider, during horizon scanning. Discussions took place at several meetings during 2020. A planned statement will bring together the conclusions from these discussions and list the research recommended by the COT.

1.74 The Committee noted that a full risk assessment could not be carried out on the potential risks to combined exposure of mycotoxins for several reasons. Firstly, therewas a lack of harmonisation of approaches/methodologies and data analysis/modelling for toxicological investigations. Secondly, the underlying mechanisms of interactions between each mycotoxin combination was yet to be fullyelucidated and understood. Research is needed on mycotoxins affecting ribosomal protein synthesis to determine whether they exhibit dose additivity in their effects, to help develop a reliable basis for their cumulative risk assessment.

1.75 Additional considerations for risk assessment include the potential toxic effects of mycotoxin mixtures on the gut microbiota and the endocrine system. Co-exposures from breastmilk and weaning foods must also be considered for infants and young children.

1.76 Furthermore, the availability of relevant food consumption data is scarce, and the development of multi-analyte methods is still not yet fully applied as standard. The management of left-censored exposure data (*i.e.,* values below the limit of detection), the use of probabilistic models and a

multi-biomarker approach should be consistent and have a well-defined approach. The Committee noted that there was a lack of UK data, particularly in biomonitoring; however, there are a number of studies ongoing. The UK will not be collecting new data for mycotoxins under the Human Biomonitoring for the EuropeanUnion (HBM4EU) initiative. However, in the future, more data could be obtained through Health Protection Research Units. Such research was considered to be a priority by the COT.

1.77 Members were of the view that the grouping of mycotoxins should be based on similarity of their modes of action (*e.g.*, cytotoxicity through inhibition of protein synthesis, genotoxicity). In order to assess the potential combined risks, co- occurrence data should be gathered and, where dose additivity had been observed or was expected, a combined margin of exposure (MoE) should be calculated. If the MoE was below 100, then amore extensive review/risk assessment should be carried out, including possible interactions between different mycotoxin groups.

1.78 The full statement and lay summary will be published on the COT website in due course.

**Potential effects that excess iodine intake may have during preconception, pregnancy and lactation**

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

1.80 Iodine is an essential component of thyroid hormones which are important in growthand 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.

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

1.82 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. The final statement will be published in due course.

## COT assurance

### Allergen risk assessment for adventitious contamination of soya in wheat flour milled and consumed in the UK

1.83 Due to the manner by which soybean and other grains, such as wheat, are grown, harvested, stored and transported, adventitious contamination of wheat flour with soya is known to occur. Soybeans and products thereof arerecognised as causing allergies and are included on the Regulation (EU) 1169/2011 annex II list of declarable allergens.

1.84 In 2014, the FSA recommended an action level of 236 mg/kg be applied by UK Flour Millers for soya protein in wheat flour, based on due diligence sampling data at the time and the conclusions from a 2013 published paper from Remington et al, 2013 (Food and Chemical Toxicology, 62:485-491). Subsequently, more data became available on the dose-response relationship for soya protein allergy, along with further soya contamination data and therefore, the FSA conducted an updated risk assessment to guide risk management actions.

1.85 The COT's assurance on the risk assessment was sought and obtained on the following key messages/conclusions to be communicated to risk managers:

a) The use of a set allergen action level to inform decisions on risk communication of soya contamination in wheat flour by food businesses selling raw/bulk product intended for further processing is not appropriate due to variation in the level of inclusion in final products, consumption amounts, and the potential effects of processing on the allergenicity and detectability of soya.

b) The current application of a set action level at the raw ingredient supply level may be hindering effective communication of risk through the supply chain and the ultimate decision on the necessity to communicate risk to the final consumer via a precautionary allergen statement, e.g., 'may contain'.

c) Alternative risk management approaches need to be explored, including business to business communication of robust quantitative cross contact information throughout the supply chain to the final product producer. Other sources of soya contamination in the supply chain should be assessed and communicated at each stage in the supply chain.

d) In the absence of a set action limit applied at the raw/bulk ingredient level, FSA risk managers should consider how the risk to soya allergic consumers could be mitigated. This might best be achieved by working with industry. A possible strategy would be to communicate industry risk assessments and analytical data down the supply chain, to the end product manufacturer to ensure consumer safety and inform their own decisions on appropriate risk communication for final products, so that the consumer can make informed food choices.

## Committee procedures

### Revision of the COT Terms of Reference and Code of Practice

1.86 The FSA is trying to ensure greater consistency between the Terms of Reference (ToR) and Codes of Practice (CoP) of the different FSA Scientific Advisory Committees (SACs). A template was developed by the FSA Science Council and the current COT ToR and CoP were revised to follow the common format. In general, this involved revising the order that information was presented in.

1.87 The Committee took the opportunity to consider the ToR and COP to ensure that it adequately reflected current working practices. A number of changes were suggested which will be incorporated into the final version.

1.88 However, unlike other FSA SACs the COT is one of three sister Committees along with COC and COM which are jointly sponsored by the FSA and the Department of Health and Social Care (DHSC) and therefore any changes will also need to be acceptable to these committees. The COC and COM will be discussing the COP and TOR at their meetings in 2021. The final version will be published on the COT website in due course.

### Exploring Dose Response Workshop Report

1.89 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 are 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 part of the 4th industrial revolution (4IR). One of the major recent scientific advancements is the development of alternative toxicity testing and computer modelling strategies for the evaluation of hazard and exposure.

1.90 The Food Standards Agency and the COT held an “Exploring Dose Response” workshop in March 2020 in a multidisciplinary setting involving regulatory agencies, Government bodies, academics and industry. The workshop provided a platform from which to address and enable expert discussions on the latest *in silico* prediction models, new approach methodologies, physiologically based pharmacokinetics (PBPK), future methodologies, integrated approaches to testing and assessment (IATA) as well as methodology validation. Through case studies including plastic particles, polymers, tropane alkaloids, selective androgen receptor modulators, the workshop outlined and explored approaches that are fit for purpose when applied to health risk assessment in the context of future food safety assessment. Possible future research to establish points of departures (PODs) using non-animal alternative models and to improve the use of exposure metrics in risk assessment was also discussed.

1.91 A summary of proceedings from this workshop (either as a COT statement and/or in the scientific literature) will be published in due course.

## PBPK for Regulators Workshop

1.92 As a follow-up to the Exploring Dose Response Workshop delivered in March 2020 where the Tox21 approach and novel approach methodologies (NAMs) for use in chemical risk assessment were discussed and explored; a workshop that focused on physiologically based pharmacokinetic (PBPK) modelling was held in December 2020.

1.93 A key aspect of the NAMs strategy is linking active concentrations *in vitro* to likely biological concentrations *in vivo*, for which PBPK modelling is essential.

1.94 The application of such alternative strategies to health risk assessment in a regulatory context requires effective collaboration between scientists including chemists, toxicologists, informaticians, computational biologists, risk assessors, and policy makers. As such, the workshop invited speakers with varied backgrounds including from academia, industry and regulatory agencies whose collective experience was diverse and multi-disciplinary.

1.95 This workshop on PBPK modelling techniques provided a platform from which to address the following objectives:

- To gain a better understanding of what PBPK models are and their application to risk assessment in regulatory fields.
- Advantages and limitations of PBPK modelling.
- What must be achieved to overcome limitations for integration into current health risk assessment practices.
- An interactive session involving a model run-through and:

- Any lessons learnt from authoritative bodies or industry.

1.96 A summary of proceedings from this workshop (either as a COT statement and/or in the literature) will be published in due course. It will also feed into the widerwork of producing a UK roadmap for using NAMs in chemical risk assessment performed by the UK FSA and the COT.

Note: Toxicology in the 21st Century (Tox21) is a US federal research collaboration testingthousands of environmental chemicals using non-animal methods for potential health effects. Further information is available on the Tox21 website. See also the US EPA'swebsite for adopting new approach methodologies.

## EFSA consultations

### EFSA consultation on the EFSA opinion on risk to public health related to the presence of ochratoxin in food

1.97 The Committee was invited to provide any comments it wished to be submitted to EFSA on the draft EFSA Opinion.

1.98 Ochratoxin A (OTA) is a mycotoxin produced by several fungal species and human exposure occurs through the consumption of contaminated food products, such as cereals and cereal products, beans, pulses, cocoa products, nuts, spices, dried fruit,

coffee, wine, beer and grape juice and in kidney, liver and blood from farm animals, where it occurs by transfer from animal feed. The most sensitive and crucial effects of OTA are on the kidneys; the extent of the kidney damage is dose- and time-dependent as OTA accumulates in the kidneys. At high concentrations, OTA induces kidney tumours in rodents.

1.99 For the non-neoplastic endpoint, the MOEs by EFSA were > 200 in most consumer groups, indicating a low health concern; the exception being high consumers in the younger age groups, where MOEs indicated a possible health concern. For the neoplastic endpoint, MOEs were lower than 10,000 for almost all exposure scenarios, including breastfed infants, indicating a possible health concern.

1.100 The Committee noted that based on its review of OTA (2018), using UK consumption data and the TWI established by EFSA at the time, no health concerns were highlighted. Overall, the Committee agreed with EFSAs conclusions and the analysis of the new data.

**EFSA Public consultation on the EFSA draft Opinion "Risk to human health related to the presence of perfluoroalkyl substances in food"**

1.101 The Committee was invited to provide any comments it wished to be submitted to EFSA on the draft EFSA Opinion. In the draft opinion, the EFSA CONTAM panel assessed 27 perfluoroalkyl substances (PFASs). They decided to use a mixtures approach and had establisheda Tolerable Weekly Intake (TWI) for the sum of four PFAS (perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS). These are currently the PFASs which contribute most to the levels observed in human serum, they share toxicokineticproperties in humans and show similar toxicological profiles.

1.102 The COT noted the measuring at different time points, after vaccination, at which measurements were made in the Abraham et al. (2020) and Grandjean et al. (2012) studies (1 and 5 and 7.5 years, respectively) could be an explanation for the difference in potency between the compounds. It was unclear whether there is a correlation between 1, 5 and 7.5 years. For children that were breastfed the impact of the mother's transfer of PFASs will be in the first year. Therefore, the data from the first year may not be as robust as data in the 5-7.5 years age groups. The COT suggested that preference should be given to using the data from the older children.

1.103 The levels of PFOS in the plasma were reported to have no relationship with vaccine response in the Abraham study but at similar levels were associated with an effect in the Grandjean study.

1.104 In the analysis of the associations (Appendix K of the EFSA opinion) it was unclear how the data were handled because 80 children had very high levels and 20 childrenhad very low levels of PFOA. These were put together in the analyses and some sortof adjustment was made for the time and number of vaccinations.

1.105 From the description of the PBPK in appendix M of the opinion there did not appear to be any information on the evaluation of the EFSA model, although the backbone of the model has been published and reasonably predicts PFAS levels. The modelling used seems to take account of the critical toxicokinetic effects.

1.106 Compared to the 2018 EFSA opinion on PFOS and PFOA there was little discussion about the uncertainty around the modelling in this draft opinion. There were a number of caveats about the modelling in the 2018 opinion.

1.107 The COT considered that either the Abraham et al (2020) or the Grandjean et al (2012) study should be used as the critical study as these are the best currently available. The NOAELs from the two studies are comparable and there are broad similarities in the observed effects and sensitivity of the two studies considered. However, there are also inconsistencies between the studies. Members felt that theywere still less than ideal, and it would be helpful to have a more robust point of departure. The mechanism of action is not known and more insights into the mechanism of action are needed.

1.108 Whilst the COT are unable to suggest an alternative TWI at this time, there will need to be strong caveats explaining the exposure estimates versus TWI relative to exposures and these would need to be considered carefully to avoid miscommunication of the data.

1.109 The pathological consequences of the reduction in vaccine response in these children are unknown. It is unknown how this effect relates to the TWI. A one hundred-fold exceedance of the TWI does not necessarily mean that there will beone hundred times greater risk.

## References:

Abraham K, Mielke H, Fromme H, Volkel W, Menzel J, Peiser M, Zepp F, Willich SN and Weikert C. (2020). Internal exposure to perfluoroalkyl substances (PFASs) and biological marker in 101 healthy one-year old children: *Archives of Toxicology*, 94(6): 2131-2147. Available at: Associations between levels of perfluorooctanoic acid (PFOA) and vaccine response.

Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P and Heilmann C. (2012). Available at: Serum Vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA. **307:** 391-397.

doi: 10.1001/jama.2011.2034.

**EFSA consultation on the EFSA opinion on risks for animals and human health related to the presence of glycoalkaloids in feed and food, in particular in potatoes and potato-derived products.**

1.110 The Committee was invited to provide any comments it wished to be submitted to EFSA on the draft EFSA opinion.

1.111 Glycoalkaloids are a group of nitrogen-containing compounds which are naturally produced by the Solanaceae plant family. This family includes popular vegetables

such as tomatoes and potatoes. The main role of glycoalkaloids is to protect against pest attacks and pathogens. Acute toxic effects such as vomiting, diarrhoea and abdominal pain have been observed following ingestion of potato glycoalkaloids.

1.112 The EFSA CONTAM panel considered that rodent data on acute toxicity was not appropriate to identify a reference point for acute exposure to potato glycoalkaloids in humans. Instead, the panel selected the LOAEL of 1 mg potato total glycoalkaloids/kg body weight per day as reference point for acute risk characterisation, based on kinetic studies and reports on intoxication in humans.

1.113 The health-based MOE value of 10 was established by EFSA to assess the possible health concern from acute exposure to potato glycoalkaloids via consumption. A MOE below 10 indicates a potential health concern, whereas a MOEhigher than 10 indicates that there is no health concern. The MOEs calculated for theyounger age groups indicate a potential health concern based on the food consumption surveys, particularly in the maximum mean exposure, as well as the 95$^{th}$ percentile exposures in all surveys. The MOEs calculated for the adult age groups indicate a potential health concern based on the food consumption surveys with the maximum 95$^{th}$ percentile exposures.

1.114 Overall, Committee Members concluded that, as the greening of potatoes where risks from potato glycoalkaloid consumption can be minimised. It was noted that the current FSA advice was to remove green, sprouting or damaged areas of potato prior to consumption. Therefore, no health concerns were highlighted.

**EFSA Public consultation on the EFSA draft "Update of the risk assessment of nickel in food and drinking water"**

1.115 The Committee was invited to provide any comments it wished to be submitted to EFSA on the draft EFSA Opinion.

1.116 In this update, the CONTAM Panel established a Tolerable Daily Intake (TDI) of 13 µg/kg bw for nickel. Due to the possibility of eczematous flare-up reactions elicitedin the skin in nickel-sensitised individuals, an approach for acute assessment was also considered necessary. A LOAEL of 4.3 µg Ni/kg bw was selected as the reference point for acute effects and an MOE of 30 or higher was considered to be indicative of low concern to human health.

1.117 EFSA established their TDI on the basis of post-implantation loss in rodents as the critical endpoint. However, Members did not consider this endpoint relevant to the infant and young children populations.

1.118 It was noted that EFSA had not referenced the Haber et al., (2017) paper (Regulatory Toxicology and Pharmacology. 87 Suppl 1:S1-S18) that the COT had used in its 2018 statement on nickel in the infant diet. The Haber paper had used the same studies as EFSA (2015) but had used a more relevant endpoint as the basis for calculating a toddler toxicity reference value (TRV) for repeat exposures to nickel. The TRV calculated (20 µg/kg bw/day) was similar to the TDI established by EFSA in its recent update (13 µg/kg bw/day).

1.119 The studies on which EFSA based their reference point for assessing the acute risk from nickel exposure are relatively old, but there were no more reliable studies available. Most recent published articles were on case studies in patients and not dose-response studies. They were therefore not of use for the purpose of dose response modelling.

1.120 The Committee agreed with the HBGVs established by EFSA

1.121 In its 2018 statement, the COT had concluded that there was potential concern fromacute exposures to nickel in infants and young children, especially those with a sensitivity to the metal. Taking into account the health-based guidance values (HBGV) in the EFSA update paper and current exposure estimates, such concern remains for the nickel sensitive population.

**EFSA consultation on the EFSA opinion on the update of the risk assessment of hexabromocyclododecanes (HBCDDs) in food**

1.123 The Committee was invited to provide any comments it wished to be submitted to EFSA on the draft EFSA opinion.

1.122 HBCDDs are additive flame retardants, which were predominantly used in expanded and extruded polystyrene applied as construction and packaging material and in textiles. General use was permitted in the EU until 2015, since then only authorised application was permitted due to health concerns. The main targets of HBCDDs toxicity in animals were the liver, thyroid hormone homeostasis, reproductive, nervous and immune system. HBCDDs are not genotoxic, and the available evidenceindicates that they are not carcinogens.

1.123 In their assessment EFSA confirmed the critical endpoint from 2011, however the COT felt it was not substantiated by any new/additional findings. A recent study in rats supporting the findings by Eriksson et al. (2006), on which the previous and the current assessment was based, was disregarded by EFSA and the Committee wereunclear regarding the justification/reasoning.

1.124 Given the effect of HBCDDs on the constitutive androstane receptor (CAR) and pregnane-X-receptor (PXR) in the liver of rodents, the Committee questions the reasoning behind the conclusions drawn by EFSA on the mode of action and would have wished for more elucidation.

1.125 The Committee acknowledged the general problem of comparing different modelling approaches such as BMDS and PROST, without the underlying algorithms and therefore would have found it useful if not only the model version but additional information on parameters underlying the specific version would have been provided.Given the limited information provided by EFSA the Committee found it difficult to follow EFSAs decision making process and approach to modelling and to identify the underlying quality control measures of the current model version.

1.126 The Committee was unable to follow and understand EFSA’s decision-making process to apply the NOAEL/LOAEL approach; especially given the previous push by EFSA to apply BMD modelling and the minimal difference in the calculated

chronic human intake from the previous (BMD) and current (NOAEL/LOAEL) approach. However, based on the NOAEL/LOAEL approach, the COT agreed with EFSA's additional uncertainty factor of 3 for the extrapolation from a LOAEL to a NOAEL and that an MOE of 24 would not be of concern.

1.127 The Committee noted that the overall decision-making process by EFSAs was unclear, however, agreed that exposure from the diet was of no concern to human health. According to EFSA's calculations and conclusions breastfed infants are the subgroup with a potential risk to health, however the Committee felt they were unable to judge whether EFSA's assessment/conclusions were conservative, as thederivation of the breastmilk exposures by EFSA was unclear to Members.

### WHO public consultation on the JECFA/JMPR update of Chapter 5 (EHC 240)

1.128 The Committee was invited to provide any comments it wished to be submitted to WHO on the draft revision of chapter 5 of the revised Environmental Health Criteria 240 (EHC 240) publication on the "principles and methods for the risk assessment ofchemicals in food", a guidance document that was released by the World Health Organisation for public consultation. The Committee noted potential discrepancies between the descriptions of the benchmark dose approach in the draft and by the Environmental Protection Agencywere addressed. Comparisons were made between the flow chart presented and that used by EFSA; it was noted that the figures serve slightly different purposes and that used by EFSA provides more detailed information on ode-response modelling.

1.129 The Committee concluded that the methodologies of the updated draft chapter and the previous version were the same, and the main differences were in the structure of the chapter.

### Working Groups

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

1.130 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. While data integration is already applied in the work of the Committees, there is a general feeling that there is no explicit explanation of the procedure used and that there also was scope for improvement in the Committees' approaches. The terms of reference are to provide an output which will combine current practice and guidance and that will be applicable and realistic.

1.131 The subgroup has suggested that its draft report should be published for public comment and concurrently trialled by the Committees before being finalised. Theoutput will be published jointly on the respective Committee's websites and publication in a scientific journal is also anticipated.

### Horizon scanning

1.132 New topics suggested included that of residues in human pharmaceuticals in food,

developments in dietary exposure assessment and evaluation of the exposome.

1.133 A programme of work on the maternal diet was planned at the request of PHE and SACN. This follows up the work on the diet of infants and young children and would specifically consider the health of the mother from 6 months prior to conception to post-delivery (see paragraphs 1.172-1.176).

1.134 The Committee had been asked to consider alternatives to plastic packaging; particularly those from plant materials (see paragraphs 1.160-1.166).

1.135 The Committee also discussed potential ideas for research including looking at bloodlevels of chemicals in relation to levels in breast milk and monitoring and undertakinga dietary survey of plant-based drinks to support the ongoing Committee work in this area.

1.136 The Committee also raised the question of the risk to users of the inhalation of substances not otherwise subject to specific regulation

### Ongoing work

### Hepatotoxicity of turmeric supplements

1.137 A review of the hepatotoxicity of dietary turmeric supplements was taken to the COT in September 2019. This review was carried out in light of the recent cases of hepatitis associated with the consumption of dietary turmeric supplements and provided a UK dietary exposure assessment in relation to the ADI for curcumin (the active ingredient). It was noted that the human case studies of hepatotoxicity presented in this paper indicate a link to turmeric because the adverse effects occurred upon challenge and were reversed afterwithdrawal of the turmeric supplement. The symptoms were considered to resemble those of an idiosyncratic drug reaction, though a role for a possible contaminant was not ruled out.

1.138 The Committee agreed there would be value in commissioning a chemical analysis of turmeric supplements available on the UK market. The commissioning of this chemical analysis in addition to a full statement are currently underway.

## Potential risks from use of topically applied CBD-containing cosmetic products

1.139 In addition to food, CBD is now being used in cosmetic products. These products could contribute to systemic CBD exposure via dermal absorption and could also have local effects. Therefore, the potential risks arising from dermal exposure to CBD originating from dermally applied cosmetic products were reviewed to see if arisk assessment could be carried out.

1.140 The Committee considered that the dermal absorption of CBD would be quite low butgiven the lipophilic nature of CBD, repeat application of these products could result inCBD accumulating. The contribution of inhalation exposure from the use of such products was also unknown.

1.141 There was insufficient information on the pharmacokinetics and toxicity of dermally applied CBD to allow an adequate risk assessment of the safety of CBD in cosmetics to be undertaken. The Committee were also unable to draw conclusions on the potential for drug interactions arising from dermal CBD exposure.

1.142 The Committee agreed that there were data gaps that needed to be addressed andthat if it was available, data on dermal absorption of pharmaceutical CBD products could be used to help assess cosmetic and consumer products.

1.143 The Committee agreed that this topic should be revisited once more data became available. Further data will be provided to the Committee in due course and the position paper on CBD (see paragraph 1.29) will be updated as required.

**Potential adverse effects associated with exposure to cannabidiol (CBD) by inhalation.**

1.144 The Committee was asked to consider whether the pharmacokinetic profile of CBD posed a safety concern or raised any safety questions regarding its use in products used for inhalation exposure.

1.145 Exposure sources may include smoking or inhaling CBD-containing plant material or oil-extract products, a solution added to an electronic nicotine (and non-nicotine) delivery systems (E(N)NDS) device, or from an aerosolised therapeutic application.

1.146 The Committee agreed that the source material has implications for risk assessment, affecting the bioavailability as well as the compounds that a consumer might be exposed to.

1.147 CBD has a long half-life of with a large volume of distribution. These characteristics, in addition to the lipophilic nature of CBD, indicated that CBD could accumulate withrepeat dosing. Conclusions on the dose-effect level could not be drawn due to uncertainties on the level of exposure. Drug interactions would be expected if systemic concentrations achieved through inhalation were similar to those from the oral route.

1.148 The Committee agreed that inhalation exposures posed a potential safety concern, but that more exposure data were needed, since the data available on inhalation exposure was even less than that for oral exposure. Effects on the central nervous system would be expected following inhalation of CBD.

1.149 The Committee agreed this topic should be reviewed once more data became available. Further data will be provided to the Committee in due course and the position paper on CBD (see paragraphs 1.29-1.45) will be updated as required.

**Review of plant-based drinks in children between 1 and 5 years of age.**

1.150 Current government advice states that “infant formula is the only suitable alternative to breast milk in the first 12 months of your baby's life. Whole cows' milk can be given as a main drink from the age of 1”. Furthermore, it is stated that “you can give your child unsweetened calcium-fortified milk alternatives, such as soya, almond and

oat drinks, from the age of 1 as part of a healthy, balanced diet".

1.151 Plant-based drinks are becoming increasingly popular and with this is mind, the COT were asked to review the safety of these products in the diets of children between 1 and 5 years of age.

1.152 For soya drinks the hazard considered was the presence of isoflavones, which raise concerns about adverse effects relating principally to their ability to mimic the female hormone, oestrogen, and therefore their potential impact on reproduction and development. For almond drinks the presence of cyanogenic glycosides (natural plant toxins that might affect the central nervous system) and aflatoxin B1, which is agenotoxic carcinogen were considered. Finally, for oats, the risk from contamination with the trichothecene mycotoxins T-2 and HT-2, deoxynivalenol (DON) which cause acute emetic effects, and ochratoxin A (OTA), which is (possibly) a genotoxic carcinogen, were evaluated.

1.153 The main challenge in the assessment of the safety of these drinks was the lack of information regarding dietary intakes for infants and young children following dairy-free or plant-based diets. Organisations providing advice on providing 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 chemicalsof concern in the different drinks. The need for consumption information for people following plant-based diets more generally was also highlighted by the Committee asthe popularity of these diets is increasing and information on realistic dietary intakes would help inform future risk assessments on similar issues.

1.154 Overall, the Committee concluded that for soya drinks, the intakes of phytoestrogens from consumption of these drinks in children aged 6 months to 5 years of age was less than the previously estimated maximum intake of 9.5 mg/kw bw per day in infants aged 0 to 6 months, who were consuming soya- based infant formula to ensure adequate nutrition, where medically necessary; hencethere was less potential concern. 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.

1.155 For almond drinks, there were no concerns for the presence of cyanogenic glycosides as bitter almonds are not used in almond drink manufacture, however the risk to health from exposure to AFB1 could not be determined based on the availabledata. Similarly, there were no concerns arising from the presence of DON and T-2 and HT-2 in oat drinks, however the risk to health from the presence of DON could not be determined based on available information.

1.156 An overarching statement covering the Committee's views on the safety of these drinks will be published in due course.

### Alternatives to Plastic Packaging

1.157 Due to the adverse environmental impacts of fossil-based plastics and owing to a large proportion of total plastic being used in packaging, there are various initiatives toreduce the amount of conventional plastic used within packaging. As a result of

government initiatives around the world, and in conjunction with pressure from consumers, recent years have therefore seen a major global increase in the development and use of biobased materials for food contact applications.

1.158 In May 2020, a paper entitled “Scoping paper: alternatives to conventional plastics for food & drinks packaging (TOX/2020/24)” was presented to the COT. This paper was based on the Fera Science report (2019) which was entitled “Bio-Based Materials for Use in Food Contact Applications” and commissioned by the FSA. The aim of the scoping paper was to identify priority materials for further review.

1.159 Members noted that further quantitative information was needed on contamination, degradation, and migration of chemicals and allergens during the manufacture of commercial bio-based food contact materials (BBFCMs), as well as environmental impacts after disposal, for example formation of micro/nano-plastics upon entering landfill or from energy-from-waste processes.

1.160 Due to the diversity of available BBFCMs for industrial use, the Committee agreed that in addition to policy priorities, it would be helpful to focus on BBFCMs that are most or most likely to be used in the UK.

1.161 Members requested the Secretariat to produce a prioritisation list of BBFCMs for health risk assessment based on hazard, extent of use (as a surrogate for exposure data where this information was insufficient), and novelty. This prioritisation list will be presented to the COT in 2021.

1.162 At the May 2020 COT meeting where alternatives to plastic packaging were discussed, it was noted that the FSA have received enquiries on chitin-based BBFCMs and chitosan-based drinking straws regarding their allergenic content. Subsequently, in September 2020, a discussion paper focussing on allergenicity of chitin and chitosan based BBFCMs was taken to the Committee.

1.163 The Committee agreed that the risk of allergenicity from chitin- or chitosan-based BBFCMs on the basis of the potential presence of allergenic proteins appears to below. However, to confirm this, additional information was needed such as relevant migration and consumption data for BBFCMs. A follow up paper will be taken to the COT in 2021 to address these issues.

### Less than lifetime exposure

1.164 The COT considered the principles produced by the COC on less than lifetime exposure to genotoxic and non-genotoxic carcinogens (COC Guidance Statement G09) and the applicability to other toxicological endpoints which are considered bythe COT. The COT concluded that it would be useful to test the principles using cases from past COT work.

1.165 Two test cases were prepared, based on the COT’s recent work on the diets of infants and young children, cadmium and fumonisins. In both cases exceedances of chronic health-based guidance values (HBGVs) had been identified in infants and/or young children. Cadmium bioaccumulates, while the fumonisins are rapidly metabolised and excreted. Following the COC principles, a Haber’s rule-based

approach had been followed for cadmium, while for the fumonisins the establishment of a short term HBGV had been considered.

1.166 The two test-cases were useful. Following the COC principles would not have changed the conclusions previously drawn by the COT on cadmium and fumonisins in the diet of infants and young children but would have strengthened the support forthe conclusions. The value of establishing short term HBGVs was discussed by the Committee. Comparison in the first instance would be to the chronic HBGV and the consideration of a short term HBGV would only be in cases where there is a need to refine the risk assessment. The COT will consider further how to approach bioaccumulative chemicals.

1.167 The COT considered that “less than lifetime” was not exactly the correct term for what could be variable exposure over a lifetime.

1.168 The COT agreed that COT-specific principles should be produced based on the COCprinciples, and this will be considered further in 2021.

### Ongoing work on the COT contribution to the SACN risk assessment on nutrition and maternal health

1.169 The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on ‘The influence of maternal, fetal and child nutrition on the development of chronic disease in later life’ (SACN, 2011) and on ‘Feeding in the first year of life’ (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered.

1.170 In 2019, SACN agreed to conduct an assessment of 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 andexcess nutrients in the diet.

1.171 SACN agreed that, where appropriate, other expert Committees would be consultedand asked to complete relevant risk assessments e.g., in the area of food safety advice.

1.172 Following a discussion, a number of components were prioritised and to this end, papers on iodine, vitamin D and dietary supplements have been presented to the Committee.

1.173 The remaining chemical and food entities included mycotoxins, phytoestrogens, resveratrol, vitamins A, C and E and caffeine, heavy metals (including arsenic), heterocyclic amines, acrylamide, dioxins and dioxin-like PCBs, non-dioxin-like PCBs,bisphenol A, selenium**,** and constituents of oily fish. It was agreed that these would be prioritised based on the likely exposure with individual or combined papers on theabove chemical entities will be presented to the Committee throughout 2021.

### Herbal Supplements Used in Pregnancy

1.174 As part of the SACN work on nutrition and maternal health described above, the Committee considered herbal supplements which might be used during pregnancy to identify priority compounds for further review.

1.175 The most frequently discussed supplements were found to be: Ginger, chamomile, raspberry leaf extract, echinacea, peppermint oil and leaves, dandelionand evening primrose oil. Of the supplements reviewed, ginger, peppermint and raspberry leaf were determined to be most regularly recommended.

1.176 The COT reviewed summaries of the available data for the most commonly recommended herbal supplements, focusing on studies relevant to pregnancy andmaternal outcomes where available.

1.177 Overall, it was noted there was some useful data from animal studies but less human data available and as such, concluded it would be useful to consider ginger, raspberry leaf tea and echinacea in more detail, with the available data on the remaining supplements to be summarised in an overarching paper.

1.178 Papers on individual supplements will be presented to the Committee in due course.

**Dioxins and Dioxin-like PCB's**

1.179 The Committee reviewed the EFSA opinion on "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food" in 2019 and2010. They focussed on the derivation of the revised tolerable weekly intake (TWI) of 2 pg TEQ/kg bw/week and subsequently considered its implications for risk management.

1.180 Due to uncertainties and inconsistencies in the description and evaluation of the key studies in EFSAs assessment, the COT could not agree with the proposed TWI and further considered the 7-fold reduction in the TWI inconsistent with the current database. The Committee noted that the European Commission (EC) has not yet adopted EFSAs new TWI due to ongoing work on the international level to review thebasis and values of the WHO toxic equivalent factors (TEFs). Hence, the Committee felt unable to comment on the dietary exposures and whether they should be compared to the EFSA proposed TWI.

1.181 The Committee recommended undertaking a review of the evidence base on dioxin to derive a health-based guidance value (HBGV). However, the Committee acknowledged that the review of the TEFs and a finalised assessment by the EC are not expected until 2022, at the earliest, and that its own review of dioxins will be an extensive and lengthy undertaking.

1.182 Any reduction in the current HBGV would take decades to reduce dioxin exposure in the population, due to the properties of dioxins, especially the 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. Thus, while the re-assessment of dioxin was a necessary and important piece of work going forward the COT does

not consider it necessary in the meantime to alter its current advice on dioxins.

## A summary of data published to date on the presence and pharmacokinetics of nicotine salts in electronic nicotine delivery systems (ENDS) products

1.183 The nicotine present in ENDS products has predominantly been in the free base form. However, some more recent products contain organic acids in the e-liquid, leading to the presence of a proportion of the nicotine in the protonated form, as asalt. Nicotine salts are less volatile than freebase nicotine and are reported to produce a less harsh experience during inhalation. Members considered the presence of nicotine salts in ENDS products and the pharmacokinetics of nicotinewhen inhaled in the salt form.

1.184 Nicotine in the form of salts decreases pH and increases palatability of the aerosol. It is inhaled more easily deep into the lungs, where there is an environment for it to be absorbed. Pharmacokinetic studies of inhaled aerosolised nicotine products indicated higher and/or faster delivery of nicotine from nicotine salts than free base nicotine.

1.185 There is a lack of information on levels of exposure to the nicotine salts in ENDS aerosol and in particular how the exposure to nicotine might differ from the use of nicotine in the form of salts compared to free base form.

1.186 It was concluded that the use of the nicotine salts resulted in increased bioavailability for ENDS users. However, whether this resulted in increased nicotine levels in the user could be influenced by user behaviour. There would be no impact on the bioavailability of nicotine to bystanders as they would not be exposed to the nicotine salt but to the free base form via exhaled breath from users.

1.187 Conclusions could not be drawn on whether there were any additional risks from the use of nicotine salts rather than freebase nicotine in e-liquids as it was unknown whether actual exposure to nicotine would be higher or not. The risks from ENDS also depended on what other substances are being inhaled from the ENDS and whether compensatory exposure to these might decrease when nicotine salts were being used compared to free base nicotine.

1.188 Further consideration of this topic by the Committee is expected in 2021.

## 2020 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 CollegeLondon

### Members

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

**Ms Jane Case**
Lay Member

**Dr Stella Cochrane** BSc PhD (from April 2019)
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

**Professor John Foster** PhD, DipRCPath, FRCPath,
Hon FBTS, FIATP
Consultant, Regulatory Science Associates

**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

**Dr John Thompson** MB ChB BMedSci, RCP FBTS (Until March 2020)
Senior Lecturer in Clinical Pharmacology, Cardiff University Director, National Poisons Information Service, Cardiff

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

**Professor Philippe Wilson** (from April 2020)
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.

## Secretariat

| | |
|---|---|
| **Ms Catherine Mulholland** BSc (Hons) | Scientific Secretary |
| **Mr Freddie Lachhman** BA (Hons) (until August 2020) | Administrative Secretary |
| **Ms Aisling Jao** (from September 2020) | |
| **Ms Britta Gadeberg** BSc (Hons) MSc | Scientific Secretary – PHE |
| **Dr David Gott** BSc (Hons) PhD (from June 2020) | |
| **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 | |
| **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 | |
| **Dr Joseph Shavila** BSc (Hons) MSc PhD | |
| **Ms Chloe Thomas** BSc (Hons) | |
| **Ms Sabrina Thomas** BSc (Hons) MSc | |
| **Ms Chara Tsoulli** BSc (Hons) MSc | |
| **Ms Frederique Uy** BSc (Hons) MSc | |

## Declaration of members interests during the period of this report

| | | |
|---|---|---|
| **Professor Alan Boobis** OBE PhD FBTS FBPhS | | |
| Personal Interest | **Employee**<br><br>Imperial College London, Department of Medicine (retired June 2017, part-time appointment from Aug 2017-May2019)<br>Full retiral June 2019.<br>Emeritus Professor of Imperial College London, National Heart & LungInstitute<br><br>**Shareholder**<br><br>Bank<br>Santander<br>Barclays Bank<br>BG Group (until 2016)BT Group<br>Centrica<br>Iberdrola SA<br>National GridLloyds | **Membership**<br><br>ILSI & ILSI HESI Board of TrusteesILSI Europe Board of Directors Science Advisory Board of Swiss Centre for Applied Human Toxicology<br>Dept. of Health Committee on theMedical Effects of Air Pollutants WHO/FAO JMPR WHO/FAO JECFA (vet)<br>WHO TobReg<br>WG10 TC126 (Intense Machine-smoking Regime for Testing Cigarettes)<br>EUROTOX<br>British Pharmacological Society, British Toxicology Society, Society of Toxicology (USA)<br>Royal Society of Biology (until 2017) Michigan State University MSU Center for Research on Ingredient Safety (CRIS) (External Advisory Committee) Agency for Innovations in Food and Chemical Safety Programme, Science, Technology and Research, Singapore (A*STAR) (Scientific Advisory Board) Owlstone Medical (Owlstone Medical) (Scientific Advisory Board) Evidence-Based Toxicology Collaboration, Bloomberg School of Public Health, Johns Hopkins, USA (Scientific Advisory Board) |
| Non Personal Interest | **Grants**<br>Horizon 2020<br>EUROMIX (until May 2019)<br>Department of Health & Social | **Membership**<br>None |

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|---|---|---|
| | Care (until March 2017)<br>Public Health England (untilJune 2017) | |
| **Dr Phil Botham** | | |
| Personal Interest | **Employee**<br><br>Syngenta - Principal Science Advisor (part time)<br>**Shareholder**<br>AstraZeneca<br>Regulatory Science Associates(Part Time Consultant) | **Membership**<br><br>British Toxicology Society, Society of Toxicology (USA)<br>European Centre for Ecotoxicologyand Toxicology of Chemicals Scientific Committee<br>European Crop Protection Association Toxicology Expert Group<br>Crop Life International Human Health Steering Team |
| Non-Personal Interest | None | None |
| **Ms Jane Case** | | |
| Personal Interest | **Employee**<br>Company Secretary of Muse InteriorsStevens & Bolton LLP as Jane Hughes)<br><br>**Shareholder**<br>Standard Life<br>Santander | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Dr Stella Cochrane** | **COT Member from June 2019** | |
| Personal Interest | **Employee**<br>Unilever<br><br>**Shareholder**<br>Unilever | **Membership / Affiliation**<br>Unilever representative on the UK FDF Allergen Steering Group (Deputy Chair),FDE Allergen Group and University of Nebraska Food Allergy Research & Resources Board |
| Non-Personal Interest | None | None |
| **Dr James Coulson** | | |

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|---|---|---|
| Personal Interest | **Employee**<br>Cardiff University<br>Director of Medical, Scientific and Toxicology Consultancy Ltd | **Membership**<br>British Medical Association British Pharmacology Society<br>British Toxicology Society National Trust<br>Royal College of Physicians of London |
| Non-Personal Interest | None | None |
| **Dr René Crevel** | | |
| Personal Interest | **Employee**<br>Unilever<br>Consultant, Réne Crevel consulting<br><br>**Shareholder**<br>Unilever<br>Centrica<br>BG Group<br>National Grid<br>Lloyds | **Membership/affiliation**<br>ILSI Food Allergy Task Force: Chair |
| Non-Personal Interest | None | None |
| **Dr Caroline Harris** | | |
| PersonalInterest | **Employee**<br>Exponent International Ltd<br><br>**Shareholder**<br>Exponent Inc | **Membership**<br>International Union of Pure and Applied Chemistry<br>**Fellowships**<br>Royal Society of Chemistry |
| Non-Personal Interest | None | **Membership**<br>Expert Committee on Pesticides |
| **Professor Gary Hutchison** | | |
| Personal Interest | **Employee**<br>Dean of Applied Sciences at Edinburgh Napier University, Professor of Toxicology | **Membership**<br>Hazardous Substances Advisory Committee, DEFRA British Toxicology Society. |
| Non-personal Interest | None | None |
| **Dr SarahJudge** | | |
| Personal Interest | **Employee**<br>Newcastle University<br>Lowcock Properties Ltd | **Membership**<br>British Pharmacology SocietyBritish Toxicology Society International Association for Neurotoxicology |
| Non-Personal Interest | **Research Funding** | None |
| **Dr Gunter Kuhnle** | **COT Member from June 2019** | |
| Personal Interest | **Employee** | **Membership** |

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| | Professor of Nutrition and Food Science, University of Reading. | None |
| Non-Personal Interest | None | None |
| **Dr David Lovell** | **COT Member from June 2019** | |
| Personal Interest | **Employee**<br>Reader in Medical Statistics<br>St Georges Medical School<br>University of London<br><br>**Shareholder**<br>National Grid -<br>Pfizer -<br>AstraZeneca (spouse shareholder)<br>National Grid plc (spouse shareholder) | **Membership**<br>HESI GTTC –<br>Biometrics Society<br>British Toxicology SocietyGenetics Society<br>Royal Society of Biology Laboratory Animal ScienceAssociation<br>Royal Statistical Society Statisticians in the PharmaceuticalIndustry<br>United Kingdom Environment Mutagen Society (UKEMS) UK National Centre of Replacement, Refinement and Reduction of Animals in Research(NC3Rs)<br>MRC EMINENT Scientific ReviewBoard<br>Also, private member of:<br>British Trust of Ornithologists (BTO)<br>English Heritage<br>Liberty<br>Campaign of the Protection of Rural England (CPRE)<br>Kew Gardens<br>Sandwich Bay Bird Observatory Trust (SBBOT)<br>Chelsea Physic Garden<br>National Trust |
| Non-Personal Interest | None | None |
| **Dr Mac Provan** | **COT Member from June 2019** | |
| Personal Interest | **Employee**<br>Director of Regulatory Science Ltd | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Ms Juliet Rix** | | |
| Personal Interest | **Employee**<br>None | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Dr Cheryl Scudamore** | | |

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| Personal Interest | **Employee**<br>Independent consultant in experimental and toxicological pathology | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Dr NatalieThatcher** | **COT Member from June 2019** | |
| Personal Interest | **Employee**<br>Mondelēz International | **Membership** |
| Non-Personal Interest | None | None |
| **Dr John Thompson** MB ChB BMedSc FRCP FBTS | **COT Member until March 2020** | |
| Personal Interest | **Employee**<br>Senior Lecturer in Clinical Pharmacology, Cardiff University, Director, National Poisons Information Service, Cardiff | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Professor Mireille Toledano** | | |
| Personal Interest | **Employee**<br>Marit Mohn Chair in Perinatal & Paediatric Environmental Epidemiology, Imperial College London | **Membership** |
| Non-Personal Interest | None | None |
| **Professor Faith Williams** | | |
| Personal Interest | **Employee**<br>Emeritus Professor, Newcastle University<br><br>**Shareholder**<br>Share in FTSE 100 quoted companies | **Membership**<br>British Toxicology Society, Society of Toxicology (US) |
| Non-Personal Interest | None | None |
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| **Professor Philippe Wilson** | | |
| Personal Interest | **Employee**<br>Nottingham Trent University<br>Rare Breeds Survival Trust | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Professor Matthew Wright** | | |
| Personal Interest | **Consultancies and Direct Employment**<br>Newcastle University | **Membership**<br>British Toxicology Society<br>Society of Toxicology (US)<br>EFSA FAF Panel<br><br>**Miscellaneous**<br>Toxicology – Associate Editor |
| Non-Personal Interest | **Support by Industry**<br>GSK<br>Lubrizol. | None |
| **Professor Maged Younes** | COT Member from June 2019 | |
| Personal Interest | **Employee**<br>Independent Expert in Toxicology and Biochemical Pharmacology | **Membership**<br>Chair of EFSA ANS panel Chair.<br>Commission on evidence-based methods in risk assessment, Federal Institute for Risk Assessment (BFr), Germany<br><br>Society of Toxicology, USA<br><br>German Society of Experimental and ClinicalPharmacology and Toxicology<br><br>Society for Risk Analysis |
| Non-Personal Interest | None | 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 2020. As always, the COM would be happy to receive any feedback from readers of this report.

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 mutagenicity testing. The membership of the Committee, declarations of their interests, agendas and minutes of meetings, and statements are all published on the internet. COM Website

During 2020, the Committee worked on a number of topics.

It continued the updating of the overarching COM Guidance Document which is now ready for completion in 2021. It worked on the associated specific Guidance documents which will accompany the overarching document on topics such as the use of QSAR models to predict genotoxicity. This followed a presentation on the approaches by Dr Richard Foster of LHASA. It completed its report on the two-day workshop on the interpretation of genotoxicity data held in 2019.

It reviewed recent work on the quantitative assessment of genotoxicity data and developed a plan for future guidance on this topic. It discussed, as part of its remit to follow new developments in the field, the topic of Mutational Spectra and Signatures of Environmental Mutagens following a presentation by Professor David Phillips of Kings

College, London.

It evaluated the genotoxicity of cannabidiol after a referral from the Committee on Toxicity (COT) following the availability of new data. It responded to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) on its draft revision of its EHC 240 chapter on genotoxicity. It was actively involved in responding to the development of OECD Guidelines for the PIG-a gene mutation assay and on the transgenic rodent somatic and germ cell mutation assays.

The COM maintained its awareness of the implications of Brexit 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 2020 and onwards.

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.

I would again like to thank the secretariat for their exceptional support to the COM and to the WRc/IEH team for the excellent work they delivered in 2020. I will single out Dr Ovnair Sepai for her outstanding commitment and assistance as the Committee's Scientific Secretary. 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. It is clear that as I write this foreword, that 2021 will be a difficult year but I hope that we will be able to adapt our ways of working to ensure that we can continue to maintain the high level of advice that the COM provides.

My term as Chair of COM ended on 31st March 2021 so I also stepped down from my ex officio role on COC. I have always enjoyed working with the COC and I have maintained and extended the close links that have been built up between the two committees as well as with the COT. I believe that during my time as COM Chair I have extended the work on those issues where the remits overlap. The investigations of the mutations which contribute to the development of cancers is a major aspect of carcinogenesis and involves interactions between experts in the two fields. This work will continue to grow in importance. Continual close working will also be needed to ensure that problems which are now becoming apparent because of Brexit can be met. This will be challenging particularly as the Covid-19 pandemic creates difficulties, but also some opportunities through virtual meeting, for how Expert Committees function. It is, in my view essential, that when conditions allow, that some 'in person' meetings resume.

I wish my successor Professor Gareth Jenkins every success at he takes over the Chair of COM. I can assure him that he has a great team of Committee members and a dedicated Secretariat who, I am sure, will ensure that the COM continues to maintain its excellent work.

**Dr D.P. Lovell (Chair)**

**PhD BSc (Hons) FBS CStat CBiol CSci**

## Ongoing Work

### COM guidance series update

2.1 The updating of the overarching COM Guidance document continued through 2020 (papers in February (MUT/2020/03), June 2020 (MUT/2020/09), and November (MUT/2020/16)). The intention was to finalise this overarching document, with the publication of the updated COM Guidance in 2021, which would then be updated as part of a rolling revision. The topic of genomics would not be included in the overarching document because it was a rapidly developing field and likely to become out of date very quickly. A separate guidance document on genomics may be developed in the future.

2.2 Other separate COM Guidance documents developed through 2020 included: Germ cell mutagens (MUT/2020/12 and MUT/2020/17); 3D models (MUT/2020/11 and MUT/2020/18); Guidance on the genotoxicity testing of nanomaterials (papers MUT/2020/10 and MUT/2020/19); and Guidance on the genotoxicity testing of impurities (MUT/2020/21). These documents would be considered further in 2021.

### Guidance statement on QSAR models to predict genotoxicity

2.3 At the February meeting a draft statement on QSAR models was presented (MUT/2020/02). There was also a presentation to the committee by Dr Robert Foster on the Lhasa Ltd *in silico* prediction models for genotoxicity. The talk introduced (Q)SAR systems, using Derek Nexus an expert rule-based model and Sarah Nexus, a statistical system, as examples, and discussed the performance of (Q)SAR systems and model development with respect to genotoxicity. For mutagenicity it was accepted that these models perform very well and are accepted for regulatory purposes. The ICH M7 guidelines state that one expert rule-based and a statistical-based model can be reviewed, however expert knowledge is needed to support the final conclusions for the mutagenic potential of impurities. Dr Foster noted that there is far greater Ames data available for model building compared to other tests for genotoxicity, such as chromosome aberration and micronucleus tests. A validation of Derek against chromosome aberration data showed that it performed well on chemicals which are expected to be DNA reactive. But Derek had low sensitivity for prediction of a set of compounds known to interact with either topoisomerase or tubulin. In Derek, chromosomal damage (CD) alerts primarily cover DNA/protein reactive compounds. This is an issue with rule-based systems where creating a valid SAR is incredibly difficult for complex, poly(hetero)aromatic ring systems. Dr Foster also demonstrated how a statistical system may be able to complement the rule-based system by creating a Sarah model for the prediction of CD. Data were taken predominantly from Vitic Nexus. Each time a compound is positive in both *in vitro* chromosomal aberration (CA) or *in vitro* micronuclei (MN) data sets it is counted as positive in CD. This model is significantly more sensitive for prediction of chromosome damage compared to Derek. However, it is important to note that Sarah was designed for the prediction of mutagenicity *in vitro* and, in line with the European Food Safety Authority (EFSA) report (2019:EN-1598 Evaluation of the applicability of existing (Q)SAR models for predicting the genotoxicity of pesticides), additional refinement would be required to the model before it could be considered for use for prediction of chromosome damage *in vitro*. Following the presentation by Dr Foster and COM discussion at the February 2020 meeting, a draft statement (MUT/2020/20) had been prepared for the November meeting. However, there was

insufficient time for members to discuss the draft document at the November meeting due to a shorted meeting duration. Members were asked to send comments by email. The comments would then be considered, and a revised document prepared for discussion at a later meeting.

### Quantitative assessment of genotoxicity data

2.4 The COM first considered quantitative approaches for assessing genotoxicity data, and how they may be used in chemical risk assessment, at its Horizon Scanning exercise in June 2013 and a guidance statement was published in 2015. EFSA released a draft guidance on the assessment of aneugenicity in 2020, which made proposals regarding the quantitative assessment of genotoxicity data. The draft EFSA document was reviewed by COM members and a Committee response to the public consultation was submitted. It was suggested that the COM guidance statement on quantitative assessment of genotoxicity data should be reviewed in light of the changes proposed in the EFSA 2020 document, and paper (MUT/2020/22) highlighted where updates could be made. The suggested updates were discussed by COM members, and it was agreed that due to a number of concerns regarding the EFSA document, the COM guidance should not be updated at this time to reflect these. An alternative approach was agreed whereby the COM would prepare a directed statement in response to the EFSA document once it had been adopted and published.

### Two-day workshop on the interpretation of genotoxicity data held in Birmingham in 2019

2.5 A draft report (MUT/2020/14) and draft paper (MUT/2020/13) relating to the 2019 Two-day workshop on the interpretation of genotoxicity data were considered by the COM. The draft paper drew together the main outcomes and consensus points from the separate breakout discussion groups at the meeting under various topic headings. Members agreed that the draft paper was a good summary and representative of the workshop. It was suggested that a paper could be submitted for publication in a journal. Members also agreed that it would be useful to explore the possibility of holding similar future meetings.

### Presentation by Professor David Phillips on mutational spectra and signatures of environmental mutagens

2.6 The COM keeps a ‘watching brief’ on the development of new methodologies for determining potential mutagenicity resulting from environmental exposures to chemicals. As part of this awareness programme, Professor David Phillips from King’s College, London, provided an overview to COM of the current status of the use of mutational spectra and signatures to identify environmental mutagens.

2.7 For clarity, the key differences between ‘spectrum’ and ‘signature’ were outlined. Spectrum was defined as a mutation in a single gene in a test system, determined over many repeats in different cells and tumours, to build up a library of mutations. A ‘signature’ was taken to refer to mutations in the exome or across the whole genome of the test system, which is determined over a smaller number of repeats. An example of TP53 mutations in human cancer was discussed which has data

available from a large number of studies (>1000). Professor Phillips described an experimental system in mice fibroblasts that his research team had developed for human TP53 genes, which showed concordance with human data in reproducing the spectrum in human tumours following environmental chemical mutagen exposure (e.g., aristolochic acid). Other mutations were also identified in the system using whole genome sequencing, with between 15,000 and 25,000 mutations identified, depending on the chemical exposure. Untreated cells have a background mutation rate of around 5000 which is thought to be due to reactive oxygen species (ROS) generation.

2.8 There are six possible base substitution point mutations, although insertions/deletions do also occur. Taking neighbouring bases into consideration, each signature has 96 possible substitution mutations in total. A study was described in which human induced pluripotent stem cells were exposed to 79 environmental agents and the base substitution signatures determined. There was no selection bias for type of mutation. Around half (n=41) of the agents produced a significant increase in mutations, once the 'cell-culture' signature, or background signature, had been subtracted. Similarity of signatures to those determined in the Sanger Institute Catalogue of Somatic Mutations in Cancer was demonstrated for aristolochic acid, benzo[a]pyrene (in presence of S9) and benzo[a]pyrene diol epoxide (with mutations similar to those seen in tumours from smokers). Other examples discussed included dibenzopyrans, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), platinum drugs, alkylating agents and ROS inducers. Dinucleotide substitutions are also possible, and solar radiation was associated with CC>TT and cisplatin with AG>TT and GA>TT. Insertion / deletion signatures were also seen with a limited number of agents (n=8), and stable signatures (i.e., reproducible) seen for 7 of these.

2.9 Professor Philips concluded that the study showed similar signatures for similar agents (e.g., cisplatin and carboplatin), however this did not apply in all cases, and, in addition, some dissimilar agents also showed similar signatures (e.g., PhIP and BaP/BPDE). It has not been possible to date to compare tissue specific signatures. The focus of research by Professor Phillips and his research team was on 3D systems, which were considered more relevant to the *in vivo* situation. Clonal organoid lines had been developed from human tissue and the assay time had been reduced by using Duplex Sequencing. Early results with a limited number of agents demonstrated proof of principle.

2.10 Following the presentation, clarification was sought around whether the methodology detected mutations in actively transcribed or silent regions and whether differences could be expected due to DNA repair. Members were informed that this was dependant on the agent. Further interesting results had been seen when early and late replicating regions had been compared as these did not mimic what was seen in tumours. As this is an evolving methodology however, it was considered possible that the mutation load may have been too small, or that the duration of exposure is important at low doses. The origin of the organoids used in the studies presented was also discussed as these can be derived from normal tissues, tumour biopsies and pluripotent stem cells; the ones described had been derived from normal tissue.

2.11 COM noted that a project being undertaken at HESI/GTTC was assessing the use of Duplex Sequencing for genotoxicity testing. The ultimate aim of this was to replace the transgenic rodent assay as the new methodology could be applied to any

repeated dose study and potentially be used for detecting mutagenicity within *in vitro* assays. Further refinement of signature detail was also discussed which could be achieved using different bioanalytical software. However, Professor Phillips cautioned that there was still much work to do to verify that signatures are caused by specific agents.

2.12 It was agreed that the COM would keep an active watching brief on further developments with the methodology, particularly with regards to its use as part of a genotoxicity testing strategy.

## COM evaluations

### Evaluation of the genotoxicity of cannabidiol update

2.13 The Food Standards Agency (FSA) previously requested an opinion from the COM on the genotoxicity of cannabidiol (CBD). This was to assist the FSA in developing its advice relating to the increasing number of requests for a health risk assessment on CBD in consumer products. The COM had considered the genotoxicity data relating to CBD in 2019 and concluded that the *in vitro* and *in vivo* data were inadequate. In January 2020, the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) received an update on available data, which included additional genotoxicity data. Therefore, the COT referred the consideration of the 'new' genotoxicity data to the COM. Paper MUT/2020/01 provided details of additional genotoxicity studies submitted to the European Medicines Agency (EMA) (available online) in relation to a medicinal form of CBD known as Epidiolex (used to treat seizures in certain medical conditions e.g., Lennox-Gastaut syndrome and Dravet syndrome).

2.14 The *in vitro* data consisted of pure CBD tested in the Ames test conducted to GLP (in Salmonella typhimurium strains TA98, TA 100, TA 102, TA 1535, and TA 1537). Members had no concerns over the reported data and agreed with the conclusion of a negative result.

2.15 Two *in vivo* studies were reported, a bone marrow micronucleus test and a comet assay for chromosome damage. Pure CBD was evaluated for its potential to increase the incidence of micronucleated polychromatic erythrocytes (MNPCEs) in rat bone marrow cells.

2.16 CBD treated rats showed mean MNPCE frequencies similar to those of the vehicle control group and fell within the laboratory's historical vehicle control range. Members noted that they could not see any information provided on whether the target tissue had been exposed (e.g., toxicokinetic or plasma levels) but assumed that because this study related to a medicinal product that appropriate toxicokinetic data would be available, which would be informative regarding bone marrow exposure. The COM agreed that from the information provided that the study appeared to be robustly conducted and gave a negative result.

2.17 In a rat alkaline comet assay, rats were given single oral gavage doses of 0 (sesame oil), 125, 250 or 500 mg/kg/day CBD oral solution. Liver samples were taken 24 hours after the initial dose. No clinical signs of toxicity were observed at any dose. Members agreed that from the information provided the study appeared to be

robustly conducted and gave a negative result.

2.18 Overall, the COM concluded that from the information provided, the studies appeared to be well conducted and gave negative results. However, the COM asked whether it could see all the relevant data for the *in vivo* studies to confirm that there was sufficient target tissue exposure and to evaluate whether there was any important species difference in metabolism (i.e., between humans and rats) because the potential for this this was mentioned in the summary information provided.

### WHO JECFA response to consultation

2.19 The Committee was provided with comments from COM members that had already been sent to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) secretariat on its draft revision of EHC 240 chapter on genotoxicity (MUT/2020/07). Members were asked whether they wished to submit any additional comments. JECFA were expected produce a final version and provide responses to any not taken into consideration. The COM had no further comments.

### Horizon scanning

2.20 It was noted that the item on the two-day workshop on the interpretation of genotoxicity data contributed to horizon scanning. For example, there was a proposal to form a working group to develop a framework or guidance (perhaps, similar to that of the Bradford-Hill criteria) on how to evaluate genotoxicity data from different sources (e.g., unpublished GLP studies conducted to OECD test guidelines and non-GLP studies published in the scientific literature). A few members expressed an interest in contributing to this. It was also noted that an additional COM led workshop could be organised in the future to further discuss unresolved questions that came out of the Birmingham meeting.

2.21 It was also anticipated that Defra would be developing a new chemical strategy. Additionally, it was expected that there would be a call for evidence in Spring relating to human health and chemicals in the environment. The COM assessors considered at that time that it was difficult to predict how the various government departments/agencies may require COM input in the future.

2.22 Members noted a few topics that the COM may need to consider in the future, and these included the baseline for spontaneous inherited mutations; environmental DNA (eDNA) collected from environmental samples (e.g., soil, water or air), which could be informative for monitoring various aspects, such as biodiversity (via DNA sequencing without having to collect individual living organisms); and new techniques for evaluating DNA damage. Additionally, it was noted that horizon scanning needed to be targeted with a need to avoid duplication or unnecessary work (e.g., in terms of regulatory response to technological changes). The COM was also informed that the COT was holding a workshop on exploring dose-response analysis at Manchester on the 11th of March 2020.

## OECD

### PIG-a Update

2.23 The COM was provided with paper MUT/2020/06 relating to the PIG-a gene mutation assay, mainly for information. This included UK comments that had been submitted to the OECD on the development of its test guideline. Member were asked if they had any additional comments.

2.24 The COM agreed this did not contain anything controversial and was generally content. It was noted that although there was nothing wrong with the assay, it did not appear to fill any useful gaps i.e., it did not enable anything to be investigated that couldn't already be done with existing methods. It would be useful if it could be developed further to examine other tissues in addition to peripheral blood.

2.25 Additionally, an update on the development of OECD Test Guideline 488 on transgenic rodent somatic and germ cell mutation assays was circulated to the COM (just a day before the meeting). Members were aware that there had been some disagreement between some countries over the text for sampling time in relation to rat germ cells. Members were also aware of reported evidence and modelling of rat spermatogenesis that suggested that a 28 day + 28-day (i.e., sampling 28 days later, after 28 days of dosing) designs was a better germ cell design than 28-day + 3-day (i.e., sampling 3 days later, after 28 days of dosing) for both the mouse and rat. The UK had previously commented that the data on appropriate sample times were not as good for the rat as the mouse. The relevant paragraph had been reworded to create a 'quick fix' for TG 488.The COM was content with the new wording that had been circulated (e.g., regarding sample times).

## 2020 Membership of the Committee on Mutagenicity of Chemicals in Food,Consumer Products and the Environment

### Chairman

**Dr David Lovell**
Emeritus Reader in Medical Statistics at St George's Medical School, University ofLondon

### Members

**Dr Carol Beevers**
Managing Scientist, Exponent International Ltd

**Mr Amit Bhagwat**
Lay Member

**Dr Stephen Dean**
Agenda Life Sciences

**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 (From 1 June 2020)**
Associate Professor, Swansea University Medical School

**Ms Julia Kenny (From 1 June 2020)**
GlaxoSmithKline

**Dr Ruth Morse**
Senior Lecturer in Human & Clinical Genetics, University of the West of England,Bristol.

**Dr Michael O'Donovan**
Independent Consultant

**Dr Andrew Povey**
Reader in Molecular Epidemiology, University of Manchester

**Mrs Madeleine Wang (From 1 June 2020)**
Lay Member

## Secretariat

| | |
|---|---|
| **Dr Ovnair Sepai** | PHE Scientific Secretary |
| **Ms C Mulholland** | FSA Scientific Secretary (from August 2019) |
| **Mrs N Blowfield** | Administrative Secretary |

## Declaration of members interests during the period of this report

| | | |
|---|---|---|
| **Dr David Lovell PhD BSc (Hons) FSS FIBiol Cstat CBiol (Chair)** | | |
| Personal Interest | **Pension**<br>Pfizer<br><br>**Shareholder**<br>National Grid plc<br>AstraZeneca (Spouse Shareholder)<br>National Grid plc (Spouse Shareholder) | **Membership**<br>Biometrics Society<br>British Toxicology Society (BTS)<br>Genetics Society<br>Royal Society of Biology (CBiol FRSB, 2003)<br>Laboratory Animal Science Association (LASA)<br>Royal Statistical Society<br>Statisticians in the Pharmaceutical Industry (PSI)<br>United Kingdom Environment Mutagen Society (UKEMS)<br>UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs) – Board Member<br>MRC EMINENT Scientific Review Board<br>British Trust of Ornithologists (BTO)<br>English Heritage<br>Liberty<br>Campaign of the Protection of Rural England (CPRE)<br>Kew Gardens<br>Sandwich Bay Bird Observatory Trust (SBBOT)<br>Chelsea Physic Garden<br>National Trust<br>HESI GTTC |
| Non Personal Interest | None | None |
| **Dr Carol Beevers** | | |
| Personal Interest | **Employee**<br>Exponent<br><br>**Pension**<br>Covance<br>Exponent | **Membership**<br>HESI GTTC(workgroup member)<br>OECD (workgroup member)<br>IWGT (work group chair)<br>United Kingdom Environmental Mutagen Society (UKEMS) |
| Non-Personal Interest | None | None |
| **Mr Amit Bhagwat** | | |
| Personal Interest | **Owner and Shareholder** | **Membership** |

| | | |
|---|---|---|
| | Research and Consulting Business | None |
| Non-Personal Interest | Bradford Teaching Hospitals NHS Foundation Trust - Public Governor (Rest of England & Wales)<br>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<br>Prescribed specialised services advisory group, DHSC – Public appointment<br>Committee on Mutagenicity, DHSC – Public Appointment |
| **Dr Stephen Dean** | | |
| Personal Interest | **Employee**<br>Imagen Therapeutics, From February 2020 (Equity Holder)<br><br>**Shareholder**<br>Standard Life | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Professor Shareen Doak** | | |
| Personal Interest | **Employee**<br>None | **Membership**<br>United Kingdom Environmental Mutagen Society (UKEMS)<br>Fellow of the Learned Society of Wales<br>British Association for Cancer Research (BACR)<br>Royal Society of Biology (FRSB)<br>ILSI HESI (committee member)<br>British Toxicology Society (BTS) |
| Non-Personal Interest | **Trustee**<br>St David's Medical Foundation (medical research & education charity)<br><br>**PhD Studentship Grants**<br>Unilever (2017 – 2020)<br>AstraZeneca (2009 – 20160<br>Unilever (2010 -2017)<br><br>**Research Grant 2008 – 2010**<br>Hoffman-LaRoche<br>Unilever | None |
| **Dr Paul Fowler** | | |
| Personal Interest | **Pension**<br>Unilever (UK)<br>Covance<br><br>**Misc**<br>De Montfort University – External Examiner | **Membership**<br>IGG (committee member)<br>UKEMS (committee member)<br>RoundTable of Toxicology Consultants (RTC)<br>British Toxicology Society (BTS)<br>In vitro toxicology Society |

| | | |
|---|---|---|
| | FSTox Consulting - Director | (Committee member) |
| Non-Personal Interest | None | None |
| **Professor David Harrison** | | |
| Personal Interest | **Employee**<br>University of St Andrews, UK<br>NuCana plc, UK<br>Benenox Ltd, UK<br><br>**Consultant**<br>University of Edinburgh<br>University of Canberra<br>University of Florida<br>Visiopharm<br><br>**Shareholder**<br>VBL Ltd, UK<br>Ryboquin Ltd, UK<br>Avipero Ltd, UK<br>Benenox Ltd, UK<br><br>**Misc**<br>Cunningham Trust – Scientific Adviser<br>University of Edinburgh, UK – Honorary Professor<br>University of Glasgow, UK – Visiting Professor<br>University of Florida, Adjunct Professor<br>VBL Ltd – Director (no salary)<br>Canon Medical Europe (part support for travel to meeting) | **Membership**<br>None |
| Non-Personal Interest | **Misc**<br>iCAIRD research consortium – Director (unpaid role)<br>Families First St Andrews (children's charity) – Trustee and Director (unpaid role)<br>Respiratory Gene Therapy Consortium (Wellcome Trust) – External scientific advisor (unpaid role)<br>AstraZeneca, research collaboration (no funding received)<br>Panakeia Ltd, UK, research collaboration (no funding received)<br>Committee on Carcinogenicity, chair, (unpaid role)<br>Nanostring, USA, research collaboration & grant support<br>Innovate UK, grant support | **None** |

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|---|---|---|
| | Medical Research Scotland, grant support<br>EU Horizon 2020, grant support<br>Chief Scientist Office, Scotland, grant support<br>Scottish Government AI Steering Group, member (unpaid role)<br>NuCana plc, research grant support | |
| **Dr George Johnson** | COM Member from 1 June 2020 | |
| Personal Interest | **Consultancy:**<br>Current –<br>Fermenich<br>Cefic<br>American Chemistry Council<br>Teva<br>Greenberg Traurig LLP<br>Galapogos<br>Janssen<br>Merck | **Membership**<br>United Kingdom Environmental Mutagen Society (UKEMS)<br>HESI (committee member)<br>President of the European Environmental Mutagenesis and Genomics Society (EEMGS) 2019-2021<br>EMA Expert Member<br>IWGT, Expert Member<br>ICEM, Committee Member |
| Non-Personal Interest | **Relevant grant funding:**<br>GSK, post-doctoral research funding – 2021-2022. nitrosamine research.<br>SCIENSANO. MYCX-IT. 2020-ongoing. | None |
| **Ms Julia Kenny** | COM Member from 1 June 2020 | |
| Personal Interest | **Employee**<br>GlaxoSmithKline<br><br>**Pension**<br>GlaxoSmithKline<br><br>**Shareholder**<br>GlaxoSmithKline | **Membership**<br>HESI GTTC (committee member)<br>UK Environmental Mutagen Society (UKEMS)<br>Cosmetic Europe – Task Force Genetic Toxicology member |
| Non-Personal Interest | None | None |
| **Dr Ruth Morse** | | |
| Personal Interest | **Employee**<br>None | **Member**<br>United Kingdom Environmental Mutagen Society<br>British Society of Toxicology<br>Genetics Society |

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|---|---|---|
| Non-Personal Interest | **Misc**<br>Medical Research Council with AstraZeneca (ITTP programme) - PhD studentship collaborative grant 2015-2020<br>Petroleum Technology Fund, Nigeria - PhD studentship 2016-2020 | None |
| **Dr Michael O'Donovan** | | |
| Personal Interest | **Employment**<br>O'Donovan GT Consulting Ltd – Director<br>Apconix - Associate<br><br>**Pension**<br>AstraZeneca<br>BASF | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Dr Andrew Povey** | | |
| Personal Interest | **Shareholder**<br>Lloyds<br>Standard Life<br>Halifax<br>Santander (Partner Shareholder)<br>Norwich Union (Partner Shareholder)<br>Roadchef Topco Ltd (Partner Shareholder)<br><br>**Misc**<br>European Crop Protection Agency – Part of consortium recently awarded grant on exposure assessment | **Membership**<br>UK Molecular Epidemiology Group (UK-MEG)<br>UK Environmental Mutagen Society (UKEMS)<br>American Association for Cancer Research (AACR)<br>Molecular Epidemiology Group (MEG)<br>British Association for Cancer Research (BACR) |
| Non-Personal Interest | **Misc**<br>RTZ – Departmental Research Grant<br>Manchester University – Research equipment bought using departmental funds from consultancies with industry and other bodies | None |
| **Ms Madeleine Wang** | COM Member from 1 June 2020 | |
| Personal Interest | **Employment** | **Membership** |

| | | |
|---|---|---|
| | None | None |
| Non-Personal Interest | None | 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 (COT Website).

We have welcomed new members virtually as we met via Teams to continue our work. This has been a challenging year I am grateful to Members, Secretariat and other contributors for ensuring that the work continues. One of the committee's primary roles has been to ensure that we provide appropriate guidance for policy makers and regulators. We have continued our review and update of guidelines and have identified some areas where a complete revision is now required. This, together with regular horizon scanning and issues directly raised by Members, should reassure that COC's advice is appropriate and timely, and allows us to think through the implications of leaving the EU may affect our work. We have continued our 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 when data relevant to human disease may be incomplete or sometimes missing completely. The multidisciplinary nature of the committee has proved its worth as we seek to give more informed and specific advice.

Professor David Harrison
MD DSc FRCPath FRCPEd FRCSEd

## COC Evaluations

## The microbiome

3.1 The microbiome had been on the COC horizon scan list and Professor Tim Gant (PHE) joined the meeting to give an overview of the area and describe some of the specific aspects of relevance to chemicals and carcinogenicity.

3.2 The microbiome represents the community of microorganisms that are resident on or in the human body and includes bacteria, viruses and fungi. The term also encompasses the environmental microbiome however the focus of the presentation and subsequent discussions was the internal one. Sequencing methods have indicated a large diversity with the total microbiome being around 30 trillion similar to the number of cells in the human body. The gene pool was estimated to be far larger than that of the human host. The ratio of bacterial to human cells though previously reported at more than 10:1 was considered to be 1:1

3.3 The microbiome has been found on any surface of the body that has a connection with the environment and in particular, where conditions favour microbial growth. Humans are thought to be born sterile with the microbiome then immediately establishing, with initial seeding reflecting that of the route of delivery.

3.4 Influences on the microbiome have been shown to be both genetic and environmental. Age is an important parameter in driving diversity of the gut microbiome, as are diet and degree of exercise. The gut microbiome provides around 70% of the energy for the gut and is particularly important for the metabolism of small molecules, including environmental chemicals. Thus, changes to the microbiome may lead to changes in host phenotype. Changes to the gut microbiome diversity may alter the types of reactions occurring both for endogenous and exogenous chemicals which may also impact on any toxicological response. Differences in toxicological response have also been reported within animal strains that were housed together and commonly used for chemical testing, which was attributed, at least in part, to differences in the gut microbiome. Such differences allowed metabolism prior to absorption from the gut to occur in some animals, and in others no metabolism occurred, resulting in a difference in the outcome following exposure which could not be predicted.

3.5 In terms of therapeutics and disease, treatment with antibiotics may adversely affect the microbiome and the reestablishment of the microbiome can be slow, following the end of a treatment regimen. Evidence is emerging suggesting an adverse effect of antibiotics on the microbiome having a role in in disease processes particularly respiratory diseases. There was some uncertainty in the epidemiology due and more evidence was required to establish the association and in particular causality. Although the microbiome may be involved in modulating toxicity it was not generally taken into account in toxicity or carcinogenicity testing.

3.6 A role for the microbiome in the development of cancer was not less established at present, though it was plausible given the role of the microbiome in metabolism of exogenous molecules. An important aspect of microbiome research that was considered missing, and which might impact on its use in risk assessment, was the lack of an agreed definition of what is considered ‘normal’ in both humans and animals. Also linked to this was the uncertainty around how to predict what proportion of intra-individual variability in response is due to differences in the microbiome.

3.7 The COC recognised that the microbiome was an area of concern to the general public who were aware of its potential involvement in the underpinning of a number of diseases. It was agreed that going forward, the Committee should assess how this may impact COC guidelines and opinions. This would best be achieved by establishing a baseline of what is currently known and what further work needs to be carried out to fill critical gaps in knowledge.

## Ongoing topics

### The tumour microenvironment

3.8 The COC has been developing a watching brief document on the tumour microenvironment in recognition of the awareness of its role in cancer development. Many of the key events associated with the interaction of neoplastic cells with the microenvironment are not considered in current risk assessment methodologies. This is an area that the Committee will be keeping awareness of in the coming years

### Joint meetings

3.9 In November 2020, the COC and COM held a joint online meeting over two half days, to which COT Members were also invited. The purpose of this meeting was to allow committee members to meet and discuss issues of joint interest and decide how to take such issues forward. In addition, the meeting allowed for discussion of recent developments in COC and COM guidance and other activities.

3.10 The discussion topics for the meeting were: updates on Committees guidance, discussion of the implications of EU exit and the end of the transition period, review of the amendments to the COT Terms of Reference and Code of Practice, joint horizon scanning, and biological relevance and statistical significance (see section below 3.12-3.13).

3.11 From the joint horizon scanning, the following topics were agreed, and the Secretariats will consider how to progress these either as joint topics or which Committee might lead on these:

- Use of toxicogenomics/omics technologies in toxicity testing
- PBPK modelling – a COT workshop was held the following week; COC members participating may wish to feed back on this.
- Next generation sequencing
- Further exploration of microplastics/microparticles and their composition – also linking with COMEAP
- Development of a dynamic cancer risk model, including consideration that pre-cancer effects are assessed as ‘general’ toxicity pathways, and other influencers on cancer/toxicity risk (e.g., shift work)
- Knowledge sharing across the three Committees, including impacts of EU Exit
- Consideration of uncertainty, use of uncertainty factors and margins of exposure – noting this also links with other activities.

### Biological Relevance and Statistical Significance

3.12 A scoping paper outlining current literature concerning assessment of biological relevance and statistical significance was presented at the November joint meeting. During the discussion, the importance of considering statistics as more than statistical significance was emphasised, with consideration of all aspects of the study being crucial for interpretation. The recommendation to move away from the use of p-values and their specific interpretation to an estimation of effect using confidence intervals (CIs) has been discussed over many years. It was considered that there is a need to encourage scientists to apply the term significance only to statistical results and not to biological meaning. In addition, in the wider scientific community, statistical significance is considered to be the primary factor, when in fact this needs to be framed within the context of biological relevance.

3.13 It was agreed that although this issue had been recognised for many years, there remained a problem when trying to implement changes in practice. One contributing factor may be that the limitations of 'p-values' had not been effectively communicated to the general public. To address this, a short non-technical paper on how the committees evaluate data, including use of WoE and meta-analysis tools would be written, and this will be taken forward in 2021 as a joint effort by all three Committees.

### Horizon scanning

3.14 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.

3.15 At the end of discussion in 2020, 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

3.16 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 IARC and the EU Scientific Committees.

## Working Groups

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

3.17 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 1.134-1.135

## Guidance statements

3.18 The Committee continued to develop the guidance statement series during 2020. This included finalising revisions to the overarching strategy for risk assessment of carcinogenicity (G01), defining points of departure and potency estimates in carcinogenic dose response (G05), and effects of combined exposures to chemical carcinogens (G08).

3.19 Updates to the cancer risk characterisation methods (G06) statements are ongoing and it is expected to be finalised in 2021.

3.20 The Committee also reviewed the guidance on hazard identification and characterisation (G03) and alternatives to the two-year bioassay (G07) and considered these should be combined. A draft scope of such a document has been presented and will be further developed in 2021.

## 2020 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

**Dr Meera Cush (From February 2020)**
Managing Consultant (Toxicologist), Ramboll

**Dr Ruth Dempsey (From February 2020)**
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 (From February 2020)
Head of Pathology UK, GlaxoSmithKline

**Dr Ray Kemp** BA MSc PhD MRTPI SIRM
Public Interest Representative

**Dr David Lovell** PhD BSc (Hons) FSS FRSB CStat CBiol
Emeritus Reader in Medical Statistics at St George's Medical School, University of London

**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

**Professor Heather Wallace** BSc(Hons) PhD FRCPath FBTS FRSC FRSB FBPS ERT
Professor in Biochemical Pharmacology and Toxicology, University of Aberdeen

**Dr Rosemary H Waring** PhD DSc FRCPath (To June 2020)
Honorary Reader in Human Toxicology, University of Birmingham

**Secretariat**

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| **Miss B Gadeberg** BSc(Hons) MSc | 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 David Harrison** | | |
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| Personal Interest | **Employee**<br>University of St Andrews, UK<br>NuCana plc, UK<br>Benenox Ltd, UK<br><br>**Consultant**<br>University of Edinburgh<br>University of Canberra<br>University of Florida<br>Visiopharm<br><br>**Shareholder**<br>VBL Ltd, UK<br>Ryboquin Ltd, UK<br>Avipero Ltd, UK<br>Benenox Ltd, UK<br><br>**Misc**<br>Cunningham Trust – Scientific Adviser<br>University of Edinburgh, UK – Honorary Professor<br>University of Glasgow, UK – Visiting Professor<br>University of Florida, Adjunct Professor<br>VBL Ltd – Director (no salary)<br>Canon Medical Europe (part support for travel to meeting) | **Membership**<br>None |
| Non Personal Interest | **Misc**<br>iCAIRD research consortium – Director (unpaid role)<br>Families First St Andrews (children's charity) – Trustee and Director (unpaid role)<br>Respiratory Gene Therapy Consortium (Wellcome Trust) – External scientific advisor (unpaid role)<br>AstraZeneca, research collaboration (no funding received)<br>Panakeia Ltd, UK, research collaboration (no funding received)<br><br>Committee on Mutagenicity, member ex officio, (unpaid role) | None |

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| | Nanostring, USA, research collaboration & grant support<br>Innovate UK, grant support<br>Medical Research Scotland, grant support<br>EU Horizon 2020, grant support<br>Chief Scientist Office, Scotland, grant support<br>Scottish Government AI Steering Group, member (unpaid role)<br>NuCana plc, research grant support | |
| **Mr Derek Bodey** | | |
| Personal Interest | **Employee**<br>None | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Dr Gill Clare** | | |
| Personal Interest | **Pension**<br>Shell Research Ltd<br>AstraZeneca<br><br>**Shareholder**<br>AstraZeneca<br>Diageo<br>Marks and Spencer<br><br>**Consultant**<br>Covance | **Membership**<br>United Kingdom Environmental Mutagen Society (UKEMS) |
| Non-Personal Interest | None | None |
| **Dr Meera Cush** | From February 2020 | |
| Personal Interest | **Employee**<br>None | **Membership**<br>Royal Society of Biology |
| Non-Personal Interest | None | None |
| **Dr Ruth Dempsey** | From February 2020 | |
| Personal Interest | **Shareholder**<br>RD Science Speaks Consultancy, Sarl (Shareholder and director)<br>Philip Morris International<br><br>**Pension**<br>Philip Morris International | **Membership**<br>British Toxicology Society<br>Swiss Society of Toxicology<br>Royal Society of Biology |

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| Non-Personal Interest | None | None |
| **Dr John Doe PhD** | | |
| Personal Interest | **Employee**<br>Parker Doe Partnership (Partner)<br><br>**Pension**<br>Syngenta<br><br>**Consultant**<br>ECETOC<br>Syngenta<br>Covance<br><br>**Misc**<br>Liverpool John Moores University (Honorary Research Fellow) | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Dr Richard Haworth** | From February 2020 | |
| Personal Interest | **Employee**<br>GlaxoSmithKline<br><br>**Shareholder**<br>GlaxoSmithKline<br>Royal Dutch Shell (Spouse Shareholder)<br>United Utilities (Spouse Shareholder) | **Membership**<br>British Society of Toxicological Pathology |
| Non-Personal Interest | None | None |
| **Dr Ray Kemp** | | |
| Personal Interest | **Director**<br>Rhodes-Kemp Law Ltd<br><br>**Non-Executive Director**<br>Dept of Business, Energy and Industrial Strategy (BEIS)<br><br>**Member**<br>Committee on Radioactive Waste Management (CoRWM)<br><br>**Independent Expert**<br>International Atomic Energy Agency – Mission to Fukushima Prefecture<br><br>**Independent Expert** | **Member -** Committee on Medical Aspects of Radiation in the Environment (COMARE)<br><br>**Member**<br>Royal Town Planning Institute Specialist<br><br>**Member**<br>Institute of Risk Management |

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| | Office for Rail and Road | |
| Non-Personal Interest | None | None |
| **Dr David Lovell PhD BSc (Hons) FSS FIBiol Cstat CBiol** | | |
| Personal Interest | **Pension**<br>Pfizer<br><br>**Shareholder**<br>National Grid plc<br>AstraZeneca (Spouse Shareholder)<br>National Grid plc (Spouse Shareholder) | **Membership**<br>Biometrics Society<br>British Toxicology Society (BTS)<br>Genetics Society<br>Royal Society of Biology (CBiol FRSB, 2003)<br>Laboratory Animal Science Association (LASA)<br>Royal Statistical Society<br>Statisticians in the Pharmaceutical Industry (PSI)<br>United Kingdom Environment Mutagen Society (UKEMS)<br>UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs) – Board Member<br>MRC EMINENT Scientific Review Board<br>British Trust of Ornithologists (BTO)<br>English Heritage<br>Liberty<br>Campaign of the Protection of Rural England (CPRE)<br>Kew Gardens<br>Sandwich Bay Bird Observatory Trust (SBBOT)<br>Chelsea Physic Garden<br>National Trust<br>HESI GTTC |
| Non-Personal Interest | None | None |
| **Professor Neil Pearce** | | |
| Personal Interest | **Employee**<br>None | **Membership**<br>None |
| Non-Personal Interest | None | None |
| **Dr Lesley Rushton OBE BA MSc PhD Cstat HonFFOM** | | |

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| Personal Interest | **Employee**<br>None | **Member**<br>Industrial Injuries Advisory Council - Chair |
| Non-Personal Interest | None | **Misc**<br>IEH Consultancy Ltd – Research Support |
| **Professor Heather Wallace BSc Hons PhD FRCPath FBTS FRSC FRSB ERT** | | |
| Personal Interest | **Shareholder**<br>Bank Santander SA<br>BT Group<br>NovaBiotics<br>Aviva<br><br>**Misc**<br>EFSA – CONTAM Panel<br>Cell ProTx - Director | **Membership**<br>EUROTOX - President<br>British Toxicological Society (BTS)<br>Medical Research Scotland – Trustee and Vice Chair<br>Paediatric Medicines Expert Advisory Group – MHRA<br>Herbal Medicines Advisory Committee – MHRA |
| Non-personal Interest | None | None |
| **Dr Rosemary Waring PhD DSc FRCPath** | To June 2020 | |
| Personal Interest | **Shareholder**<br>Tharos – Director and Shareholder<br>Centrica and National Grid<br>Ateria Health | **Membership**<br>None |
| Non-Personal Interest | None | None |