Committee on Toxicity

Committee on Carcinogenicity

Committee on Mutagenicity

Annual Report 2019

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

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Contents

About the Committees

This is the twenty-eighth 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 relevant references from the Committee's administrative secretary or from the internet sites listed below.

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 General Advisory Committee on Science, 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 addresses:
COT: http://cot.food.gov.uk
COC: https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food- consumer-products-and-the-environment-coc
COM: https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in- food-consumer-products-and-the-environment

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

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

Preface

I am pleased to present this report, which summarises the work of the Committee on Toxicity (COT) during 2019. 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.

At the request of the Scientific Advisory Committee on Nutrition, the Committee has continued its programme of work reviewing the risks to infants and young children from a variety of contaminants and other chemicals in their diet. An overarching statement was published collating the Committee's views on those contaminants and other chemicals for which a major new review was considered unnecessary. The compounds included in this overarching statement were the mycotoxins moniliformin, fusarenon-X, cyclopiazonic acid, aflatoxins, patulin, tropane alkaloids, and the fumonisins and the contaminants tetrabromobisphenol A, 2-MCPD, 3-MCPD and esters, and low/no-calorie sweeteners

Building on the well received work on 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 begun collaborating in a Working Group to examine the Synthesis of Epidemiological and Toxicological Evidence (SETE) Such topics use the complementary knowledge and skills of sister SACs to great effect.

Another ongoing programme of COT work relates to assessing the safety of 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 toxicity in adolescents, young children and other bystanders, and exposure of users to ingredients and emissions, including flavourings and nicotine.

The other topics discussed by the Committee this year have been very varied and have included the safety of cannabidiol (CBD) in food, PBPK modelling, the effect of xenobiotics on the gastrointestinal microbiome, microplastics, soya drinks, and

turmeric and curcumin in food supplements There have also been continuing discussions on the fortification of wheat flour with folic acid, an assessment of phosphate-based flame retardants, and the potential effects of energy drinks in adolescents.

This year the Committee said goodbye to Professor Roy Harrison, Dr Mark Graham and Dr Brian Lake and would like to thank them for all their valuable contributions during their time on the Committee.

In preparation for the UK's exit from the European Union, the capacity of the Committee has been significantly expanded. We welcomed eight new Members to the Committee. These new Members are Dr Stella Cochrane, Professor Gary Hutchison, Professor Gunter Kuhnle, Dr David Lovell, Dr Michael Routledge, Dr Cheryl Scudamore, Dr Natalie Thatcher and Professor Maged Younes,
Three Joint Expert Groups have also been established as part of the FSA Scientific Advisory Committee (SAC) structure which 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 in due course.

I would like to thank the Secretariat for their continued and much appreciated support, both during and between meetings, and my fellow Committee Members for all their hard work and valuable contributions to the work of the Committee through the year.

Professor Boobis
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COT evaluations

Folic Acid – statement on the tolerable upper level (TUL)

1.1 Supplementation with folic acid has been shown to reduce the risk of having a neural tube defect (NTD) affected pregnancy. This is where the brain, spine or spinal cord do not form properly in an unborn baby and results in life-long health problems or can even be fatal. UK Government advice is that women should take a 400 µg supplement of folic acid daily before getting pregnant and up to the third month of pregnancy; women who have already had an NTD affected pregnancy are advised to take a 5 mg supplement.

1.2 The Scientific Advisory Committee on Nutrition (SACN) is reviewing the scientific evidence that bears on the Government's dietary recommendations for infants and young children. The Committee on Toxicity (COT) was asked to review the risks of toxicity from chemicals in the diet of infants aged 0 – 12 months and children aged 1 – 5 years. This statement focuses on possible risks from cadmium in the diet of these age groups.

1.3 However, as many women do not take supplements and many pregnancies are unplanned, the rate of affected pregnancies has not significantly changed since this advice was issued. Consequently, advisors to the government have recommended that wheat flour should be fortified with folic acid to ensure that all population groups receive adequate amounts of this vitamin. This recommendation was accompanied by advice that folic acid levels in supplements and foods that are currently fortified such as breakfast cereals should be adjusted so that there is no increase in the number of people who were currently consuming more folic acid than is necessary.

1.4 Safe levels (sometimes called Safe Upper Levels or Guidance Levels (or equivalent)) for folic acid have been established by a number of risk assessment bodies. All of these bodies set a maximum recommended intake of 1 mg/day folic acid based on the observations of nerve damage in patients with pernicious anaemia.

1.5 Pernicious anaemia is an auto-immune disease (where the immune system of the patient destroys healthy cells of the body). In the case of pernicious anaemia, the immune system destroys cells that line the stomach. These cells secrete a substance that allows the body to absorb vitamin B12, therefore these patients become deficient in vitamin B12 regardless of the amount of vitamin B12 present in the diet. Vitamin B12 is an essential vitamin which is necessary for producing haemoglobin – the oxygen carrying molecule in blood; and for producing the myelin sheath that surrounds and protects the nerves of the body. If the myelin sheath become damaged and is not repaired by new myelin, then the messages carried from the brain to the extremities of the body, can be disrupted resulting in numbness and/or muscle weakness. The damage caused to the nerves in pernicious anaemia can be permanent.

1.6 Often the first symptom of pernicious anaemia to be identified is extreme tiredness resulting from anaemia (low blood haemoglobin) which can be identified through a simple blood test. There are many causes of anaemia, one of which can also be low dietary folate (the natural form of folic acid found in the diet). Should a patient with pernicious anaemia dramatically increase their intake of folic acid or folate, then their anaemia and associated symptoms may improve

but the damage to the nerves would continue unchecked. This has been called "masking vitamin B12 deficiency".

1.7 The COT reviewed the safe level for folic acid and the studies on which it was based. Although the studies were limited, the COT agreed that, from the information available, it was appropriate to base a safe level on the masking of vitamin B12 deficiency. They also agreed that 1mg/day of folic acid in the form of supplements (not including dietary folates) was still the most appropriate level to use but noted that the data on which this was based were poor.

1.8 The COT also noted that currently reliable diagnostic tests for pernicious anaemia were not routinely or consistently applied across the UK. Should this situation change, with diagnosis becoming more reliable, then there were would be no need to stipulate an upper level for folic acid.

The full COT statement can be found here:

https://cot.food.gov.uk/sites/default/files/cotfolicacidstatement.pdf

Overarching statement on the potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

1.9 The Committee on Toxicity (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 0-12 months) and young children (age 1-5 years). The reviews will identify new evidence that has emerged since the Government's recommendations were formulated and will appraise that evidence to determine whether the advice should be revised.

1.10 The COT identified a number of chemicals in 2015, which may be present in the diets of infants and young children and for which advice may be needed. The following statement discusses the conclusions of the COT regarding a number of these chemicals:

- Alcohol: In the absence of any more recent information, the COT confirmed its previous advice for breastfeeding women to not drink more than 1 or 2 units of alcohol once or twice a week. As children aged 0 to 5 years would not be consuming alcohol directly, the current statement does not require any further assessment in this age group.

- Caffeine: In the absence of any more recent information, the COT confirmed its previous advice for pregnant and breastfeeding women to consume less than 200 mg caffeine per day. As children aged 1 to 5 years would not be expected to be consuming high-caffeine beverages no further assessment for this age group is required.

- Food additives: Food additives are regulated under EU law and therefore outside the remit of the COT.

- Legacy chemicals: The COT concluded, in line with the 2012 overarching statement, that there is no indication of concern for human health at present levels of these chemicals in the diet of infants and young children. It was also noted that levels of these chemicals are expected to decline further over time.

- Soya phytoestrogens: In the absence of any more recent information, the COT concluded that uncertainties remain about the safety of soya-based formula in infants and young children, and that in the absence of medical needs, soya-based formula should be used only in exceptional circumstances and under medical supervision.

- Vitamin A: Following its update in 2017, the COT concluded that the possibility of adverse effects cannot be excluded in high consumers, primarily those who regularly eat liver. However, if effects did occur it would be in a small proportion of consumers. The COT found no scientific basis for a change in current Government advice, including the recommendation that infants over 6 months of age should not have more than one portion of liver per week.

- Trans fatty acids: SACN is currently reviewing saturated fat, including information on how intakes of trans fatty acids are changing over time. No advice from COT is currently needed.

- Perchlorate: In the absence of any recent UK-specific data, the COT based its assessment on a recent evaluation by the European Food Safety Authority (EFSA). The chronic and short-term exposures for all age groups of infants and young children are of potential concern, particularly in the case of those with mild to moderate iodine deficiency.

- Chlorate: In the absence of any recent UK-specific data, the COT based its assessment on a recent evaluation by EFSA. Chronic dietary exposure is of potential concern to high consumers in all age groups of infants and young children, particularly to those individuals with mild to moderate iodine deficiency. Single acute exposure to chlorate at levels found in food and drinking water are unlikely to cause adverse effects, including in vulnerable individuals.

- Furan: The exposures in the diet of infants and young children are of potential concern to human health. However, the COT acknowledges that its assessment is based on worst case assumptions. There have been efforts to reduce concentrations of furan (and methylfurans) in food and such efforts should therefore continue.

- Chromium: The COT concluded that the estimated dietary exposures of infants and young children do not indicate excessive chromium intake and are not of toxicological concern. Similarly, environmental exposures from dust, soil and air are not of toxicological concern.

- Selenium: The COT concluded that the dietary exposure from breastmilk or other foods in infants and young children are unlikely to be of toxicological concern.

- Zinc: The COT concluded that the estimated dietary exposures do not indicate excessive zinc intake and are unlikely to be of toxicological concern. The COT however noted, that all health based guidance values (HBGVs) and upper level (UL) are derived from adults, making it difficult to identify a HBGV or UL that is applicable for all age groups of infants and children.

1.11 Chemicals identified for review and not included in this statement have been or will be subject to a full review or will be published in a subsequent addendum to

the overarching statement at a later date. The remaining chemicals are listed in Annex 1 of the overarching statement.

The full COT statement can be found here:

https://cot.food.gov.uk/sites/default/files/cotoverarchingstatement.pdf

Statement on the potential risks from "energy drinks" in the diet of children and adolescents.

1.12 Highly caffeinated soft drinks (known as "energy drinks") have become widely popular since their introduction in Austria in 1987. Drinks that contain 150 milligrams (mg) or more of added caffeine per litre are required by EU law to display the warning: "High caffeine content. Not recommended for children or pregnant or breast-feeding women". In addition, the amount of caffeine in mg per 100 ml of drink must appear on the can.

1.13 Recently, media have drawn attention to concerns that the free access by children and adolescents to "energy drinks" may be detrimental to their health and may cause "problem behaviour", particularly in school. Several major retailers have voluntarily restricted the sale of "energy drinks" to try to reduce their consumption by individuals under 16 years old.

1.14 The British Soft Drinks Association, the trade body for soft drink manufacturers, produced a Code of Practice in 2015, laying down rules for the labelling and the responsible marketing of "energy drinks" to the effect that consumers are aware of the potential effects of drinking these products and that the exposure of school-age children to related advertising is kept to a minimum. 4 Government is now considering a legal ban on the sale of "energy drinks to children rather than a voluntary agreement.

1.15 In the light of these concerns, the COT was asked to examine the issue of "energy drinks" to determine whether there is scientific evidence that adolescents are particularly sensitive to their ingredients or are more likely than adults to drink them in excess and thus suffer ill effects.

1.16 In addition to caffeine, "energy drinks" may contain a variety of other ingredients such as taurine (a type of amino acid found naturally in the body), glucurono-gamma-lactone (a glucose-like compound produced normally in the body) and extract of guarana (a plant with coffee-like stimulant properties). However, the substance largely responsible for their stimulant effect is caffeine, which is also found in coffee, tea and chocolate. Levels of caffeine vary, depending on the brands involved, but some brands of coffee from high street coffee shops contain more caffeine per serving than that commonly found in some "energy drinks".

1.17 Caffeine acts at various sites in the nervous system and initially increases alertness but large amounts can cause nervousness, sleeplessness and an upset stomach. Very large amounts can be fatal but to reach this level of intake voluntarily is very rare and is usually a consequence of taking caffeine in tablet or powder form.

1.18 Caffeine consumption increases blood pressure and may not be advisable for people with underlying heart and circulatory conditions. Caffeine has well documented effects on sleep and may lead to daytime sleepiness, through sleep deprivation, and reduced mental and physical performance.

1.19 The major brands of “energy drinks” (and many “soft” drinks) are marketed in different varieties, which often contain large amounts of sugar, but there are now “light” and sugar free versions available. There is a new tax on beverages containing more than 5 g of sugar per 100 millilitres (ml). Manufacturers must now reformulate their products or pay the duty and thence possibly absorb the cost or pass it on to the consumer. High sugar intake is related to the development of obesity and type-2 diabetes. There is little evidence for any additional stimulant effect due to the presence of caffeine and sugar together.

1.20 Adolescents are known to consume “energy drinks” and consumption is influenced by various factors, including taste, the stimulant effect, peer pressure and degree of adult supervision. Social factors and the effects of normal brain development in adolescence confound the interpretation of studies investigating the effects of “energy drinks” on adolescent behaviour.

1.21 People who consume “energy drinks” in combination with alcohol have been reported to be at an increased risk of “risky” behaviour, such as drink-driving, fighting and unsafe sex. In the UK it is illegal for retailers to sell alcohol to people under 18 years of age, although under-age drinking still occurs and causes problems even without the addition of “energy drinks”.

1.22 Overall the consumption of “energy drinks” by children and adolescents is a complex social issue. The acute effects of the main active constituents of “energy drinks”, caffeine and sugar, are well documented, while those of other ingredients are either negligible or reported inconsistently. New legislation should reduce the amount of sugar in “energy” and “soft” drinks. Only a small proportion of children and adolescents admit to “energy drink” use at levels likely to cause them problems. Although the effects of regular long-term consumption of these drinks are unknown, children and adolescents have long consumed caffeine and its breakdown products in tea, coffee, cola and chocolate. The natural behavioural development of adolescents may contribute to the behaviour that has been attributed to “energy drink” use

The full statement can be found here:

https://cot..food.gov.uk/sites/default/files/cotenergydrinksstatement.pdf

Manganese – Statement on the health effects of manages in the diets of infants aged 0-12 months and children aged 1-5 years

1.23 The Scientific Advisory Committee on Nutrition (SACN) is reviewing the evidence behind the Government recommendations for the diets of infants and young children. The SACN have requested that the Committee on Toxicity (COT) review the risk posed by certain chemicals, including manganese, in the diets of infants and young children up to 5 years of age.

1.24 Manganese is found naturally in the environment and can also be released as a

result of industrial activity. It is an essential nutrient in the human diet, acting as a necessary component of a number of enzymes and has a role in other biological processes.

1.25 Long-term intake of excessive levels of manganese has been found to produce a range of effects on the nervous system which combine, in severe cases, to form a Parkinson disease-like syndrome called Manganism. Primary effects include reduced response speed, reduced scores in intelligence tests, mood changes and compulsive behaviour in the initial stages to more prominent irreversible effects in more severe cases. Cases of Manganism are primarily associated with occupations such as mining and welding, where inhalation of manganese from the air is the primary route of exposure.

1.26 Safe levels (sometimes called Safe Upper Levels (SUL) or Guidance Levels (GL)) for manganese have been established by a number of risk assessment bodies. The UK Expert Group on Vitamins and Minerals concluded in 2003 that there were not sufficient data to set an SUL for manganese but they did set a GL of 0.2 mg/kg bw/day for total manganese, at or below which exposure was considered unlikely to cause adverse effects in adults. The World Health Organisation (WHO) established an SUL of 60 µg/kg (0.06 mg/kg) body weight in 2011 based on exposure through drinking water.

1.27 The COT reviewed studies that had been published since the EVM opinion in 2003. These focussed primarily on the association between levels of manganese in hair, blood or tooth samples and IQ scores or other neurological effects in children such as behaviour. The Committee concluded that the available evidence indicates that excessive exposure to manganese from all sources in children can lead to effects on the nervous system which may not be reversible.

1.28 From the evidence available, it is not possible to conclude whether exposure to manganese from the diet is sufficient to cause effects on the nervous system. For example, there is considerable uncertainty on how much manganese is absorbed from the gut, and many of the studies in which changes in behaviour were observed were complicated by exposures to other substances, such as lead, that can have effects on the nervous system.

1.29 Overall, the Committee concluded that it was not possible to attribute the adverse effects observed in human studies to exposure to manganese from the diet and therefore it is not possible to reach clear conclusions on the effects of current dietary intakes of manganese on the nervous system of children aged 0-5 years. Further data are required to draw firm conclusions, although any risk at current dietary intakes is likely to be low.

The full statement can be found here:

https://cot.food.gov.uk/sites/default/files/manganesestatementab.pdf

Statement on phosphate-based flame retardants and the potential for neurodevelopmental toxicity: lay summary

1.30 Due to stringent requirements of the Furniture and Furnishings (Fire) (Safety) Regulations introduced in 1988 in the UK, flame retardants are used extensively in the UK. The restrictions on PBDEs have led to an increase in the use of

alternative chemical flame retardants, some of which include phosphate-based flame retardants (PFRs), or commercial mixtures of PFRs and non-polybrominated diphenyl esters (PBDEs).

1.31 PFRs have been found ubiquitously in household dust and biomonitoring data suggest that exposure is widespread and increasing over time as PFRs replace BFRs as flame retardants. Young children and infants have been identified as a potentially susceptible subpopulation due to their greater exposure via the oral, inhalation and dermal routes.

1.32 PFRs share a structural similarity to other classes of organophosphates, such as organophosphate (OP) pesticides and other OP compounds, which have been shown to interfere with neurodevelopment by cholinergic and noncholinergic (serotonergic and dopaminergic) pathways.

1.33 Therefore, the Committee was asked for an opinion on the potential for PFRs to cause developmental toxicity, and in particular neurodevelopmental toxicity.

1.34 OPs need to possess a number of structural features to elicit neurotoxicity by an established mechanism for such compounds, such as interference with cholinergic pathways, and these are not fulfilled by PFRs. Further, the Committee concluded that the experimental data do not support an established OP-related mechanism of action for any neurotoxic effect of PFRs at anticipated human exposures. Adequately conducted studies would be needed to exclude potential effects via other mechanisms.

1.35 Due to the neurotoxicity of ortho-TCP, which can be present as a contaminant at very low concentrations (< 0.1%) in commercial TCP mixtures, the Committee recommends continued efforts to keep concentrations of this isomer in commercial mixtures low.

1.36 The limited human data available provide some evidence for neurodevelopmental effects of PFRs in exposed populations, primarily an association with reduced cognitive performance and poorer social behaviours in children. However, the Committee noted inconsistencies in the findings between studies. Limitations included study design and a lack of specificity in the relationships identified.

1.37 The Committee concluded that the chemical and experimental evidence indicated that PFRs were different from other OPs in terms of their biological activity, and thus, PFRs were very unlikely to share the neurodevelopmental effects of other OPs. However, the Committee could not exclude the possibility that PFRs could produce neurodevelopmental toxicity by some other mechanism. Overall, the available evidence indicates that PFRs do not pose a risk of developmental toxicity at anticipated exposure levels.

The full COT statement can be found here:

https://cot.food.gov.uk/sites/default/files/cotphosphatebasedflameretardantsdevelopment_0.pdf

Committee procedures

EFSA consultation on phthalates

1.38 The COT was asked to comment on EFSA's draft assessment of five phthalates used in plastic food contact materials at their meeting in March 2019. Comments were submitted to EFSA and these were responded to or taken account of when the final EFSA statement was published in December 2019. The COT comments submitted related to the data considered by EFSA in the opinion, the conclusions on DINP. The COT comments can be accessed alongside others using the following link:

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2019.EN-1747

Working Groups

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

1.39 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.

1.40 The subgroup will publish its output on the respective Committees websites and is also anticipating publication in a scientific journal.

Ongoing work

Potential risk from chemicals in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

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

1.42 Between 2012 and 2019 individual statements have been produced for a

range of chemicals in relation to the infant diet. These are acrylamide, aluminium, arsenic, copper, cadmium, hexabromocyclododecane, iodine, lead, methylmercury, nickel, ochratoxin A, polybrominated biphenyls, polybrominated diphenyl ethers and T-2 toxins, HT-2 toxins, neosolaniol and manganese.

1.43 The COT has evaluated the information provided by EFSA on dioxins and dioxin-like compounds and will await the final publication before deciding if a full re-evaluation of its current advice is required. The same applied to bisphenol A and phthalates, which are currently under re-evaluation by EFSA. The COT has evaluated the information provided by EFSA on perfluorooctanesulfonic acid and perfluorooctanoic acid in 2018 and a statement will be published in 2020.

1.44 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 (see paragraph 1.9 above).

1.45 Reviews on tropane alkaloids, tetrabromobisphenol A, monochloropropane diol, polycyclic aromatic hydrocarbons, hexachlorocyclohexane, the most commonly used sweeteners in the UK (aspartame, acesulfame K, saccharine, sorbitol and xylitol, steviol glycosides, sucralose) and 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) have been presented to the COT from February to December 2019 and summaries will form part of the Addendum to the Overarching Statement, due to be published early in 2020.

The effects of xenobiotics on the gut microbiota.

1.46 Following horizon scanning, a paper was presented to the Committee outlining recent work on the effects of a range of dietary xenobiotics on the balance of gut microbial populations. Most of the data were obtained from experimental animals, mostly mice. The substances covered were metals, pesticides, antibiotics, environmental pollutants, artificial sweeteners, ethanol, pharmaceuticals, mycotoxins and food contact materials.

1.47 All of these xenobiotics had some effects on the balance of gut microbial populations, which many of the authors extrapolated to possible consequences for humans such as obesity and type 2 diabetes. However, the Committee decided that such extrapolations were of limited value because of the variability in the population of the human gut microbiota and the large uncertainties in ascribing the direction of causation of any observed changes.

1.48 The Committee requested a follow-up paper on this subject, highlighting current knowledge on the human gut microbiome and the uncertainties in differentiating normal fluctuations in its composition from toxic responses

caused by exposure to xenobiotics. This will be presented to the COT in 2020.

The potential risks of exposure to microplastics

1.49 As part of horizon scanning, two COT Members raised the potential risks from microplastics as a topic the COT should consider. Public Health England has further expressed an interest in this topic especially with regards to microplastics in the air.

1.50 Following the discussion of this topic in October 2019, the COT concluded that a risk assessment could not currently be performed due to the lack of relevant human or related data, however, it was proposed that an initial risk assessment could be based on microplastic exposure from tyre wear.

1.51 The requested additional data and the statement are being prepared to be published in early 2020.

Hepatotoxicity of turmeric supplements

1.52 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 to 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 after withdrawal of the turmeric supplement. The symptoms were considered to be an idiosyncratic drug reaction, though a role for a possible contaminant was not ruled out.

1.53 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.

Cannabidiol (CBD)

1.54 Cannabidiol (CBD) is a type of cannabinoid found in the Cannabis plant. Although CBD is classified as a novel food, that requires authorisation before being placed on the market, it has been increasingly used in foods and food supplements on the UK market. As risk assessment advice on cannabidiol (CBD) has been increasingly requested, it was considered timely for the available toxicological information on CBD to be reviewed.

1.55 The Committee noted that some CBD products would not only contain CBD but also other cannabinoids such as tetrahydrocannabinol (THC), often due to the different extraction and production methods used. The Committee agreed that there was potential for interactions between the cannabinoids present in CBD products and this in turn, could affect the potential adverse effects of CBD.

1.56 The Committee agreed that overall there was a lack of data on CBD. However, based on the currently available in vitro and in vivo data, CBD appears to have the following adverse effects: hepatoxicity, immunotoxicity, reproductive toxicity, changes to organ weights and alterations to drug metabolizing enzymes (P450), suggesting that both adverse effects and interactions with pharmaceuticals and alcohol could occur in consumers.

1.57 It was agreed that the data from the medicinal/pharmaceutical sector on CBD would be very useful if it could be obtained as most of it was currently not publicly available. However, it was important to note that the safety profile of food grade CBD products might be different to medical grade products due to differences in composition.

1.58 The Committee agreed that it could not reach a conclusion on the safety in use of CBD products based on the information presented. The Committee agreed this topic should be reviewed once more data became available.

1.59 As the genotoxicity data were conflicting but indicated genotoxic potential in some but not all in vivo studies, the Committee recommended the genotoxicity data be referred to COM for consideration (see paragraphs 2.10 to 2.16).

Risk assessment of residues of non-permitted additives and veterinary products

1.60 In 2019, the COT was requested to consider and provide advice on a number of issues with commercial implications. These topics are being considered as reserved business. The minutes will be published at a future date.

Risk assessment of endocrine disruptors

1.61 The COT considered a paper which summarised different endocrine systems, briefly touched on the criteria, tests and guidance used to identify endocrine disruptors, and summarised the considerations in recent reports and opinions relevant to the risk assessment of endocrine disruptors, i.e. whether thresholds exist for endocrine disruptors, low-dose effects, non-monotonic dose-response relationships and critical windows of susceptibility.

1.62 The COT discussed the cases made for and against the existence of thresholds for endocrine disruptors. A number of well conducted studies across a wide range of doses had demonstrated a marked point of inflection in the dose-response curve, consistent with a threshold. In addition, knowledge of receptor activation, signalling and regulation of hormonal effects through homeostatic feedback provided mechanistic support for a threshold. Members agreed that there would almost certainly be a threshold in most cases. However, thresholds could not be proven experimentally, and the COT did not consider that consensus amongst the scientific community could be reached.

1.63 The COT was not convinced about the existence of claimed low-dose effects, nor of non-monotonic dose response relationships occurring at low doses. Its view could change if there were consistently reproducible evidence of such effects. If endocrine disrupting chemicals exhibit non-monotonic dose-response relationships, then it is difficult to understand why mixtures of similarly acting substances show monotonic dose-response relationships over a wide range of doses. For example, dose addition models based on biologically-relevant reductions in fetal testosterone had accurately predicted postnatal reproductive tract alterations by a mixture of phthalates in rats.

1.64 The COT agreed that critical windows of susceptibility to endocrine disruptors exist, primarily in utero. They considered the extent to which standard toxicology tests were sufficient to cover these windows of susceptibility. There are suitable studies, for example, the extended one generation reproductive toxicity study. However, they have not been used for many chemicals assessed by the COT.

1.65 The COT agreed that it would be able to conduct risk assessments for endocrine disruptors if sufficient data were available.

Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)

1.66 A number of papers were presented to the COT in 2019 covering known constituents and potential adverse health outcomes arising from exposure to EN(N)DS aerosols, following earlier papers in 2016, 2017 and 2018. In addition, further aspects considered were bystander exposure, exposure to flavouring components and nicotine toxicity.

1.67 As statement is due to be considered by the Committee and published in 2020.

Application of PBPK modelling in chemical risk assessment

1.68 A scoping paper on physiologically-based pharmacokinetic (PBPK) modelling used for human health risk assessment was considered by the COT in July 2019. This paper focused on applications of PBPK models in risk assessment, approaches to building PBPK models, methods of model fitting, and model validation. The Committee discussed ways to assess the reliability of human PBPK models in the absence of human pharmacokinetic data. The Committee agreed that it would be useful to have further information in the form of case studies where PBPK models have been applied in health risk assessment.

1.69 These case studies were taken to the COT in December 2019. The Committee recognised that although PBPK modelling is of current interest in the field of chemical risk assessment, PBPK models were not applied routinely applied in risk assessment or assessed by regulatory bodies because they were generally complex, specific to individual chemicals or groups of chemicals and labour and

data intensive.

1.70 Since the last workshop on PBPK modelling was hosted by the COT in 2003, a joint workshop on potency estimation and PBPK modelling is being organised for March 2020. The aims of this workshop are to explore the generation of quantitative estimates of potency and exposure from non-animal methods, and to provide direction for future research efforts so that they are relevant to risk assessment.

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

1.71 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”. Plant-based drinks are becoming increasingly popular and with this is mind, the COT have been asked to review the safety of these products in the diets of children between 1 and 5 years of age. Soya milk was reviewed in 2019, and other plant-based drinks will be reviewed in 2020 with a view to producing a statement covering all plant-based drinks.

Environmental, health and safety alternative testing strategies: Development of methods for potency estimation

1.72 The combined advances in discovery and clinical sciences, data science and technology has resulted in the potential for significant changes to toxicity testing in the future. Many different types of *in silico* methods have been developed to characterize and predict toxic outcomes in humans and environment. This will be particularly important in risk assessment scenarios where limited or no direct information is available on the toxicity of a chemical.

1.73 The COT were updated on some of these in silico methods and novel approach methodologies. These included databases, different kinds of quantitative structure activity relationship (QSAR) methods, adverse outcome pathways (AOPs), high throughput screening (HTS), read across models, molecular modelling approaches, machine learning, data mining, network analysis tools, and data analysis tools using artificial intelligence (AI).

1.74 The COT noted that improved *in silico* technologies presents an opportunity in toxicology to bridge the communication gap and collaboration with scientists from industry, academia and regulatory agencies to develop, maintain and utilise appropriate models.

1.75 The COT and FSA Secretariat have planned a workshop for March 2020 where these topics will be explored in more detail.

Dioxins and Dioxin-like PCB's

1.76 In 2018, the COT was asked to submit comments to EFSA on their revised risk assessment for dioxins and dioxin-like PCB's which has now been finalised and published on the EFSA website. The revised TWI is significantly lower than the previous one. The COT has been asked by the FSA for a more detailed consideration of the basis of the TWI. Initial discussions took place in 2019 but further information on this topic will be considered by COT in 2020.

2019 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

Professor Alan Boobis OBE PhD CBiol FRSB FBTS
Professor of Toxicology (part-time) in the Faculty of Medicine at Imperial College London

MEMBERS

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

Ms Jane Case
Lay Member

Dr Stella Cochrane BSc PhD (from April 2019)
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 Mark Graham BSc PhD (until March 2019)
Director, MG Toxicology Consulting Ltd

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

Professor Roy Harrison OBE PhD DSc C.Chem FRSC FRMetS HonFFOM HonMFPH (until March 2019)
Professor of Environmental Health, School of Geography, Earth & Environmental Sciences, University of Birmingham

Professor Gary Hutchison (from April 2019)
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 (from April 2019)
Professor of Nutrition and Food Science

Professor Brian G Lake BSc PhD DSc FBTS (until March 2019)
Head of Molecular Sciences Department, Leatherhead Food Research

Dr David Lovell (from April 2019)
Emeritus Reader in Medical Statistics at St George's Medical School, University of London

Dr Mac Provan (from April 2019)
Director of Regulatory Science Ltd

Ms Juliet Rix
Lay Member

Dr Michael Routledge (from April 2019)
Associate Professor of Environmental Toxicology in the School of Medicine at Leeds

Dr Cheryl Scudamore (from April 2019)
RCVS Specialist in Veterinary Pathology (laboratory animals) working as independent consultant in experimental and toxicological pathology

Dr Natalie Thatcher (from April 2019)
Mondelēz International

Dr John Thompson MB ChB BMedSc
FRCP FBTS *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 Matthew Wright BSc, PhD
Professor of Toxicology, Institute of Cellular Medicine, Newcastle University

Professor Maged Younes (from April 2019)
Independent expert on toxicology and biochemical pharmacology.

SECRETARIAT

Dr D Gott BSc (Hons) PhD (to July 2019)	Scientific Secretary
Ms C A Mulholland BSc (Hons) (from July 2019)	Scientific Secretary
Mr Freddie Lachhman BA (Hons) (from August 2019)	Administrative Secretary
Mrs Hetty Gbormittah (to July 2019)	
Ms B Gadeberg BSc (Hons) MSc	Scientific Secretary – PHE

Ms R Acheampong BSc (Hons) MSc (to June 2019)
Dr Alexander Cooper BSc (Hons) MSc PhD
Dr B Doerr BSc (Hons) MSc PhD
Dr D Hedley BSc (Hons) MSc PhD
Ms F Hill BSc (Hons) MSc
Ms Cleanncy Hoppie BSc (Hons) MSc (from November 2019)
Mr B Maycock BSc (Hons) MSc
Mr Daniel Medlock BSc (Hons) MSc (June to October 2019**)**
Dr O Osborne BSc (Hons) (Exon) PhD
Ms C Potter BSc (Hons) MSc
Dr J Shavila BSc (Hons) MSc PhD
Ms Chloe Thomas BSc (Hons) (from September 2019)
Ms Sabrina Thomas BSc (Hons) MSc (from June 2019)
Ms C 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 CBiol FSB FBTS		
Personal Interest	**Employee** Imperial College London, Department of Medicine (full time until June 2017, part-time from Aug 2017) **Shareholder** Bank Santander Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds	**Membership** ILSI & ILSI HESI Board of Trustees ILSI Europe Board of Directors Science Advisory Board of Swiss Centre for Applied Human Toxicology Dept. of Health Committee on the Medical Effects of Air Pollutants
Non Personal Interest	**Grants** Horizon 2020 EUROMIX Department of Health & Social Care Public Health England	**Membership** WHO/FAO JMPR WHO/FAO JECFA (vet) WHO TobReg WG10 TC126 (Intense Machine-smoking Regime for Testing Cigarettes) EUROTOX British Pharmacological Society British Toxicology Society Society of Toxicology (USA) Michigan State University MSU Center for Research on Ingredient Safety (CRIS) (External Advisory Board)
Dr Phil Botham		
Personal Interest	**Employee** Syngenta - Principal Science Advisor (part time) **Shareholder** AstraZeneca	**Membership**
Non-Personal Interest	None	**Membership** British Toxicology Society Society of Toxicology (USA)

		European Centre for Ecotoxicology and Toxicology of Chemicals Scientific Committee European Crop Protection Association Toxicology Expert Group Crop Life International Human Health Steering Team
Ms Jane Case		
Personal Interest	**Employee** Company Secretary of Muse Interiors Stevens & Bolton LLP as Jane Hughes) **Shareholder** Standard Life Santander	
Non-Personal Interest	None	
Dr Stella Cochrane	COT Member from June 2019	
Personal Interest	**Employee** Unilever **Shareholder** Unilever	
Non-Personal Interest	None	**Membership** British Society of Immunology
Dr James Coulson		
Personal Interest	**Employee** Cardiff University Director of Medical, Scientific and Toxicology Consultancy Ltd	
Non-Personal Interest		**Membership** British Medical Association British Pharmacology Society British Toxicology Society National Trust Royal College of Physicians of London
Dr René Crevel		

Personal Interest	**Employee** Unilever Consultant, Réne Crevel consulting **Shareholder** Unilever Centrica BG Group National Grid Lloyds	**Membership/affiliation** ILSI Food Allergy Task Force: Chair
Non-Personal Interest		
Professor John Foster	None	
Personal Interest	**Employee** Emeritus Professor & Senior Consultant Pathologist, Regulatory Science Associates	
Non-Personal Interest		
Dr Mark Graham	COT Member until March 2019	
Personal Interest	**Employee** MG Toxicology Consulting Ltd	
Non-Personal Interest	None	
Dr Caroline Harris		
Personal Interest	**Employee** Exponent International Ltd **Shareholder** Exponent Inc	
Non-Personal Interest		**Member** International Union of Pure and Applied Chemistry **Fellowships** Royal Society of Chemistry
Professor Roy Harrison OBE, FRS	COT Member until March 2019	
Personal Interest	**Employee** University of Birmingham **Consultancy**	**Member** Defra Air Quality Expert Group Dept. of Health Committee on the Medical Effects of Air Pollutants

	King Abdulaziz University (Saudi Arabia) Environment Agency **Support by Industry** Jaguar Land Rover **Shareholder** Halifax/Lloyds Renovare Fuels NQ Minerals AB Packaging	
Non-Personal Interest	None	**Membership** Fellow, The Royal Society Royal Society of Chemistry Royal Meteorological Society Faculty of Public Health (honorary) Faculty of Occupational Medicine (honorary) Chartered Institute of Environmental Health (honorary)
Professor Gary Hutchison		
Personal Interest	**Employee** Dean of Applied Sciences at Edinburgh Napier University, Professor of Toxicology	**Membership** Hazardous Substances Advisory Committee, DEFRA
Non-personal Interest	None	**Membership** British Toxicology Society.
Dr Sarah Judge		
Personal Interest	**Employee** Newcastle University Lowcock Properties Ltd	
Non-Personal Interest	**Research Funding**	**Membership** British Pharmacology Society British Toxicology Society International Association for Neurotoxicology
Professor Gunter Kuhnle	COT Member from June 2019	
Personal Interest	**Employee** Professor of Nutrition and Food Science, University of Reading.	

Non-Personal Interest	None	
Professor Brian Lake	COT Member until March 2019	
Personal Interest	**Employee** Part time Associate Toxicologist at Concept Life Sciences (CLS), Dundee, Scotland **Misc** Consultancy for CLS and other clients	
Non-Personal Interest		**Membership** British Toxicology Society National Trust Society of Toxicology (USA) Member of the editorial board Xenobiotica
Dr David Lovell	COT Member from June 2019	
Personal Interest	**Employee** Reader in Medical Statistics St Georges Medical School University of London **Shareholder** National Grid - Pfizer - AstraZeneca (spouse shareholder) National Grid plc (spouse shareholder)	**Membership** UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs)
Non-Personal Interest		**Membership** HESI GTTC – Biometrics Society British Toxicology Society Genetics Society Royal Society of Biology Laboratory Animal Science Association Royal Statistical Society Statisticians in the Pharmaceutical Industry United Kingdom Environment Mutagen Society (UKEMS) MRC EMINENT Scientific Review Board

		British Trust of Ornithologists (BTO) English Heritage Liberty Campaign of the Protection of Rural England (CPRE) Kew Gardens Sandwich Bay Bird Observatory Trust (SBBOT) Chelsea Physic Garden National Trust
Dr Mac Provan	COT Member from June 2019	
Personal Interest	**Employee** Director of Regulatory Science Ltd	
Non-Personal Interest		
Ms Juliet Rix		
Personal Interest	None	
Non-Personal Interest	None	
Dr Cheryl Scudamore	COT Member from June 2019	
Personal Interest	**Employee** Independent consultant in experimental and toxicological pathology	
Non-Personal Interest	None	
Dr Natalie Thatcher	COT Member from June 2019	
Personal Interest	**Employee** Mondelēz International	
Non-Personal Interest	None	
Dr John Thompson MB ChB		

BMedSc FRCP FBTS		
Personal Interest	**Employee** Senior Lecturer in Clinical Pharmacology, Cardiff University, Director, National Poisons Information Service, Cardiff	
Non-Personal Interest	None	
Professor Mireille Toledano		
Personal Interest	**Employee** Marit Mohn Chair in Perinatal & Paediatric Environmental Epidemiology, Imperial College London	
Non-Personal Interest	None	
Professor Faith Williams		
Personal Interest	**Employee** Emeritus Professor, Newcastle University **Shareholder** Share in FTSE 100 quoted companies	
Non-Personal Interest		**Membership** British Toxicology Society Society of Toxicology (US)
Professor Matthew Wright		
Personal Interest	**Consultancies and Direct Employment** Newcastle University	**Membership** EFSA ANS Panel **Miscellaneous** Toxicology – Associate Editor
Non-Personal Interest	**Support by Industry** GSK	**Membership** British Toxicology Society

	Lubrizol.	Society of Toxicology (US)
Professor Maged Younes	COT Member from June 2019	
Personal Interest	**Employee** Independent Expert in Toxicology and Biochemical Pharmacology	**Membership** Chair of EFSA ANS panel
Non-Personal Interest	None	

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

Foreword by David Lovell – Chair

I am pleased to present this report on the work of the Committee on Mutagenicity (COM) during 2019. 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. https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in-food-consumer-products-and-the-environment

During the course of 2019, the Committee worked on a number of topics:
It continued its review of the COM's 2011 guidance on a strategy for genotoxicity testing of chemical substances. The guidance has now been updated and a series of separate papers being developed were prepared and considered, including on QSAR models, manufactured nanomaterials, 3D-models under development and on germ cell mutagens. These separate short guidance statements will form part of the revised guidance document and are being developed so that they can be updated independently of the main document as new information related to them becomes available.

In June 2019 the COM organised a two-day workshop in Birmingham on “The interpretation of genetic toxicology data in a regulatory environment". Participants included members of the Committee, assessors from the UK and Europe and other invited experts. The workshop involved presentations on the scientific developments in the field and viewpoints from regulators. The meeting provided the basis for both the short-term review of the COM's current guidelines and for the longer-term

development of guidelines for later in the 2020's which would reflect the developments now underway in the field.

The COM continued throughout 2019 to take an active interest in the work of the OECD (Organisation for Economic Cooperation and Development) on test guidelines particularly those related to nanoparticles, tests for in vivo genotoxicity, the Pig-a assay and the various 'mini' versions of Ames-type tests that have been developed.

The COM received a presentation on the ToxTracker assay which uses six unique reporter cell lines to detect genotoxicity and carcinogenicity as well as providing information relating to the mode of genotoxic action. Based upon this and other information, the COM agreed to keep a watching brief on how the regulatory acceptance of ToxTracker develops and how it progresses through the OECD process.

The Committee evaluated the genotoxicity of a number of specific compounds during the year including azodicarbonamide, cannabidiol and patulin in response to requests from Government Agencies and other expert committees.

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

The COM maintained its awareness of the implications of 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.

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 2019. 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 forward, that 2020 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.

Dr D.P. Lovell Chair
PhD BSc (Hons) FBS CStat CBiol CSci

ONGOING WORK

COM Guidance Series Update

2.1 In 2018, a review of the COM guidance on a strategy for genotoxicity testing of chemical substances was initiated. This document was last updated in 2011. As there had been no significant changes to strategy developments or assay methodologies that merited a total re-write of the COM guidance the focus was to review content for accuracy and update references where necessary. MUT/2019/01 and MUT/2019/12 document the amendments and comments from members. Four new stand-alone sections have been drafted which will be published once complete. Methods for the assessment of the genotoxicity of nanomaterial were reviewed including OECD and EU projects. The guidance statement will include an opinion about the use of the Ames test in the testing of manufactured nanoparticles, and the use of cytochalasin B in the micronucleus assay (MUT/2019/02). Members previously considered a scoping paper (MUT/2018/2) on the use of QSARs to predict genotoxicity in February 2018, which formed the basis of the draft Guidance Statement (MUT/2019/03). The members concluded that that QSAR models should not be used to overrule test results but can be used to aid interpretation of test data. A paper on 3D models provided a summary of models currently used for genotoxicity testing and those under development and/or validation (MUT/2019/04). This is an area which is developing rapidly, and members were aware of imminent publications thus this statement would be reviewed in the near future. The original guidance document discussed germ cell and somatic cell mutagens, a separate guidance statement has been drafted on testing for germ cell mutagens (MUT/2019/05). The aim of producing these separate short guidance statements is to be able to update or edit sections independently as new methods or evidence is published.

ToxTracker

2.2 The ToxTracker assay is a stem cell-based screening platform which utilises six unique reporter cell lines[1] to detect potential genotoxicity and carcinogenicity and provide information relating to the mode of genotoxic action, if present. The COM first evaluated the technology in 2014. Since that time, ToxTracker has undergone further validation and development and Giel Hendriks from 'Toxys', the Dutch Biotech company that developed the assay, presented an update of recent developments, to the COM in October 2019.

2.3 The assay responds to DNA damage (e.g. mutagenic lesions and DNA double strand breaks), activation of p53, oxidative stress and protein damage and indicates this via Green Fluorescent Protein (GFP) induction in the reporter cell lines determined by flow cytometry.

[1] Bscl2-GFP (mutagenic DNA lesions); Rtkn-GFP (DNA double strand breaks); Btg2-GFP (activation of p53); Srxn1-GFP (oxidative stress); Blvrb-GFP reactive oxygen species production); Ddit3-GLP (protein damage).

2.4 ToxTrackerACE (Aneugen and Clastogen Evaluation) includes the addition of DNA staining in wild type (wt) stem cells to detect aneugenicity leading to cell cycle block and polyploidy. To date, a large number (>1000) and range of substances have been tested using ToxTracker including: single molecules; polymers; complex mixtures; nanomaterials; and intermediates. As such, there is a growing trend to include the assay for early screening and hazard identification purposes, in addition to its use in follow up testing, identifying mode of action (MoA), for quantitative dose response modelling, threshold of toxicological concern (TTC) and for weight of evidence (WoE) considerations.

2.5 Technical in-house validation of ToxTracker indicated sensitivity and specificity to both be around 90% and this was supported by the findings of a small inter-laboratory validation exercise where two laboratories screened 28 blinded compounds. A much larger international inter-laboratory validation exercise was in progress, coordinated by a Validation Management Team, with the aim of evaluating and the adoption of the assay by The European Centre for the Validation of Alternative Methods (ECVAM) and The Organisation for Economic Co-operation and Development (OECD). This included eight independent laboratories in the US, EU and Japan analysing 64 blinded compounds, with findings expected to be reported in early 2020.

2.6 The sensitivity of ToxTracker in terms of being able to detect individual chromosome deletions was also considered. In this regard, if the deletion triggers an effect on cell cycle progression then it will be picked up in the assay. Members discussed the added value of using ToxTracker, particularly when equivocal data has been found using ‘standard’ in vitro testing methods. It was considered that information on the MoA provided by ToxTracker could help explain equivocal findings, particularly from standard in vitro assays. In addition, ToxTracker could be used where in vivo follow up studies are not permitted following a positive Ames test (for example when testing cosmetics).

2.7 Increased or more widespread use of ToxTracker was seen as necessary to trigger its inclusion in the standard battery of genotoxicity assays and to gain regulatory acceptance. The ongoing discussions of the development of ToxTacker within the OECD process has been positive to date, and the eventual outcome for these newer developments will decide if an OECD technical guideline is needed for the screening assay. However, although there has been much interest from industry in using ToxTracker, the longer-term issue remains as to whether compounds can be accepted within a regulatory process if there is no approved OECD technical guideline.

2.8 In conclusion, it was agreed that the COM would keep an active watching brief on developments with the ToxTracker platform, particularly with regards to regulatory acceptance of its use for genotoxicity testing.

COM EVALUATIONS

Risks to human health from the use of azodicarbonamide as a food additive (MUT/2019/07)

2.9 This was considered as a reserved in confidence item.

Review of genotoxicity of cannabidiol (MUT/2019/10)

2.10 Cannabidiol (CBD) is a type of cannabinoid produced by the cannabis plant (Cannabis sativa). Research into the potential medicinal use of CBD has been conducted over a number of years including clinical trials for its use in treating seizures from epilepsy.

2.11 CBD has been added to a number of food and beverages (e.g. beer, spirits, wine, coffee and soda style drinks), liquids (tinctures, drops, syrup and oils), chewables (gum drops) and chocolate. Claims have been made that the added CBD helps people to feel more relaxed and can help reduce anxiety. The composition and the amount of CBD in the different types of products can vary (e.g. depending on the type of product and the extraction and manufacturing process).

2.12 The Food Standards Agency previously sought toxicity advice from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). The COT concluded in July 2019 that there was evidence for hepatotoxicity, immunotoxicity, reproductive toxicity, changes in organ weight and alterations in drug metabolising enzymes (e.g. P450s). The COT could not conclude on the safety of CBD products and requested advice on mutagenicity from the COM.

2.13 Regarding the available genotoxicity data, some in vitro studies in bacteria gave negative results, but some in vitro studies with mammalian cells indicated positive results. An oral in vivo micronucleus test in mice gave a negative result, while an earlier 1980s intraperitoneal administration micronucleus test in mice gave a positive result. Due to the conflicting genotoxicity data, the COM was asked to review the available data presented in paper MUT/2019/10 and to give its opinion.

2.14 The COM considered that an Ames test reported by Marx et al., 2018[2] used high purity CBD, was conducted to OECD Test Guidelines and gave a clear negative result. It was noted that this negative result may not be applicable to other lower purity CBD extracts. Regarding the in vitro tests in mammalian cells, members noted negative results reported for adverse chromosomal effects in V79 Chinese hamster lung cells (Marx et al., 2018)

[2] Marx, T.K., Reddeman, R., Clewell, A.E., Endres, J.R., Béres, E., Vértesi, A., Glávits, R., Hirka, G. and Szakonyiné, I.P., 2018. An Assessment of the Genotoxicity and Subchronic Toxicity of a Supercritical Fluid Extract of the Aerial Parts of Hemp. *Journal of toxicology*, 2018.

and a negative result for the comet assay conducted in Caco-2 cells by Aviello et al., 2011[3]. However, members had concerns over the reported positive results in a comet and micronucleus test conducted in human cells (HepG2 and TR146) by Russo et al., 2019[4]. A summary table provided micronuclei data but did not provide data for the comet assay. The unexpectedly high percentage of cells in necrosis and apoptosis (e.g. 33 and 37%, respectively at the highest tested dose) raised concern over whether the test had been conducted adequately and whether cytotoxicity was a potential cause of the observed positive result. Also, the fold increase in micronuclei appeared to be higher than would be expected and positive control data were not presented. Additionally, evidence for oxidation was reported for the comet assay, which may provide an explanation for the observed positive result.

2.15 Regarding the in vivo data, members considered that there was insufficient information provided on the study that gave a positive result (i.e. the in vivo intraperitoneal micronucleus test by Zimmerman and Raj 1980)[5] to interpret the positive result reported e.g. insufficient information on the extraction method and whether there were potentially impurities or metabolites present in the test material. The Marx et al 2018 in vivo micronucleus test was agreed to be well conducted and negative.

2.16 Overall, the COM considered that an appropriate range of genotoxicity studies had not been conducted (either in vitro or in vivo) to conclude on the mutagenic potential of CBD. Additional information would be required on extraction methods and CBD purity in the studies conducted. Each study would need to be evaluated on a case by case basis depending on the test material e.g. considering the presence of impurities and metabolites. A negative result in one test under a particular exposure condition or with one test material may not be sufficient for an overall evaluation on the mutagenicity of CBD.

Review of genotoxicity of patulin (MUT/2019/11)

2.17 Patulin is a mycotoxin produced by certain species of the genera Aspergillus and Penicillium (i.e. it arises from common spoilage microorganisms present in apples). The International Agency for Research

[3] Aviello, G., Romano, B., Borrelli, F., Capasso, R., Gallo, L., Piscitelli, F., Di Marzo, V. and Izzo, A.A., 2011. Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol on experimental colon cancer. *Journal of molecular medicine*, 90(8), pp.925-934

[4] Russo, C., Ferk, F., Mišík, M., Ropek, N., Nersesyan, A., Mejri, D., Holzmann, K., Lavorgna, M., Isidori, M. and Knasmüller, S., 2019. Low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) cause DNA damage and chromosomal aberrations in human-derived cells*. Archives of toxicology*, 93(1), pp.179-188.

[5] Zimmerman, A.M. and Raj, Y., 1980. Influence of cannabinoids on somatic cells in vivo. *Pharmacology*, 21(4), pp.277-287.

on Cancer (IARC 1986) classified patulin in Group 3, i.e. not classifiable as to its carcinogenicity, due to limited evidence for carcinogenicity in experimental animals. A factsheet published by the World Health Organization in 2018, stated that patulin is considered to be genotoxic but has not demonstrated carcinogenicity.

2.18 The Joint FAO/WHO Expert Committee on Food Additives (JECFA 1990) evaluation of patulin established a Provisional Tolerable Weekly Intake (PTWI) of 7 micrograms per kilogram of body weight per day (µg/kg bw/day). In 1995, JECFA updated its opinion and recommended a Provisional Maximum Tolerable Daily Intake (PMTDI) of 0.4 µg/kg bw/day, which was subsequently endorsed by the EU Scientific Committee (SCF 2000).

2.19 A review of the potential risks of patulin in the diet of infants aged 0 to 12 months and children aged 1 to 5 was presented to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in May 2019. The COT concluded that the new toxicological data (excluding the genotoxicity data) available from 1995 to 2018 would not change the current health-based guidance value. However, the data on genotoxicity was considered to be variable and therefore a view from the COM on the available genotoxicity data was requested by the COT.

2.20 Paper MUT/2019/11 presented a review of the available genotoxicity data on patulin and the COM was asked to provide its opinion. Members agreed that although many in vitro studies had been conducted, they were mainly non-standard genotoxicity studies that were poorly described (i.e. insufficient details on how each study had been conducted) with many being quite old. This meant that the available in vitro data were difficult to interpret. However, a number of positive in vitro responses were reported (e.g. induction of micronuclei in human lymphocytes), which could not easily be discounted on a weight of evidence basis. There was also some evidence of oxidative stress, which may provide an explanation for the observed positive results. Members suggested that there was a possibility for the occurrence of publication bias, due to the large interest in conducting studies on potential anti-oxidative properties and mycotoxins, which was a popular area of investigation (i.e. a potential danger of a bias towards the publication of positive results compared with negative results).

2.21 The in vivo studies also consisted of non-standard genotoxicity studies that were poorly reported or inadequately conducted (e.g. involving single doses and intraperitoneal administration) and therefore could not be interpreted. Positive results were reported in in vivo comet assays. However, there was no description of measures of toxicity or oxidative stress, so it was not possible to determine whether the positive response was due to direct or indirect interaction with DNA. Again, for in vivo studies (e.g. MN, chromosome aberrations and comet), members agreed that there was an indication of a positive response in sub-standard studies, which were inadequately conducted or described, and often complicated by co-administration of anti-oxidants. Therefore, the in vivo studies could

not be interpreted.

2.22 Overall, the COM concluded that the in vitro and in vivo genotoxicity studies were inadequate. There was some evidence of positive results (particularly in vitro, but also in vivo), but in non-standard tests with insufficient details on how they were conducted. Therefore, the observed positive responses could not be interpreted, but were also difficult to discount. It was suggested that a standard regulatory genotoxicity tests should be conducted to acceptable standards (i.e. Ames test and in vitro micronucleus test) and that it would also be useful to investigate whether any positive response was due to oxidative stress.

HORIZON SCANNING

2.23 At the February 2019 meeting the committee discussed potential items for further discussion under Horizon Scanning, which included the following:

2.24 It was suggested that in vitro multi-endpoint test systems were likely to become more important, including high-throughput test systems, imaging systems and 3D cell cultures. These could be used to evaluate a number of endpoints in addition to mutation that are relevant to cancer e.g. cell division rates and suppression of apoptosis. It was suggested that the COM could consider other such endpoints rather than focusing solely on mutation to give a clearer overall picture in terms of genotoxicity and cancer.

2.25 Another suggestion was for the COM to consider a weight of evidence approach to evaluating genotoxicity data and mutation potential. This could involve bringing various aspects together (e.g. mode of action, non-linear dose response relationships, quantitative genotoxicity analysis etc.) to aid consistency in the interpretation of data. The multi-endpoint test systems (e.g. MultiFlow and Toxtracker) could also help with this.

2.26 The Pig-a in vivo assay was highlighted as a test that had the potential to be used to a greater extent in the future. Currently it is only used in blood cells. However, it was suggested that it could be conducted in other tissues and that this would provide a further option in addition to the in vivo transgenic rodent (TGR) gene mutation test, which was currently the only option for an in vivo gene mutation test.

2.27 A further suggestion was that the COM should consider a more holistic approach when considering potential harms to the public (e.g. disinfection by-product mixtures in swimming pools) rather than focussing on just the mutation aspect (i.e. consider the overall public health concern).

2.28 In June 2019, a two-day workshop “on the interpretation of genetic toxicology data in a regulatory environment” was held that brought together key people with an interest in developing views on the interpretation of genotoxicity data and discussed new methods and challenges for future testing strategies. From this workshop two papers

were produced. The first paper (MUT/2019/08) provided notes of the presentations given and discussion sessions. The second paper (MUT/2019/09) provided an assimilated summary of the workshop. There was support for the publication of the workshop summary, once finalised. In addition, some members confirmed interest in helping to develop guidance to evaluate genetic toxicology data, one of the recommendations from the workshop. In addition, a further workshop, possibly in conjunction with UKEMs, was supported, with COM as the lead.

OECD

2.29 During the year, the COM was kept updated on developments relating to OECD test guidelines on genotoxicity testing:

- the *in vitro* mammalian cell micronucleus assay test guideline (TG 487) to be applicable for testing nanomaterials.
- the *in vivo* transgenic rodent gene mutation assay test guideline (TG 488) which was being reviewed and updated.
- the development of a new guideline for a 3D reconstructed skin micronucleus assay.

2.30 The Chair of COM had acted as an observer for peer review on the validation of the Pig-A assay.

2019 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 of London

MEMBERS

Dr Carol Beevers
Managing Scientist, Exponent International Ltd

Mr Amit Bhagwat
Lay Member

Dr Gill Clare BSc PhD (to May 2019)
Independent Consultant

Dr Stephen Dean
Agenda Life Sciences

Professor Shareen Doak
Institute of Life Science, Swansea University Medical School

Dr Paul Fowler
FSTox Consulting (from September 2019)

Mrs Philippa Hardwick (To May 2019)
Lay Member

Professor David Harrison MD DSc FRCPath FRCPEd FRCSEd
Professor of Pathology, University of St Andrews

Professor Gareth Jenkins (To March 2019)
Institute of Life Science, Swansea University, Honorary Non-clinical Senior Lecturer, Swansea NHS Trust

Professor David Kirkland (To March 2019)
Principal, Kirkland Consulting

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

SECRETARIAT

Dr Ovnair Sepai	PHE Scientific Secretary
Dr D Gott BSc(Hons) PhD	FSA Scientific Secretary (to July 2019)
Ms C Mulholland	FSA Scientific Secretary (from August 2019)
Mrs N Blowfield	Administrative Secretary

Declaration of members interests during the period of this report

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Personal Interest	**Employee** Reader in Medical Statistics St Georges Medical School University of London **Pension** Pfizer **Shareholder** National Grid plc AstraZeneca (Spouse Shareholder) National Grid plc (Spouse Shareholder)	**Membership** HESI GTTC (committee member) Biometrics Society British Toxicology Society (BTS) Genetics Society Royal Society of Biology (CBiol FRSB, 2003) Laboratory Animal Science Association (LASA) Royal Statistical Society Statisticians in the Pharmaceutical Industry (PSI) United Kingdom Environment Mutagen Society (UKEMS) UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (Board Member) MRC EMINENT Scientific Review Board British Trust of Ornithologists (BTO) English Heritage Liberty Campaign of the Protection of Rural England (CPRE) Kew Gardens Sandwich Bay Bird Observatory Trust (SBBOT) Chelsea Physic Garden National Trust
Non - Personal Interest	**None**	**None**
Dr Carol Beevers		
Personal Interest	**Employee** Exponent **Pension** Covance	**Membership** ILSI HESI (workgroup member) OECD (workgroup member) United Kingdom Environmental Mutagen Society (UKEMS)

	Exponent	
Non-Personal Interest	**None**	**None**
Dr Gill Clare	COM Member to May 2019	
Personal Interest	**Pension** Shell Research Ltd AstraZeneca **Shareholder** AstraZeneca Diageo Marks and Spencer **Misc** Covance – Consultant	**Membership** United Kingdom Environmental Mutagen Society (UKEMS)
Non-Personal Interest	**None**	**None**
Dr Stephen Dean		
Personal Interest	**Employee** WIL Research, Europe (Jan – March 2019) (Equity Holder) **Shareholder** Standard Life **Director** Scientific Services for Agenda Life Sciences	**Membership** United Kingdom Environmental Mutagen Society (UKEMS) Society of Toxicology
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Professor Shareen Doak		
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		Royal Society of Biology (FRSB) ILSI HESI (committee member) British Toxicology Society (BTS)
Non-Personal Interest	**Trustee** St David's Medical Foundation (medical research & education charity) **PhD Studentship Grants** Unilever (2017 – 2020) AstraZeneca (2009 – 20160 Unilever (2010 -2017) **Research Grant 2008 – 2010** Hoffman-LaRoche Unilever	
Dr Paul Fowler	COM Member since September 2019	
Personal Interest	**Pension** Unilever (UK) Covance **Misc** De Montfort University – External Examiner FSTox Consulting - Director	**Membership** IGG (committee member) UKEMS (committee member) Rountable of Toxicology Consultants (RTC) British Toxicology Society (BTS) In vitro toxicology Society (committee member)
Non-Personal Interest	**None**	**None**
Mrs Philippa Hardwick	COM Lay Member to May 2019	
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Non-Personal Interest	**None**	**None**
Professor David Harrison		
Personal Interest	**Employee** University of St Andrews, UK NuCana Biomedical, UK (part-time) **Consultant** University of Canberra University of Florida	**None**

	Pneumagen Ltd, UK **Shareholder** Ryboquin Ltd, UK Avipero Ltd, UK Benenox Ltd, UK (Shareholder and Director) **Misc** University of Dundee – External Examiner Cunningham Trust – Scientific Adviser Definiens AG – Advisor University of Edinburgh, UK – Honorary Professor University of Glasgow, UK – Visiting Professor	
Non-Personal Interest	**Misc** iCAIRD research consortium – Director (unpaid role) Families First St Andrew's (children's charity) – Trustee Director Gene Therapy Consortium (funded by Wellcome Trust) – Unpaid external scientific advisor Systems Biology Ireland – Unpaid external scientific advisor	
Professor Gareth Jenkins	COM Member until March 2019	
Personal Interest	**None**	**Member** United Kingdom Environmental Mutagen society (UKEMS)
Non-Personal Interest	**Research Grant 2008 – 2010** Unilever	**None**
Professor David Kirkland	COM Member to March 2019	
Personal Interest	Kirkland Consulting – Principal **Consultant**	**Membership** United Kingdom Environmental Mutagen society (UKEMS)

	Multiple pharmaceutical, chemical, agrochemical, food and cosmetics **Shareholder** Saga	European Environmental Mutagen and Genomics society (EEMGS) – Member and Trustee Environmental Mutagen and Genomics Society (EMGS) – Emeritus member ILSI HESI – Steering Committee Member and Workgroup Leader ILSI Europe Packaging Materials Task Force
Non-personal Interest	**None**	**None**
Dr Michael O'Donovan		
Personal Interest	O'Donovan GT Consulting Ltd – Director Apconix - Associate **Pension** AstraZeneca BASF	
Non-Personal Interest	**None**	**None**
Dr Andrew Povey		
Personal Interest	**Employee** Reader in molecular epidemiology, University of Manchester. **Shareholder** Lloyds Standard Life Halifax Santander (Partner Shareholder) Norwich Union (Partner Shareholder) Roadchef Topco Ltd (Partner Shareholder) **Misc** European Crop Protection Agency – Part of consortium recently awarded grant on exposure assessment	**Membership** UK Molecular Epidemiology Group (UK-MEG) UK Environmental Mutagen Society (UKEMS) American Association for Cancer Research (AACR) Molecular Epidemiology Group (MEG) British Association for Cancer Research (BACR)

Non-Personal Interest	**Misc** RTZ – Departmental Research Grant Manchester University – Research equipment bought using departmental funds from consultancies with industry and other bodies	**None**
Dr Ruth Morse		
Personal Interest	**Employee** Senior Lecturer in Human & Clinical Genetics, University of the West of England	**Member** United Kingdom Environmental Mutagen Society British Society of Toxicology Genetics Society
Non-Personal Interest	**Misc** Medical Research Council with AstraZeneca (ITTP programme) - PhD studentship collaborative grant 2015-2020 TETFUND, Ebonyi State University - PhD studentship 2014-2019 Petroleum Technology Fund, Nigeria - PhD studentship 2016-2020	**None**
Mr Amit Bhagwat		
Personal Interest	**Owner and Shareholder** Research and Consulting Business	**None**
Non-Personal Interest	Bradford Teaching Hospitals NHS Foundation Trust - Public Governor (Rest of England & Wales) British Computer Society – the Chartered Institute for IT - Chair/Volunteer for Learned Events and Public Service Activities	NHS England subsidiary board on Mental Health Digital Programme – Public Member Prescribed specialised services advisory group, DHSC – Public appointment Committee on Mutagenicity, DHSC – Public Appointment

COMMITTEE ON THE CARCINOGENCITY 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 (https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc).

I am grateful to the Members, Secretariat and other experts for their continued commitment to the work of the committee. A major ongoing task is to generate updates of guidelines to reflect current knowledge and understanding. These are intended for use by assessors but also to be more generally available. To that end we have sought in the introduction to have an explanation in plain English.

We are aware that our understanding of cancer has increased in many ways including by use of new technologies and adoption of deep learning and other computational tools. However, on a practical level we still face the challenge of offering meaningful advice with less evidence than is optimal. For that reason, we will embark on a wide-ranging exercise to think in terms of risk modifiers of cancer rather than the more traditional view of whether or not a substance causes cancer in the next couple of years. This will include considering emerging evidence in immunology and the nascent tumour microenvironment. We hope that this work will better inform how we use information to produce more useful advice.

Professor David Harrison
MD DSc FRCPath FRCPEd FRCSEd

COC EVALUATIONS

Chemical Carcinogenicity Revisited

3.1 The COC is currently considering whether new scientific approaches and understanding of the carcinogenic process may provide an updated paradigm for assessing carcinogenic risk. To initiate discussions, Dr John Doe presented to the COC in March 2019 the key messages from a series of three papers, of which he was a co-author, and that challenged the current chemical carcinogenicity assessment paradigm.

3.2 It was noted that the current paradigm was set up over 40 years ago, and the usefulness of identifying carcinogens per se using a long-term rodent bioassay was now being questioned for assessing carcinogenic risk in humans. The stochastic nature of the cancer process was outlined, in which the probability of a cancer outcome being influenced by the number of replications of cells, hereditary related errors and environmental stressors (directly acting on the genome and/or increasing cell replication) was assumed.

3.3 The aetiology of cancer was also described. It was emphasised that a proliferative environment needed to be maintained to allow for the progression of tumourigenic development. The “current gold standard” for carcinogenicity testing, the 2-year rodent bioassay, was considered biased towards providing such a sustained proliferative environment due to use of the maximum tolerated dose. This may therefore give a greater likelihood of tumour findings compared to controls.

3.4 An updated paradigm that moves away from identifying carcinogens as a classification process, to one that assesses carcinogenic potential as part of risk characterisation was proposed. It was considered that as cancer occurs as a downstream consequence of genotoxicity and/or toxicity, prevention of these through setting of guidance values would also prevent cancer. A suggested risk assessment approach using structure-activity relationship and/or toxicity testing for mutagenicity as the starting point for cancer evaluation was outlined.

3.5 The COC noted that epidemiology studies had identified most chemical carcinogens, and that the proposed outline model might not fit all new carcinogens and the findings might be secondary to epidemiological evidence. In contrast, it was also recognised though that epidemiology studies would not be available for all chemicals and animal data should not be dismissed for deriving health-based guidance values.

3.6 The proposed approach was also thought to benefit from consideration of the importance of scale within the cancer

process, being able to inform on the microenvironment around the cell; this is key to cancer progression and does not get taken into account when considering large scales such as whole organs or bodies

3.7 Logistics of replacing the existing paradigm were also raised. The Committee agreed that the presentation had given an excellent overview of current issues in carcinogenic risk assessment and the proposed model provided a useful starting point for re-assessing the process.

Published paper: Experimental and pan-cancer genome analyses reveal widespread contribution of acrylamide exposure to carcinogenesis in humans

3.8 The Committee discussed a publication considering a mutational signature of glycidamide, which is the postulated reactive metabolite of acrylamide. This signature had been found in one-third of the tumour genomes, and observed in over 50% of cancers of the lung, liver, kidney, bile duct and cervix, as well as being present to a lesser extent in other cancer types.

3.9 The COC queried the specificity of the mutational signature as a marker of glycidamide, and noted that the information from the controls in the study had not been presented. Overall the Committee considered that the paper provided only weak evidence of a widespread contribution of acrylamide in all human cancers.

Update on OECD Integrated Approach to Testing and Assessment (IATA) on Non-genotoxic carcinogens

3.10 An update of the work being undertaken on the OECD Integrated Approach to Testing and Assessment (IATA) of non-genotoxic carcinogens (NGTxC) was presented by Dr Miriam Jacobs (PHE) at the July COC meeting. The remit of the IATA steering group was to identify key mechanisms and chemical applicability domain gaps, evaluate promising assays for inclusion in an IATA and, to design a framework in which the assays could sit.

3.11 Initial steps involved the reordering of the ‘Hallmarks of Cancer’ and associated modes of action, as Adverse Outcome Pathways (AOPs) based on 4 levels of operation from subcellular through to whole organism level. The IATA used different assay blocks to allow early, mid and late key events in the carcinogenic process to be identified, to obtain equivalent or better levels of information for human and environmental heath than the rodent cancer bioassay.

3.12 The COC welcomed the update on the work, and noted its

potential to influence some of its guidance statements. It was agreed that the OECD work would be kept under review as it developed.

ToxTracker

3.13 At the November COC meeting, the Committee had a presentation on the ToxTracker assay, from Dr Giel Hendriks (toxys). This is a stem cell-based screening platform which utilises six reported cell lines to detect changes that may indicate carcinogenicity, including genotoxic and non-genotoxic mechanisms of action.

3.14 The presentation outlined the assay and outcomes from the large number and range of substances that had been tested using it. It was noted that in addition to screening and hazard identification, there were proposals for use of the assay in dose-response modelling and threshold of toxicological concern or weight of evidence assessments.

3.15 The future regulatory use and acceptance of ToxTracker was also considered to be critically important. At the present stage of development and validation, there is no intention to replace standard assays, and it is finding use as a follow up to explain equivocal findings coming from current standard assays.

3.16 The COC noted that the assay was undergoing a validation exercise, and agreed to keep a watching brief on developments, including discussions with the OECD with respect to regulatory acceptance. The potential for use of the assay as an initial screen for general toxicity as well as for characterisation and understanding of AOPs was also noted.

Potential toxicological risks from electronic nicotine and non-nicotine delivery systems (E(N)NDS – e-cigarettes) – update of available data on carcinogenicity

3.17 The COC had looked at the available evidence on potential carcinogenicity of E(N)NDS in 2018 and concluded “that relative risk of E(N)NDS compared to conventional cigarettes appeared to be lower, but there was still some risk associated with the chemicals and particles in the emissions from E(N)NDS. This risk should be emphasised to new users. In addition. Members concluded that the possibility of bystander effects should also be considered”. This advice had been provided to the COT to support its review of the toxicological risks from these products.

3.18 Since the 2018 COC consideration, two further papers (a study in mice and an *in vitro* study) had been published, and the COT had requested a view from COC on these additional papers. The COC considered that there were a number of confounding issues with both studies that prevented any robust conclusions

being drawn. COC agreed that the papers did not alter their previous conclusions on the potential carcinogenicity of E(N)NDS.

Horizon scanning

3.19 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.

3.20 As part of the 2019 horizon scanning discussion a short update was given on recent International Agency for Research on Cancer (IARC) conclusions, which could be relevant to bear in mind during chemical risk assessment, in particular shift work was discussed. A short outline of the role of immunological and stromal cells in the tumour microenvironment was provided, and this area would be taken forward in 2020.

3.21 At the end of discussion, it was agreed that the priority topics were:

- IARC assessment of shift work and how that might affect assessment of chemicals and carcinogenicity
- View on the future of assessment of carcinogenicity including use of animal models, in vitro and in silico data as well as new approaches encompassing artificial intelligence and analysis of big data.
- The cellular microenvironment and role in carcinogenicity

3.22 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

3.23 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 1.39-1.40

Guidance statements

3.24 The Committee continued to develop the guidance statement series during 2019. This included finalising a set of principles for consideration of risk due to less than lifetime exposure (G09).

3.25 Further discussion papers on 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) and were also considered. These documents are expected to be finalised in 2020.

2019 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

CHAIR

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 John Doe PhD DipRCPath
Consultant in Toxicology, Parker Doe Partnership

Dr Richard Haworth MA VetMB DPhil FRCPath DipECVP DABT (co-opted from November 2018)
Head of Pathology UK, GlaxoSmithKline

Dr Ray Kemp BA MSc PhD MRTPI SIRM
Public Interest Representative

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Dr Rosemary H Waring PhD DSc FRCPath
Honorary Reader in Human Toxicology, University of Birmingham

Professor Saman Warnakulasuriya BDS, FDSRCS, DipOralMed, PhD, DSc (to 31 March 2019)
Professor of Oral Medicine & Experimental Pathology, King's College London

SECRETARIAT

Miss B Gadeberg BSc(Hons) MSc	PHE Scientific Secretary
Dr D Gott BSc(Hons) PhD	FSA Scientific Secretary (to July 2019)
Ms C Mulholland	FSA Scientific Secretary (from August 2019)
Mrs N Blowfield	Administrative Secretary

Declaration of members interests during the period of this report

Professor David Harrison		
Personal Interest	**Employee** University of St Andrews, UK NuCana Biomedical, UK (part-time) **Consultant** University of Canberra University of Florida Pneumagen Ltd, UK **Shareholder** Ryboquin Ltd, UK Avipero Ltd, UK Benenox Ltd, UK (Shareholder and Director) **Misc** University of Dundee – External Examiner Cunningham Trust – Scientific Adviser Definiens AG – Advisor University of Edinburgh, UK – Honorary Professor University of Glasgow, UK – Visiting Professor PathAlba Ltd - Director	**None**
Non-Personal Interest	**Misc** iCAIRD research consortium – Director (unpaid role)	**None**

	Families First St Andrew's (children's charity) – Trustee Director Gene Therapy Consortium (funded by Wellcome Trust) – Unpaid external scientific advisor Systems Biology Ireland – Unpaid external scientific advisor	
Mr Derek Bodey		
Personal Interest	**None**	**None**
Non-Personal Interest	**None**	**None**
Dr Gill Clare		
Personal Interest	**Pension** Shell Research Ltd AstraZeneca **Shareholder** AstraZeneca Diageo Marks and Spencer **Consultant** Covance	**Membership** United Kingdom Environmental Mutagen Society (UKEMS)
Non-Personal Interest	**None**	**None**
Dr John Doe PhD Dip R C Path		
Personal Interest	**Employee** Parker Doe Partnership (Partner) **Pension** Syngenta **Consultant** Concept Life Sciences ECETOC Syngenta	**None**
Non-Personal Interest	**None**	**None**

Dr Richard Haworth (Co-Opted Member)		
Personal Interest	**Employee** GlaxoSmithKline **Shareholder** GlaxoSmithKline Royal Dutch Shell (Spouse Shareholder) United Utilities (Spouse Shareholder)	**Membership** British Society of Toxicological Pathology
Non-Personal Interest	**None**	**None**
Dr Ray Kemp		
Personal Interest	**Shareholder** Ray Kemp Consulting	**None**
Non-Personal Interest	**None**	**None**
Dr David Lovell PhD BSc (Hons) FSS FIBiol Cstat CBiol		
Personal Interest	**Employee** Reader in Medical Statistics St Georges Medical School University of London **Pension** Pfizer **Shareholder** National Grid plc AstraZeneca (Spouse Shareholder) National Grid plc (Spouse Shareholder)	**Membership** Biometrics Society British Toxicology Society (BTS) Genetics Society Royal Society of Biology (CBiol FRSB, 2003) Laboratory Animal Science Association (LASA) Royal Statistical Society Statisticians in the Pharmaceutical Industry (PSI) United Kingdom Environment Mutagen Society (UKEMS) UK National Centre of Replacement, Refinement and Reduction of Animals in

		Research (NC3Rs) – Board Member MRC EMINENT Scientific Review Board British Trust of Ornithologists (BTO) English Heritage Liberty Campaign of the Protection of Rural England (CPRE) Kew Gardens Sandwich Bay Bird Observatory Trust (SBBOT) Chelsea Physic Garden National Trust HESI GTTC
Non-Personal Interest	**None**	**None**
Professor Neil Pearce		
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Non-Personal Interest	**None**	**None**
Dr Christopher J Powell, FRCPath, FBTS, FRSB	COC Member to 31 March 2019	
Personal Interest	**Employee** GlaxoSmithKline **Shareholder** GlaxoSmithKline	**None**
Non-Personal Interest	**None**	**Member** British Toxicology Society – President (Trustee)
Dr Lesley Rushton OBE BA MSc PhD Cstat		
Personal Interest	**Consultancy**	**Member**

	Review of Global Burden of unsafe water, unsafe sanitation, unsafe hygiene and lead in water	Industrial Injuries Advisory Council - Chair HSE Science, Engineering and Environmental Assurance Committee (SEAC)
Non-Personal Interest	**None**	**Misc** IEH Consultancy Ltd – Research Support
Professor Heather Wallace BSc Hons PhD FRCPath FBTS FRSC FRSB ERT		
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Non-personal Interest	**None**	**None**
Dr Rosemary Waring PhD DSc FRCPath		
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Non-Personal Interest	**None**	**None**
Professor Kasturi Warnakulasuriya FDS, PhD, DSc	COC Member until 31 March 2019	
Personal Interest	**Shareholder** National Grid Post Office Ltd	**None**
Non-Personal Interest	Cancer Research UK - Advisory	**Member** Oral Health Foundation