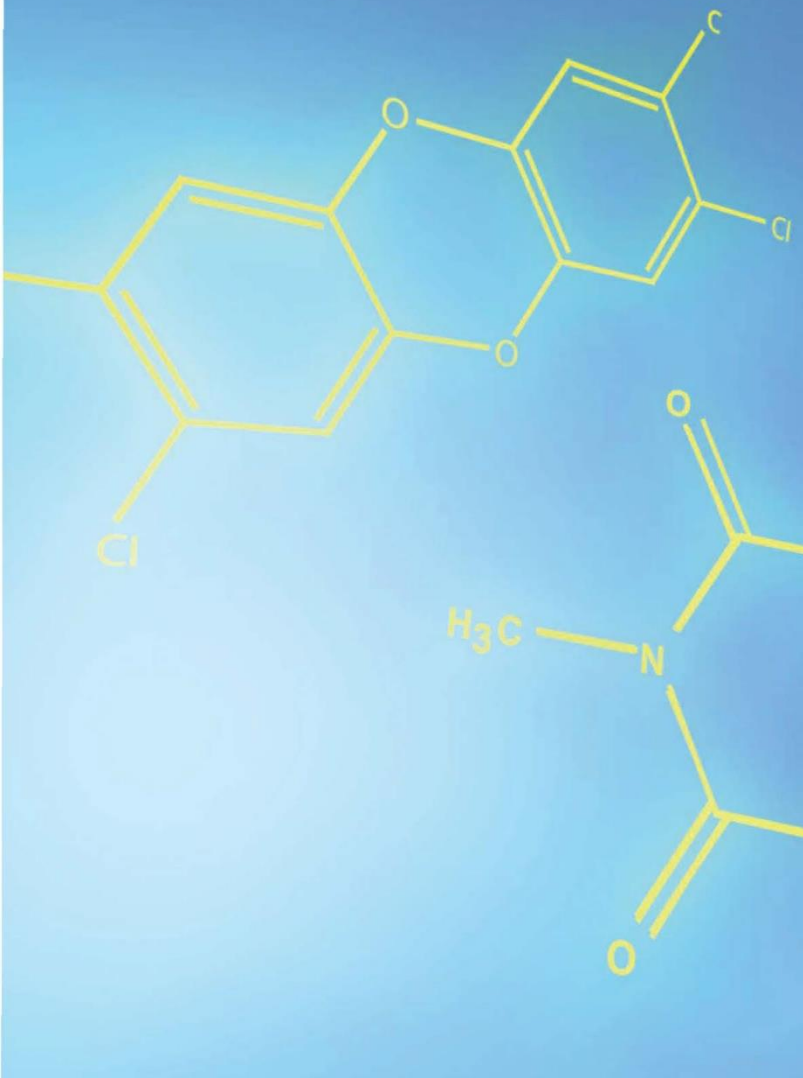
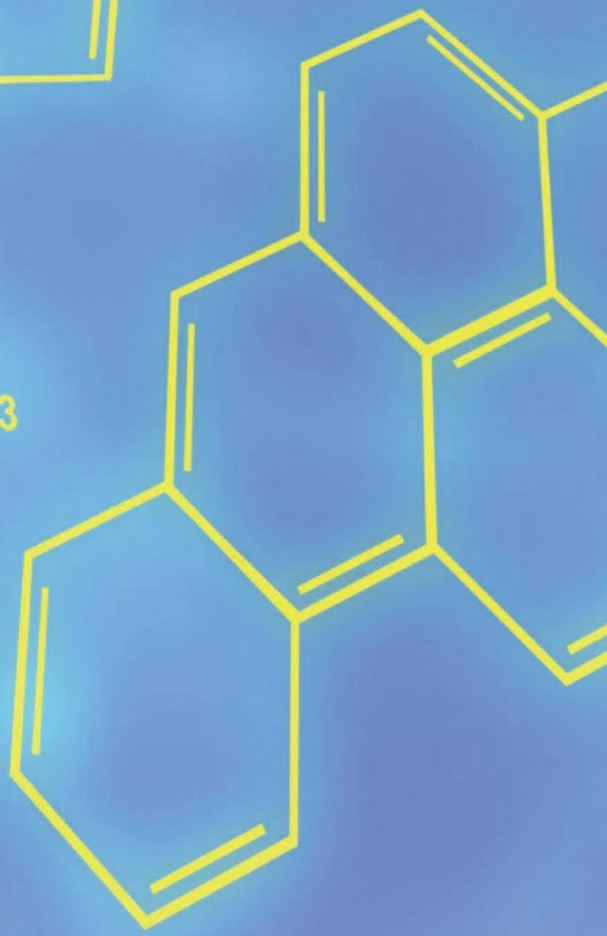
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment





Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2018

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

Annual Report 2018

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 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 2018. 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. One of the meetings was over two days to allow COT Members to hold an extensive session on horizon scanning and work prioritisation.

COT and COC Members have been collaborating in a joint Working Group on the Synthesis of Epidemiological Evidence (SEES). Such activities use the complementary knowledge and skills of our SACs to great effect. The findings of the Working Group were discussed by the individual Committees and the final report published. It is hoped that this work can be extended to consider the synthesis of other types of evidence.

The committee heard a presentation on Risk 21 (risk assessment in the 21st century), a framework for the synthesis and communication of information on potential risks from chemical exposure developed by the Health and Environmental Sciences Institute.

At the request of the Scientific Advisory Committee on Nutrition (SACN), 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 the diet. The substances reviewed included manganese, chlorate, perchlorate, furans, tropane alkaloids, zinc, selenium and phthalates. Reviews were also completed, and statements published on the methyl mercury, cadmium, nickel, copper and the mycotoxins ochratoxin A and T2-toxin, HT2-toxin and neosolaniol.

Another ongoing programme of COT work relates to assessing the safety and 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 on e-cigarettes discussed included exposure to metals, silicon and silicates in aerosols, the assessment of the main components propylene glycol and glycerol and an initial review of nicotine.

The other topics discussed by the Committee this year have been very varied and have included 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 Janet Cade and would like to thank her for all her contributions during her time on the Committee. We also welcomed Dr Mirielle Toledano, a senior lecturer in epidemiology, to the Committee.

As the date of the UKs exit from the European Union draws near, the Committee has been working with the FSA Secretariat to ensure that it will be ready to undertake whatever tasks will be required in the future, both in terms of expert capacity but also ensuring our approaches to risk assessment reflect the most up to date science.

I would like to thank the Secretariat for their continued support and my fellow Committee Members for all of their hard work and valuable contributions to the activities of the Committee through the year.

Professor A Boobis (Chairman)
OBE PhD CBiol FRSB FBTS FBPhS

COT evaluations

Statement on potential risks from methylmercury in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

1.1 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). This statement gives an overview of the potential risks from methylmercury(MeHg) in the diets of infants and young children in the UK.

1.2 Mercury (Hg) is a metal that is released into the environment from both natural sources and human activity. After release into the environment, it undergoes a range of transformations and cycles between atmosphere, land and aquatic systems. Mercury can exist in a number of chemical forms. The three forms occurring most commonly in the environment are (i) elemental or metallic mercury, (ii) inorganic mercury compounds and (iii) organic mercury, mainly as methylmercury. It is the last form (iii) that is by far the most common in the food chain.

1.3 All forms of mercury entering the aquatic environment are converted into methylmercury by microorganisms.

1.4 The general population is exposed to inorganic mercury and methylmercury through food, drinking water, soil and in trace amounts from the air. The diet, and especially fish consumption, is the main route of exposure to methylmercury. Since methylmercury tends to persist in aquatic organisms, older, predatory fish, which eat smaller fish, are more likely to have higher methylmercury concentrations than smaller and/or younger fish.

1.5 Methylmercury is readily absorbed following oral exposure. It can cross into the brain, cross the placenta and is excreted in breastmilk. Thus, it can reach the developing fetus, where it tends to accumulate in the brain. It can also accumulate in the hair, where measurement can be used to estimate long-term exposure. It has a long half-life and is eliminated less efficiently in newborns than in older children.

1.6 The main adverse effect associated with exposure to methylmercury is toxicity to the developing nervous system. As a consequence of its build-up in the body over time, exposure of the fetus to methylmercury depends on the maternal exposure up to a year prior to conception. Infants and young children can also be exposed to methylmercury via breast milk.

1.7 The European Food Safety Authority (EFSA) and the Joint Food and Agriculture Organisation of the United Nations and the World Health Organisation Expert Committee on Food Additives (JECFA) have published risk assessments on exposure to methylmercury in food. In 2003, based on the results of epidemiological studies in high-fish consuming populations, the JECFA established a Provisional Tolerable Weekly Intake (PTWI) for methylmercury of 1.6 µg/kg bw. In 2012, after reviewing updates on said epidemiological studies, the EFSA established a Tolerable Weekly Intake (TWI) of 1.3 micrograms per kilogram of bodyweight (µg/kg bw).

1.8 In their 2004 evaluation, the COT concluded that the PTWI of 1.6 µg/kg bw established by JECFA in 2003 was sufficient to protect against neurodevelopmental effects on the fetus and should be used in assessing risks from dietary exposure to methylmercury in women who are pregnant or may become pregnant the following year. The Government, therefore, currently advises that breastfeeding mothers should avoid eating more than one portion of shark, swordfish or marlin per week and that pregnant women, women trying to get pregnant and children should avoid eating these species. Consumption of up to two 140g portions of fresh tuna, or up to four 140g portions of canned tuna, per week, before or during pregnancy would not be expected to result in adverse effects on the developing fetus.

1.9 In this review, the COT estimated exposure of UK infants and young children to methylmercury from different food sources, based largely on recent UK data on methylmercury levels in food, and compared them to the TWI established by EFSA in 2012. New information on the effects of methylmercury in exposed populations, published since EFSA's 2012 review, were also considered.

1.10 For infants aged 0-6 months old who are fed breast milk exclusively, as well as infants and young children (0-18 months) non-exclusively fed breast milk, or exclusively fed ready to feed drinks and powdered formula, the exposures to methylmercury are below the TWI and are therefore not of toxicological concern. In children consuming a mixed diet, assuming that all of the mercury in fish is methylmercury, the TWI is slightly exceeded in the age groups of 12 to <15, 15 to <18 and 18 to<24 months old at the top end range of exposures from fish. However, methylmercury content in fish varies greatly depending on species of fish, size, age and their diet, and it is very unlikely that children of this age would be exclusively consuming large predator fish, e.g. swordfish with high methylmercury content. Hence, when the conservatism in the exposure assumptions is taken into account, the risk to health from the potential minor exceedance of the TWI in these groups is low. It is concluded that it would be prudent to maintain existing advice regarding consumption of large predator fish.

1.11 The full statement can be found at:
https://cot.food.gov.uk/sites/default/files/cotstatementonmethylmercury.pdf

COT statement on the potential risks from cadmium in the infant diet

1.12 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.

1.13 Cadmium is a heavy metal that is found widely in the environment, coming from both natural sources, such as volcanic activity, and human activities, such as the smelting of metals. Cadmium in the soil, water and air enters the human food chain through being taken up by crops, which are consumed by food animals. Once in the body, this metal accumulates over many years, where it may cause damage to the kidneys and loss of bone tissue. It can also cause cancer.

1.14 Infants and young children can be exposed to cadmium from breast milk, food, air and ingested soil and domestic dust.

1.15 In 2009, the European Food Safety Authority (EFSA) conducted a review of the risks of exposure to cadmium. EFSA established a tolerable weekly intake (TWI) for cadmium, based on an adverse effect on the kidneys, to determine the level of exposure of people below which there would be no cause for concern. The TWI is defined as the amount of cadmium that can be taken in by a person every week throughout their life without causing adverse effects on health. This value was very low, at 2.5 micrograms (millionths of a gram) per kilogram body weight.

1.16 The COT compared cadmium exposure of UK infants and young children to this TWI. The results indicated that estimated exposure to cadmium from breast milk was below the TWI but for infant food, in some cases, estimated exposure exceeded the TWI, by up to about 2.5-fold. The COT noted, however, that the EFSA TWI erred greatly on the side of caution and was meant to cover several decades of life, not the short period for which infants or young children would be eating infant food.

1.17 Exposure to cadmium from air, dust and soil *per se* was not found to be a cause for concern. Whilst it is possible that some allotment land, and crops grown thereon, could be more contaminated than commercial fields, it was noted that the sources of historic contamination, i.e. metal smelting sites and incinerators, are now much less polluting than in the past.

1.18 The COT concluded that the levels of cadmium in the environment and food are not a cause for concern for the health of infants and young children. However, considering the cumulative nature of cadmium toxicity, efforts to minimise the levels of this metal in the environment should continue.

1.19 The full COT statement can be found at:
https://cot.food.gov.uk/sites/default/files/cotstatementoncadmium.pdf

COT statement on the potential risks from copper in the infant diet

1.20 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 copper in the infant diet.

1.21 Copper is a metal that is widely used in plumbing, coins and other consumer products. Copper is found widely in the environment, coming from both natural sources such as erosion of copper-bearing ores and human activities such as the smelting of metals. Copper is an essential micronutrient in humans, and is involved in important chemical reactions in cells. Either too little or too much copper can be detrimental, but deficiency is unlikely because it is so widely available.

1.22 Infants and young children are exposed to copper in breast milk, food, air and any soil or domestic dust that is swallowed. Drinking-water from copper pipes can be a major source of dietary copper, especially if the system is new and water is left to stand in contact with the pipes.

1.23 The Expert Committee on Vitamins and Minerals (EVM) derived a Safe Upper Level for copper consumption of 0.16 mg/kg body weight/day.

1.24 The intake of copper by infants from 0 to 12 months and children aged 1 to 5 years through consumption of breast milk, infant formula, food and drinking water is below the Safe Upper Level derived by the EVM and is thus there is no toxicological concern for the health of infants and young children[1].

1.25 The contribution of environmental sources (soil, dust and air) is very small compared with intake from the diet and is not of toxicological concern.

1.26 The Committee noted that the current advice from NHS Choices on making up infant formula did not explicitly reflect advice from the Drinking Water Inspectorate (DWI) that water from the mains tap was preferable to tank-stored water when preparing food and drink unless the tank was intended, set up and maintained adequately to store drinking water. DWI also advise running the tap for several seconds before use. Following this advice could help reduce the intake by infants of copper and other drinking water contaminants.

1.27 The full COT statement can be found at: https://old.food.gov.uk/sites/default/files/cotstatementoncopper.pdf

Statement on the results of the 2014 survey of metals and other elements in infant foods

1.28 Food surveys are carried out on a regular basis by the Food Standards Agency (FSA) and are an important part of the UK Government's surveillance programme for chemicals in food. Survey results are used to estimate dietary exposures of the general UK population or specific sub-populations (e.g. infants) to chemicals in food, such as nutrients and contaminants, to identify changes or trends in exposure and make assessments on the safety and quality of the food supply.

1.29 The FSA has completed a survey of 15 elements in the 2014 survey of metals and other elements in infant formula, commercial infant foods, and other foods (not specifically manufactured or intended for infants, but known to be or may be consumed by infants (e.g. bread, fruit and vegetables)). The results of the survey provide information on the concentrations of aluminium, antimony, arsenic (including inorganic arsenic), cadmium, chromium, copper, iodine, iron, lead, manganese, mercury, nickel, selenium, tin and zinc in these foods. Estimates of dietary exposures have been calculated for each element for UK

[1] Those rare individuals with a genetic abnormality in how they handle copper (e.g. Wilson Disease) should be receiving medical advice on how to minimise exposure to copper.

infants and young children aged 4 to 18 months using food consumption data taken from the Diet and Nutrition Survey of Infants and Young Children.

1.30 This evaluation considers only those reported levels of elements above those necessary for normal nutrition and not where potential deficiencies in the elements were observed, since this is outside of the remit of the COT.

1.31 To assess the risk, these exposure estimates were then compared to available health-based guidance values (HBGVs) or evaluated using a margin of exposure (MOE) approach using appropriate reference values.

1.32 The Committee concluded that the current estimated dietary exposures did not indicate excessive intakes for copper, iodine, iron, selenium or zinc, and that these were not of toxicological concern (but this conclusion does not necessarily apply to those with inborn errors of copper or iron metabolism). Current estimated dietary exposures of chromium, aluminium, antimony, mercury, nickel and tin were not of toxicological concern for the general population. It is not possible to determine whether there is a risk of sensitisation to nickel in infants and young children exposed to nickel through the diet. The effect from ingestion of an acute exposure of nickel in sensitised individuals could be a dermal reaction, which although unpleasant is not lifethreatening.

1.33 Although manganese exposures were below the available HBGVs the Committee considered that the way in which the respective HBGVs were derived was not robust. Therefore, it would not be appropriate to use these HBGVs to characterise the potential risks from exposure to manganese. The committee will address this in a forthcoming statement.

1.34 Not all calculated exposures for all elements were below an HBGV. Thus, in some instances cadmium exposures exceeded the HBGV, but these were small in magnitude and would not be expected to remain at these levels over the decades of exposure necessary to reach the reference value used by EFSA in setting the HBGV. On the basis of the MOEs calculated, the Committee considered that current average dietary inorganic arsenic exposures would be of low concern, but high-level exposures could present a small risk to consumers. The Committee also concluded that any risk posed by the current estimated dietary exposures to lead were small. There are other potentially more important sources of exposure to lead such as water and soil.

1.35 The full COT statement can be found at:
https://cot.food.gov.uk/sites/default/files/2014infantmetalssurveystatement.pdf

Statement on potential risks from nickel in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

1.36 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) had been asked to review the risks of toxicity from chemicals in the diet of infants (aged 0-12 months) and young children (aged 1-5 years). This statement addresses the risks from high levels of nickel in the diet of young children aged 0-5 years.

1.37 Nickel is a metal that exists in various mineral forms and is present throughout the environment. It is used in a wide variety of processes including electroplating and alloy production, and is present in a wide range of consumer products. Nickel concentrations in the environment reflect both natural and anthropogenic contributions.

1.38 The general population is primarily exposed to nickel via food and drinking water. Higher levels of nickel have been found in legumes, nuts and oilseeds and cocoa beans and cocoa products. Inhalation from ambient air and exposure through the skin are minor sources of exposure. Following oral exposure in humans, nickel is bioavailable at levels from 1% up to 40% and has lower bioavailability when in the presence of food than in the presence of drinking water alone.

1.39 In humans, the effects of oral exposure to nickel include effects on the gastrointestinal, haematological, neurological, and immune systems. Exposure to nickel through skin or by inhalation may lead to nickel sensitisation; although oral exposure is not known to lead to sensitisation, it may be able to elicit eczematous flare-up reactions in the skin of nickel-sensitised individuals.

1.40 Haber et al., (2017)[2] established a tolerable daily intake (TDI) of 20 µg/kg bodyweight (bw) for the toddler population and an acute reference dose (ARfD) of 4.0 µg/kg bw for sensitised individuals. A reference point of 1.1 µg/kg bw for a margin of exposure (MOE) approach, was established by the European Food Safety Authority (EFSA) (2015)[3] for exposures of sensitised individuals to nickel.

1.41 Nickel exposures from dust, soil and air were considerably lower than from dietary exposures for infants aged 0 to 12 months and young children aged 1 to 5 years.

1.42 Chronic nickel exposures for all age groups and food categories were below the TDI of 20 µg/kg bw. The Committee concluded that there was no toxicological concern to the long term health of infants aged 0 to 12 months and young children aged 1 to 5 years.

1.43 Assuming an MOE reference point of 1.1 µg/kg bw: EFSA concluded that an MOE of 10 or greater would be indicative of low health concern for acute nickel exposures. Apart from average and high level consumption of breast milk, with a low concentration of nickel, all other exposures result in an MOE value of less than 10. Hence, there is the possibility of a dermal response to an oral exposure of nickel at the concentrations currently found in food in sensitised individuals.

1.44 Assuming an ARfD of 4.0 µg/kg bw: Acute nickel exposures show exceedance of the ARfD of up to about 2-fold for high level food and formulae consumers aged 4 to 60 months. Average consumers in this age group may slightly exceed the ARfD. There may be some risk to sensitised individuals from nickel exposure aged 4 to 60 months. However, there are

[2] Haber LT, Bates HK, Allen BC, Vincent MJ, Oller AR. (2017). Derivation of an oral toxicity reference value for nickel. Regul Toxicol Pharmacol. 87 Suppl 1:S1-S18. doi: 10.1016/j.yrtph.2017.03.011. Epub 2017 Mar 12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28300623

[3] EFSA (2015) 'Scientific opinion on the risks to public health related to the presence of nickel in food and drinking water' EFSA Journal 13 (2) pp.4002 Available at: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1351.pdf

uncertainties associated with the exposure assessment due to the significant degree of combining of food items into groups in the Total Diet Study (the data from which were used to calculate the exposures). In particular, it is not possible to reliably estimate the contribution of specific food items to total exposure for refining the assessment to reduce these uncertainties.

1.45 It is not possible to determine whether there is a risk of sensitisation to nickel in infants and young children exposed to nickel through the diet. The effect from ingestion of an acute exposure of nickel in sensitised individuals could be a dermal reaction, which although unpleasant is not life-threatening.

1.46 The full COT statement can be found at: https://cot.food.gov.uk/sites/default/files/statementonpotentialrisksofnickel.pdf

Statement on potential risks from ochratoxin A (OTA) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

1.47 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). This statement gives an overview of the potential risks from ochratoxin A (OTA) in the diets of infants and young children in the UK.

1.48 OTA is a mycotoxin produced by several fungal species and has been detected in a variety of plant commodities such as cereals and cereal products, coffee beans, beans, pulses, cocoa products, nuts and spices and dried fruit all over the world. It has also been detected in a number of plant-derived products such as coffee, wine, beer and grape juice and in kidney, liver and blood from farm animals, where it occurs by transfer from animal feed.

1.49 Human exposure occurs through the consumption of contaminated food products. OTA is rapidly absorbed following oral ingestion and most of the compound present in the blood is bound to plasma proteins. It has been detected in human blood, urine and breast milk.

1.50 The most sensitive and crucial effects of OTA are on the kidneys and these have been observed experimentally in rats and pigs. The extent of the kidney damage is dose- and time-dependent as OTA accumulates in the kidneys. At high concentrations, OTA induces kidney tumours in rodents. Both JECFA and EFSA have concluded that on the basis of the available mechanistic data, toxicity to the pig kidney is the most appropriate effect on which to base the risk assessment of OTA.

1.51 In 2006, the European Food Safety Authority (EFSA) derived a tolerable daily intake (TDI) of approximately 18 ng OTA/kg bw per day. However, given the relatively long half-life of OTA, EFSA considered that a tolerable weekly intake (TWI) would be more appropriate and therefore established a TWI of up to 120 ng/kg bw. This is a level that can be consumed weekly, over a lifetime without any risk to health. EFSA confirmed this TWI in a statement in 2010.

1.52 The COT calculated estimates of exposure of UK infants and young children to OTA from different food sources and compared them to the TWI established by EFSA. For infants aged 0-6 months old who are fed breast milk, ready to feed drinks and powdered formula the exposures to OTA are not of toxicological concern.

1.53 The available breast milk data suggest generally low exposures to OTA. At the top end of the range of exposures from breast milk a small risk cannot be ruled out for 0-6 months old infants. However, considering the relatively short duration of breastfeeding and the fact that a continuous exposure to such a high concentration of OTA is unlikely, adverse effects on health would not be expected.

1.54 In infants and young children (4 months to 5 years), consuming commercial foods, exposures were well below the TWI and hence there is no toxicological concern for OTA exposure in these groups.

1.55 The full COT statement can be found here: https://cot.food.gov.uk/sites/default/files/cotstatementon-ota.pdf

Statement of T2-toxin (T2), HT2-toxin (HT2) and neosolaniol (NEO) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

1.56 T2 and HT2 toxins are type A trichothecene fungal toxins and are produced by a variety of Fusarium and other fungal species. Fusarium species grow and invade crops and produce T2 and HT2 under cool, moist conditions prior to harvest. T2 and HT2 are found predominantly in cereal grains (particularly oats) and their products. NEO is a hydrolytic phase I metabolite of T2 and may be formed in fungi and mammals. NEO has been found in some brewed coffee samples, in a sample of cereal-containing baby food and at trace level in some barley field malt samples.

1.57 T2 and HT2 have been assessed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2001, the Scientific Committee on Food (SCF) in 2002 and the European Food Safety Authority (EFSA) in 2011 and 2017. NEO was included in the EFSA 2017 evaluation of T2 and HT2.

1.58 There is very little information on the in vivo absorption of T2 and HT2 in animals after oral administration. T2 is rapidly absorbed after direct administration into the small intestine and is extensively hydrolysed to HT2 and other metabolites. It is rapidly distributed to the liver, kidney and other organs without accumulation. Excretion is also rapid. The metabolism of T2 and HT2 in humans and other species is complex and a number of phase I and phase II metabolites are produced. No data have been identified for the toxicokinetics of NEO.

1.59 Several acute and subacute toxicity studies had been published since the European Food Safety Authority (EFSA) 2011 evaluation, focussing predominantly on the anorectic effects of T2 and HT2 at low doses (mink, pig and mouse). Subchronic toxicity studies published since 2011 had investigated similar endpoints to those used by EFSA in its 2011 evaluation for establishing a health-based guidance value (HBGV). They tended to be of longer duration than the pig studies used but confirmed the immunotoxicity and haematotoxicity of T2 and HT2.

1.60 Prior to 2017, chronic HBGVs had been established for T2 and HT2 by JECFA, SCF and EFSA. In their 2017 Opinion, EFSA established a group acute reference dose (ARfD) of 0.3 µg/kg bw for T2, HT2 and NEO and a group TDI of 0.02 µg/kg bw for T2 (x1), HT2 (x1) and NEO (x0.3) [values in parentheses are correction factors for potency].

1.61 As levels of NEO were below the LOD in all samples of wheat, maize, oat and rye-based products analysed in two UK surveys, no exposure assessment was performed for this metabolite.

1.62 Acute and chronic exposures were calculated for the sum of T2 and HT2 using occurrence data from a retail survey of oat-based products commissioned by the FSA in 2015 and consumption data from NDNS and DNSIYC. Exposures in 0 to 4-month old infants are negligible as infants in this age range are unlikely to consume solid foods, including oat based products. Mean and 97.5th percentile acute exposures ranged from 0.022 – 0.032 and 0.056 – 0.11 µg/kg bw, respectively. These were all below the ARfD of 0.3 µg/kg bw and are therefore not of toxicological concern.

1.63 Mean and 97.5th percentile chronic exposures were calculated and ranged from 0.0099 – 0.014 and 0.029 – 0.063 µg/kg bw/day, respectively. All the mean exposures were below the TDI of 0.02 µg/kg bw and were therefore not of toxicological concern. The chronic 97.5th percentile exposures ranged from 145 – 315% of the EFSA TDI. Whilst an effect on health cannot be entirely excluded it is doubtful that children would be regularly exposed to these levels, which were measured in a year in which levels of T2/HT2 in oat grains were particularly high, over a prolonged period. In most years, levels of T2 and HT2 will be much lower than those observed in this harvest. It is therefore unlikely that dietary exposure levels of T2, HT2 or NEO would be of any toxicological concern in infants and young children.

1.64 The full COT statement can be found at:
https://cot.food.gov.uk/sites/default/files/cotstatement-t2ht2andneosolaniol.pdf

Guidance on information required by COT for consideration of irritant sprays and their formulation

1.65 As part of the evaluation of new active substances or formulations of irritant sprays, the Home Office Centre for Applied Science and Technology (now Dstl) requests review of the safety of these from the COT. To support such an evaluation, the Committee requests that certain information be provided or justification given if not available or appropriate.

1.66 The full COT Guidance can be found at:
https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2018/guidance-on-information-required-by-cot-for-consideration-of-irritant-sprays-and-their-formulation

COT statement on new formulation of CS - Sabre 540010-01

1.67 In 2015, the Home Office Centre for Applied Science and Technology received a submission for the reformulation of 2-chlorobenzylidene malononitrile (CS) using a new non-flammable solvent, trioctyl phosphate (TOP; tri-(2-ethylhexyl phosphate); CAS No. 78-42-2), and asked for it to be referred to the COT for expert advice.

1.68 The Committee considered that the data on the new formulation did not indicate any additional risk over the previous formulation and that there was sufficient information available to support approval of the product.

1.69 The Committee recommended monitoring in use should be followed for this formulation, in line with its advice on previously approved products. Further surveillance data was requested if available.

COT statement on TW1000, a new formulation of PAVA

1.70 PAVA (nonivamide; N-pelargonylvanillylamide; CAS No. 2444-46-4) is the synthetic equivalent of capsaicin, the ingredient in peper (Capsicum species) giving rise to gustatory "heat" (sensation of burning). The COT has previously considered the use of PAVA as an irritant spray and the most recent formulation, Captor II, has been in use in UK police sprays since 2007.

1.71 Information on a new formulation of PAVA, known as TW1000, has now been considered by the COT, following a request from the Home Office Centre for Applied Science and Technology (CAST).

1.72 The COT concluded that the information provided on TW1000 was sufficient to enable it to reach an opinion. The Committee was satisfied that there is no evidence of any increased risk from exposure to TW1000 compared to exposure to sprays currently in use, in particular Captor II.

1.73 Guidance is given to a UK police force which uses Captor II with detailed instructions on when and where the spray may be used, in order to protect vulnerable members of the public. The COT would expect similar instructions to be issued for the use of TW1000. The Committee also recommends that monitoring in use should be followed for TW1000, in line with its advice on previously approved products.

Committee procedures

EFSA consultation on draft EFSA/ECHA guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

1.74 The COT was invited to provide any comments it wished to be submitted to EFSA on this draft guidance.

1.75 This guidance brought together a number of existing approaches used in hazard identification to provide a single source for how to identify compounds that are endocrine disruptors, as defined by the criteria adopted within the EU for pesticides and biocides. The scope was very much limited to those modes of action involving the oestrogenic, androgenic and thyroid systems (EATS). In general, the information was clearly presented and provided a logical approach to ED (EATS) identification. The figures were clear and easy to follow. In particular, the COT supported the approach that in vivo data are necessary (Level 3, 4 and 5) even if in vitro results are negative (Level 2), given that endocrine systems are complex and involve different cells, tissues and organs.

1.76 However, it could be emphasised that extensive toxicity data are available for plant protection products and biocides, such that a conclusion might well be possible on ED identification without the generation of extensive additional data for this purpose as this would otherwise result in a significant increase in animal testing. The COT recognised that there will be cases in which additional data will be required. However, it requested that the guidance emphasise that the existing data should be evaluated first, using weight of evidence (WoE). In some cases it might still be possible to reach conclusions without an ideal data set based on overall WoE.

1.77 Perhaps the most significant gap was the issue of non-EATS modes of endocrine disruption. These were mentioned briefly in a few places, but there was no clear indication of what would, should or could be done in this area and how such effects would impact on the overall assessment of a compound for ED potential. A couple of paragraphs explaining this would be useful, recognising that it is not possible to provide specific guidance at present but at least it should be possible to help the reader understand what would be expected at present.

1.78 It was not clear if assessors are required to report non-EATS evidence or not, if available. Some of the tests will provide non-EATs evidence. For example, adrenal weight atrophy together with adverse neuro effects could indicate disruption of the hypothalamic-pituitary adrenal axis (stress hormone response).

1.79 The COT supported the approach that the MOA key events need to be postulated, if possible, between the endocrine activity and adverse effect (postulating the key events between the very first molecular initiating event (MIE) and endocrine activity may be very difficult, given lack of data). The authors dis explain that the MOA is between the endocrine activity and adverse effect in detail on page 3, and in other places. However, it would aid understanding, particularly for some readers, who think of the MOA starting with exposure, if it was detailed every time the MOA was mentioned. For example, in the glossary of terms MOA was defined as “Biologically plausible sequence of substance-specific key events, starting with exposure…”.

1.80 It did not appear that glucocorticoid levels would be tested in these guidelines. If these were to be included in future recommendations, as there was growing evidence that insecticides and herbicides can disrupt the stress response, it would not be sufficient to recommend just measuring corticosterone/cortisol levels. The hypothalamic-pituitary-adrenal (HPA) axis would need to be challenged with a stressor to determine if the endocrine system had been disrupted.

1.81 The COT additionally made a number of detailed comments on the text.

1.82 The EFSA Opinion was published in June 2018

EFSA consultation on draft guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health

1.83 The COT was invited to provide any comments it wished to be submitted to EFSA on this draft guidance. This draft was the third version of EFSA guidance on nanomaterials and

took into account developments that had occurred in other pieces of EFSA guidance, for example, it followed a tiered approach. The guidance applied only to oral exposure.

1.84 The approach was to first characterise the material; to consider if the material remains in the nano form in the gastrointestinal tract, and to assume that it does if this possibility could not be excluded; and to consider if there was oral exposure. The guidance then contained a framework to consider what toxicity data were required. The COT discussed which materials were in the scope of the guidance. It was indicated that these would be materials which met a recommended definition by the European Commission of containing 50% or more of particles in the number size distribution with one or more external dimensions in the size range 1 nm – 100 nm, plus materials with less than 50% of particles in the number size distribution having one or more external dimensions in the size range 1 nm – 100 nm, plus materials which contained particles with a size above 100 nm which could retain properties that are characteristic of nanoparticles.

1.85 Any powdered material would contain some particles in the nanoscale and the COT wondered what percentage should be a cut-off if this was set at less than 50%. This could depend on whether the toxicity of the nanomaterial was increased compared to the non-nano form. A material could have a particle size a little greater than 100 nm and still have the properties of a nanomaterial but the guidance was not clear what characteristics a particle larger than 100 nm would need to possess to be considered within scope. Page 16 of the draft guidance listed 11 characteristics but most of these were not specific to nanomaterials, e.g. bioaccumulation. Quantum effects were specific to nanoparticles but would only occur for very small nanoparticles.

1.86 The guidance implied that nanomaterials may have greater toxicological potency for any toxicological effect than non-nano forms of the same material, and the COT questioned what the available evidence for this was. It recognised that there was evidence of local reactions in the wall of the gastrointestinal tract for some nanomaterials.

1.87 A Member wondered why conventional toxicological testing was not considered sufficient for nanomaterials, as it would test the consequences of such materials in the diet.

1.88 The COT noted that the gastrointestinal tract removes insoluble materials. Molecules with molecular weights more than 1500 Da are not absorbed and few nanomaterials would be smaller than that. In addition, the likelihood that material would remain in the nano form once it had reached the gastrointestinal tract was very low, due to processes such as dissolution and aggregation/agglomeration.

1.89 The Committee continued to work through the guidance, following the general outline in Figure 1 and considering the text in the guidance for each step. After characterising the material as being a nanomaterial or having properties characteristic of the nanoscale, the guidance asked whether the material quickly and fully degrades in in vitro digestive tract conditions. PHE's Group Leader of their Nanoparticle Inhalation Research Group had questioned the security of the degradation rate cut-off of "12% or less of the material is present as particles after 30 minutes of intestinal absorption." The COT considered that this cut-off would work for homogenous materials but not heterogenous materials as only the larger particles would have been degraded.

1.90 The next step was to assess the stability in lysosomal fluid and in vitro testing. The assumption was that nanoparticles were taken up by lysosomes and only if they persist and were not degraded were they a concern. However, this did not indicate what might be happening elsewhere in the cell. The authors of the draft guidance had perhaps considered that this would be identified by the other in vitro tests.

1.91 A Member questioned how the data from a suite of in vitro cytotoxicity tests should be interpreted. It was difficult to see how it would be possible to conclude that there was no effect. It was presumed that the intention was that experience would be built up over time. However, there was no guidance provided on which test methods to use or on establishing in vitro methods that were fit for purpose.

1.92 Regarding in vivo testing it was noted that the design of the 90-day study should be guided by the toxicokinetic studies, showing where the nanoparticles were distributed.

1.93 Regarding exposure, the Committee observed that the worst-case scenario assumed in the absence of evidence to the contrary, was that 100% of nanomaterial added to a food or feed product would be ingested and absorbed.

1.94 Chapter 7 on nano-specific risk characterisation was not considered specific to nanomaterials. Section 6.9, on considerations when testing nanomaterial, contained the aspects which were specific to nanomaterials. Similarly, chapter 8 on uncertainty was largely not specific to nanomaterials. It was suggested that section 8.2 could be replaced with links to existing guidance on uncertainty.

1.95 The EFSA Opinion was published in July 2018.

EFSA consultation on draft guidance on threshold of toxicological concern approach

1.96 The COT considered this consultation document. No substantive comments were made and therefore no response to this consultation was submitted.

EFSA public consultation on draft Scientific Opinion on evaluation of the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels

1.97 This document presented an evaluation of the applicability of the ARfD established for cyanide in raw apricot kernels for other foods containing cyanogenic glycosides, an evaluation of the relevance of chronic effects related to human dietary exposure to cyanogenic glycosides, estimations of acute and chronic dietary exposure to cyanogenic glycosides and an assessment of human health risks related to acute dietary exposure to cyanogenic glycosides.

1.98 Members comments on this were sent to EFSA ahead of the deadline.

Public consultation on the EFSA Opinion on "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food."

1.99 The European Food Safety Authority's Panel on Contaminants in the Food Chain (CONTAM) were asked for a scientific opinion on the risks for animal and human health related to the presence of dioxins and DL-PCBs in feed and food.

1.100 Following a review of available animal and epidemiological data it was decided that the human risk assessment would be based on effects observed in humans and the animal data to be used as supportive evidence. Based on observations from the Russian Children's Study, the CONTAM Panel has established a Tolerable Weekly Intake (TWI) of 2 pg TEQ/kg bw/week.

1.101 The Committee were provided with a summary of the approach used by the CONTAM Panel to establish the TWI and a brief summary of the risk characterisation.

1.102 The Members discussed the Opinion and the COT's views were submitted to EFSA and are now published in the Report for the Information Session held by EFSA.

EFSA public consultation on the MIXTOX guidance

1.103 The European Food Safety Authority (EFSA) have launched a public consultation on a draft Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. The document described harmonised risk assessment methodologies for combined exposure to multiple chemicals for all relevant areas within EFSA's remit.

1.104 The Members were invited to discuss about the guidance, the Committee's comments were agreed and submitted to the EFSA prior the deadline of the 15th of September.

Horizon Scanning

1.105 At their February 2018 meeting, the COT had been invited to consider emerging or developing topics of importance within the COT remit, which might be included in future agendas for detailed discussion. Members noted the list of agenda items that were planned or underway for 2018, and discussed several other topics that might also be considered.

Ongoing items

1.106 There are a number of ongoing items, either on the current agenda or scheduled for further discussion at a future meeting:

- COT input into the Scientific Advisory Committee on Nutrition (SACN) review of complementary and young child feeding focussing on children age 1 to 5.
- Electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)
- Developing Methods for Potency Estimation research project

Potential discussion topics

Consultations of the European Food Safety Authority (EFSA)

1.107 EFSA frequently consults on draft documents on issues of generic relevance across its remit, or that are particularly high profile. When these have been of particular importance to the Food Standards Agency, the COT has been invited to respond to the consultation (e.g. aspartame, bisphenol A, acrylamide and caffeine). Similarly, EFSA documents on toxicological risk assessment approaches with potential relevance to the working practice of the COT have also been discussed (e.g. default values to be used in risk assessment in the absence of actual measured data, and draft guidance on uncertainty). It is anticipated that further relevant EFSA documents will be presented to COT during 2018.

Items carried forward from the 2017 horizon scanning

Analysis of the evidence gap for postulated human health effects of Endocrine Disrupting Chemicals

1.108 Members agreed that a systematic review of the health effects of Endocrine Disrupting Chemicals (EDCs) would be useful but recognised that this would be a major task. A similar task had been conducted by the WHO but more focussed questions would have been helpful. Without a coordinated systematic review to understand the evidence base (possibly an “umbrella” review of reviews to obviate author selection bias) the impact of EDCs was uncertain. In the first instance, a paper on the evidence gaps should be prepared by PHE but other priorities have meant that this item has not been progressed. This is likely to continue to be the case in 2017.

Update on the COT 2008 Trans and multigenerational toxicity statement

1.109 Members noted that the knowledge base on this topic had moved on since the last COT statement was published in 2008. The Committee agreed that the statement should be updated, however resource constraints have not permitted progress during 2017. Due to the interest from COM and COC in PHE held a joint symposium of all three Committees in 2017.

Role of chemicals altering the microbiome and potential human health effects

1.110 The Committee agreed that since the importance of the microbiome in many areas of health and disease was becoming increasingly apparent, the effects of xenobiotics on the microbiota and of the microbiota on xenobiotics should be considered in a short discussion paper. Both the makeup of the microbiological population, i.e. the species of bacteria and other microorganisms present, and its functional makeup, i.e. the biochemical pathways contributed by the total mass of microorganisms, would be taken into account, along with other potential interactions, for example between air pollution, microorganisms in the respiratory tract and the development of asthma. Progress has not been possible during 2016 and 2017 due to other Committee priorities.

Risk Assessment in the 21st Century (RISK21)

1.111 The International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) created the Risk Assessment in the 21st Century (RISK21) Project. This multi-sector, international initiative began in 2009 and has involved the active participation of over 120 individuals from 12 countries, 15 government institutions, 20 universities, 2 nongovernmental

organizations, and 12 corporations. RISK21 has developed a conceptual framework called the roadmap and a simple exposure-toxicity comparison matrix. The matrix enables exposure and hazard to be evaluated and compared effectively and transparently using all relevant sources of information sufficient for decision-making to address the specific problem formulated. The overarching principles of the RISK21 approach and an introduction to the roadmap and visualization matrix are described by Pastoor et al. (2014) and application of the RISK21 roadmap in risk assessment is described in detail by Embry et al. (2014) Annexes 1 & 2 respectively.

1.112 The Committee received a presentation on the RISK21 approach at the May meeting in 2018.

Modelling kinetics

1.113 The Committee agreed that it would be useful to keep abreast of developments in the area of physiologically-based toxicokinetic (PBTK) modelling, particularly as it might be asked in the future to advise on risk assessments using such models. This issue was also discussed in the context of the COT symposium on the implications of obesity on the kinetics of persistent organic pollutants held in March 2015.

1.114 Insufficient data had been presented at the COT symposium to consider building PBTK models. It was considered that compared to pharmaceutical drugs, for environmental chemicals there was usually a lack of good PBTK data which can be used in modelling. The US had made a heavy investment into the replacement, reduction and refinement of animals in research (the 3Rs) and had started to take a bottom-up in vitro and in silico approach, in which toxicokinetic extrapolation plays a key role. It was noted that the COT should keep a watching brief on this topic.

Items discussed at the 2017 Joint COC, COM and COT Horizon Scanning meeting in October 2017

1.115 A Joint Committee Horizon Scanning took place in October 2017 and a number of items were discussed which could be discussed at future COT meetings. Minutes from the meeting, along with the Horizon Scanning papers from each of the Committees are included in Annex A.

1.116 Briefly, the following topics could be of interest to the COT: uncertainty in risk assessment (including modelling approaches and toxico-kinetics); extrapolation from lifetime animal studies to early human less than lifetime exposure; balance between environmental exposure and food exposure; by-products of various drinking water disinfection treatments.

1.117 It was suggested that data presented to the COT during consideration of the heat-not-burn tobacco products could be used in a case study of the RISK21 framework.

1.118 A potential concern over natural products and “new” natural products had been raised. There is no overall framework or systematic approach to natural food products in general. It was suggested that it would be useful to know if there is a potential health risk from taking these products before taking this further, and a brief survey using the National Poisons Information Service could be undertaken in the first instance.

1.119 The use of epidemiological evidence in a health risk assessment was discussed. It was noted that a sub group of the COT and COC was finalising a document on synthesising epidemiological evidence and how this could be used by Committees. The question of how to deal with poor published studies was raised. Members noted that such studies could cause difficulties for various expert Committees, where poor studies were used to question Committee opinions in some cases. It was noted that EFSA currently required scoring of individual papers and used a weight of evidence approach in its evaluations using its PROMETHEUS approach.

1.120 In terms of priorities for joint Committee consideration, it was suggested one important area was how to evaluate the biological or toxicological relevance of a reported response or perturbation, especially where this may be an atypical endpoint and how statistics can, and should, be used to help determine this. This should encompass how the Committees could judge whether the statistics used were appropriate. Consideration of sufficient levels of health protection and dealing with uncertainty could also be useful, for example, the degree of confidence over a non-significant result in relation to health protection. Another area of importance was how to deal with different sources of evidence considered by the Committees (e.g. predatory journals and poor quality non-standard tests), which could be a follow up to the SEES group work. In addition, a watching brief should be maintained on nanomaterials, especially as size distribution is of relevance for e-cigarettes and also heat-not-burn tobacco products.

New suggestions for topics

1.121 The Secretariat would welcome members views on whether the current structure of three separate Committees remains appropriate and sustainable in light of future challenges or whether they should explore other possibilities in consultation with the Secretariats of COC and COM and departmental sponsors.

1.122 No additional items were highlighted by the Secretariat

Balance of expertise on the Committee

1.123 It has previously been agreed that the following types of specialist expertise are required by the Committee for some or all of its evaluations:

Analytical techniques	Biochemistry
Bioinformatics	Cell biology
Clinical practice	Dietary exposure assessment
Endocrinology	Environmental exposure assessment
Epidemiology	Human toxicology
Immunology	Mathematical Modelling
Mechanistic toxicology	Molecular biology
Neurotoxicology	Nutrition
Paediatrics	Pharmacokinetics
Pharmacology	Probabilistic modelling
Reproductive toxicology	Respiratory toxicology
Risk assessment	Statistical aspects of experimental design

Statistics	Systems biology
Toxicogenomics	Toxicological pathology
Xenobiotic metabolism	

1.124 It would not be necessary to have an individual member for each listed expertise as some people would have a combination of the required skills. Additional key experts are also invited to attend meetings for specific topics to supplement missing knowledge.

1.125 The Full Horizon Scanning paper can be found at: https://cot.food.gov.uk/sites/default/files/tox2018-11.pdf

1.126 The Minutes of the discussion can be found at: https://cot.food.gov.uk/sites/default/files/finalcotminutesfeb2018.pdf

Representation at The Science and Technology Committee (STC) evidence sessions:

1.127 A COT submission, supported by COC and COM, was made to the Science and Technology Committee enquiry on e-cigarettes, outlining the Committees evidence assessment on heated tobacco products, published in December 2017, and on the ongoing review of electronic nicotine, and non-nicotine, delivery systems (e-cigarettes). Professor David Harrison, COC Chair and former COT member, presented on this evidence to the STC at the evidence hearing held on 27th February 2018. The recording and transcript of the meeting are available on the STC website: https://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/inquiries/parliament-2017/e-cigarettes-17-19/.

1.128 The Science and Technology Committee (STC) evidence session on the health effects of energy drinks attended by Dr. John Thompson, Member of the COT, was held on 12 June 2018. The recording and transcript of the meeting are available on the STC website: https://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/news-parliament-2017/energy-drinks-evidence-17-19/

Working Groups

Report of the Synthesising Epidemiological Evidence Subgroup (SEES) of the Committee on Toxicity and Committee on Carcinogenicity: Executive Summary

1.129 The Synthesising Epidemiology Evidence Subgroup (SEES) of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) and Committee on Carcinogenicity (COC) was set up in 2015. Its aim was to review and document current practice, given recent international and national development of methods by which evidence is synthesised, and to make recommendations for COT/COC guidance.

1.130 Human studies can provide direct evidence of health impacts of particular exposures. However, much of the evidence comes from observational epidemiological studies, where control of chance, bias (including exposure misclassification) and confounding may be problematic. Systematic review and meta-analysis are gold standard methods for

combining epidemiological studies, but may not be available, or practical or possible to conduct for many of the questions considered by COT/COC.

1.131 Epidemiological reviews leading to statements or opinions in the last 10 years by COT/COC were identified and reviewed. A wide range of topics were identified relating to infant feeding, alcohol consumption, asbestos exposure, organophosphate exposure and vitamin E intake. The review methods used by the Committees varied by topic and requirement.

1.132 Evidence synthesis in the World Health Organization (WHO), the International Agency for Research on Cancer (IARC) and European Food Safety Authority (EFSA) was discussed and a number of well documented major systems for evidence synthesis were reviewed. These were:

• Systems initially designed for clinical medicine but now applied more widely, the Cochrane collaboration, GRADE (Grading of Recommendations Assessment Development and Evaluation) and SIGN (the Scottish Intercollegiate Guidelines Network). GRADE, with modifications, is being increasingly used in systematic reviews of environmental exposures.

• US Federal programmes, the National Toxicology Program (NTP)-OHAT, National Toxicology Program (NTP)-Report on Carcinogens and EPA-IRIS – these programmes were considered too time-consuming and resource intensive to be replicated in their entirety for COT/COC

• The Navigation Guide, first published in 2014, designed to speed up implementation of health protection measures for hazardous chemicals in the environment.

1.133 SEES considered evidence synthesis methodologies and tools available in order to draw up guidance points for scoping, conducting and reporting. For systematic reviews and meta-analysis, SEES recommended use of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance. Quality assessment of studies was considered an integral part of review. A large number of numerical scoring tools are available; the subgroup did not recommend any one tool and considered that if employed, these should be used (i) to aid narrative assessment rather than in place of it and (ii) can help direct sensitivity analyses of the meta-analysis e.g. by exclusion of low-scoring studies. Specific issues related to quantitative risk assessment and meta-analysis were identified, particularly around consideration of study heterogeneity. Documentation of uncertainty and of (potential conflict of) interests was considered important.

1.134 SEES also considered methods for combining epidemiological and toxicological evidence. These are less well developed than those for systematic review, particularly in a quantitative framework. There 4 are currently international initiatives in this area e.g. the Systematic Review and Integrated Assessment (SYRINA) and COT/COC will need to keep this methodological area under regular review.

1.135 The report was published and its conclusions were presented at EUROTOX. The full report can be found at: https://cot.food.gov.uk/cotreports/cotjointreps/synthesising-epidemiology-evidence-subgroup-sees-report

Ongoing work

COT statement on the potential risks from Manganese in the infant diet: lay summary

1.136 The COT had been asked to consider the toxicity of chemicals in the infant diet and the diet of young children aged 1-5 years, in support of a review by the SACN of Government recommendations on complementary and young child feeding. A scoping paper (TOX/2015/32), highlighting some of the chemicals for possible consideration for the diet of young children aged 1-5 years was discussed by the COT in October 2015. Members concluded that a review on the potential risks from manganese in the diet of infants and young children aged 1-5 years should be completed.

1.137 The COT discussed a review of the literature on manganese and a statement was drafted ready for publication.

1.138 Given the current interest in the potential health effects of dietary manganese and the lack of studies providing a useful comparison of dietary intakes and toxicological effects, the Secretariat considered that a publication in the peer-reviewed literature based on the discussion paper and draft statement may be of value. The discussion paper and draft statement had not yet been placed in the public domain in anticipation of this. The secretariat hope to publish a paper in 2019.

Risk assessment of residues of a veterinary product

1.139 In 2018, the COT were 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.

Toxicity of chemicals in the infant diet and the diet of young children aged 1 to 5 years

1.140 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 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. The recommendations cover diet from birth to five years of age.

1.141 Condensed draft statements on perchlorate, chlorate, furan, chromium, selenium and zinc have been presented to the COT in 2018 and together with sections on alcohol, caffeine, food additives, legacy chemicals, soya phytoestrogens, vitamin A and trans fatty acids form part of the overarching statement on the potential risk from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. This will be published in 2019.

1.142 Reviews on tropane alkaloids and 4,15-diacetoxyscirpenol have been presented to the COT and will form part of an addendum to the overarching statement and will be published in 2019.

1.143 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 (BPA) and phthalates, which are currently under re-evaluation by EFSA. The COT has evaluated the information provided by EFSA on perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in 2018 and a statement will be published later in 2019.

Folic acid – statement on the Tolerable Upper Level (TUL)

1.144 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 a NTD affected pregnancy are advised to take a 5 mg supplement.

1.145 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.

1.146 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.

1.147 The Committee was asked to review the Safe Upper Level for folic acid to ensure that it was still pertinent. The Department of Health and Social Care will use the COT findings to take forward proposals for fortification of wheat flour. A statement will be published in 2019.

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

1.148 A number of papers were presented to the COT in 2018 covering known constituents and potential adverse health outcomes arising from exposure to EN(N)DS aerosols, following earlier papers in 2016 and 2017. In addition further aspects considered were exposure to metals and solvents (propylene glycol and vegetable glycerine/glycerol), the presence in the vapour of silicon/silicate particles, nicotine toxicity, including potential for developmental toxicity and a possible role of nicotine in schizophrenia spectrum disorders in adolescents.

1.149 Further topic areas would be considered in 2019.

Phosphate-based flame retardants and the potential for developmental toxicity

1.150 Phosphate-based flame retardants (PFRs) are being increasingly used due to restrictions on other flame retardants. The COT have been asked to look at PFRs as they share some structural similarity with organophosphate (OP) pesticides, which have been shown to interfere with neurodevelopment by inhibition of cholinergic and noncholinergic esterases. A scoping paper was presented to the Committee and aimed to investigate the potential for developmental toxicity following exposure to PFRs, with a focus on children and the developing fetus, and provides background information on proposed mechanism of action, exposure, biomonitoring and toxicity of PFRs.

1.151 Given the limited information available on the topic of PFRs and developmental toxicity, a short Committee view, including discussion of the other potential neurotoxic mechanisms would be published in 2019.

Submission of data on PSI PRO irritant spray

1.152 Data were considered on a new irritant spray product 'PSI PRO', at the request of Dstl, and the Committee requested further information to aid its evaluation.

Interim position paper on potential risks from "energy drinks" in the diet of children and adolescents.

1.153 "Energy drinks" are defined by the presence of compounds, mainly high amounts of caffeine, added for their stimulant properties, as opposed to "sports" drinks, which are formulated to replace water and electrolytes lost during exercise. "Energy drinks" are also intended to be consumed cold. They often, but not always, contain significant amounts of sugar. As there is no official definition, drinks containing added caffeine above 150 mg per litre are referred to as "energy drinks" throughout this document.

1.154 The EU has had legislation in place since 2011 that requires all drinks (excluding tea and coffee) containing over 150 mg of caffeine per litre to bear the statement "High caffeine content. Not recommended for children or pregnant or breast-feeding women". In addition, the amount of caffeine in mg per 100 ml (mg/100ml) of drink must appear after this statement. Although additional caffeine labelling was required from 2004, at that time only the statement "High caffeine content" was required along with the level of caffeine in mg/100ml.

1.155 The Department of Health and Social Care (DHSC) is currently consulting on a proposal to ban the sale of "energy drinks" to children (up to 16 or 18 years of age). The COT has been asked for its views on the safety aspects of "energy drink" consumption by children and adolescents, specifically the effects of caffeine and other components associated with "energy drinks". The COT has not been asked to look at potential benefits or health claims relating to these products.

1.156 An initial scoping paper was discussed in July 2018 on the potential risks to children and adolescents from the consumption of “energy drinks”4. Due to the time frames involved, the COT has produced this interim position paper based on its preliminary discussions, which will be submitted to the DHCS in response to its consultation. A full statement will be produced in the near future following literature searching on additional aspects and when further committee discussions on these have taken place.

1.157 In 2016, more than 20 brands of “energy drinks” were on sale in the UK5. Sales of “energy drinks” constituted 13.4% of the soft drinks market in the same year6.

1.158 EFSA carried out a comprehensive review of the literature on caffeine and “energy drinks” in 2015, prepared by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Due to the extensive database, the panel reviewed previous risk assessments from authoritative bodies worldwide to identify the major health concerns which were relevant (EFSA, 2015). The COT will use this EFSA review extensively in the final statement, but a literature search will also be carried out for studies that specifically look at children and young people. For the purposes of their review, EFSA considered children and adolescents together, which included ages 1 – 18 years.

1.159 In addition to caffeine, “energy drinks” vary in their lesser components. Common ingredients include taurine; B-group vitamins; D-glucurono-□-lactone; guarana (a tropical shrub, the berries of which contain caffeine, theophylline and theobromine); ginseng; gingko biloba; L-carnosine; inositol; or a mixture of these and other minor components (Higgins et al (2010). It was noted that low- and zero-calorie “energy drinks” are also available.

1.160 “Energy drinks” contain variable amounts of caffeine as their main active constituent, included for its stimulant properties; the effects of other non-caffeine, non-sugar constituents are at levels such that they are unlikely to be of toxicological or pharmacological concern (Higgins et al, 2010).

1.161 The Committee was clear that caffeine in “energy drinks” should be considered in the context of total caffeine consumption. Coffee can contain higher amounts of caffeine and sugar than “energy drinks”. Whilst the temperature of hot beverages may go some way to slow down their consumption, it would not affect the rate of absorption once the beverage has been ingested. The other components of “energy drinks” such as taurine and D-glucurono-□-lactone are unlikely to change the potency and activity of the caffeine in these beverages. The Committee noted that, according to EFSA, “energy drinks” were not the largest source of caffeine in the diets of adolescents or children surveyed across Europe between 2000-2012. In toddlers (12-36 months of age), tea and chocolate (including cocoa drinks) were the main sources of caffeine in all countries surveyed except Belgium where cola was the main source. In children (3-10 years of age), chocolate was the primary source followed by tea and cola in all surveys. Adolescents (10-18 years of age) were more variable, with chocolate being the primary source in 6 surveys, coffee in 4 surveys, cola in 3

[4] Available at: https://cot.food.gov.uk/sites/default/files/tox2018-27_0.pdf
[5] https://www.statista.com/statistics/308493/leading-brands-of-energy-drinks-excluding-colas-or-mixers-for-alcoholic-drinks-in-the-uk/
[6] https://www.statista.com/statistics/422739/soft-drink-market-share-by-category-in-the-united-kingdom/

surveys and tea in two surveys. The highest contribution to total caffeine intake from "energy drinks" was 11% in the UK, followed by 8.1% in the Netherlands and 5.3% in Belgium (EFSA, 2015). However, it should be noted that these are population figures, and some individuals may be particularly high consumers.

1.162 Whilst some "energy drinks" contain significant amounts of sugar and will be subject to the new Soft Drinks Industry Levy, the levels of sugar are similar to those found in other soft drinks and therefore "energy drinks" do not pose a unique risk with regards to their sugar content. The Committee noted that drinking large quantities of high-sugar soft drinks will have adverse effects on metabolism and could be a contributory factor towards obesity.

1.163 The Committee recognised that caffeine was a diuretic at high doses and had effects on heart rate and blood pressure as well as sleep duration and sleep onset. The response to caffeine is influenced by the dose, presence of food, and individual's intrinsic metabolism, acquired tolerance, withdrawal status and by psychological factors, such as consumer expectations and societal drivers of consumption.

1.164 Children and adolescents have, until recently, had full access to "energy drinks" but new voluntary restrictions by some food retailers limit this. The taste of these products is a common driver for consumption but overall, drinking "energy drinks" is influenced by various, sometimes conflicting, factors including perceived stimulation, availability, warnings on packaging, advertising, peer pressure and parental influence. Most surveys suggest that boys consume a greater volume of "energy drinks" than girls.

1.165 Use of "energy drinks" has been associated with adverse effects including poor sleep, reduced attention in school and nervousness or anxiety. "Energy drinks" are also consumed mixed with alcohol in older adolescents, which may be associated with "risky" behaviours. However, many of the studies on "energy drinks" are cross-sectional and involve self-reported questionnaires from which cause and effect cannot be determined and which are prone to subjective bias. There are few if any longitudinal studies following "energy drink" consumers over time. Much of the evidence is also anecdotal or based on surveys from energy drink users, relying on self-reporting. Many of the studies are subject to confounding by other dietary and life style factors as well as psychological effects such as expectation.

1.166 Members reiterated their agreement with the EFSA approach for estimating acute risk of caffeine, by extrapolating from adults to children on a body weight basis, given the lack of direct data in children and considering that the rate of caffeine clearance in children and adolescents is at least that of adults. The enzyme primarily responsible for caffeine metabolism, CYP1A2, reaches full expression between ages of 1 and 3 years (Xie, 2017). Current data are inadequate to differentiate between the effects of energy drinks in younger children and older adolescents.

1.167 Overall the consumption of "energy drinks" by children and adolescents is a complex social issue and while the effects of acute consumption have been documented, chronic effects of caffeine and any lasting effects from consumption while brain development is still ongoing remain to be determined. Further research would be required before more definitive conclusions could be made on the long-term effects of caffeine consumption by children and adolescents.

2018 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
Global Head of Product Safety for Syngenta

Professor Janet Cade BSc PhD (until 31st March 2018)
Professor of Nutritional Epidemiology and Public Health, University of Leeds

Ms Jane Case
Lay Member

Dr James Coulson Bsc MBBCh Dip Med Tox Dip Therapeutics MD MRCP ERT
Clinical Senior Lecturer at Cardiff University

Dr René Crevel
Director, René Crevel Consulting Limited

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

Dr Mark Graham BSc PhD
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
Professor of Environmental Health, School of Geography, Earth & Environmental Sciences, University of Birmingham

Dr Sarah Judge BSc, PhD
Staff Scientist in the Medical Toxicology Centre and Institute of Neuroscience at Newcastle University

Professor Brian G Lake BSc PhD DSc FBTS
Head of Molecular Sciences Department, Leatherhead Food Research

Ms Juliet Rix
Lay Member

Dr John Thompson MB ChB BMedSc FRCP FBTS
Senior Lecturer in Clinical Pharmacology, Cardiff University
Director, National Poisons Information Service, Cardiff

Professor Mireille Toledano (appointed 1st April 2018)
Chair in Perinatal and Paediatric Environmental Epidemiology, Faculty of Medicine, School of Public Health, Imperial College London

Professor Faith M Williams MA PhD FBTS
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

SECRETARIAT

Dr D Gott BSc (Hons) PhD	Scientific Secretary
Ms H Gbormittah	Administrative Secretary
Ms B Gadeberg BSc (Hons) MSc	Scientific – PHE

Ms R Acheampong BSc (Hons) MSc
Dr B Doerr BSc (Hons) MSc PhD
Dr Alexander Cooper BSc (Hons) MSc (22nd October 2018)
Dr D Hedley BSc (Hons) MSc PhD
Ms F Hill BSc (Hons) MSc
Mr B Maycock BSc (Hons) MSc
Ms C A Mulholland BSc (Hons)
Dr O Osborne BSc (Hons) (Exon) PhD
Ms C Potter BSc (Hons) MSc
Dr J Shavila BSc (Hons) MSc PhD
Ms C Tsoulli BSc (Hons) MSc
Ms Frederique Uy BSc (Hons) MS

c (19th of November 2018.)

Declaration of members interests during the period of this report

Professor Alan Boobis OBE PhD CBiol FSB FBTS		
Personal Interest		**Non 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 ”		**Grants** Horizon 2020 EUROMIX Department of Health 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		**Non Personal Interest**
Employee Syngenta		None
Shareholder AstraZeneca **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		

Professor Janet Cade		
Personal Interest		**Non Personal Interest**
None		Kellogg - PhD student
Ms Jane Case		
Personal Interest		**Non Personal Interest**
Company Secretary of Muse Interiors **Shareholder** Standard Life Santander		None
Dr James Coulson		
Personal Interest		**Non Personal Interest**
None		**Membership** British Medical Association British Pharmacology Society British Toxicology Society National Trust Royal College of Physicians of London
Dr René Crevel		
Personal Interest		**Non Personal Interest**
Shareholder Unilever Centrica BG Group National Grid Lloyds		None
Employee Unilever		
Membership/affiliation ILSI Food Allergy Task Force: Chair		
Professor John Foster		
Personal Interest		**Non Personal Interest**
Dr Mark Graham		

Personal Interest		Non Personal Interest
Employee MG Toxicology Consulting Ltd		None

Dr Caroline Harris

Personal Interest		Non Personal Interest
Employee Exponent International Ltd		**Fellowships** Royal Society of Chemistry
Shareholder Exponent Inc		
Member International Union of Pure and Applied Chemistry		**Misc** Advisory Committee on Pesticides Steering Committee for ACROPOLIS

Professor Roy Harrison OBE, FRS

Personal Interest		Non Personal Interest
Employee University of Birmingham		**Member** 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)
Consultancy King Abdulaziz University (Saudi Arabia) Environment Agency		**Support by Industry** Jaguar Land Rover
Shareholder Halifax/Lloyds Renovare Fuels NQ Minerals AB Packaging		
Member Defra Air Quality Expert Group Dept. of Health Committee on the Medical Effects of Air Pollutants		

Dr Sarah Judge		
Personal Interest		**Non Personal Interest**
Employee Newcastle University		**Research Funding** National Institute for Health Research
Membership British Toxicology Society International Association for Neurotoxicology		
Professor Brian Lake		
Personal Interest		**Non Personal Interest**
Employee Part time Associate Toxicologist at Concept Life Sciences (CLS), Dundee, Scotland		**Member** British Toxicology Society National Trust Society of Toxicology (USA)
		Member of the editorial board Xenobiotica
		Misc Consultancy for CLS and other clients
Ms Juliet Rix		
Personal Interest		**Non Personal Interest**
None		None
Dr John Thompson		
Personal Interest		**Non Personal Interest**
None		None
Professor Mireille Toledano		
Personal Interest		**Non Personal Interest**
Professor Faith Williams		

Personal Interest		**Non Personal Interest**
Emeritus Professor of Toxicology, Institute of Cellular Medicine, The Medical School, Newcastle University		ILSI Working Group
		Current and recent research funding None

Professor Matthew Wright

Personal Interest		**Non Personal Interest**
Consultancies and Direct Employment Newcastle University		**Support by Industry** GSK
Membership BTS IVTS		**Miscellaneous** EFSA Toxicology – Associate Editor
Specific Interests Hepatology Toxicology		

COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Preface

I am pleased to present this report on the work of the Committee on Mutagenicity (COM) during 2018. 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 2018, the Committee worked on a number of topics:

It reviewed the genotoxicity data for electronic nicotine (or non-nicotine) delivery systems (E (N) NDS) in conjunction with the COT's work on this topic. It considered the implications of the safety evaluation carried out by European Food Safety Authority (EFSA} of some specific flavouring substances. It also responded to the EFSA consultation on 'Genotoxicity of Mixtures'. It evaluated recent experimental work on para-choroaniline (PCA).

It began a review of the COM's guidance series documents and considered scoping papers on the use of QSAR's to predict genotoxicity and a guidance update on the evaluation of in vivo genotoxicity assays.

It received a presentation on the CRISPR gene editing technology and discussed the potential genotoxicity associated with it and a statement from the joint committee workshop (COM/COC) on the use of epigenetics in chemical risk assessment was updated.

The Committee carried out its annual Horizon scanning exercise, identifying a number of 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 continued throughout 2018 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.

The COM maintains an awareness of the implications of Brexit on its work and is alert to the continuing uncertainty as to how the UK's regulatory environment and its relationships with international organisations will develop.

I again thank the secretariat for their exceptional support to the COM and to the members of the WRc/IeH team for the excellent work they delivered in 2018. I am, as always, 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.
Dr D.P. Lovell Chair
PhD BSc (Hons) FBS CStat CBiol CSci

ONGOING WORK

COM Guidance Series Update

2.1 The COM considered how to update the guidance on a strategy for genotoxicity testing of chemical substances. This guidance was last updated in 2011.

2.2 Members considered that there had been no significant changes to strategy developments or assay methodologies that merited a total re-write of the COM guidance presently. However, there are aspects which should be updated. Members considered the guidance in more detail and determined which areas would be updated (MUT/2018/09 and MUT/2018/13).

2.3 The committee considered two papers one on the use of (Q)SAR models to predict genotoxicity (MUT/2018/02) and a COM Guidance update – evaluation of in vivo genotoxicity (MUT/2018/03)

2.4 The COM had previously agreed that when no genotoxicity data were available an initial assessment of potential genotoxicity could be based on publicly available Structure Activity Relationships (SAR) and Quantitative Structure Activity Relationships (Q)SAR models. An initial investigation was undertaken to determine whether Stage 0 (Preliminary Considerations prior to genotoxicity testing) of the COM 2011 Guidance on a Strategy for genotoxicity testing of chemical substances needed to be amended and updated in relation to developments in (Q)SAR models. A scoping paper (MUT/2018/2) had been prepared that provided a brief summary of ten (Q)SAR models, covering knowledge-based, statistical and hybrid models. For each (Q)SAR model considered, information was collated on a range of topics, such as the endpoints covered, the size of the data set and any statistics applied to test the robustness of the model.

2.5 Concerns were raised over the lack of transparency of the data on which the various models were based and the impacts on subsequent predictions (e.g. relating to the proprietary nature of the data contained within many (Q)SAR models, the quality of the data and the chemicals included). The Committee suggested that it is often necessary to run several models, which may have differing quality. These issues will be considered further, and a statement will be produced as part of the update to the COM guidance.

2.6 MUT/2018/03 provided a summary of regulatory requirements relating to three *in vivo* genotoxicity assays, namely UDS, transgenic mutation and the comet assay and publications outlining significant changes since 2011. The COM guidance will be reviewed and published in sections to allow ease of update in the future. New sections on QSARs, 3D models, nanomaterial testing, and germ cell mutagens will be developed. These separate sections could be published on the COM website which would facilitate more frequent update as necessary rather than an overall Guidance document.

CRISPR gene editing technology - is there potential for genotoxicity?

2.7 Clustered Regularly Interspaced Short Palindromic Repeats, commonly abbreviated to CRISPR, are a series of specific repeated bacterial DNA sequences which are interspersed with viral DNA sequences following infection. The functions of CRISPR and CRISPR-associated (Cas) genes are essential in adaptive immunity in select bacteria and archaea, allowing the organisms to respond to and eliminate subsequent virus or plasmid infection.

2.8 subsequent virus or plasmid infection. These sequences are the basis of CRISPR technology which has been developed as a precise and efficient gene editing tool.

2.9 CRISPR technology, its application as a genome editing tool in human medicine and the potential for viral vector-mediated genotoxicity was discussed by the COM in June 2018 (MUT/2018/10). The COM considered CRISPR to be an interesting technique and expressed the need for an expert overview presentation before further consideration could be given. The specific issue the COM wanted to evaluate was the potential mutation hazard from this technology and any associated direct or indirect risk to human health.

2.10 Dr Mike Fellows from the Innovative Medicines & Early Development Biotech Unit at Astra Zeneca, UK, presented his research in this area to the COM in October 2018, in a presentation entitled 'Nucleotide therapeutics: preclinical safety case studies'. The development of precise genome editing techniques in general (including CRISPR) as research tools and the process by which these were being translated to the clinic were outlined, followed by a more detailed explanation of the mechanism behind the CRISPR/Cas9 methodology, which has applications to multiple types of genetic perturbations. It was emphasised that therapeutic CRISPR is still at an early stage and pre-clinical safety considerations surrounding the occurrence and consequences of off-target (as seen with gene therapy trials) and on-target effects will be crucial to the acceptance of the use of CRISPR. Currently used standard *in vitro* and *in vivo* genotoxicity assays are unsuitable for pre-clinical assessment, however more suitable approaches are being developed; these include bioinformatics analysis, next generation sequencing, detection of off target translocations and assessment of tumourogenicity using a humanised mouse model. It was considered that the safety paradigms adopted will depend on whether delivery of therapy is *ex vivo* or systemic. The importance of monitoring and adequate regulatory control of this technology was also highlighted.

2.11 Members agreed that the regulation of CRISPR technologies and associated guidelines was a requirement and acknowledged that efforts were being undertaken to put this in place in ICH guidance, for example. It was thought pragmatic to review and comment on such guidance when released, rather than produce a COM guidance document in the area.

2.12 Currently, there are issues in assessing the pre-clinical safety of the CRISPR technology, due to many of the existing standard techniques not being suitable as testing methods, however, more appropriate models are being developed. Members considered that these novel methods could also be valuable tools in the wider field of genotoxicity testing.

2.13 In conclusion, it was agreed that the COM should keep a watching brief on mutagenicity aspects, particularly those associated with environmental exposure.

Statement from a joint committee workshop on the use of epigenetics in chemical risk assessment - updated first draft

2.14 A joint meeting of COT, COC and COM held in 2017 discussed "Whether epigenetics should be used in chemical risk assessment?" A first draft statement (MUT/2018/04) from this joint committee meeting was discussed. One of the conclusions was that toxicological tests that are currently carried out are sufficient to detect toxicological changes, although it may be useful to further understand what tests would be available to investigate epigenetic changes. COM members considered how epigenetic endpoints may correlate with genotoxicity tests and how to extrapolate from in vivo data to humans. Members had no further comments on the update first draft of the statement.

COM EVALUATIONS

Consideration of the EFSA safety assessment of certain flavouring substances

2.15 This paper (MUT/2018/01) was considered as reserved business as it relates to commercially sensitive information.

2.16 The safety assessment of flavouring agents is carried out in the European Union by the European Food Safety Authority's (EFSA) Panel of Food Contact Materials, Enzymes, Flavourings and Processing Aids. EFSA experts assess the intake levels, absorption, metabolism and toxicity of flavouring substances, which are grouped into structurally related "flavouring groups". Toxicity data from one compound is often used to read-across to other structurally related substances. The views of the panel are published in the form of Flavouring Group Evaluations (FGE's). COM were asked to evaluate a specific flavouring where the FGE concluded it to be genotoxic. The use of historical controls as part of the evaluations as well as requests for further tests were discussed. The COM conclusions were used by FSA to inform their policy views and discussions.

2.17 Some of the general aspects from this evaluation initiated a discussion with experts in EFSA and led to a proposal for a workshop to discuss advances in genotoxicity testing.

EFSA consultation on genotoxicity of mixtures

2.18 The European Food Safety Authority (EFSA) launched a consultation on its draft Guidance statement on 'Genotoxicity assessment of chemical mixtures' in July 2018. COM submitted comments (MUT/2018/12). The members had concerns over the following *in vivo* test strategies in light of recommendations from the International Workshops on Genotoxicity Testing (IWGT) e.g. tissue selection; a recommendation that mixtures containing a large number of substances with positive *in vitro* results should be considered to be genotoxic without *in vivo* follow up testing; lack of consideration of concentrations of genotoxic substances (which is inconsistent with the EU Classification, Labelling and Packaging (CLP) regulations and guidance); use of dose addition when applying Margin of Exposure (MoE) or Threshold of Toxicological Concern (TTC) approaches i.e. different genotoxicants

in a mixture may have different modes of genotoxic action; no discussion of dose response modelling to determine a point of departure for *in vivo* genotoxicity data; a heavy reliance on hazard rather than risk; and lack of consideration of low levels of exposure to genotoxic substances as part of a mixture.

Review of the genotoxicity data for para-chloroaniline

2.19 The COM evaluated new data on the genotoxicity of para- chloroaniline (PCA) as positive for genotoxicity *in vivo*; however, insufficient information was available to distinguish whether the genotoxicity involved direct or indirect modes of action. The indirect genotoxic mode of action proposed was considered to be plausible, but further evidence is needed to demonstrate that this is the only mode of action.

E-cigarettes e(n)nds genotoxicity

2.20 The Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) considered the potential toxicological risks of electronic nicotine (or non-nicotine) delivery systems (E(N)NDS). COM considered the available papers on genotoxicity. The aim was for the COM to assess absolute risks from E(N)NDS and relative risk compared to conventional cigarettes, and if available to heated tobacco products (MUT/2018/08).

2.21 Members noted that studies sponsored by industry and conducted to OECD Test Guidelines showed negative results, whilst the non-test guideline studies, usually conducted independently of industry, generally reported positive results but did not show consistency and had not been repeated by other investigators. Members expressed concern that some studies reported genotoxicity only when wider toxic effects were also observed. It was possible to conclude that this limited evidence base did not indicate any specific mutagenic risks from E(N)NDS that were not observed with conventional cigarette products. However, members considered that greater consistency and demonstrable reproducibility in both product, exposure and methodologies were needed before any view could be taken on absolute risks of E(N)NDS products.

Horizon scanning

2.22 The COM undertakes an annual ‘Horizon Scanning’ exercise, which provides an opportunity for Members and assessors from Government Departments/Agencies to discuss and suggest topics for further work.

2.23 The COM members discussed future topics of interest. COM wish to keep a watching brief on the effects? of epigenetic changes in the germ-line and the transmission of epigenetic changes to the next generation. The COM guidance is in the process of being updated taking into account current advances in genotoxicity testing. Members expressed a concern over publication bias in that positive results are more likely to be published and these are in some cases given more weight as compared to negative results in regulatory studies.

2.24 The COM member Professor David Kirkland gave a presentation on evaluations conducted by a working group of the IWGT (International Workshops on Genotoxicity Testing) on *in vivo* genotoxicity testing strategies. The IWGT came to a number of conclusions, such as if there was systemic exposure to an *in vivo* mutagen, then a positive genotoxic response would be detected by use of a combination of the bone marrow micronucleus test and a liver comet test. Also, when systemic exposure to a substance did not occur, then a sample from a single tissue in the GI tract (e.g. the duodenum in a comet assay) would be sufficient to detect a gastrointestinal site of contact *in vivo* mutagen. The COM would continue to consider strategies for *in vivo* genotoxicity testing and explore ways of harmonising the approach to *in vivo* genotoxicity testing.

OECD test guidelines

2.25 The OECD will re-initiate Project 4.95 – A Guidance document on the adaptation of *in vitro* mammalian cell-based genotoxicity Test Guidelines for testing manufactured nanomaterials. The OECD is intending to hold a meeting in January or February in 2019 to discuss, COM will keep abreast of developments.

GUIDANCE STATEMENTS

None

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

DECLARATION OF INTERESTS DURING THE PERIOD OF THIS REPORT
(1st January 2018 to 31st December 2018)

	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Dr David Lovell PhD BSc (Hons) FSS FIBiol CStat CBiol (Chair)	National Grid	Shareholder		
	Pfizer	Pension Scheme Member		
	HESI GTTC	Committee Member		
	Biometrics Society	Member		
	AstraZeneca	Spouse Shareholder		
	National Grid plc	Spouse Shareholder		
	British Toxicology Society (BTS)	Member		
	Genetics Society	Member		
	Royal Society of Biology (CBiol FRSB, 2003)	Member		

	Laboratory Animal Science Association (LASA)	Member		
	Royal Statistical Society	Member		
	Statisticians in the Pharmaceutical Industry (PSI)	Member		
	United Kingdon Environment Mutagen Society (UKEMS)	Member		
	Board Member of the UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs)	Member		
	MRC EMINENT Project Review Board	Member		
Dr Carol Beevers	Covance (Jan – Aug)	Salary Pension Employee	None	None
	Exponent (Sept – Dec)	Salary Pension Employee		
	ILSI HESI	Workgroup member		
	OECD	Workgroup member		
	United Kingdom Environmental Mutagen Society (UKEMS)	Member		
Dr Gill Clare	Covance	Consultant	None	None
	AstraZeneca	Shareholder		
	Diageo	Shareholder		
	Marks and Spencer	Shareholder		
	Shell Research Ltd	Pension		
	AstraZeneca	Pension		
	United Kingdom Environmental Mutagen Society (UKEMS)	Member		
Dr Stephen Dean	WIL Research, Europe (Jan – March 2016)	Salary Employee Equity Holder		
	UKEMS	Member		
	Standard Life	Shareholder		
	Society of Toxicology	Member		
	Scientific Services for Agenda Life Sciences	Director		

Prof Shareen Doak	United Kingdom Environmental Mutagen Society (UKEMS)	Member	Unilever	PhD Studentship Grants 2017 – 2020
	British Association for Cancer Research (BACR)	Member	AstraZeneca	PhD Studentship Grants 2009 – 2016
	Royal Society of Biology (FRSB)	Member	Unilever	PhD Studentship Grants 2010 – 2017
	ILSI HESI	Committee Member	Hoffman-LaRoche	Research Grant 2008 – 2010
	British Toxicology Society (BTS)	Member	Unilever	Research Grant 2008 – 2010
Mrs Philippa Hardwick	Unilever plc	Pension	None	None
Professor David Harrison	University of Canberra	Consultant	Melville Trust (cancer research charity)	Trustee
	University of Florida	Consultant	Families First St Andrew's (children's charity)	Trustee Director
	University of Dundee	External examiner	Gene Therapy Consortium (funded by Wellcome Trust)	Unpaid external scientific advisor
	Ryboquin Ltd, UK	Consultant, Shareholder	Systems Biology Ireland	Unpaid external scientific advisor
	Cytosystems Ltd, UK	Consultant	iCAIRD research consortium	Director (unpaid role)
	Cunningham Trust (registered charity)	Scientific Adviser		
	Avipero Ltd, UK	Shareholder		
	Ryboquin Ltd, UK	Shareholder and Director		
	Benenox Ltd, UK	Shareholder and Director		
	Pneumagen Ltd, UK	Consultant		
	Aquila Ltd, UK	Consultant		
	NuCana Biomedical, UK	Part time employee		
	Definiens AG	Advisor		
	University of St Andrews, UK	Salary		
	University of Edinburgh, UK	Honorary Professor Consultant		
	University of Glasgow, UK	Visiting Professor		
Prof Gareth Jenkins	None	None	Unilever	Research Grant 2008 – 2010
Prof David Kirkland	Kirkland Consulting	Principal	None	None
	Saga	Shareholder		
	ILSI HESI	Steering Committee Member and Workgroup Leader		

	ILSI Europe Packaging Materials Task Force	Task Force member		
Prof Francis Martin (To 31 March 2018)	ReVivoCell Ltd	Shareholder and Chief Scientific Officer	Crown Paints	Consultancy 2016/2017
	Biocel Ltd	Shareholder and joint Director	Unilever	PhD Studentship 2014 - 2018
			Barfoots	PhD Studentship 2016 - 2019
Dr Michael O'Donovan	O'Donovan GT Consulting Ltd	Director	None	None
	Apconix	Associate		
	AstraZenca	Pension Scheme Member		
	BASF	Pension Scheme Member		
Dr Andrew Povey	UK Molecular Epidemiology Group (UK-MEG)	Member	RTZ	Departmental Research Grant
	UK Environmental Mutagen Society (UKEMS)	Member		
	American Association for Cancer Research (AACR)	Member		
	Molecular Epidemiology Group (MEG)	Member		
	British Association for Cancer Research (BACR)	Member		
	European Crop Protection Agency	Part of Consortium recently awarded grant on exposure assessment		
	Lloyds	Shareholder		
	Standard Life	Shareholder		
	Halifax	Shareholder		
	Santander	Partner shareholder		
	Norwich Union	Partner shareholder		
	Roadchef Topco Limited	Partner shareholder		
Prof Helga Drummond (To 14 February 2018)	None		None	
Dr Ruth Morse	United Kingdom Environmental Mutagen Society	Member	Medical Research Council with AstraZeneca (ITTP programme)	PhD studentship collaborative grant 2015-2020
	British Society of Toxicology	Member	TETFUND, Ebonyi State University	PhD studentship 2014-2019

	Genetics Society	Member	Petroleum Technology Fund, Nigeria	PhD studentship 2016-2020
Mr Amit Bhagwat	None	None	None	None

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).

The COC held two meetings in 2018 and discussed a range of topics from electronic nicotine (and non-nicotine) deliver systems (E(N)NDS or e-cigarettes) to assessing the effects of combined exposures to chemicals. At the meeting in November, Professor Nigel Gooderham from Imperial College London presented to the Committee to begin consideration on the effect of the immune system and stromal cells on cancer risk.

I wish to extend my gratitude to all the Members of the Committee with whom I have worked this year, to the expertise of the Secretariat and staff at the National Centre for Environmental Toxicology at WRc plc and IEH Consulting. I also wish to extend special thanks to Dr Peter Greaves who finished his third term of office on the Committee this year and has given 9 years of dedicated service.

Professor David Harrison
MD DSc FRCPath FRCPEd FRCSEd

COC Evaluations

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

3.1 The COC assessed the available data with respect to carcinogenicity as part of the COT assessment of the relative and absolute toxicological risks from E(N)NDS compared to conventional cigarettes, and where feasible heated tobacco products.

3.2 The Committee raised concern around the use of flavourings in E(N)NDS products and queried whether there was an 'approved' list for use in such products. The extent of carcinogenicity testing of the flavourings via the inhalation route was considered as a potential issue, with most testing presumed to be by the oral route. In addition, thermal decomposition of flavourings and other materials was a potential risk, though it was difficult to draw any conclusions on relative risks compared to conventional cigarettes based on the available evidence.

3.3 It was noted that the risk to new users taking up the use of E(N)NDS products had not been considered. One paper had compared the risk associated with using conventional cigarettes, heated tobacco products and E(N)NDS products. The Committee considered that the risk for tobacco-containing products was implicit to the user as tobacco does not need to be heated to be carcinogenic. For E(N)NDS products, the available evidence suggested that nicotine itself was not a carcinogen.

3.4 There was some discussion on the potential risks to bystanders from exhaled aerosols and whether there was a difference between second hand smoke from conventional cigarettes when compared to E(N)NDS products. It was noted that only limited data were available on this topic.

3.5 The COC 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.

Presentation on Immunological and stromal cell modulations relevant to cancer risk by Professor Nigel Gooderham

3.6 The COC is currently considering the wider role of immunomodulation in cancer development. As an initial step in these considerations, Professor Nigel Gooderham from Imperial College, London, presented his research in the area of metabolism and its interaction with the inflammatory system in cancer to the COC in November 2018.

3.7 In a presentation entitled 'Immunological and stromal cell modulations relevant to cancer risk', Professor Gooderham outlined his early research investigating a possible link between the exposure of humans to heterocyclic amines (HAs) from cooked meat in the diet and

colon cancer. He outlined the hypothesis that the genotoxicity of the metabolites of HAs absorbed from cooked meat in the diet was a major driver for colorectal cancer. However, this hypothesis was not supported by the findings of a study of 500 incident colon cancer cases in which patients showed depressed hepatic cytochrome P450 activity (involved in HA metabolism), probably as a result of systemic infection and inflammation.

3.8 The above mentioned finding led to further investigations of the 500 incident colon cancer cases and the effects of HAs on the immune system. Increased expression of CYP1B1 and 2E1 was demonstrated, both of which are involved in carcinogen metabolism, in tumour tissue, and a distinct inflammatory microenvironment, with a number of pro-inflammatory cytokines (COX-2, IL-1 β , IL-6, NF-kB-p65) being elevated. One of these, IL-6, was known to induce tumour CYP2E1 via the activation of JAK2 and STAT3 and mediated tumour CYP1B1 induction by reducing the expression of miR27b, an inhibitor of CYP1B1, to relieve its inhibition. Within the tumour microenvironment, IL-6 mediated immune and epithelial cancer cell cross-talk via miRNA and cytokines to sustain chronic inflammation and promote pro-metastatic cancer cell behaviour. In addition, miRNAs were indicative of a tissue-specific response making them good biomarkers. It was suggested that CYP1B1, 2E1, IL-6, the JAK/STAT pathway and IL-6-mediated miRNAs could be therapeutic opportunities for colorectal cancer.

3.9 The Committee considered that there might be value in further investigation of the utility of miRNAs for the diagnosis of early stages of disease, for example as part of ongoing epidemiology studies or by the screening of samples collated as part of the BioBank initiative. In addition, it was questioned whether or not elevated levels of miRNAs in pre-tumour tissue indicate a causal mechanism in tumour development and provide therapeutic opportunities. It was recognised that the gut microbiome may have some effect on the miRNA profile in patients as the gut microbiome had its own miRNAs; however, the function of gut microbiome miRNAs had not yet been established.

3.10 In conclusion, it was agreed that the presentation had been and excellent introduction and that the COC would investigate further aspects of the role of immunomodulation in cancer in due course.

Horizon scanning

3.11 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.

3.12 In 2018, the Committee considered the list of topics of interest from 2017, and discussed potential new topics on the microbiome and follow up to the Synthesising Epidemiological Evidence subgroup of the COT and COC on integrating epidemiological and toxicological evidence. Additional interest was also noted in unusually potent non-genotoxic carcinogens, for which BRAF inhibitors and pioglitazone could be examples.

3.13 Following this discussion, the list of COC priority topics (in no specific order) was:

- Immunological and stromal cell modulations relevant to cancer risk – to continue discussion from November 2018
- Presentation to provide background on the microbiome
- Unusually potent non-genotoxic carcinogens
- Integrating toxicological and epidemiological evidence, with COT as follow up to SEES subgroup
- Nanomaterials
- Mechanisms incorporating genomics and the Cancer Genome Atlas
- Effect of early life exposure to cigarettes, depending on COT deliberations on developmental effects of nicotine
- *In vitro* systems - to be undertaken when resource allows

3.14 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 synthesising epidemiological evidence

3.15 Following the COC consideration of the draft report from the subgroup in 2017, the report was published in 2018 and its conclusions presented at EUROTOX. More information can be found in the COT section of this report (para 1.129).

Guidance statements

3.16 The Committee continued to develop the guidance statement series during 2018. Updates were agreed for five papers in the series: Hazard identification and characterisation: conduct and interpretation of animal carcinogenicity studies (G03), The use of biomarkers in carcinogenic risk assessment (G04), Defining a point of departure and potency estimates in carcinogenic dose response (G05), Risk characterisation methods (G06), and Alternatives to the 2-year bioassay (G07). In addition, a non-technical introduction to the series of statements, written in plain English, was agreed.

3.17 Further discussion papers on developing a framework for consideration of risk due to less than lifetime exposures were discussed. Two papers on effects of combined exposures to chemical carcinogens were also considered. Both these are expected to become guidance in 2019.

3.18 These developments, updates and revisions to the guidance statements will continue to be addressed in 2019.

2018 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

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

MEMBERS

Mr Derek Bodey MA
Public Interest Representative

Dr Gill Clare BSc PhD
Independent Consultant

Dr John Doe PhD DipRCPath
Consultant in Toxicology, Parker Doe Partnership

Dr Peter Greaves MBChB FRCPath (until 31st March 2018)
Consultant Pathologist and Honorary Senior Lecturer, University of Leicester

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

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

Professor Neil Pearce BSc DipSci DipORS PhD DSc FRSNZ FMedSci FFPH
Professor of Epidemiology and Biostatistics, London School of Hygiene and Tropical Medicine

Dr Christopher Powell BSc PhD DipRC Path FRC Path FBTS FRSB
Vice President Safety Assessment, GlaxoSmithKline

Dr Lesley Rushton OBE BA MSc PhD CStat
Emeritus Reader in Occupational Epidemiology, Imperial College London

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

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

Professor Saman Warnakulasuriya BDS, FDSRCS, DipOralMed, PhD, DSc
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
Mrs N Blowfield	Administrative Secretary

DECLARATION OF INTERESTS DURING THE PERIOD OF THIS REPORT

Member	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Professor David Harrison	University of Canberra	Consultant	Melville Trust (cancer research charity)	Trustee
	University of Florida	Consultant	Families First St Andrew's (children's charity)	Trustee Director
	University of Dundee	External examiner	Gene Therapy Consortium (funded by Wellcome Trust)	Unpaid external scientific advisor
	Ryboquin Ltd, UK	Consultant, Shareholder	Systems Biology Ireland	Unpaid external scientific advisor
	Cytosystems Ltd, UK	Consultant	iCAIRD research consortium	Director (unpaid role)
	Cunningham Trust (registered charity)	Scientific Adviser		
	Avipero Ltd, UK	Shareholder		
	Ryboquin Ltd, UK	Shareholder and Director		
	Benenox Ltd, UK	Shareholder and Director		
	Pneumagen Ltd, UK	Consultant		
	Aquila Ltd, UK	Consultant		
	NuCana Biomedical, UK	Part time employee		
	Definiens AG	Advisor		
	University of St Andrews, UK	Salary		
	University of Edinburgh, UK	Honorary Professor Consultant		
	University of Glasgow, UK	Visiting Professor		
Mr Derek Bodey	None		None	
Dr Gill Clare	Covance	Consultant	None	None
	AstraZeneca	Shareholder		
	Diageo	Shareholder		
	Marks and Spencer	Shareholder		
	Shell Research Ltd	Pension		
	AstraZeneca	Pension		
	United Kingdom Environmental Mutagen Society (UKEMS)	Member		
Member	**Personal Interest**	**Non-Personal Interest**	**Member**	**Personal Interest**

Dr John Doe	Parker Doe Partnership	Partner		
	Concept Life Sciences	Consultant		
	Syngenta	Pension		
	ECETOC	Consultant		
	Syngenta	Consultant		
Dr Peter Greaves (to 31 March 2018)	AstraZeneca, Cambridge	Consultant		
	Bristol-Myers Squibb, Princeton, NJ, USA	Consultant		
	Eisai Inc, Woodclife Lake, NJ, USA	Consultant		
	Scynexis Inc, Jersey City, NJ, USA	Consultant		
	Pioneer HI BRED International, USA			
	Novo Nordisk A/S, Måløv, Denmark	Consultant		
	UCB Biopharma SA, Brussels, Belgium	Consultant		
	Verona Pharma Plc, London	Consultant		
Dr Richard Haworth (Co-Opted Member from 8 November 2018)	GlaxoSmithKline	Shareholder and Salary	None	None
	British Society of Toxicological Pathology	Member		
	Royal Dutch Shell	Spouse shareholder		
	United Utilities	Spouse shareholder		
Dr Ray Kemp	Ray Kemp Consulting	Shareholder		

Member	Personal Interest	Non-Personal Interest	Member	Personal Interest
Dr David Lovell	National Grid	Shareholder		
	Pfizer	Pension Scheme Member		
	HESI GTTC	Committee Member		
	Biometrics Society	Member		
	AstraZeneca	Spouse Shareholder		
	National Grid plc	Spouse Shareholder		
	British Toxicology Society (BTS)	Member		
	Genetics Society	Member		
	Royal Society of Biology (CBiol FRSB, 2003)	Member		
	Laboratory Animal Science Association (LASA)	Member		
	Royal Statistical Society	Member		
	Statisticians in the Pharmaceutical Industry (PSI)	Member		
	United Kingdon Environment Mutagen Society (UKEMS)	Member		
	Board Member of the UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs)	Member		
	MRC EMINENT Project Review Board	Member		
Professor Neil Pearce	None	None	None	None
Dr Christopher J Powell	GlaxoSmithKline	Shareholder and Salary	None	None
	British Toxicology Society	President		

Member	Personal Interest	Non-Personal Interest	Member	Personal Interest
Dr Lesley Rushton	Review of Global Burden of unsafe water, unsafe sanitation, unsafe hygiene and lead in water	Consultancy	IEH Consulting Ltd	Research Support
	Industrial Injuries Advisory Council	Chair		
	HSE Science, Engineering and Environmental Assurance Committee (SEAC)	Member		
Professor Heather Wallace	Bank Santander SA	Shareholder		
	EFSA	Contam Panel		
	BT Group	Shareholder		
	NovaBiotics	Shareholder		
	Antoxis	Shareholder		
	Cell ProTx	Director		
	EUROTOX	President		
	Paediatric Medicines Expert Advisory Group – MHRA	Member		
	Herbal Medicines Advisory Committee – MHRA	Member		
	Medical Research Scotland	Trustee		
Dr Rosemary Waring	Centrica and National Grid	Shareholder	None	None
	Tharos	Director and Shareholder		
	Ateria Health	Shareholder		
Professor Kasturi Warnakulasuriya	National Grid plc	Shareholder	Oral Health Foundation	Panel member
	Post Office Ltd	Shareholder	Cancer Research UK	Advisory