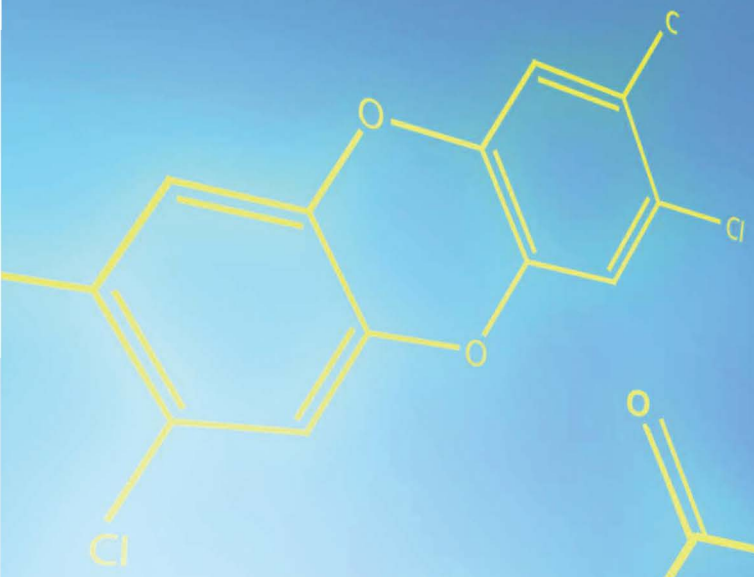
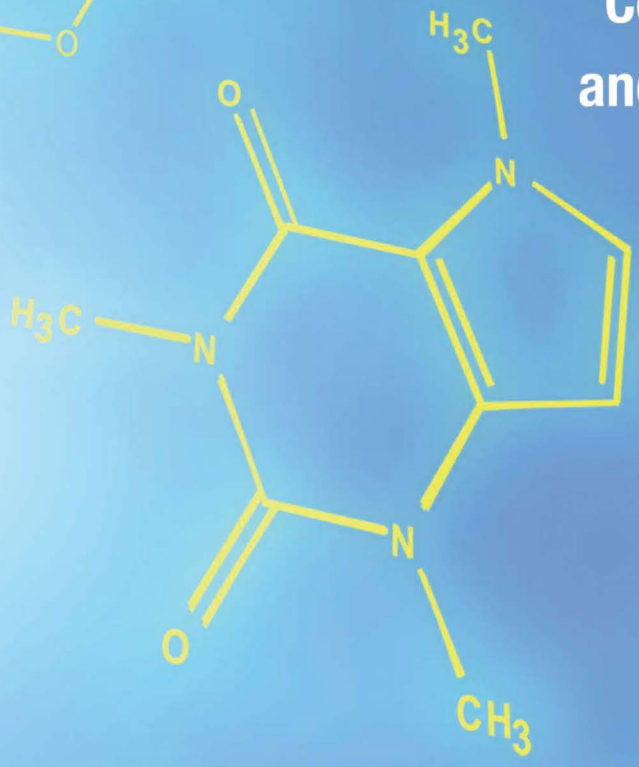
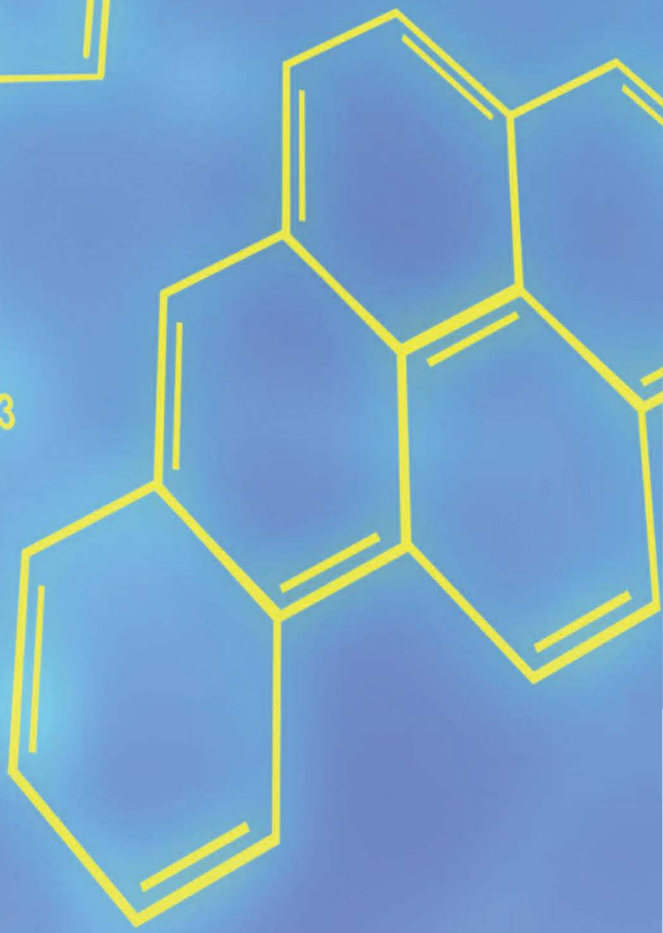
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment







Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2017

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

Annual Report 2017

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About the Committees

This is the twenty-sixth 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 – ACP).

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 2017. 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, 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 which included two joint meetings with COC and COM. The first of these was a joint session on heat not burn tobacco products and the second a workshop on epigenetics combined with a joint Committee horizon scanning session. There was also an urgent request for advice during the year with a request during August to peer review the FSA's risk assessment of Fipronil in eggs and egg products.

The Committee said goodbye to several long serving members during the year and I would like to express my thanks to Dr Nick Plant, Mr Derek Bodey, Professor Rob Smith, Dr Anna Hansell, Professor David Harrison, Professor Brian Houston and Professor Ian Morris for their many and varied contributions over the years. We also said a fond farewell to Dr Diane Benford, who retired from the Food Standards Agency in May having been Scientific Secretary since 2000. Unfortunately, we were unable to say goodbye to Diane personally as she was still recovering from the serious injuries she suffered in a road traffic accident earlier in the year. I would like to put on record the committee's appreciation of Diane's dedicated and professional support of the Committee over her whole time as Scientific Secretary.

Of course, whilst goodbyes may be sad they are balanced by welcoming new members appointed to the Committee bringing with them different skills and perspectives. I was therefore pleased to welcome Professor John Foster, Professor Matthew Wright, Dr Phil Botham and Dr Sarah Judge as new specialist members and Ms Juliet Rix and Ms Jane Case as our new public interest representatives.

From the completed and on-going work described in this report, I would like to highlight several joint pieces of work which have either drawn on complementary skills and knowledge of our sister Committees (COC and COM) or the various pieces of work with the Scientific Advisory Committee on Nutrition which have allowed us to combine our individual outputs on risk (COT) and benefit (SACN) into agreed risk benefit evaluations. These risk benefit evaluations have provided risk managers with robust scientific summaries of the weight of evidence and the associated uncertainties which should have made their evaluation of options easier. We have also been pleased to welcome Professor Peter Aggett's contribution as a conduit between ourselves and SACN on the infant diet work improving communication and minimising misunderstandings.

I would like to acknowledge the contribution of our joint Secretariat from the Food Standards Agency and Public Health England in a challenging year which allowed the Committee to focus our attention on the critical questions.

Finally, I would like to thank all members of the Committee and the secretariat for their support and hard work over the year. It helped make my task as chair much easier.

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

COT evaluations

Iodine in the diet of infants and young children

1.1 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 young children (aged 1-5 years). This statement addresses the risks from high levels of iodine in the diet of young children aged 0-5 years. This statement does not look at risks associated with insufficient intakes of iodine.

1.2 Iodine is an essential nutrient in the human diet, required for the production of thyroid hormones. These hormones are necessary for cell metabolism, growth and development at all stages of life. The most obvious sign of iodine deficiency is goitre – an enlargement of the thyroid gland in the neck but other, more subtle effects can be noted, in IQ and physical development, at lower levels of deficiency.

1.3 The consequences of too much iodine vary considerably between individuals. The adult thyroid gland secretes about 80 µg thyroxine per day which requires a dietary intake of between 100 and 150 µg/day of iodine. Humans have a number of mechanisms by which they can counter an excess of iodine. Most people can tolerate a chronic excess of iodine of up to 2 g of iodine per day but there will be some individuals who experience effects at much lower levels, close to the upper recommended limit for intake.

1.4 Some sensitive individuals with pre-existing thyroid conditions can experience hypothyroidism (reduced production of thyroid hormones by the thyroid gland) following excess iodine in the diet. The iodine status of an individual will also affect the consequences of excess iodine. The normal thyroid gland will adapt relatively easily to excess iodine. Populations who are slightly iodine-deficient can experience hyperthyroidism (excessive production of thyroid hormones by the thyroid gland), with even low-level increases in iodine intake. The mechanism for this is still uncertain.

1.5 The richest dietary sources of iodine are marine fish, sea salt and cows' milk with children having a greater iodine intake than adults due to their higher intake of cows' milk.

1.6 The Committee looked at a range of scientific papers and an assessment of dietary intakes for children aged 0-12 months and 1-5 years. They concluded that some sectors of the population may be at risk from the effects of excess iodine in the diet. These include exclusively formula-fed infants and high-level consumers at all age groups except breast-fed infants.

1.7 Overall the COT concluded that some children may be exposed to levels of iodine that may cause adverse effects. However, the Committee also noted that the window between iodine deficiency and excess intake was very narrow and measures to reduce exposure in some targeted groups may increase the proportion of children receiving inadequate iodine which would also be detrimental. Members highlighted the need for the COT to work closely with the Scientific Advisory Committee on Nutrition to ensure that advice on iodine to government was suitably co-ordinated.

1.8 The full COT statement can be found at: https://admin.food.gov.uk/sites/default/files/statementiodine0to5.pdf

Heat-not-burn tobacco products and their safety

1.9 The COT, with support from the COC and the COM, was requested to assess the toxicological risks from novel heat-not-burn tobacco products, and compare these risks to those from conventional cigarettes.

1.10 To date, two novel heat-not-burn tobacco products have been notified to PHE in accordance with the Tobacco and Related Products Regulations 2016.

1.11 In heat-not-burn tobacco products, processed tobacco is heated in a controlled device instead of being burnt as is the case for conventional tobacco products.

1.12 A recent consultation by HM Treasury noted there is a range of heat-not-burn tobacco products where:

a. processed tobacco is heated directly to produce vapour

b. processed tobacco is designed to be heated in a vaporiser

c. devices produce vapour from non-tobacco sources, where the vapour is then passed over processed tobacco in order to flavour the vapour

1.13 The two products assessed by the Committees fall into the first and last of these groups, and as a result the temperature to which the tobacco is heated varies considerably between them. For one product where the tobacco is heated directly, a maximum heating temperature of up to 350 °C was reported, while for the other product in which the tobacco is heated by a vapour, the maximum temperature of the tobacco was reported to be less than 50 °C. For comparison, when tobacco in cigarettes is burnt it reaches temperatures of at least 800 °C.

1.14 The two manufacturers of products notified in the UK before November 2016 were asked to present the relevant toxicity data they hold. In addition to the

manufacturers' data, a literature search was undertaken to identify any available independent data on these products. This was very limited.

1.15 Investigations on both products that were assessed by the Committees, showed a decrease in the harmful and potentially harmful compounds (HPHCs) to which the user would be exposed, compared to the HPHCs from a conventional cigarette. For both products, there were some HPHCs where the reduction was approximately 50%, and the reduction in other HPHCs was greater than 90%.

1.16 The Committees also requested data on additional contaminants from the devices themselves. The available data presented and discussed with the manufacturers provided no evidence for exposures other than from compounds also present in conventional cigarette smoke.

1.17 The design of the devices means that any potential sidestream emissions from them will be very different to those from the burning tip of conventional cigarettes. In terms of environmental exposure to bystanders, assessments showed that while some of the measured components increased above background with the use of the heat-not-burn tobacco products, much greater increases occurred following use of conventional cigarettes.

1.18 In compiling the list of information requested by the Committees for this evaluation, there was a focus on cancer, respiratory, cardiovascular and liver-related health effects.

1.19 Both products are already available on the market in the UK and other countries around the world. Post-marketing surveillance is being undertaken by both manufacturers in these countries, but it is too early for epidemiological information on health impacts to be available.

1.20 A number of differences were identified between the two products notified in the UK, the most obvious being the temperature to which the tobacco is heated, which will potentially have an impact on the number and amount of compounds that thereby become volatile and can be inhaled by the user. There is also a difference in the source of the nicotine. In the product where the tobacco is heated directly, the nicotine is derived from the tobacco in the device, while for the other product the nicotine is present within the liquid that is aerosolised and passed through the tobacco.

1.21 The Committees were unable to assess the absolute risk of heat-not-burn tobacco products given the nature of the data available.

1.22 The data indicated that the aerosol generated from these products contains HPHCs, some of which are mutagenic and carcinogenic, and therefore there will be some risk to health from use of these products. The normal recommendation of the Committees is that exposure to such chemicals is kept as low as reasonably

practicable, but it was recognised that these products could provide harm reduction for people who would otherwise smoke cigarettes.

1.23 There would likely be a reduction in risk for conventional smokers deciding to use heat-not-burn tobacco products instead of smoking cigarettes. However, stopping smoking entirely would lead to the greater reduction in risk.

1.24 A reduction in risk would also be experienced by bystanders where smokers switch to heat-not-burn tobacco products.

1.25 The Committees were concerned over the potential for non-smokers including children and young people, who would not otherwise start to smoke cigarettes, to take up using these products, as they are not without risk. There was also concern over whether the use of these products would lead to cigarette smoking by non-smokers. Information on this should be obtained before the overall impact on public health can be assessed.

1.26 The data considered by the Committees was not sufficient to comment on the relative risks of heat-not-burn tobacco products and e-cigarettes, though this is of interest.

1.27 The Committees considered the potential risks from use of these products during pregnancy. The current UK advice to pregnant women is to stop smoking entirely. However, the advice states: “If using an e-cigarette helps you to stop smoking, it is much safer for you and your baby than continuing to smoke”. There is no direct data on the risk to the unborn child following use of heat-not-burn tobacco products by the mother. Based on reduced exposure to compounds of concern with heat-not-burn tobacco products compared to conventional cigarettes, the Committees considered that, though the aim should be for pregnant women to stop smoking entirely, the risk to the unborn baby is likely to be reduced if using these products during pregnancy instead of smoking.

1.28 The Committees emphasised that nicotine itself is addictive, and can have harmful effects on health. In addition, users of any nicotine product would use it in such a way, and in such quantity, as to achieve a similar effect to that they were used to from their previous smoking products. Depending on the concentrations of nicotine in different products, relative exposure to other compounds of concern could be increased or decreased in the process of achieving the desired nicotine effect. For example, a user might take a fewer or greater number of puffs, or use these products more often or for longer than they did with conventional cigarettes.

1.29 It is well recognised that using tobacco is carcinogenic and its use has other harmful effects on human health.

1.30 Using heat-not-burn tobacco products involves breathing in a number of compounds of concern, some of which are carcinogens.

1.31 The levels of the different compounds in the aerosol from heat-not-burn tobacco products are different to the levels in smoke from conventional cigarettes.

1.32 Heat-not-burn tobacco products contain nicotine and are designed to deliver similar levels of nicotine to conventional cigarettes; their use will not reduce nicotine exposure or the risk to health from and possibility of addiction to nicotine.

1.33 The Committees conclude that there will be a risk to health from using heat-not-burn tobacco products.

1.34 It is currently not possible to quantify this risk. Heat-not-burn tobacco products are new and there is insufficient data available to enable a full assessment.

1.35 The exposure to compounds of concern in using heat-not-burn tobacco products is reduced compared to that from conventional cigarette smoke. It is likely that there is a reduction in overall risk to health for conventional smokers who switch to heat-not-burn tobacco products.

1.36 While the Committees conclude there is a likely reduction in risk for smokers switching to heat-not-burn tobacco products, a risk remains and it would be more beneficial for smokers to quit smoking entirely.

1.37 A reduction in risk would be expected to be experienced by bystanders where smokers switch to heat-not-burn tobacco products.

1.38 The risk to the unborn child from use of these products by mothers during pregnancy is difficult to quantify and current NHS advice is to stop smoking entirely. The Committees consider that the risk to the unborn baby is likely to be reduced if these products were used during pregnancy instead of smoking, although the aim should be to stop smoking entirely.

1.39 Overall, the Committees conclude there are toxicological risks from novel heat-not-burn tobacco products though data on impacts to human health is very limited. Compared with the known risks from conventional cigarettes, they are probably less harmful. Even so, smokers would do better to quit entirely.

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

PBDE's in the diet of infants and young children (Addendum)

1.41 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 young children (aged 1-5 years). This addendum addresses the risks from high levels of

polybrominated diphenyl esters (PBDEs) in the diet of young children aged 1-5 years and updates conclusions on infants aged 0-12 months, who were considered in the previous COT statement.

1.42 Technical mixtures of PBDEs have been widely used as flame retardants incorporated in polymers and textiles, construction materials, furniture, and electrical equipment. International agreements on bans and regulations on production and use of technical mixtures of PBDEs have been introduced since 2004, leading to declining levels in the environment. However some PBDE congeners are especially persistent in the environment.

1.43 Food is the main source of exposure to PBDEs in the general population. Infants can be exposed to such chemicals through their presence in breast milk as well as other foods, and in dust.

1.44 No new data have been published on the safety of PBDEs since the previous statement in 2015. From the data that are available, there is evidence in experimental animals for effects on the liver, thyroid hormones, and the reproductive and nervous systems. Observations in human populations have not given consistent results, and do not allow conclusions on the levels of exposure at which adverse effects could occur.

1.45 The available data are insufficient to establish health-based guidance values, for PBDEs, and as an alternative, the COT considered the ratios between the highest doses that had been found not to cause adverse effects in animal studies (reference points) and the estimated exposures of infants and young children. Such ratios are known as “margins of exposure” (MOEs), and their interpretation should take into account uncertainties in the toxicological database, in extrapolation from animals to humans, and in the estimation of exposures.

1.46 The 2015 COT statement indicated a possible concern with respect to exposure of infants to BDE-99 and (to a lesser extent) BDE-153 from food, other than commercial infant food. The current analysis indicated that exposure of young children aged 1-5 years to these PBDEs from such food was unlikely to be a health concern.

1.47 Since the previous statement, new data have become available on PBDEs in infant formula and commercially produced infant foods. Exposures from these products are lower than from breast milk and are unlikely to be a health concern.

1.48 This new analysis for young children indicates a potential concern for BDE-99 and -153 exposures from breast milk at age 12-18 months, and for exposure to BDE-99 and -209 in dust and soil in children aged 1-5 years. These conclusions are consistent with the 2015 COT statement relating to infant exposure.

1.49 This does not necessarily imply that toxicity is occurring and the absence of clear evidence for adverse effects in epidemiological studies gives some reassurance. Nevertheless, the risk assessment does not give the assurance of safety that would be desirable.

1.50 Given that most uses of PBDEs have been phased out, and that the main dietary sources of exposure to residual environmental PBDEs are breast milk and dairy products, options for reducing exposure are limited. A priority for further research is continued monitoring of PBDEs in breast milk and food to check that levels are declining as expected.

1.51 The 2015 COT statement can be found at: https://cot.food.gov.uk/sites/default/files/PBDEstatementfinal.pdf

1.52 The 2017 COT addendum can be found at: https://cot.food.gov.uk/sites/default/files/statementpbdes.pdf

Potassium-based replacements for sodium chloride and sodium-based additives

1.53 In order to reduce blood pressure and numbers of strokes in the population, the government is committed to reducing the intake of sodium from food. Sodium is present in both table salt and in a number of food additives such as raising agents and preservatives.

1.54 As part of the sodium reduction strategy, manufacturers have been encouraged to reduce the sodium in food by reformulating their products. However, the food industry have stated that it would be very difficult to reduce added sodium any further by changing recipes, because in some foods, sodium compounds have a function other than providing a salty taste. Hence, industry would like to use potassium based replacements for the sodium compounds. This has not been previously recommended because it was felt that it would be better that consumers gradually became used to less salty foods and because there were concerns that the increase in potassium could be harmful for people with reduced kidney function. However, it is possible that use of potassium based replacements for sodium compounds would enable further reductions in the amount of added sodium in some foods.

1.55 The UK Government's Scientific Advisory Committee on Nutrition (SACN) were asked to consider the use of potassium replacements for sodium and as part of this process they asked the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to assess the safety of using potassium based replacements for sodium.

1.56 Potassium is important for the correct functioning of cells, particularly heart and nerve cells. Blood potassium is kept under tight control by the body with excess potassium being rapidly excreted in urine via the kidney.

1.57 If kidney function is reduced and the excess potassium cannot be excreted, levels of potassium in the blood begin to increase; this is known as hyperkalaemia. The organs affected by hyperkalaemia are the heart, nerves and muscles and the gastrointestinal system. Patients may complain of vague feelings of not feeling well, gastrointestinal symptoms or generalised weakness. At higher levels of blood potassium, changes in the rhythm of the heart start to occur, increasing in severity as blood potassium increases further, these changes can become very serious and are potentially fatal. A rapidly increasing concentration of potassium is more serious than a slow one.

1.58 In individuals with normal kidney function, hyperkalaemia from excess potassium intake is very uncommon, with short term intakes of up to approximately 15 g/day potassium not significantly affecting serum potassium levels. Current average intake of potassium by UK adults is around 3 g/day.

1.59 The large majority of cases of hyperkalaemia occur when potassium excretion is reduced by a medical condition, most commonly chronic kidney disease (CKD) or by the use of certain medications in patients with reduced renal function. However, dietary salt substitutes, potassium supplements, penicillin potassium therapy and drinking potassium softened water may also cause hyperkalaemia in these vulnerable individuals.

1.60 This means that increasing potassium in food could have potential adverse effects in vulnerable individuals who could be at risk of hyperkalaemia due to impaired or immature kidney function. These groups could include the elderly (as kidney function decreases with age), very young children and individuals with CKD.

1.61 Some individuals with CKD are required to consume a low potassium diet, and would need to avoid products containing potassium-based salt replacers, but many individuals with CKD are unaware of this, and hence might consume such foods, leading to adverse effects because of the increased levels of potassium in their diet.

1.62 The COT assessed information on the possible vulnerable groups, in particular considering infants and young children and, individuals with impaired kidney function. There was limited information on the implications for individuals with undiagnosed CKD or otherwise reduced kidney function. In a clinical audit conducted for the COT in a London hospital, it was found that life-threatening hyperkalaemia occurred in a number of individuals with a range of different conditions, not all of whom would have been advised to avoid potassium. The results of this study were extrapolated to the UK population.

1.63 Modelling was used to estimate the possible increase in potassium intake from food by individuals of different ages and with different levels of consumption.

1.64 There are few data available on the effects of excess potassium in infants and young children; however, data on renal development suggest that they would not be any more sensitive to potassium excess than older children or adults. In addition, it is not expected that infants would be exposed to potassium-based sodium replacers before age 6 months.

1.65 However, potassium-based replacement could threaten the health of people with major impairment of renal function because of CKD, and those taking particular medications that reduce renal excretion of potassium. Most, but by no means all of these individuals will be elderly.

1.66 Although such patients could be advised to avoid foods in which sodium has been replaced by potassium, this will only be practical if the food products concerned are clearly labelled, and suitable alternatives are readily available that do not contain potassium-based replacements.

1.67 Among people who are vulnerable because of undiagnosed kidney disease, it is estimated that salt-replacement in the UK might lead to as many as 9,800 additional cases of life-threatening hyperkalaemia presenting to hospital per year. However, this figure is subject to substantial uncertainty and could be out by as much as a factor of 10. This uncertainty could be reduced by further survey work.

1.68 In deciding whether to permit or encourage potassium-based replacement of sodium chloride and sodium-based additives, policy-makers will need to balance the expected benefits against these potential adverse effects.

1.69 If replacement of sodium chloride and sodium-based additives with potassium based equivalents were to be implemented, it would be advisable to monitor its application, and any trends in the incidence of life-threatening hyperkalaemia.

1.70 The full COT statement can be found at:

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

Vitamin A in the diet of infants and young children (addendum)

1.72 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 young children (aged 1-5 years). This addendum addresses the risks from high levels of vitamin A in the diet of young children aged 1-5 years only as infants aged 0-12 months were

considered in the previous COT statement. This statement does not look at risks associated with insufficient intakes of vitamin A.

1.73 SACN have advised that some children maybe deficient in vitamin A and therefore children from 6 months of age to 5 years of age that are receiving less than 1 pint of infant formula per day are advised to consume Healthy Start vitamins which contain vitamins A, C and D daily.

1.74 Vitamin A is an essential vitamin which is required for healthy vision, reproductive processes and cell development. There are two dietary sources of vitamin A – preformed vitamin A in foods of animal origin, and provitamin A carotenoids in fruit and vegetables (such as beta-carotene in carrots and other orange vegetables). Preformed vitamin A is more active biologically than provitamin A carotenoids. Rich sources in the diet include dairy products, fish and fish oils and especially liver which can contain very high levels. It is currently recommended that if solid foods are introduced before age 6 months then liver should be avoided. Children over the age of 6 months (and also adults) are recommended not to eat more than one portion of liver per week, because the vitamin A content in the liver can be harmful in large amounts.

1.75 Vitamin A toxicity arises from high intakes of preformed vitamin A, and does not result from high intakes of provitamin A carotenoids. Too much preformed vitamin A can be harmful to the body with the most sensitive groups being the developing fetus and older people who are more prone to osteoporosis (thinning of the bones). Reversible signs of vitamin A toxicity include joint pain, dry and scaly skin, headache and nausea or vomiting. More serious symptoms include hair loss, drowsiness, liver and bone damage and visual problems. Some of these symptoms may be irreversible depending on the amount and length of time over which the vitamin A was consumed.

1.76 In 2002, the European Scientific Committee on Food set a tolerable upper level (TUL) for vitamin A toxicity. This is the maximal level that can be consumed daily for a long period of time which would not be expected to result in adverse effects. The TUL can vary between life stages, for example, in the case of vitamin A, the elderly are more sensitive to the effects of vitamin A than other population groups and therefore the TUL for the elderly may be lower than for other groups.

1.77 The COT reviewed a range of scientific papers describing cases of vitamin A toxicity in young children and an assessment of dietary intakes for children aged 1-5 years. The committee observed that high level consumers were near to or exceeding the levels found in the literature to cause adverse effects in some individuals. Therefore, a very small proportion of the population may be consuming too much vitamin A and therefore may experience adverse effects as a result.

1.78 There is evidence that a very small proportion of young children eat foods containing liver. Frequently consuming liver at the levels reported could lead to the TUL being exceeded. Therefore, the COT supported the current Government recommendation that infants over the age of 6 months should not have more than one portion of liver per week.

1.79 Overall the COT concluded that there is potential for some children to exceed the TUL and that the possibility of adverse effects from such exceedances cannot be excluded, but if they do occur, it is likely to be in only a very small proportion of infants.

1.80 The 2013 COT statement can be found at: https://cot.food.gov.uk/sites/default/files/cot/cotstavita.pdf

1.81 The 2017 COT addendum can be found at: https://cot.food.gov.uk/sites/default/files/statementaddendumvitamina.pdf

Committee procedures

EFSA consultation on draft guidance on biological relevance

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

1.83 The draft guidance appeared to apply primarily to experimental data rather than observational epidemiological data.

1.84 Homeostasis per se should probably not be considered as an example of an adaptive response. Adaptation might be one type of homeostatic response, but not vice versa. The text completely separated mode of action (MoA) and adverse outcome pathways (AOPs). However, these are functional almost the same and there are important learnings to be acquired from respective practitioners. Separate conceptualisation will act as a barrier to this.

1.85 The document described “disease signature” and “network perturbations” as terms used in epidemiology but Members were not familiar with such uses.

1.86 The COT noted that the Bradford-Hill considerations were not criteria and suggested that it would be helpful for the document to list the modified Bradford-Hill considerations to which it referred. Confounding was not one of the Bradford-Hill considerations.

1.87 The COT disagreed with a statement in the document that a threshold could never be proven experimentally “as a matter of principle.” This is a very strong statement and perhaps it relates to empirical observation rather than experiment per se. The

document should make clear what type of threshold it was referring to in this statement and what is meant by “experimentally”.

1.88 The COT questioned what was meant by the statement that chemical risk assessment usually addresses risks at the population level. Risk assessments are intended to cover the majority of individuals within a population. It was suggested that the text be amended to avoid confusion with ecotoxicological risk assessments of effects on population size.

1.89 The document stated that lack of statistical significance should not be the sole rationale for concluding a lack of a treatment- or exposure- related effect. In practice there is always uncertainty about this possibility, as it would require acceptance of the null hypothesis. However, there is a difference between uncertainty about whether there could be an effect and concluding that there is one. The document should indicate what information would allow such a conclusion in the absence of statistical significance.

1.90 Where the document discussed “background variability for the control group”, this appeared to be related to historical control data. If so, it might be helpful to reference published work on the use and misuse of such data. If the discussion of how a treatment-related effect which falls within the background variability could be considered irrelevant for risk assessment was intended to apply to epidemiological data, then it should be noted that a small shift in a distribution whilst a small change on average could result in a substantial effect in some individuals at an end of the distribution.

1.91 The document discussed effects that were not in themselves adverse or beneficial but are linked directly or indirectly to an adverse or beneficial outcome. This should be linked to emerging concepts on the use of key events in MoAs and AOPs.

1.92 The COT made a number of other comments to improve the clarity of the document. The COT congratulated the EFSA Scientific Committee for tackling the topic and producing the draft guidance, which, with input from stakeholders during the consultation, could become a very valuable document.

EFSA consultation on draft guidance on weight of evidence

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

1.94 The conceptual framework was observed to differ from that in the COT’s draft SEES report.

1.95 Every evaluation involves weight of evidence assessments. For example, in most standardised procedures there will still need to be weight of evidence considerations for a number of effects (e.g. genotoxicity, carcinogenicity,

reproductive toxicity, systemic toxicity) and even for individual effects for a given endpoint (e.g. liver toxicity, renal toxicity, cardiotoxicity). The COT suggested that the document be more explicit about the type of problems it was aiming to address.

1.96 The document incorrectly described the Bradford-Hill considerations as criteria and stated that they are frequently used as a checklist in risk assessments, which is not how they were intended to be used.

1.97 Evidence rating systems had been grouped together. Whilst these had some superficial similarity, they were very different, and questioned whether such overall grouping was appropriate. For example, GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was formulated for a clinical setting and rates the strength of evidence, downgrading evidence based on observational epidemiological evidence, whereas the International Agency for Research on Cancer (IARC) classifications synthesise the totality of different pieces of evidence in a different way.

1.98 The COT saw quantification as a tool, rather than an end in itself as appeared to be the case in the draft guidance. The draft guidance mentioned standard statistical methods used in meta-analysis, but not other aspects such as pooling.

1.99 The COT considered the categories for weight of evidence methods given in the draft guidance as opaque, thus the approach taken to an assessment would need to be forced to fit into one of the groups.

1.100 The COT disagreed that quantitative analysis was necessarily more rigorous than other methods. A quantitative analysis might be possible but inappropriate, depending on the context.

EFSA consultation on draft guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age

1.101 Health based guidance values do not apply to infants below 16 weeks of age (or below 12 weeks for JECFA evaluations). However, risk assessment may still be necessary for chemicals in food to which young infants may be exposed. Such chemicals could be either contaminants or a limited number of approved additives. The draft guidance included exposure assessment, knowledge of organ development in human infants, and the overall toxicological profile of substances obtained by standard testing strategies, before considering the risk assessment process as a whole. The COT was invited to provide any comments on this draft guidance document for submission to EFSA.

1.102 The COT considered that the guidance document was a useful compilation of information.

1.103 The Committee were concerned that the decision tree could be interpreted as suggesting that an extended one generation reproductive toxicity study would be necessary for a substance to be assessed, when it would be more appropriate to use alternative methods to obtain information in the first instance. In fact, the decision tree was referring to the small number of chemicals deliberately added to food, for which such a study would be required before they could be approved e.g. the additives used in infant formula. The use of the mini-pig was discussed in the guidance, but it was unclear whether this was being recommended as the species of choice.

1.104 It was considered that the guidance should apply to term infants only, since the physiology of pre-term infants could be very different, particularly with regard to phase 1 metabolic enzymes and gastrointestinal absorption.

1.105 The guidance document noted that an additional uncertainty factor of 3 should be considered in certain situations to allow for extra toxicokinetic differences. This is presumably because this would apply to an age group which would normally be excluded from the ADI so that the conventional uncertainty factors of 10 x 10 would not apply; however, it might be useful to clarify this.

Draft EFSA protocol for a systematic review on health outcomes related to the age of introduction of complementary food for the scientific assessment of the appropriate age of introduction of complementary feeding into an infant's diet

1.106 Members were asked for comments on this consultation. No substansive comments were received and therefore no consultation response was sent.

Horizon scanning

1.107 At their February 2017 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 2017, and discussed several other topics that might also be considered. A follow-up paper was presented at the March meeting with an action plan.

COT future items*

Item	Plan
COT input into the Scientific Advisory Committee on Nutrition (SACN) review of complementary and young child feeding focussing on children age 1 to 5.	Ongoing work.

Advice to Department of Health on novel tobacco products	Ongoing work on heat-not-burn products.
e cigarettes	To be considered after heat-not-burn products
The COT-COC synthesising epidemiological evidence subgroup (SEES)	The draft report to be considered by the COT and COC at their March meetings.
Consultations of the European Food Safety Authority (EFSA)	Relevant documents to be considered by the COT as they are released for consultation by EFSA. To include the draft EFSA/ECHA guidance on endocrine disrupters.
Analysis of the evidence gap for postulated human health effects of Endocrine Disrupting Chemicals	A paper on the evidence gaps to be prepared by PHE but other priorities mean this is not likely to be progressed during 2017. COT to consider the draft EFSA/ECHA guidance on endocrine disrupters in 2017, as above, and then reconsider this item.
Update on the COT 2008 trans- and multi-generational toxicity statement	Joint symposium of COT, COC and COM to be held on 9th October 2017.
Role of chemicals altering the microbiome and potential human health effects	A short write up of a symposium on "Toxicology and the human microbiome" at the 2017 BTS Annual Congress to be provided to the COT for further consideration.
Risk Assessment in the 21st Century (RISK21)	To receive a presentation on the RISK21 approach in the future but to hold until more papers have been published.
Potential application of AOPs in risk assessment	

*In addition to the topics listed, requests for COT advice are often received at short notice. The FSA has a substantial programme of surveys to monitor the safety and quality of food, details of which are available at http://food.gov.uk/science/surveillance/foodsurvprog. Where appropriate, the Committee's advice will be sought on the results.

1.108 A Member had noted that the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) were jointly preparing guidance on identifying endocrine disrupters and the COT could respond to the consultation on the draft guidance.

1.109 Members agreed that they would like a presentation on the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) Risk Assessment in the 21st Century (RISK21) approach. At the March meeting Members agreed that most of the papers from the RISK21 work had been

published and to receive a presentation on the RISK21 approach in September or October.

1.110 It had been proposed that the Committee be provided with a short write-up of a symposium at the 2017 British Toxicology Society Annual Congress on “Toxicology and the Human Microbiome,” after which Members could discuss the priority of this topic and approaches to taking it forward. The COT interest would be the application of knowledge of the microbiome in risk assessment. Members agreed that the COT should consider this topic, and a Member suggested that the COT could produce a position note.

1.111 A joint symposium of the COT and the Committees on Carcinogenicity (COC) and Mutagenicity (COM) on trans- and multi-generational toxicity was being arranged for the 6th or 9th October, to be held at PHE in Chilton. A draft programme was tabled. The speaker names included were provisional. Members were asked for any suggestions of areas to include or speakers.

1.112 One Member had suggested that the application of adverse outcome pathways (AOPs) to risk assessment, at the present time, be considered by the COT. In March, Members agreed that it would be useful to explore the issues around adverse outcome pathways (AOPs) and how they could be used in chemical risk assessment.

1.113 A Member requested that there be a mechanism whereby the Secretariat could feed back to the COT on EFSA work. Members agreed that it would be useful to start capturing information on what EFSA is working on.

Risk Assessment in the 21st Century (RISK21)

1.114 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 decisionmaking 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.

1.115 The Chair has suggested that the Committee have a presentation on the RISK21 approach

Modelling kinetics

1.116 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.

1.117 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.

Balance of expertise on the Committee

1.118 It was confirmed that the following types of specialist expertise are required by the Committee for some or all of its evaluations:

Analytical techniques	Biochemistry
Bioinformatics	Biomonitoring
Cell biology	Clinical practice
Dietary exposure assessment	Endocrinology
Environmental exposure assessment	Epigenetics
Epidemiology	Human toxicology
Immunology	Mathematical Modelling
Mechanistic toxicology	Molecular biology
Neurotoxicology	Nutrition
Occupational health epidemiology	Paediatrics
Pharmacokinetics	Pharmacology
Probabilistic modelling	Reproductive toxicology
Respiratory toxicology	Risk assessment
Statistical aspects of experimental design	Statistics
Systems biology	Toxicogenomics
Toxicological pathology	Xenobiotic metabolism

1.119 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 expertise.

1.120 At the March meeting, Members considered the balance of expertise of the Committee. It would be useful to recruit one Member with expertise in computational biology, including modelling and systems biology.

Peer review by EU-ANSA agencies

1.121 Due to the there being insufficient time for discussion, Members were requested to send in any comments on this paper by email. If required, this item could be brought back to the next meeting for a full Committee discussion.

Working Groups

COT/COC Subgroup on synthesising epidemiological evidence

1.122 The COT and COC set up a subgroup to review the approaches to synthesising epidemiological evidence that are used by the Committees in chemical risk assessments and to make recommendations for COT/COC guidance. The terms of reference are to provide guidance that can be used by expert advisory committees for synthesis of epidemiological evidence, to review recent practice by expert advisory committees for synthesis of epidemiological evidence, with a focus on systematic reviews, to identify key points of current best practice methodologies used in systematic review and meta-analysis, and to identify and make recommendations for areas requiring further work. Further information on the subgroup can be found at: http://cot.food.gov.uk/cotwg/cot-coc-epi-sub-group. The subgroup is expected to publish its report in 2018.

COT/SACN Subgroup on the timing of introduction of allergenic foods into the infant diet

1.123 A comprehensive risk assessment of infant and young child feeding in the UK was previously considered by the Committee on Medical Aspects of Food Policy (COMA) in its report ‘Weaning and The Weaning Diet’, published in 1994.

1.124 The Scientific Advisory Committee on Nutrition (SACN) therefore requested its Subgroup on Maternal and Child Nutrition (SMCN) to review recent developments in this area. To complement this work, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) conducted a review of the risks of toxicity from chemicals in the infant diet, and examined the evidence relating to the influence of infant diet on development of food allergy, and atopic and auto-immune disease. A joint SACN-COT working group was established to undertake a benefit-risk assessment on the timing of introduction of allergenic foods into the infant diet. The COT statement identified significant findings related to the timing of introduction of foods containing peanut and hen’s egg into the infant diet and the risk of developing peanut and hen’s egg allergy respectively. The working group therefore restricted its assessment to these foods.

1.125 The benefit-risk assessment indicated that there was insufficient evidence to support the existence of a “window of opportunity” for the introduction of peanut before six months of age. Evidence that the introduction of hen’s egg before six months might be beneficial was limited and derived from randomised control trials (RCTs) where participants were not representative of the general population.

1.126 The benefit-risk assessment also indicated that there were insufficient data to demonstrate that the introduction of peanut or hen’s egg into the infant diet before six months of age reduced the risk of developing food allergy to any greater extent than introduction from around six months.

1.127 There was reasonable evidence to demonstrate that the deliberate exclusion or delayed introduction of peanut or hen’s egg beyond six to twelve months of age may increase the risk of allergy to the same foods. Importantly, once introduced, these foods should continue to be consumed as part of the infant’s usual diet, in order to minimise the risk of allergy to peanut or hen’s egg developing after initial exposure. Families of infants with a history of early-onset eczema or suspected food allergy may wish to seek medical advice before introducing these foods.

1.128 There are differences in the evidence base for peanut and hen’s egg: there are more RCTs investigating earlier introduction of hen’s egg in a number of geographically-diverse areas; earlier age at presentation of clinical allergy (which might be related to hen’s egg being introduced earlier during complementary feeding); greater heterogeneity in the food matrix in which the hen’s egg is consumed. Despite differences in the available evidence, there is a need to maintain simple and consistent public health advice: at the present time peanut and hen’s egg should be treated in the same way. Recommendations for health care professionals may need to take into account different clinical scenarios, and that targeted advice may be appropriate for individuals at a higher risk of developing a food allergy.

1.129 The COT made the following recommendations:

a) The government should continue to recommend exclusive breastfeeding for around the first six months of life.

b) Advice on complementary feeding should state that foods containing peanut and hen’s egg need not be differentiated from other complementary foods.

1.130 The final report of the sub-group can be found at: https://cot.food.gov.uk/sites/default/files/jointsacncotallergystatementfinal2.pdf

Ongoing work

Maternal and infant dietary exposures and risk of development of atopic outcomes and autoimmune disease

1.131 In 2016, the COT was asked for their opinion on a systematic review looking at maternal and infant dietary exposures and the development of atopic outcomes or autoimmune disease. This review was commissioned by the Food Standards Agency and will be used to direct future policy in this area. The contractors have updated their systematic review in 2017 and their final manuscript has been accepted by a peer-reviewed journal subject to some amendments. The COT statement will be published at the same time as the manuscript early in 2018.

Proposal for a breaskmilk analysis study using pre-existing samples held by Imperial College London.

1.132 The COT has recently been reviewing scientific evidence relating to the diets of infants and young children as part of a wider government review of infant feeding. This is being led by the Scientific Advisory Committee on Nutrition (SACN) who is examining the nutritional basis of dietary advice to this age group. The COT was asked to review the risks of toxicity from chemicals in the diet of infants.

1.133 At the beginning of this process, the COT identified a number of chemicals which they considered should be looked at in detail. For these chemicals, literature searching has been carried out in order to identify relevant toxicity and exposure data which can be used to determine the risk posed by these chemicals in the diets of infants and young children. During this process, it has become apparent that data on chemicals in UK breastmilk are sparse for many of the chemicals of interest.

1.134 The COT secretariat has been made aware of an ongoing project, co-ordinated by Imperial College London, where breastmilk samples are available for analysis. The FSA has been offered the opportunity to become involved in this work and part-fund this project. In return, the FSA would receive access to the large amount of data already collected, and be able to help direct the future analyses of these samples.

1.135 Members discussed the study in depth. It was noted that designing and commissioning a new study of breastmilk that would fill the data gaps identified by the Committee would be prohibitively expensive and given the difficulties in collecting samples, would still not result in a perfect dataset. Therefore, collaboration in this pre-existing study would be a value for money alternative that would give the FSA and COT the opportunity to recommend future analyses as well as gain access to useful data from analyses that have already been funded. Members were clear that prioritisation of chemicals needed to take into account the

amount of toxicological data: exposure data with little or no toxicological background data would not be useful. Overall, given the lack of robust breastmilk data available at the time, the committee considered that this would be a valuable addition to the current dataset.

1.136 The Committee asked the Secretariat to liaise with the study co-ordinators to produce a list of priority chemicals to fill the data gaps for chemicals for which exposure reduction may be a possibility, for discussion at a future COT meeting.

Survey of metals and other elements in infant foods

1.137 In 2014, the FSA completed a survey of 15 metals and other elements in infant formula, commercial infant foods, and other foods (i.e. those which were not specifically manufactured or intended for infants and young children but were known to be or could be consumed by them such as bread, fruit and vegetables). The results of the FSA's survey had provided 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. Based on these concentration data, and food consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC), dietary exposures to these elements had been estimated for UK infants and young children aged 4 to 18 months.

1.138 Discussion paper TOX/2016/29 provided the aforementioned concentration data and exposure estimates, alongside brief summaries of the toxicology of each element and comparisons of the exposure estimates with the relevant health-based guidance values. A statement will be finalised in 2017 and a Food Surveillance Information Sheet (FSIS) will be drafted by the FSA both of which will be published in 2018; the FSIS will incorporate the COT's comments and conclusions.

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

1.139 The COT has been asked to consider aspects of the toxicity of chemicals in the diet of infants and of young children aged 1 to 5 years, in support of the SACN review of Government recommendations on complementary and young child feeding. The COT reviews aim to identify whether current advice is appropriate in relation to potential toxicity, or whether there is a need for new or revised advice. Between 2012 and 2017 statements had been produced for a number of chemicals in relation to the infant diet. Reviews of manganese, chromium and copper commenced in 2017 and will continue in 2018. Further evaluation will also be

conducted. Mycotoxins were reviewed in 2017 and full reviews of T2, HT2 and neosolaniol and ochratoxin A commenced in 2017. Further evaluations on mycotoxins will be carried out in 2018.

1.140 Statements on nickel and cadmium had been finalised in 2017 and will be published in 2018.

Potential toxicological risks from electronic nicotine, or non-nicotine, delivery systems (e-cigarettes)

1.141 During the horizon scanning session in 2016, the Committee agreed that the possible human health effects of electronic nicotine, or non-nicotine, delivery systems (ENDS), also known as e-cigarettes, should be evaluated by the Committee. A scoping paper was discussed in 2016, and it was then agreed that the topic would be considered after the evaluation of heat-not-burn tobacco products.

1.142 At the end of 2017, a paper on the characterisation of the aerosol particle fraction was discussed. This will be followed in 2018 by papers on exposure to metals from the device components, risks from inhalation of the main constituents and emissions, bystander exposure, and the risks from inhalation of flavouring chemicals.

Guidance on submission of papers to COT regarding irritant sprays and information required

1.143 The Home Office Centre for Applied Science and Technology, CAST, regularly seeks expert advice from the Committee on the safety-in-use of formulations of irritant sprays for use by the police. Following the most recent discussions, it was decided that the COT should provide guidance to applicants on the type of information that should be supplied to enable the Committee to develop an opinion about the safety of the formulation.

1.144 This guidance has been discussed at three meetings this year, and will be finalised in early 2018.

New formulation of PAVA irritant spray

1.145 In 2015 and 2016, the Committee discussed a new formulation of pelargonylvanillylamide (PAVA) irritant spray. A draft statement was discussed in early 2017, and following discussion with the Home Office Centre for Applied Science and Technology, CAST, it is expected that the statement will be published in early 2018.

New formulation of CS as an irritant spray

1.146 In 2015, the Committee discussed a new formulation of 2-chlorobenzylidene malononitrile (CS) irritant spray and asked for further information. This was provided and discussed by the Committee in 2017. A draft statement has been prepared and following discussion with the Home Office Centre for Applied Science and Technology, CAST, it is expected that the statement will be published in early 2018.

2017 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 Biochemical Pharmacology and Director of the Toxicology Unit (supported by Public Health England and the Department of Health) in the Faculty of Medicine at Imperial College London

MEMBERS

Mr Derek Bodey MA (until 31st March 2017)
Public Interest Representative

Dr Phil Botham BSc, PhD (appointed 1st April 2017)
Global Head of Product Safety for Syngenta

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Dr D Gott BSc (Hons) PhD	Scientific Secretary (from May 2017)
Ms H Gbormittah	Administrative Secretary
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Declaration of members interests during the period of this report

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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)
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None		Kellogg - PhD student
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Company Secretary of Muse Interiors **Shareholder** Standard Life Santander		None
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None		**Membership** British Medical Association British Pharmacology Society British Toxicology Society National Trust Royal College of Physicians of London
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Shareholder Avipero		**Research collaboration** Myriad Genetics Cytosystems Antoxis Ltd Biopta Ltd MDX Health Nucana Ltd
		Misc Office of the Scottish Charity Regulator - Board member

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Consultancies and Direct Employment Simcyp Xenotech GSK Pfizer		**Support by Industry** GSK Pfizer Lilly Servier
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Specific Interests Drug Metabolism & Pharmacokinetics		
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None		None
Professor Robert Smith		
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None		None
Dr John Thompson		

Personal Interest		**Non Personal Interest**
None		None
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Professor Matthew Wright		
Personal Interest		**Non Personal Interest**
Consultancies and Direct Employment Newcastle University		**Support by Industry** GSK
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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 2017. 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 genotoxicity 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 2017, the Committee worked on a number of topics. The COM reviewed the genotoxicity evidence on novel heat-not-burn tobacco products as part of Committee on Toxicity's (COT) toxicological evaluation. It discussed quantitative approaches to the assessment of genotoxicity data and a document related to this was to be published early in 2018. Further, it consolidated discussions on issues related to germ cell mutations. The committee joined with its sister committees: the COT and the Committee on Carcinogenicity (COC) for a one-day symposium on "Whether epigenetics should be used in chemical risk assessment" at Public Health England (PHE), Chilton in October 2017.

The Committee also carried out its annual Horizon scanning exercise, identifying a number of potential topics for future work. The COM is interested in obtaining information from Government Departments on how its advice is acted upon.

Throughout 2017 the COM continued to take an active interest in the work of the OECD (Organisation for Economic Cooperation and Development) on test guidelines. It commented on the OECD’s reviews of old test guidelines (TGs) and the development of new TG’s.

The COM also maintained an awareness of the possible implications of Brexit on its work and was aware that there remained uncertainty in how this may affect the regulatory environment and the UK’s relationship with international organisations.

I want to thank the secretariat for their work and the members of the Department of Health's Toxicology Unit who maintained their usual high standard of work up until the end of the Unit's contract. We look forward to working with WRC/IeH in the future. I am again grateful for the support of the individual members of the committee for their expert advice, the time they put in and their support throughout the year.

Dr D Lovell Chair
PhD BSc (Hons) FRSB CStat CBiol CSci

COM EVALUATIONS

Toxicological risks from heat-not- burn tobacco products: Overview of genotoxicity data submitted (Confidential)

2.1 As part of the COT assessment of the toxicological risks from novel heat-not-burn tobacco products, the COM assessed the available genotoxicity data. The COM participated in a joint discussion with COT and COC where the two manufacturers of products notified in the UK before November 2016 presented the relevant toxicity data held.

More information on the assessment and a link to the COT statement is available in the COT section of this report (paragraph 1.9)

Quantitative approaches to the assessment of genotoxicity data II and First Draft Quantitative risk assessment statement

2.2 At the COM meetings in October 2016 and March 2017, members considered papers on recent developments in Quantitative approaches to the risk assessment of genotoxicity data. This included overviews of reports from the International Workshops on Genotoxicity Testing (IWGT) working group on quantitative approaches to genetic toxicology risk assessment (the QWG); publications arising from a workshop organised by the Health and Environmental Sciences Institute (HESI); and publications in a recent edition of Mutagenesis on this topic. Aspects, such as, the development of different benchmark dose (BMD) software (PROAST[1] and US EPA BMDS), point of departure metrics, and application in carcinogenicity risk assessment were considered.

2.3 A first draft had been produced (MUT/2017/03) for consideration and comment by members. Overall, the COM considered that quantitative dose-response analysis of genotoxicity data was work in progress and that further work was required. It was important to address a number of the points referred to above such as, the most suitable BMD software; documentation and explanation of the various versions of the BMD software; clearer explanation of the analytical quantitative approaches; difference between quantal and continuous data; suitable sampling time; a cut-off point for poor quality data; suitable genotoxic endpoint and tissues; biological relevance of critical effect size (CES) or benchmark response (BMR); and analysis of a larger number of chemicals and classes with different modes of genotoxic action.

A final statement was published in 2018.

[1] This includes the EFSA-PROAST platform

Consolidated Summary of germ cell mutation discussions

2.4 The COM considered germ cell mutation at a meeting in June 2013, October 2015 and in February 2016.

2.5 COM discussed appropriate sampling times to detect mutations in sperm and the potential implications for current guidance on germ cell gene mutation assays (e.g. OECD Test Guideline 488). Members were aware of suggestions that a sampling time of 28 days post dosing in *in vivo* studies may be more appropriate than the current recommendation of a 3 day post dosing sampling time to detect DNA effects in sperm. It was agreed that this should be addressed in the COM summary document.

2.6 The COM noted that there was evidence that the number of mutations in sperm increased as paternal age increased. It was not clear whether this increase in mutations was due to an individual being older per se (i.e. due to the aging process) or whether it was a consequence of a longer duration of exposure to environmental mutagens.

2.7 Regarding the suggestion that air pollution was a germ cell mutagen, the COM considered that the sperm assays used in providing evidence for this assertion had not been sufficiently validated for detecting germ cell mutations. Members had previously agreed that the sperm chromatin structure assay (SCSA) and the terminal deoxynucleotidyl transferase (TdT) dUTP nick-end labelling (TUNEL) assays were difficult to interpret in terms of germ cell mutagenicity and had not been sufficiently validated for detecting mutation.

HORIZON SCANNING

2.8 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.

2.9 COM considered statements by the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA), which have caused concern. The first statement was that for *in vivo* genotoxicity assays the intraperitoneal (IP) route of administration should be preferred over oral and inhalation as it leads to a by-pass of some first pass metabolism in the liver, and therefore, produces a more sensitive test. The second statement was that for the *in vivo* mouse micronucleus test, even if a test compound is detected in the plasma, it does not necessarily indicate that the target tissue in the bone marrow had been sufficiently exposed to the test compound. The third statement was that even if it can be demonstrated that a test chemical has reached the bone marrow at a concentration that exceeds

anticipated human exposure, it may not be considered adequate, as higher exposure could have been achieved in an *in vivo* site-of-contact comet assay. The fourth statement was that the glandular stomach (in addition to the liver and duodenum) should be sampled for site of contact assays to help account for tissue variables; such as tissue structure/function, pH conditions, absorption rates and differences in breakdown products. These statements were discussed as part of the horizon scanning exercise and the COM acknowledged that these issues were going to be considered by the IWGT and the HESI Genetic Technical Committee (GTTC).

2.10 A joint horizon scan exercise was carried out at the Joint COM/COC and COT meeting in October 2017.

OECD

2.11 The committee kept up to date with discussions at OECD with regard to genotoxicity test guidelines.

ONGOING WORK

Joint committee workshop – Use of epigenetics in chemical risk assessment

2.12 The field of epigenetics research and the potential role of epigenetic changes in toxicology has been considered previously by COC, COM and COT, and all have recently recommended maintaining a watching brief on developments in their respective Horizon Scanning exercises. To fulfil this brief, a workshop for Members of all three Committees was organised in October 2017 with the aim of considering the overarching question; 'Whether epigenetics should be used in chemical risk assessment'.

A joint statement on the discussion of the topic is in draft and will be finalised in 2018.

2017 Membership of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM)

CHAIRMAN

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

MEMBERS

Dr Carol Beevers
Genetic Toxicology, Covance Laboratories Ltd (to end of August 2017),
Managing Scientist, Exponent International Ltd (from September 2017)

Dr Gill Clare BSc PhD
Independent Consultant

Dr Stephen Dean
Agenda Life Sciences

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

Professor Helga Drummond
University of Liverpool

Mrs Philippa Hardwick
Lay Member - District Councillor, Chichester District Council, Barrister, Fountain Court Chambers

Professor David Harrison BSc MB ChB MD DSc FRCPath FRCPEd FRCSEd *Professor of Pathology, University of St Andrews*

Professor Gareth Jenkins
Institute of Life Science, Swansea University, Honorary Non-clinical Senior Lecturer, Swansea NHS Trust

Professor David Kirkland
Principal, Kirkland Consulting

Professor Francis Martin PhD FIBMS
University of Central Lancashire

Dr Michael O'Donovan
Independent Consultant

Dr Andrew Povey

Reader in Molecular Epidemiology, University of Manchester

SECRETARIAT

Dr Ovnair Sepai	PHE Scientific Secretary
Dr D Benford BSc(Hons) PhD	FSA Scientific Secretary *(until May 2017)*
Dr D Gott BSc(Hons) PhD	FSA Scientific Secretary *(from May 2017)*
Mrs N Blowfield	Administrative Secretary

DECLARATION OF INTERESTS DURING THE PERIOD OF THIS REPORT

	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Dr D P Lovell (Chairman)	National Grid plc	Shareholder		
	Pfizer	Pension Scheme Member		
	ILSI HESI	Committee Member		
	Biometrics Society	Member		
	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 Kingdom Environmental Mutagen Society (UKEMS)	Member		
	Grant Funding Panel of the UK National Centre for Replacement, Refinement and Reduction of Animals in Research (NC3Rs)	Member		
	MRC EMINENT Project Review Board	Member		
	AstraZeneca	Spouse Shareholder		
	National Grid plc	Spouse Shareholder		

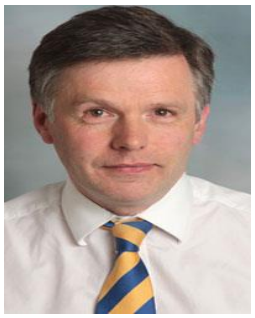
	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Dr Carol Beevers	Covance (Jan – Aug)	Salary Pension Employee	None	None
	Labcorp (Jan-Aug)	Equity Holder		
	Exponent (Sept – Dec)	Salary Pension Employee		
	ILSI HESI	Workgroup member		
	United Kingdom Environmental 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		
Dr Stephen Dean	WIL Research, Europe (Jan – March 2016)	Salary Employee Equity Holder		
	Smithers Viscient (Aug 2016 to Dec 2017)	Managing Director		
	UKEMS	Member		
	Standard Life	Shareholder		
	Society of Toxicology	Member		
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
Prof Philippa Hardwick	Unilever plc	Pension	None	None

	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
Prof David Harrison	University of Canberra	Consultant	Cytosystems Ltd	Research Collaboration
	University of Florida	Consultant	Nucana plc	Part time employee
	University of Edinburgh	Consultant	Office of the Scottish Charity Regulator	Deputy Chair of the Board
	University of Cambridge (examiner)	Consultant		
	Ryboquin Ltd	Consultant		
	NucanBiomed Ltd	Consultant		
	Cytosystems Ltd	Consultant		
	Cunningham Trust	Scientific Adviser		
	Avipero Ltd	Shareholder		
	Melville Trust (cancer research charity)	Trustee		
	Families First St Andrews (children's charity)	Trustee		
	Ryboquin Ltd	Shareholder and Consultant		
	Benenox Ltd	Shareholder and Consultant		
Prof Gareth Jenkins	None	None	Unilever	Research Grant 2008 – 2010
Prof David Kirkland	Kirkland Consulting	Principal	None	None
	United Kingdom Environmental Mutagen Society	Fellow		
	European Environmental Mutagenesis and Genomics society	Member and Trustee		
	Saga	Shareholder		
	ILSI HESI	Steering Committee Member and Workgroup Leader		
	U.S. Environmental Mutagenesis and Genomics Society	Member		
Prof Francis Martin	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

	Personal Interest		Non-Personal Interest	
	Company	**Interest**	**Company**	**Interest**
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)	Treasurer	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		
	Institut national de la sante et de la recherhce medicale (INSERM)	Grant reviewer		
	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	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 three meetings in 2017 plus two joint committee meetings.

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 to the Imperial College London Toxicology Unit, who have supported the PHE (and predecessor organizations) Secretariat over many years in preparing discussion papers for the Committees, and the staff at WRc plc and IEH who have now taken on this contract of work for their invaluable support. I also wish to extend special thanks to Professor Julian Peto, following his resignation from the Committee, for his contributions over the past 5 years.

Professor David Harrison
BSc MB ChB MD DSc FRCPath FRCPEd FRCSEd

COC Evaluations

Toxicological risks from heat-not-burn tobacco products

3.1 As part of the COT assessment of the toxicological risks from novel heat-not-burn tobacco products, the COC assessed the available data with respect to carcinogenicity. The COC participated in a joint discussion with COT and COM where the two manufacturers of products notified in the UK before November 2016 presented the relevant toxicity data held.

3.2 More information on the assessment and a link to the COT statement is available in the COT section of this report (paragraph 1.9)

OECD guidelines: Standard Project Submission Form for the ToxTracker assay

3.3 The COC considered a submission made to the OECD Test Guidelines programme for a stem cell-based reporter assay for mechanistic genotoxicity and carcinogenicity hazard assessment, called the ToxTracker assay. The COC were asked to comment on the assay in general and in particular on the use of the assay for detection of non-genotoxic carcinogenicity.

3.4 The COC was informed that the COM had previously considered the assay and concluded that it could be used as an early screen before *in vivo* testing, or where such testing is not permitted. The COM had also noted that the assay could aid interpretation of weak positive results, and possibly identify non-genotoxic carcinogens, through exploring mechanisms.

3.5 The COC queried the reasoning for using mouse cells rather than human, organ specific, or induced pluripotent stem cells, and likewise the reasoning for using rat liver S9 extract rather than a metabolic system based on human metabolism.

3.6 With respect to non-genotoxic activity, there was little mention of this within the provided documentation, and no evidence provided to support the unfolded protein response. Overall the Committee noted that non-genotoxic activity covers multiple mechanisms, and given the assay is based on a single cell line system, this would not be expected to cover all possible mechanisms. In particular the assay would be expected to have poor performance in detecting mechanisms such as immune suppression or hormone related effects.

3.7 In terms of performance, it was noted that toxicity varied between the labs. Additionally, the statistics were based on positive prediction, and the COC acknowledged that it would not be possible for the assay to determine that a substance is not a carcinogen.

3.8 The Committee commented that the OECD has previously had reservations about proprietary studies especially with only one source of the cells.

3.9 Overall the COC concluded that based on the information provided in the submission, the ToxTracker was assay not ideally placed as screening assay to detect a non-genotoxic carcinogenicity effects.

Presentation on Adverse Outcome Pathways

3.10 Professor Heather Wallace gave an overview presentation on adverse outcome pathways (AOPs), introducing the AOP concept, the overlap with the mode of action framework, the linear structure of an AOP from molecular initiating events through key events to the adverse outcome, and how they are developed. It was highlighted that AOPs are not chemical-specific, they are modular, and a pragmatic simplification of biology. In use, networks of AOPs are likely to be needed as there are interactions between individual AOPs, and they will develop overtime as information on key events evolve and new key events are identified. The presentation concluded that currently AOPs have good potential for prioritisation, e.g. in drug development to determine compounds to progress, or for development of *in vitro* tests. However there are challenges with respect to the complexity of biology, quantification of dose-response relationships, how exposure assessment and toxicokinetic data are accounted for in AOPs, and how AOPs are evaluated.

3.11 In discussion, it was noted that epidemiology and toxicology can learn from each other, as epidemiology uses a relationship of cancer risk as x^{n-1}, where n is the number of steps in the cancer process, though it needs to be known which cancers this will work for. Probability can be associated with each step and if rates are available for each step as well then incidence can be estimated.

3.12 For the mode of action framework it was noted that human relevance was also considered. For AOPs, information would be needed on whether the pathway between the molecular initiating event and the adverse outcome were conserved between species. Where this information is available, AOPs would be useful for REACH applications, where *in vivo* data are not necessarily available for chemicals being considered.

3.13 Whether the pathways were reversible, and if adaptation could be captured in a pathway, were considered, as AOPs were appealing in their simplicity but represented complex biology that has in built redundancy.

Horizon scanning

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

3.15 In 2017 the Committee participated in the joint horizon scanning discussion as part of the joint COC, COM and COT meeting in October 2017. These were further discussed at the November meeting alongside the COC list from the previous year. Following this discussion, the list of COC priority topics (in no specific order) was:

- Immunological and stromal cell modulations relevant to cancer risk
- Nanomaterials
- Mechanisms incorporating genomics and the Cancer Genome Atlas
- E-cigarettes (if referral from COT) and effect of early life exposure to cigarettes
- *In vitro* systems - to be undertaken when resource allows

3.16 The Committee continues to have a standing agenda item for each meeting on horizon scanning topics and to update the COC on upcoming topics for IARC and the EU Scientific Committees.

Papers of interest

Mutational signatures associated with tobacco smoking in human cancer – and associated editorial paper

3.17 A recent journal paper and associated editorial paper on mutational signatures associated with tobacco smoking was discussed. The Committee suggested that this paper could be considered when the guidance statement on biomarkers (G04) undergoes a full version revision.

Alcohol effects on the epigenome in the germline: Role in the inheritance of alcohol-related pathology

3.18 The Committee noted that the paper on inheritance of alcohol effects through the epigenome, indicated a three generation effect through the male line following *in utero* exposure to alcohol, though these results needed to be reproduced. The paper also highlighted the complexity of such investigations.

Cancer etiology and causal inference

3.19 The Committee discussed the topic of causal inference, which was part of an ongoing debate within the epidemiological field about balancing causality evidenced from randomized controlled trial that relies on the availability of an intervention for the disease of interest, and drawing together all the available evidence, often from other types of epidemiological studies, to infer causality of

the disease in question. The example of obesity was used, where IARC have established that obesity causes cancer, but as obesity is a state of health rather than an intervention it is not possible to prove such causality by means of a randomized controlled trial.

3.20 The relevance of the discussions about causal inference to the work of the COC was noted. The Committees draw together information from human, animal and *in vitro* studies, with toxicological studies providing additional important mechanistic information that cannot always be obtained from epidemiological studies. In addition, evidence is assessed not just by the nature of the experimental design but more importantly from the information contained in the studies considered. Diverse forms of evidence are encouraged including negative findings, and the Committee often needs to make an evaluation on limited data.

3.21 Overall the Committee agreed that disciplines working together, such as in the Committee structure, is important to draw together the available evidence on a topic and make an appropriate assessment.

Working Groups

COT/COC Subgroup on synthesising epidemiological evidence

3.22 The COC considered the draft report from the subgroup in 2017, and the subgroup is expected to publish its report in 2018. More information can be found in the COT section of this report (para 1.122).

Ongoing work

Use of epigenetics in chemical risk assessment

3.23 The COC participated in the joint COC, COM and COT workshop on 'Whether epigenetics should be used in chemical risk assessment' in October 2017. More information can be found in the COM section of this report (para 2).

IGF-I

3.24 Insulin-like Growth Factor 1 (IGF-1) is a growth factor which has a variety of biological effects including the promotion of cell division and growth. It had been proposed that exposure to dietary IGF-1 could increase the risk of certain cancers, and the COC is evaluating the evidence on this.

3.25 The COC is considering an extensive range of data which covers dietary absorption, levels of IGF-1 in food and the association between blood levels of IGF-1 and the risk of certain types of cancer. In 2017, the COC considered the draft statement on the topic and it is expected that this will be published in 2018.

Guidance statements

3.26 The Committee continued to develop the guidance statement series during 2017, including discussing updates to the published documents in light of new developments. These included developments in benchmark dose modelling, the Threshold of Toxicological Concern (TTC). Further discussion was also held on how to consider risk when exposures do not occur across the whole lifetime, and how to consider margins of exposure for children where exposure is limited in duration or where lifetime exposure is unlikely to be of concern.

3.27 These developments and revisions to the guidance statements will continue to be addressed in 2018.

2017 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

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MEMBERS

Mr Derek Bodey MA
Public Interest Representative

Dr Gill Clare BSc PhD
Expert Member

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Dr Peter Greaves MBChB FRCPath
Consultant Pathologist and Honorary Senior Lecturer, University of Leicester

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Professor Julian Peto MA MSc DSc FMedSci (until October 2017)
Professor of Epidemiology, London School of Hygiene and Tropical Medicine

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

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

Professor Saman Warnakulasuriya BDS, FDSRCS, DipOralMed, PhD, DSc
Professor of Oral Medicine & Experimental Pathology, King's College London

SECRETARIAT

Miss B Gadeberg BSc(Hons) MSc	PHE Scientific Secretary
Dr D Benford BSc(Hons) PhD	FSA Scientific Secretary *(until May 2017)*
Dr D Gott BSc(Hons) PhD	FSA Scientific Secretary *(from May 2017)*
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	Examiner	Gene Therapy Consortium (funded by Wellcome Trust)	Unpaid external scientific advisor
	Ryboquin Ltd, UK	Consultant, Shareholder		
	Cytosystems Ltd, UK	Consultant		
	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 Shareholder		
	University of St Andrews, UK	Salary		
	University of Edinburgh, UK	Honorary professor Consultant		
Mr Derek Bodey	None		None	
Dr Gill Clare BSc PhD	Covance	Consultant	None	
	AstraZeneca	Shareholder		
	Diageo	Shareholder		
	Marks and Spencer	Shareholder		
	Shell Research Ltd	Pension		
	AstraZeneca	Pension		
Member	**Personal Interest**	**Non-Personal Interest**	**Member**	**Personal Interest**
	Parker Doe Partnership	Partner		

Dr John Doe PhD Dip R C Path	ILSI	Member of Steering Group for RISK 21 project		
	Syngenta	Pension		
	ECETOC	Chairman of Task Force - Bringing Potency into Classification for Carcinogenicity and DART		
Dr Peter Greaves	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		
Professor Ray Kemp BA	Ray Kemp Consulting	Shareholder		

Member	Personal Interest	Non-Personal Interest	Member	Personal Interest
Dr David Lovell PhD BSc (Hons) FSS FIBiol Cstat Cbiol	National Grid	Shareholder		
	Pfizer	Pension Scheme Member		
	ILSI HESI	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		
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	Statisticians in the Pharmaceutical Industry (PSI)	Member		
	United Kingdon Environment Mutagen Society (UKEMS)	Member		
	Grant Funding Panel 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
Professor Julian Peto MA MSc DSc FMedSci	None	None	None	None
Dr Christopher J Powell, FRCPath, FBTS, FRSB	GlaxoSmithKline	Shareholder and Salary	None	None
	British Toxicology Society	President		

Member	Personal Interest	Non-Personal Interest	Member	Personal Intere
Dr Lesley Rushton OBE BA MSc PhD Cstat	Economic Burden of Occupational Cancer	Consultancy	IEH Consulting Ltd	Research Support
	Deputy Editor Occupational and Environmental Medicine Journal	Deputy Editor		
	HSE Science, Engineering and Environmental Assurance Committee (SEAC)	Member		
Professor Heather Wallace BSc Hons PhD FRCPath FBTS	Bank Santander SA	Shareholder		
	EFSA	Contam Panel		
	BT Group	Shareholder		
	NovaBiotics	Shareholder		
	Antoxis	Shareholder		
	Cell ProTx	Director		
	EUROTOX	President-Elect		
	Paediatric Medicines Expert Advisory Group – MHRA	Member		
	Herbal Medicines Advisory Committee – MHRA	Member		
Dr Rosemary Waring PhD DSc FRCPath	Centrica and National Grid	Shareholder	None	None
	Tharos	Director and Shareholder		
	Ateria Health	Shareholder		
Professor Kasturi Warnakulasuriya FDS, PhD, DSc	National Grid plc	Shareholder	Oral Health Foundation	Panel member
	Post Office Ltd	Shareholder	Cancer Research UK	Advisory

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https://www.gov.uk/government/organisations/committee on mutagenicity of chemicals in food consumer products and the environment

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