COT/COM/COC Annual Report 2022

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About the Committees

This is the 32nd joint annual report of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) and the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC).

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

In common with other independent advisory committees, Committee members are required to follow a Code of Conduct which also gives guidance on how commercial interests should be declared. Members are required to declare any commercial interests on appointment and, again during meetings if a topic arises in which they have an interest. If a member declares a specific interest in a topic under discussion, and it is considered to be a conflict of interest, he or she may,

at the Chairman's discretion be allowed to take part in the discussion but is

excluded from decision-making. Annex 1 contains the terms of reference under which the Committees were set up. The Code of Conduct is at Annex 2 and Annex 3 describes the Committees' policy on openness.

Annex 4 is the Good Practice Agreement for Scientific Advisory Committees. Annex 5 contains a glossary of technical terms used in the text. Annex 6 is an alphabetical index to subjects and substances considered in previous reports. Previous publications of the Committees are listed at Annex 6.

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

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

Committee on Toxicity

Committee on Carcinogenicity

Committee on Mutagenicity

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

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COT Preface - 2022

In this guide

Preface

Head and shoulders Image of Prof Alan Boobis, standing in front of a patterned background. Prof Boobis is wearing half framed glasses and a light-coloured striped shirt.

The Committee met on eight occasions during the year. In addition to their seven regular meetings, an extraordinary meeting was held to discuss the draft EFSA opinion on bisphenol A (BPA). As ever, the Committee have undertaken a busy and varied programme of work.

2022 brought a welcome return to face-to-face meetings, though now with the use of hybrid technology to allow the participation of Members not wishing or able to attend in person; this also allows the easier attendance of interested external observers, increasing the reach of the COT.

The Committee continued its review of components and contaminants in the maternal diet in support of the risk assessment currently being undertaken by the Scientific Advisory Committee on Nutrition (SACN). A number of new topics were considered as part of this work including lead, cadmium and ergot alkaloids along with ginger and raspberry leaf tea supplements.

Other topics discussed by the Committee this year have covered a wide range including nicotine pouches, ocean bound plastics, cows’ milk, per and polyfluoroalkylated substances (PFAS), the inhalation exposure of microplastics, the genotoxicity of acrylamide and approaches to mixture risk assessment. The COT also started work on a review of the aircraft cabin air environment, considering a number of potential chemicals that could be present.

In 2022, the work of the Committee started to include overseeing and assuring the risk assessment of regulated products that were previously assessed in Europe. Joint Expert Groups (JEGs) were established as part of the FSA Scientific the Advisory Committee (SAC) structure to advise the FSA on these products;

AEJEG covers enzymes, additives and other regulated products, while the FCM JEG covers food contact materials, respectively; along with the other SACs, the COT oversees the work of these Groups. A number of regulated product authorisations have now been reviewed by the Committee and this workstream will increase in the future as the authorisation process matures. The Committee are also being tasked with requests for advice from the Nutrition Labelling Composition and Standards Policy Group who co-ordinate the policy approach in this area across the UK; this has led to work on the safety of green tea catechins and fortificants in bread and flour.

The Committee also contributed comments to a number of public consultations from EFSA, including BPA, acrylamide and nitrosamines.

The joint COT and SACN Working Group continues its benefit- risk assessment of plant-based drinks consumed as an alternative to cows' milk. It is hoped this WG will report in 2023.

The Committee held a workshop Opportunities and outlook for UK Food and Chemicals regulation post EU Exit which took place in Liverpool in July 2022. The purpose of the workshop was to review the food and chemical regulatory landscape from a number of different organisational perspectives, with a particular focus on the REACH classification process for chemicals. The workshop provided an opportunity for invited experts and organisations to share their knowledge, have roundtable discussions on the topic bringing representatives from industry, academia and regulatory agencies.

This year, the Committee said goodbye to Dr Caroline Harris and Dr Rene Crevel. On behalf of all Members, I would like to express the COT's sincere thanks to them for all their invaluable contributions to the work of the Committee over the years. We also welcomed a new Member, Dr Silvia Gratz from the Rowett Research Institute to the Committee and look forward to working with her.

Next year, the Committee will hold a workshop to kick-start the process of updating its guidance on the risk assessment of chemicals in food and the environment, last revised several decades ago. This will be an opportunity to bring together a number of topics on which the Committee has been working over the last few years, including new approach methodologies (NAMs), dose-response assessment, assessing data-poor chemicals, and evidence integration. It is also proposed that, together with the COC and COM, a more holistic approach to assessing toxicity and carcinogenicity be explored.

I would like to thank my fellow Committee Members for their continuing support and expert contributions to the work of the COT and its sub-groups over the year. On a personal note, and on behalf of all Members, I very much appreciate the considerable support provided to the Committee by the joint Scientific Secretaries and all of their staff. They face many demands on their time and resources, and we are very grateful at how effectively they ensure the functioning of the COT.

Professor Alan Boobis (Chair)

OBE PhD CBiol FRSB FBTS FBPhS

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COT evaluations

Statement on the effects of Vitamin D on maternal health

1.1 In 2019, The Scientific Advisory Committee on Nutrition (SACN) agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet. The Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was consulted, and decided that Vitamin D should be considered for a detailed risk assessment.

1.2 There are two forms of vitamin D; these are vitamin D2 (also known as ergocalciferol) and D3 (also known as cholecalciferol). Vitamin D2 can be found in plants and fungi and therefore is only available to humans via the diet. Vitamin D3 is made in human skin via ultraviolet radiation from the sun and can also be found in oil rich foods or supplements of animal origin such as cod liver oil. Vitamin D3 is reported to be about three times more potent than vitamin D2.

1.3 Both forms of vitamin D are converted in the body by the liver to analogous substances called 25-hydroxyvitamin D (25(OH)D) and the 25OHD is further converted in the kidney to analogous substances called 1,25-dihydroxyvitamin D (1,25(OH)2D); this is the active form of vitamin D.

1.4 Vitamin D (in reality two forms as described in paras 3-4) plays an important role in maintaining healthy bones by ensuring adequate uptake of calcium. It also helps maintain healthy muscles by aiding muscle contraction and

helps nerves and the immune system to function. However, consuming too much vitamin D from food sources and supplements can cause adverse health effects.

1.5 Too much vitamin D in the body can lead to hypercalcaemia (higher than normal calcium levels in the blood), which can lead to hypercalciuria (higher than normal levels of calcium in urine), demineralisation of bones, kidney and cardiovascular issues. Other side effects of excess vitamin D may include vomiting, nausea, constipation and diarrhoea.

1.6 It is important to note that whilst too much vitamin D can be consumed from foods and supplements it is not possible to make too much vitamin D via ultraviolet radiation from the sun. This is because there are inbuilt biochemical mechanisms in our skin that prevent vitamin D3 reaching toxic levels from exposure via skin.

Effects of vitamin D during pregnancy and lactation

1.7 There is currently no information available on the adverse health effects that excess vitamin D might cause during the period preceding conception.

1.8 Information on the adverse health effects caused by excess vitamin D during pregnancy and lactation is limited, but hypercalcemia (higher than normal calcium levels in the blood) can occur during pregnancy, especially in individuals that have mutations in genes involved in vitamin D metabolism. Individuals with these mutations have experienced hypercalcemia after consuming up to 1,250 µg per month of vitamin D. Hypercalcemia during pregnancy may increase risk of fetal and neonatal morbidity. Excess vitamin D during pregnancy may also result in fetal and neonatal hypercalcemia, which can lead to adverse effects on the digestive system, behaviour and growth.

1.9 There is limited evidence for adverse health effects that could arise due to excess vitamin D exposure during lactation. However, hypercalciuria could possibly occur, with one clinical study reporting it in women that consumed supplements of 700 µg per week vitamin D. However, participants in this study had low levels of calcium before consuming the supplements that increased their levels to be in “possible hypercalciuria” range.

1.10 In 2003, the Expert Group on Vitamin and Minerals (EVM) set an intake level of 25 µg per day as the level of vitamin D that would not be expected to result in adverse health effects – i.e. a safe level of intake. More recently The European Food Safety Authority (EFSA) developed a tolerable upper limit (TUL) of

100 µg per day for the general adult population, including pregnant women. This TUL was endorsed by the COT.

1.11 This risk assessment showed that women attempting conception, pregnant and lactating women who consume vitamin D only from food (and not supplements) are very unlikely to be at risk of adverse health effects from vitamin D as their exposure levels are below the TUL of 100 micrograms per day.

1.12 Only a minority of women attempting conception, pregnant and lactating women who consume vitamin D from both food and supplements are above the TUL of 100 micrograms per day. It is important to note that this would only be of health concern if their intakes were sustained long-term. Pregnant women with mutations in the genes involved in vitamin D metabolism may be more likely to experience adverse health effects such as high blood calcium levels and high calcium levels in the urine.

1.13 Ultimately the COT concluded that consumption of higher strength vitamin D supplements alone or in combination with food can result in exceedance of the TUL and pose a potential health concern. However, consumption of lower strength supplements that are aimed at pregnant and breast-feeding women, either alone or in combination with food is very unlikely to result in excess vitamin D intake or adverse health effects related to excess vitamin D intake.

1.14 The full COT statement can be found at: Statement 01/22 Vitamin D.

Statement on the potential effects that excess iodine intake may have during preconception, pregnancy and lactation

1.15 The Scientific Advisory Committee on Nutrition (SACN) is currently conducting a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

1.16 The Committee on Toxicity was consulted and decided that iodine should be considered for assessment of the risks associated with excess intake.

1.17 SACN agreed that, where appropriate, other expert committees would be consulted and asked to complete relevant risk assessments e.g. in the area of food safety advice to support their review. Therefore, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked

to consider whether exposure to excess iodine would pose a risk to maternal health, as part of this review.

1.18 In the environment, iodine is usually found in the form of iodate salts, or in the form of organo-iodide compounds produced by algae and bacteria. Iodine is essential in the human diet because it is required for the synthesis of the thyroid hormones tri-iodo- and tetra-iodothyronine (T3 and T4 which is also known as thyroxine). This takes place in the thyroid gland. The thyroid hormones help regulate metabolism and ensure that the heart, brain and other organs function in a healthy manner. They are also involved in brain development and bone growth especially in the fetus. The fetus is exposed to iodine via the placenta, and both maternal iodine deficiency and excess can have profound effects on both mother and offspring.

1.19 Excess iodine may lead to the occurrence of goitre in adults and children.

1.20 Goitre is a condition where a lump or swelling at the front of the neck caused by a swollen thyroid.

1.21 There are currently three health-based guidance values (HGBV) set for iodine. Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a Provisional Maximum Tolerable Daily Intake (PMTDI) of 17 µg/kg bw/day (equivalent to 1020 µg/day for a 60 kg adult) for iodine from all sources. The Expert Group on Vitamins and Minerals (EVM) set a guidance level for iodine of 15 µg/kg bw/day. The European Scientific Committee on Food (SCF) established a Upper Limit (UL) for total iodine intake of 600 µg/day.

1.22 Overall, the Committee concluded that there are no toxicological concerns at the levels of iodine exposure in the general population, however, high consumers of seaweed may be exposed to levels of iodine that could pose a toxicological risk to maternal health. Currently, available data are not sufficient to assess the applicability of the HBGVs to pregnant women, and there is a lack of exposure data in relation to pregnancy and lactation to enable a risk assessment to be performed.

The full COT statement can be found at: Statement on the potential effects that excess iodine intake may have during preconception, pregnancy and lactation | Committee on Toxicity (food.gov.uk).

Statement on the effects of excess Vitamin A on maternal health

1.23 In 2019, SACN agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet. The Committee on Toxicity was consulted, and decided that Vitamin A should be considered for assessment of the risks associated with excess intake.

1.24 Vitamin A (also known as retinol) is found in foods of animal origin (such as liver, paté and cod liver oil) and is also formed in the body when beta-carotene – the colouring matter in red and yellow, and leafy green vegetables – is broken down. The NHS lists significant food sources of vitamin A as cheese, eggs, oily fish, fortified low-fat spreads, milk, yoghurt and liver and liver products such as paté. Significant sources of beta-carotene include vegetables such as carrots, sweet potatoes, red peppers and spinach, and some fruit such as mango, papaya and apricots.

1.25 Retinol is converted, after it is eaten, into other chemical forms that are involved in several biological functions, such as the proper growth of the fetus in pregnancy (in a form called retinoic acid) and how the retina in the eye senses light (in a form called retinal). Most of the effects of vitamin A are caused by retinoic acid, which, among other things, influences bone development and secretion of hormones from the thyroid gland and stimulates the immune system improving resistance to infections. Different chemical forms of vitamin A and synthetic substances that mimic it are also used as medicines, for example, to treat severe acne.

1.26 Although Vitamin A is vital to health and has many benefits, too much of it can cause health problems. A very high dose of vitamin A in the form of retinol can cause tiredness, joint pain, dry skin, headache, sickness, hair loss, drowsiness, liver and bone damage and sight problems. Vitamin A also accumulates in the liver and taking it over a long period of time can cause dry thickening of the skin, cracking of lips, damage to the eyes, skin reddening, hair loss, brittle bones, joint pain, lasting headache, increased pressure inside the skull and liver damage. Some, but not all, of these effects are reversible on reducing vitamin A intake.

1.27 Although it is broken down in the body to produce retinol, eating vegetables that are rich in beta-carotene, or consuming beta-carotene itself, does not result in adverse effects (except possibly high dose supplements in smokers) because less than one-third of beta-carotene from plant sources gets absorbed by the body.

1.28 Eating fat-rich food increases the absorption of vitamin A from the digestive system. The vitamin is carried on proteins in the blood to the liver, where it is stored and then distributed to the rest of the body to perform its functions. Vitamin A is excreted from the body largely in the urine, but as it accumulates in the liver, more is released in the bile, which may prevent the liver from being exposed to too much vitamin A.

Effects of vitamin A on reproduction

1.29 Vitamin A is necessary for the proper functioning of the male and female reproductive systems, both inadequate and excessive amounts can harm the unborn fetus. The statement on vitamin A is concerned with the effects of excessive amounts of vitamin A (rather than inadequate amounts) and ill-effects from over-exposure. Excessive amounts of vitamin A can cause malformations to the fetus that include spina bifida (abnormal development of the spine), small or no eyes, harelip, cleft palate, absent or deformed ears, and deformities of limbs, kidneys, genitals, heart, thyroid gland and skeleton.

1.30 The UK Government recommends that, in order to avoid possible harm to the unborn child, pregnant women, or women thinking about having a baby or trying to conceive, should not consume liver or liver products such as paté, or supplements that contain vitamin A, including fish liver oil, unless they are advised to do so by a doctor. EFSA set a TUL for vitamin A of 3,000 µg per day for women of childbearing age, based on the risk of damage to the liver and to any unborn child. The UK Expert Committee on Vitamins and Minerals (EVM) considered that an intake greater that 1,500 µg per day was “inappropriate”, based on possible effects on bone. The World Health Organisation (WHO) recommends that vitamin A supplements should not be given to pregnant women except to prevent night blindness in places where vitamin A deficiency is a severe public health problem (which does not include the UK).

1.31 Taking food supplements, like fortified food products and vitamin pills, is the most common way for people, including pregnant women and those considering pregnancy, to be exposed to high doses of vitamin A. Scientific studies have surveyed the effects of supplements on development of the fetus in humans where women have taken higher dose supplements during pregnancy. Malformations have been seen, but as the number of women taking these supplements was low, the actual amount of vitamin A that causes deformities in humans remains uncertain.

1.32 Treatment of acne by taking tablets of the drug isotretinoin, a potent synthetic form of retinoic acid, is very effective but has raised concern as a possible cause of malformations when taken by pregnant women. Some countries, including Canada and the EU countries advise women against becoming pregnant while taking isotretinoin. But there are still a few women who become pregnant while taking this drug, putting the fetus at potential risk.

1.33 Treating acne with creams and ointments that contain forms of vitamin A and/or synthetic substances that mimic it, appears to pose a much lower level of risk to the unborn child than treatments given by mouth. However, since these preparations are also known to be able to produce the same adverse effects on the fetus as tablets, when given at a sufficiently high dose, their use is likewise not recommended during pregnancy.

1.34 Concerns have been raised about a link between isotretinoin use and an increased risk of depression and suicide. However, recent evidence suggests that having acne can itself cause depression and hence, if anything, treatment with vitamin A analogues can improve mental health. Nevertheless, as explained above, women who are pregnant or trying to conceive should avoid taking isotretinoin because of the possible risk to the fetus.

1.35 The effects of vitamin A may be affected by:

a. Other components in the diet, including vitamins D, K, C and folate, some fats and zinc,

b. alcohol,

c. Medicines including antibiotics, treatments for fungal infections, drugs for epilepsy, and

d. Chemicals in the environment including biocidal shop antifouling paints (i.e. paints that discourage growth of marine organisms) and flame retardants, for example form furniture.

1.36 One way they can do this is by affecting the rate of breakdown of vitamin A and its active products.

1.37 Consuming large amounts of beta-carotene, for example by eating a lot of carrots daily, may lead to some skin yellowing and a fall in the levels of vitamin A in the liver but, unlike intake of pre-formed vitamin A, studies on animals have shown no ill-effects of beta-carotene on their offspring.

1.38 A study showed that high intake of beta-carotene supplements, as part of a clinical trial, unexpectedly increased the incidence of lung cancer and overall mortality in smokers. However, smoking itself can damage the fetus, regardless of any additional adverse effects caused by consumption of beta-carotene, so women are anyway strongly advised against smoking during pregnancy.

1.39 In parts of Africa and south-west Asia, there is more concern about vitamin A deficiency and the harmful effects this has upon the health of unborn children. In developed countries (like the UK, USA and those in Europe), however, the concern is more about excess intake, as many people regularly consume more than the recommended daily amount, and in some cases, more than EFSA's tolerable upper limit.

1.40 EFSA has estimated that most European adults consume between 816 and 1,498 µg of retinol per day. The UK Government dietary advice, on the NHS.uk website recommends a daily vitamin A intake from food, for those aged 19 to 64, of 700 µg for men and 600 µg for women. Official estimates are that in the UK women between 16 and 49 years of age actually have an intake of between 760 and 2600 µg per day, and the small number who regularly eat liver and liver products such as paté may consume up to 3 times this amount. Supplements containing vitamin A in the form of retinol can add 300 – 906 µg per serving. Pregnant women and women thinking about having a baby are therefore specifically warned to avoid taking supplements containing vitamin A and not to eat liver and liver products to avoid potential harm to the unborn child, unless specifically advised to do so by their Doctor. No other food provides as much vitamin A on its own, although some fortified spreads and "health foods" may, in combination, provide more than the recommended limit.

1.41 Food supplements containing beta-carotene do not have warnings against their use by pregnant women and women thinking about having a baby because this nutrient is considered low risk.

1.42 There is still a lot of uncertainty about how much vitamin A is likely to cause deformities in unborn children, therefore the COT agreed that the current UK Government advice to pregnant women and those planning pregnancy – as set out on NHS.uk website – that they should limit their intake of vitamin A to reduce this risk, remains appropriate.

1.43 The full COT statement can be found at: Statement 04/22 Vitamin A in the maternal diet (food.gov.uk).

Position paper on bamboo composites in food contact materials

1.44 Risk assessment advice on biobased food contact materials (BBFCMs) has been increasingly requested from the Food Standards Agency (FSA), hence it was considered timely for the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to review the available toxicological information on BBFCMs.

1.45 The COT acknowledged the challenges and complexities associated with BBFCMs and highlighted several limitations and knowledge gaps on BBFCMs research and regulation. These included labelling, composition (including biodegradability), contamination and standardisation.

1.46 The COT undertook a more detailed review of the potential health risks of bamboo composites in Food Contact Materials (FCMs) due to the increased number of incidents reported of non-compliant bamboo composite items (e.g. coffee cups) being placed onto the European market.

1.47 Until December 2020, reports in relation to bamboo composite FCMs were predominantly related to misleading labelling on packaging and/or their advertisement, as well as incidences of formaldehyde/melamine migration levels exceeding legal limits. Since 2021, and due to the EU’s conclusion that bamboo is an unauthorised additive within plastic FCMs, reports received by the FSA have predominantly been of non-compliance of plastic-bamboo FCMs in the European market. This included the advertisement of products from UK businesses on EU facing markets. No action appeared to have been taken on that basis prior to this year.

1.48 In 2019, the EFSA panel on FCMs was asked by the European Commission to assess whether the authorisation of untreated wood flour and fibres (FCM no. 96) as an additive in plastic food contact materials was still in accordance with EC Regulation 1935/2004, and also to consider whether bamboo could be considered under the scope of this authorisation. EFSA concluded that wood and bamboo should be considered distinct and each material regarded on a case-by-case basis. In addition, the food safety authorities of Belgium, Luxembourg and the Netherlands (Benelux) published a joint letter calling for the market withdrawal of bamboo-melamine plastics (NVWA, 2021a). In April 2021, the EC recommended that Member States should take stringent action on bamboo composite FCMs and set out a coordinated control plan. The UK FSA is aware of the stance by the EC and of the individual Member States and is

considering an appropriate course of action based on scientific evidence.

1.49 The COT previously assessed the reports by the German Federal Institute for Risk Assessment (BfR) and the Netherlands Food and Consumer Product Safety Authority (NVWA) and noted that the BfR applied their own tolerable daily intake (TDI) of 0.6 mg/kg/day for formaldehyde whereas the NVWA and EFSA used a lower TDI of 0.15 mg/kg/day (BfR 2020; NVWA 2021b; COT 2021c). Overall, the COT concluded that the exposure assessments were conservative but not necessarily worst-case. It was agreed that although the NVWA and BfR opinions took slightly different approaches, in general the same conclusions were reached. Based on the assessment of the BfR and NVWA reports the Committee concluded that the migration of formaldehyde and melamine from bamboo composite cups was a potential concern to human health (COT 2021c).

1.50 Due to insufficient UK data, the COT was unable to make recommendations on bamboo bio-composites FCMs. A UK study assessing the risks associated with bamboo composites and other biobased food contact materials is currently underway. The study aims to address migration levels of formaldehyde and melamine, and also the potential presence of other chemicals, such as heavy metals and pesticide residues. Data from this study is expected to be available in March 2022. Once, UK data is available, a full risk assessment will be undertaken.

1.51 The full COT statement can be found at: COT Position Paper Bamboo Composites.

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

1.52 In 2019 the Scientific Advisory Committee on Nutrition (SACN) agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) were asked to review the risks of toxicity from chemicals in the maternal diet.

1.53 Cadmium is a heavy metal found widely in the environment, coming from both natural sources, such as volcanic activity, and human activities, such as the smelting of metals. Cadmium in the soil, water and air enters the human food chain through being taken up by crops, which are consumed by food

animals. Once in the body, this metal accumulates over many years, where it may cause damage to the kidneys and loss of bone tissue. It can also cause cancer.

1.54 Those of childbearing age (16-49 years) can be exposed to cadmium from food, drinking water, air, dust and ingested soil. Smoking is the main non-dietary source of exposure of cadmium and can lead to a similar internal exposure as the obtained from the diet.

1.55 In 2009, the EFSA CONTAM panel established a tolerable weekly intake (TWI) based on the adverse effect on the kidneys, to determine the level of exposure of people below which there would be no cause for concern. The TWI is defined as the amount of cadmium that can be taken in by a person every week throughout their lifetime without causing adverse effects on health. This value was very low at 2.5 micrograms (millionths of a gram) per kilogram body weight. The COT had previously concluded that the EFSA TWI for cadmium was an acceptable value to use for risk assessment.

1.56 The COT concluded that the levels of cadmium in water, soil and dust only contribute a small amount of exposure and overall, cadmium in the maternal diet does not appear to be a health concern.

1.57 The COT highlighted that the consumption data used for the exposure assessment was for women of childbearing age and therefore may not be fully representative of the maternal diet, leading to an under/overestimation of the actual exposure. The COT also noted that women who give up smoking while pregnant will still carry a higher body burden of cadmium than those who had never smoked.

1.58 The full COT statement can be found at: Cadmium in the Maternal Diet - Introduction | Committee on Toxicity (food.gov.uk).

Statement on the potential effects of excess vitamin D intake during preconception, pregnancy and lactation

1.59 In 2006, the European Commission established a minimum vitamin D content in infant- and follow-on formulae of 1 µg per 100 kcal (Directive 2006/141/EC). Subsequently in 2016, in Commission Delegated Regulation 2016/127, this was doubled to 2 µg per 100 kcal. This new regulation became applicable in Great Britain from the 1st of January 2021.

1.60 In order to inform discussion across the four nations on whether existing advice around vitamin D supplements remains appropriate or needed updating in

light of the increase in the minimum vitamin D content of infant- and follow-on formulae, the FSA conducted an exposure assessment to determine whether this increase could result in infants (0-12 month-olds) and young children (1-4 year-olds) exceeding their tolerable upper levels (TULs).

1.61 A draft statement was prepared which provides an exposure assessment for infants and young children, regarding their vitamin D intake from infant formulae products, vitamin D supplements, and other dietary sources (including breast milk), and comparison to the relevant EFSA TULs.

1.62 The Committee concluded that the new minimum vitamin D content in infant formulae did not lead to excessive vitamin D exposure in infants or young children, as minor exceedances of their respective TULs occurred only when, in combination with other sources such as the recommended supplements, the quantities of infant formula consumed reached 1000 ml. Current NHS guidance is that supplementation is not needed if more than 500 ml infant formula is being consumed. The Committee agreed with the recently revised TUL of 35 µg/person/day for 6-12 month-olds, and also that the exposure assessment indicated that the current guidance did not give rise to any toxicological concerns.

1.63 The full COT Statement can be found at: Vitamin D in infant formula statement.

Potential approaches to address unintentional mixture risks for future UK REACH assessments

1.64 In September 2020, the UK Chemicals Delivery Board had agreed that the Environment Agency should prepare a report on whether the use of a mixture assessment factor (MAF) is a useful approach to address the potential risks arising from unintentional (coincidental) mixtures of chemicals under the UK REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) Regulation. Risks from intentional mixtures are already covered under the current regulatory system. This approach was also being considered by the European Union under EU REACH. Subsequently, the UK Health Security Agency (UKHSA) had agreed that they would work with the Environment Agency to prepare a joint report.

1.65 The COT considered the draft version of the joint EA/UKHSA report on this topic in March and May 2022 to review and comment on the human health aspects prior to finalisation of the report.

1.66 A number of recommendations and comments were made by the COT in March, which were addressed in the version presented in May. The COT recognised that while there were publications hypothesising that environmental mixtures of chemicals might have an additive effect, the evidence available suggested that any potential effects were almost always driven by exposure to a small number of chemicals, even when there were a large number of substances in the mixtures considered. Similar findings had also been reported in three EFSA retrospective cumulative risk assessments of dietary exposure to mixtures of pesticide residues. The Committee noted the lack of research available to address the question of whether there was dose addition for chemicals present in a mixture at concentrations below their health-based guidance values (HBGVs). In many studies, whilst findings at effect levels were consistent with dose addition, they were also consistent with response addition (independent action). Hence, whilst dose addition might be a reasonable default at exposure levels above health-based guidance values, it was highly questionable whether this was the case at lower levels and consequently whether a MAF was needed.

1.67 Overall, the COT agreed with the conclusions of the report and in particular that there was strong scientific evidence within the report to support not adopting the use of a MAF in human health risk assessments.

1.68 The EA/UKHSA report “Evaluation of the potential approaches to risk assessment of unintentional chemical mixtures for future UK REACH assessments” was published following comments from COT and Defra’s Hazardous Substances Advisory Committee (HSAC) and is available from: Evaluation of the potential approaches to risk assessment of unintentional chemical mixtures for future UK REACH assessments - GOV.UK (www.gov.uk).

1.69 Contribution for update paper (2022 paper to give an indication on the level of information is available at: Update on Advice (food.gov.uk).

Potential approaches to address unintentional mixture risks for future UK REACH assessments

1.70 The EA/UKHSA report “Evaluation of the potential approaches to risk assessment of unintentional chemical mixtures for future UK REACH assessments” was published following comments from COT and Defra’s Hazardous Substances Advisory Committee (HSAC) in August 2022, and is available from: Evaluation of the potential approaches to risk assessment of unintentional chemical mixtures for future UK REACH assessments - GOV.UK (www.gov.uk).

1.71 In December 2022, a stakeholder workshop was hosted by Defra to discuss options for addressing unintentional mixtures under UK REACH. The report and the outputs from this workshop will be considered by Defra to inform the development of policy options.

Review of potential risks of Aflatoxin in foodstuffs at the new proposed Codex Alimentarius maximum levels - RESERVED Business

1.72 The FSA asked the Committee to review the toxicity of aflatoxins in certain foodstuffs. This item is currently reserved as it relates to developing policy.

Review of potential risk of Ochratoxin A in spices at the proposed Codex Alimentarius Levels (RESERVED Business)

1.73 The FSA asked the Committee to review the toxicity of Ochratoxin A in spices. This item is currently reserved as it relates to developing policy.

Discussion paper on the request for assessment of a coating in canned food packaging materials

1.74 Members discussed the information provided to the Committee on a can coating as well as the assessment and discussions of the Joint Expert Group on Food Contact Materials (FCM JEG) and sister Committee on Mutagenicity (COM). The work is ongoing, but a final assessment is expected in spring 2023. This item is reserved as the data are commercially confidential.

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Response to EFSA consultation on “Re-evaluation of the risks to public health from bisphenol A (BPA) in foodstuffs”

1.75 In December 2021, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) published a draft opinion re-evaluating the health risks arising from the presence of bisphenol A (BPA) in food. The panel proposed a significant reduction to the current temporary Tolerable Daily Intake (TDI) of 4 µg/kg body weight (bw) to 0.04 ng/kg bw. This reduction would mean that both

mean and high level consumers for all age groups would exceed the new TDI by 2-4 orders of magnitude.

1.76 Due to the size and complexity of the draft opinion, the COT held an extraordinary meeting to discuss it, before feedback was then provided to EFSA as part of their consultation process. The Committee considered the Health Outcome Category (HOC)/cluster approach used by the EFSA CEP panel to conduct the evaluation comparing it to the approach taken by the COT and COC Synthesis and Integration of Epidemiological and Toxicological Evidence subgroup (SETE). The Committee also discussed the benchmark dose modelling used by EFSA including the uncertainty analysis and derivation of the Health Based Guidance Value (HBGV). The Committee then considered the toxicokinetics along with the specific endpoints of immunotoxicity, reproductive and developmental toxicity, neurotoxicity and developmental neurotoxicity, genotoxicity, and other minor endpoints; the approach to epidemiology, metabolic effects, cardiotoxicity, and carcinogenicity.

1.77 The comments agreed by the Committee were submitted to EFSA as part of their public consultation process. The final EFSA opinion is expected to be published towards the end of 2022.

EFSA Draft Opinion for Public Consultation on “Re-evaluation of the existing health-based guidance values for copper and exposure assessment from all sources

1.78 The European Food Safety Authority Scientific Committee were asked by the European Commission to review the existing scientific evidence and all new relevant studies with the aims:

- to provide a scientific opinion on an ADI for copper which can be used as a reference value for copper containing regulated products.
- to take into account all sources of exposure and integrate different approaches and scenarios, to perform a new estimation of the overall copper intake which includes contributions from all major sources of exposure.

1.79 The Committee considered the approach used by the EFSA Scientific Committee to establish the Acceptable Daily Intake (ADI) for copper and the studies used by the Scientific Committee to reach their conclusions. The pivotal studies used by EFSA to determine the HBGV were Turnlund et al., (2005) and Harvey et al., (2003) which examined copper homeostasis. The Committee

discussed these studies and highlighted that there was a limited number of participants which were all male that could have an impact on the reliability of the HBGV. However, it was noted that the homeostatic response would not vary in relation to age, sex or pregnancy.

1.80 In conclusion, the Committee agreed that EFSA's proposed new HBGV of 5 mg per day and the harmonised approach used to establish it were acceptable.

1.81 The comments agreed by the Committee were submitted to EFSA as part of their public consultation process.

Draft FSA/HSE/VMD report on approaches to chronic dietary exposure assessment for chemicals in food

1.82 The COT was asked to comment on a report drafted by FSA, the Health and Safety Executive (HSE) and the Veterinary Medicines Directorate (VMD) on approaches to chronic dietary exposure assessment for chemicals in food. The draft report was also being taken to the Expert Committee on Pesticides (ECP) and the Expert Committee on Pesticide Residues in Food (PRiF) for comment before being finalised.

1.83 The work had been undertaken because there were differences in the current approaches to chronic dietary exposure assessments undertaken by the HSE for pesticides, VMD for veterinary medicines and FSA for chemical contaminants and other chemicals in food. Furthermore, there were differences in how these assessments were conducted internationally for pesticides and emerging differences for veterinary medicines. In addition, following exit from the EU, it was timely for UK regulators to consider the approaches they might wish to take in the future.

1.84 The draft report discussed the principles of dietary exposure assessments and described the current approaches to chronic dietary exposure assessments being taken by the FSA and for pesticides and veterinary medicines. It discussed the current differences in approach and the reasons for them, uncertainties in exposure assessments, considered the possibilities for common approaches to be taken in the future and the approaches to substances with multiple uses (e.g. as both pesticides and veterinary medicines). It also included some considerations on cumulative and aggregate exposure assessment and referred to the recent considerations of less than lifetime and variable exposure over a lifetime by the COT and COC.

1.85 The draft report made a number of recommendations. These included increasing collaboration between FSA, HSE and VMD on topics such as exposure assessments for substances with multiple uses, the setting of common Maximum Residue Levels (MRLs) and Health Based Guidance Values (HBGVs), and on methodologies for cumulative risk assessments; continuing international collaborations; periodically reviewing exposure assessment methodologies for fitness for purpose and considering their uncertainties; and having up-to-date comprehensive food consumption data, which are contained within a central database to which staff from each of the departments/agencies have access and training on their use.

1.86 The COT advised that the recommendations be separated out from the conclusions. The FSA's approach was noted to be usually closer to actual consumer exposures compared to regulatory approaches for approvals of pesticides and veterinary medicines. If joint exposure assessments were to be performed it would need to be agreed what degree of conservatism there should be. The COT supported the desire for more information on cumulative and aggregate exposures but the methods were not fully developed yet and there were still improvements that could and should be made to exposure assessments for single substances first. Probabilistic modelling was included in the report as a high tier model but that was not being conducted to much extent at the moment, though the software was available and it could be used more. There was also agreement with the recommendation of a central database for food consumption data.

1.87 The COT considered that it was a good idea to conduct exposure assessments more consistently across chemical areas; however, it was noted that for applicants there was also the international consideration and to them it would be preferable for there to not be too many differences in the approaches used between regions internationally, e.g. between the UK and Europe.

1.88 The COT noted that EFSA had taken one approach to the cumulative risk assessments of pesticides and a different approach to other chemicals. While they had produced guidance it was not clear whether they were currently routinely undertaking cumulative risk assessments for chemicals other than pesticides. Where such cumulative risk assessments had been performed, a constrained approach tended to have been taken, for example, grouping chemicals in the same regulatory area that have similar structures. At present, there did not appear to be have been any move to conder, for example, all chemicals across all sectors that cause hepatic steatosis as a single group, for

regulatory purposes. The COT suggested that the report should recognise the difficulties as well as the possibilities of performing combined exposure assessments across different regulatory areas.

1.89 The COT observed differences in the age ranges being used currently to define infants and children, asked for justification for the use of the 97.5th percentile to represent high consumers to be included in the report, and discussed the extent to which the National Diet and Nutrition Survey (NDNS) adequately covered ethnic groups and groups such as vegans. The NDNS reflected the whole population but focused studies would be needed to reflect the consumption patterns of groups that comprise only small percentages of the entire population, to ensure their adequate statistical characterisation.

1.90 It was noted that exposure assessors are constrained by the data that they can obtain. For example, JECFA and JMPR do not have access to consumption data with the level of granularity that the FSA has, and hence would have considerable difficulties in performing probabilistic modelling.

1.91 The draft report would be revised and published after the ECP and PRiF had also commented.

Statement on the EFSA Opinion on the risks to human health related to the presence of perfluoroalkyl substances in food

1.92 The European Food Safety Authority (EFSA) was asked, by the European Commission, to prepare an Opinion on the risks to human health related to the presence of perfluoroalkylated substances (PFASs) in food, and to consider existing hazard assessments and available occurrence data. The statement was published in September 2020.

1.93 The Committee on Toxicity of Chemicals in Food, Consumer products and the Environment (COT) have reviewed the “EFSA Opinion Risk to human health related to the presence of perfluoroalkyl substances in food” (2020) alongside UK exposure data to assess the potential risks to the UK population from PFASs (predominantly through exposure via the diet).

1.94 Per- and polyfluoroalkyl substances (PFASs) with a minimum of six carbons in their backbone, are a class of over 12,000 fluorinated substances (US EPA CompTox Dashboard 2022). They have been produced since the 1940s and are, or have been, used in a broad range of consumer products and industrial applications (Glüge *et al*., 2020). Their structure enhances their utility in a variety

of applications including the production of water- and oil-resistant clothing, electronics, non-stick cookware, carpets, and food packaging materials.

1.95 Many PFASs are environmentally long-lived and individuals are exposed to them through all environmental sources, i.e. drinking water, air, dust, and the diet and through the placenta and breastfeeding for developing offspring (Sunderland *et al*., 2019).

1.96 The tolerable weekly intake (TWI) was established by EFSA based on epidemiological studies of an effect on the immune system, as this was considered, by the EFSA CONTAM Panel, to be the critical effect. Two studies on this (Abraham *et al*., 2020 and Grandjean *et al*., 2012) were considered by EFSA as suitable for hazard characterisation. One of these studies, Abraham *et al.* (2020), was amenable to dose-response modelling (i.e. analysis of the response of an organism, as a function of exposure (or doses) to a chemical after a certain exposure time); which resulted in a benchmark dose limit value (BMDL10) for blood serum of 17.5 ng/mL for the sum of the four main PFASs present. This value was then used as the reference point to calculate the corresponding tolerable daily intake for a mother, to protect their offspring, considered the most sensitive population, which was 0.63 ng/kg body weight (bw) per day. This was then converted to a weekly value, because of the long persistence of PFASs in the body, the TWI, of 4.4 ng/kg bw per week for the sum of the four PFASs PFOS, PFOA, PFHxS and PFNA, for use as the health-based guidance value.

1.97 The COT agreed that, on the basis of the information reviewed by EFSA, qualitatively the appropriate health endpoint had been selected but quantitatively, questioned the calculations. Overall, there were some reservations about the choice of the critical study (Abraham *et al.*, 2020) and the specific effect that was selected. However, the COT agreed that the critical study was the best available; and, in the absence of more appropriate studies, its use was understandable. Therefore, it was not unreasonable that this study was selected.

1.98 The COT had significant reservations about the dose-response model used, including the modelling approach, and the TWI which had been established, due to the uncertainties and the caveats involved.

1.99 The COT agreed that the use of the sum of the four PFASs was acceptable as a first approximation for exposures of PFASs but had reservations about the calculations due to the uncertainties.

1.100 The diet is the predominant route of exposure to PFASs, however, other possible sources of exposure include dust by ingestion and indoor air by inhalation, and these exposures have been considered. There may also be some exposure via the skin, however these have not been calculated.

1.101 The values for the BMDL and TWI were low and there was a lot of uncertainty surrounding the data used by EFSA.

1.102 Estimated breast milk exposures for UK infants all exceed the TWI of 4.4 ng/kg bw per week. However, EFSA cautions that “the higher exposure of breastfed infants is taken into account in the derivation of the TWI (i.e. it is assumed that those later exposed have already received this exposure) and the intake by infants should therefore not be compared with this TWI”.

1.103 Blood serum level modelling of the four PFASs indicates that the lower bound estimates of exposure (assuming that levels below detection are zero) is a more accurate prediction of the exposure than the upper bound estimates (assuming that levels below detection are present at that level), which would lead to a much higher exceedance of the critical blood serum levels. Lower bound mean estimated dietary exposures for adolescents, adults, the elderly and the very elderly approximate the TWI, that for other children is approximately twice the TWI, and for infants and toddlers are several times the TWI.

1.104 Estimated exposures from household dust at average median PFASs concentrations for all UK populations, for individual PFASs, are below the TWI. For exposures estimated from average maximum PFASs concentrations in household dust the TWI is exceeded for PFOS, PFOA and PFHxS by infants, toddlers and children.

1.105 The EFSA CONTAM Panel, in their evaluation of PFASs, assessed exposure both to individual compounds and using a mixtures approach (i.e. a probabilistic model for representing the presence of subpopulations within an overall population, without requiring that an observed data set should identify the sub-population to which an individual observation belongs) for the sum of four PFASs: PFOS, PFOA, PFHxS and PFNA. All exposure estimates were compared to the TWI of 4.4 ng/kg bw per week. The CONTAM Panel considered that the impact of the uncertainties on the risk assessment for the sum of PFOA, PFNA, PFHxS and PFOS is high.

1.106 The exceedances of the TWI at lower bound exposure estimates indicate a potential health concern.

1.107 Whilst the COT is unable to suggest an alternative TWI at this time due to the lack of data, there are strong caveats when comparing the exposure estimates with the TWI established by EFSA. There is considerable uncertainty as to the appropriateness of the derivation of the TWI and of the biological significance of the response on which it is based.

1.108 The COT suggested that in future reviews it could use the averages for exposures for the four PFASs added together to provide a reasonable estimation of combined PFASs exposure for comparison to the TWI.

1.109 The full statement can be found at: Statement on the EFSA Opinion on the risks to human health related to the presence of perfluoroalkyl substances in food .

Response to draft EFSA opinion on the human health risks related to the presence of N-nitrosamines (N-NAs) in food

1.110 EFSA published a draft Scientific Opinion on the human health risks related to the presence of N-nitrosamines (N-NAs) in food for consultation October 2022. The COT were asked to provide comments on this draft.

1.111 Nitrosamines are the reaction products formed from nitrosating agents, such as nitrites or nitrogen oxides, and amino-based substances, such as secondary amines. They may be formed in a variety of foods (e.g., cured meat products, processed fish, beer and other alcoholic and non-alcoholic beverages, cheese, soy sauce, oils and processed vegetables) under processing conditions in the presence of these reactants.

1.112 It was considered that the draft Opinion provided a good summary in terms of ADME and genotoxicity data. It was commented that the main issues open to question were the method of benchmark dose (BMD) analysis and how compounds were aggregated (grouped).

1.113 Positive feedback was provided on the draft Opinion, which Members considered to be a comprehensive review of the topic. The comments agreed by the Committee were submitted to EFSA as part of their public consultation process.

Ongoing Work - COT 2022

In this guide

Lead in the Maternal Diet

1.114 As part of the work on the maternal diet, the COT was asked to consider the potential effects that excess lead intake may have in the maternal diet.

1.115 Lead is a heavy metal that occurs naturally in the Earth's crust, chiefly as lead sulphide (PbS). Lead is ubiquitous in the environment and is thus present in the diet of the general population, including women of childbearing age. Despite this, dietary levels have fallen since the phasing out of lead in petrol, plumbing and paints.

1.116 Potential risks from maternal exposures to lead were characterised by margins of exposure (MOEs), calculated as the ratio of the benchmark dose level (BMDL) to estimated exposures from diet, soil and air. A BMDL01 has been set for the reduced development of intellectual function in offspring. Specifically, a dietary exposure of 0.5 µg/kg bw/day was associated with a 1% change in full scale IQ score (EFSA 2010).

1.117 As the BMDL was for a small effect, it is likely to be conservative and protective for all other adverse effects of lead in all populations, including the mother. EFSA concluded that a margin of exposure of 10 or greater should be sufficient to ensure that there was no appreciable risk of a clinically significant effect on IQ. At lower MOEs, but greater than 1, the risk is likely to be low, but not such that it could be dismissed as of no potential concern (EFSA, 2010). In 2013, the COT added that an MOE of >1 can be taken to imply that at most, any risk is likely to be small. MOEs <1 do not necessarily indicate a concern, but scientific uncertainties mean that a material risk cannot be ruled out.

1.118 Lead was initially discussed at the February 2022 COT meeting. The Committee considered issues such as exposure to food, drink and air. It was determined that other sources of exposure should also be considered such as soil and dust due to the ubiquitous nature of lead in the environment; this was discussed at the May 2022 meeting.

1.119 It was concluded that while MOE values were ≥1 for all exposure scenarios, lead toxicity would depend on total exposure from all sources, therefore an aggregate exposure to determine an overall likely level of risk was appropriate.

1.120 A statement setting out the views of the Committee on will be published in 2023.

Potential risk to human health of turmeric and curcumin supplements

1.121 The FSA has been monitoring incidents related to consumption of raw and powdered turmeric and its supplements. In light of these incidents and due to the uncertainties surrounding the composition and possible contamination of these commodities, the COT was asked to comment on the risk to human health from turmeric and curcuminoids in their various forms which include supplements.

1.122 To aid this discussion a survey of 30 products was undertaken by Fera Science Ltd in 2021. All samples were analysed for the curcuminoids: curcumin, bisdemethoxycurcumin (BDMC) and demethoxycurcumin (DMC) as well as the black pepper derived alkaloid, piperine; and a comprehensive analysis of 69 trace elements which included the heavy metals lead (Pb), mercury (Hg), arsenic (As) and cadmium (Cd). A further 70 turmeric products were analysed for Pb in 2022.

1.123 After reviewing the results of the survey, the Committee concluded that Pb contamination of turmeric products was not likely to be the reason for hepatotoxicity incidents.

1.124 The COT further concluded that substantial exceedances of the dietary ADI, which may occur from consumption of currently available supplements, represented a potential health risk to humans, especially if other medicines are being taken concomitantly and for individuals with altered hepato-biliary function. Furthermore, in rare individuals, consumption of turmeric at the levels found in supplements, even at low concentrations where exposure was below the ADI) may pose a risk of adverse effects to the liver, due to idiosyncratic responses. This possibility of an unexpected idiosyncratic response should be considered when providing guidance on the use of such supplements.

1.125 A final COT statement is due to be published early 2023.

Oral Nicotine pouches

1.126 The COT was requested by the Tobacco team in the Office of Health Improvement and Disparities at DHSC (OHID) to consider the toxicological risk for nicotine-free or nicotine pouches.

1.127 In 2022, the COT discussed updated paper providing publicly available data on the ingredients in these products along with an assessment of the oral bioavailability of nicotine. Following this, a first draft statement was presented on

the bioavailability of nicotine from the use of oral nicotine pouches and assessment of the potential toxicological risk to users.

1.128 The COT agreed with the overall conclusions presented in the statement; several minor comments on the general structure and content of the draft statement would be addressed by correspondence. It is anticipated that the statement would be finalised in 2023.

Risk assessment of potential constituents and contaminants in cow's milk

1.129 Plant-based drinks have become increasingly popular in the United Kingdom (UK) both for individuals with an allergy to cows' milk or lactose intolerance and those who wish to avoid dairy products for other ethical or cultural reasons.

1.130 Current UK Government advice regarding the use of plant-based drinks for infants and young children is that unsweetened calcium-fortified plant-based drinks, such as soya, oat and almond drinks, can be given to children from the age of 12 months as part of a healthy balanced diet; rice drinks should not be given due to the levels of arsenic in these products (NHS, 2018).

1.131 The Committee agreed during their meeting of July 2021 the main comparator for plant-based drinks should be cow's milk and that a discussion paper should be produced looking at the potential chemical risks in the consumption of this for the population group of interest, children aged 6 months to 5 years.

1.132 Over the course of 2021 two discussion papers were produced reviewing a range of compounds found in cow's milk. The compounds covered included veterinary medicines, pesticides, nitrate and nitrite, bisphenol A, phthalates, dioxins and dioxin-like biphenyls, non-dioxin-like polychlorinated biphenyls, polycyclic aromatic hydrocarbons and isoflavones. A selection of heavy metals, iodine, chlorate and perchlorate, mycotoxins, naturally occurring oestrogens in cows' milk, insulin like growth factor, per- and polyfluoroalkyl substances, brominated flame retardants and microplastics were also considered.

1.133 Following this work, over the course of 2022 two draft statements were drafted and presented for the COT regarding cow's milk. Within these draft statements, iodine and aflatoxin M1 were indicated as being of low concern and risk relating to isoflavones was considered uncertain due to a lack of health-based

guidance values for young children.

1.134 A final statement will be published in 2023.

Microplastics – exposure via the inhalation route

1.135 As part of horizon scanning exercise, the COT identified the potential risks from microplastics as a topic it should consider to inform Food Standards Agency (FSA) discussions on this. Since then, several discussion papers have been presented to the COT and in 2021, an overarching statement on the potential risks from exposure to microplastics was published (COT Statement 2021/02). This provided a high-level overview of the current state of knowledge, data gaps and research requirements with regards to this topic. This was followed by a sub-statement which considered the potential effects of oral exposure to microplastics in more detail.

1.136 As there is evidence for the presence of plastic particles in both indoor and outdoor air inhalation is a possible route of exposure. The Committee is therefore discussing a sub-statement on inhalation exposure to microplastics to provide more detailed, supplementary information on this topic.

1.137 A final statement will be published in 2023.

Chitin and chitosan in food packaging materials

1.138 The COT is currently assessing whether there are any potential health risks posed by bio-based food contact materials (BBFCMs). One of the first materials to be reviewed was food packaging materials which contain chitin or chitosan.

1.139 Chitin and chitosan can be derived from fungi, insects, or shellfish. As there are potential concerns for allergic individuals, the Committee agreed that during its manufacture, the protein content in the specification of chitosan needs to be considered.

1.140 The Committee noted that due to a scarcity of relevant data in the scientific literature, it is not currently possible to undertake a reliable exposure assessment due to the uncertainties involved.

1.141 The COT further noted that whilst the risk of allergenicity from these BBFCMs appears to be low, it would be useful to have an indication or estimation of total exposures to allergenic proteins from BBFCMs, for example the upper

bound levels of ingestion, or range of amounts of BBFCMs in contact with different foods.

1.142 A position paper on chitosan will be prepared in 2023.

Statement paper on the guidance levels for the fortificants in the bread and flour regulations

1.143 The Bread and Flour regulation (BFR) stipulates the levels of calcium carbonate, iron, thiamin (also known as vitamin B1) and nicotinic acid that must be present in flour. In 2022, the Department for Environment, Food and Rural Affairs (Defra) held a consultation on the BFR 1998 review and asked whether the consultees agreed with the proposal to raise the minimum levels of calcium carbonate, iron and niacin added in non-wholemeal wheat flour to 15% of the nutrient reference values (NRV) supplied by 100g of flour as stated in point 1 of Part A of Annex XIII of regulation EC No. 1169/2011. NRVs are established guidelines for the recommended daily energy and nutrient consumption. The minimum amount of thiamin required to be present in non-wholemeal wheat flour will remain the same at 19% of the NRV.

1.144 The COT were asked by DHSC to provide a risk assessment on the dietary exposure of calcium carbonate, iron, nicotinic acid and thiamin at the current and proposed fortification levels to identify if there were any potential adverse health effects. The Committee considered the the potential exposures from the proposed changes and the adverse effects associated with high calcium, iron and thiamine intakes.

1.145 Acute and chronic intakes for all minerals (calcium, iron niacin and thamin) at the current and proposed fortification levels in food did not exceed the levels considered to be acutely toxic and were not considered to be a health concern.

1.146 Intakes of calcium from supplements alone did not exceed the guidance level. However, daily intakes of iron, niacin and thamin from supplements alone may result in exceedance of Health Based Guidance Values when higher dosage supplements are consumed. However, not all of the population consume supplements. Therefore, any potential health risks will only occur in individuals who consume high dosage iron, niacin and thiamin supplements.

1.147 Intakes of calcium from both food and supplements would not result in exceedance of HBGVs for calcium. However, intakes of iron, niacin and thamin

from food and supplements combined could lead to these being exceeded. Given, that exceedance occurs from supplement consumption alone, the exceedances of iron, niacin and thiamin here would only be of toxicological concern to individuals that also consume high dosage of iron, niacin and thiamin through supplements.

1.148 Overall, the COT concluded that the proposed increased in the fortification level of calcium, iron and niacin in non-wholemeal flour would not result in any excess risk. However, there would be a possible exceedance in individuals that consume supplemental iron, niacin and thiamin alongside food containing and/or fortified with these minerals.

1.149 A final statement will be published in 2023.

Ginger in the maternal diet

1.150 As part of the current programme of work on the maternal diet, the Committee considered the use of herbal dietary supplements during pregnancy. These were supplements that were not officially recommended by the relevant authorities, but which were promoted by anecdotal evidence and unofficial sources as having various purported benefits. Ginger was identified as one of the supplements that should be considered in more detail.

1.151 Ginger (**Zingiber officinale**) is a flowering tropical plant originating in Southeast Asia and grown in warm climates including China, India, Africa and the Caribbean. The rhizome (underground stem) of the ginger plant is commonly used as a spice and flavouring in many countries around the world and is increasingly growing in popularity as a natural remedy due to its purported immune system-boosting properties and also for motion sickness and post-operative nausea and vomiting.

1.152 The COT have previously reviewed the potential effects of ginger and in particular, the use of ginger supplements during pregnancy and lactation, reviewing the available data on toxicity to the mother, effects on the development of the fetus or embryo, and possible interactions with medicines. In 2022, the Committee worked on a statement setting out their views. The statement is being revised to include information on the National Institute for Health and Care Excellence (NICE) and the European Medicines Agency (EMA) guidelines available on the on the use of ginger for nausea in pregnancy. And clarification on the exposure to ginger in the form of concentrated drinks and shots.

1.153 Further, the weight of evidence on spontaneous abortion as an outcome should be considered, along with the probability of this effect.

1.154 The statement will be finalised by the COT in 2023.

The potential risks from ergot alkaloids in the maternal diet

1.155 As part of the ongoing programme of work on the maternal diet, the Committee were asked whether exposure to ergot alkaloids (EAs) would pose a risk to maternal health.

1.156 Ergot alkaloids (EA) are secondary metabolites produced by the fungi families **Clavicipitaceae** and **Trichocomaceae**, with Claviceps purpurea being the most widespread **Clavicepsspecies** in Europe. Based on their occurrence and the available toxicological data the European Food Safety Authority (EFSA) considered six EAs in their risk assessment in 2005, namely: ergotamine, ergocornine, α-ergocryptine, ergosine, ergocristine (peptide ergot alkaloids) and ergometrine (a lysergic acid amide). EFSA further included both forms (-ine and inine) in their assessment, while the -inine forms are considered biologically inactive interconversion occurs under various conditions (EFSA, 2005, Tasker and Wipf, 2021). Bromocriptine is synthetic ergoline derivate and it is used in the treatment of Parkinson’s disease and pituitary tumours (Herdman et all., 2001).

1.157 The EA were discussed at July 2022 COT meeting. The Committee considered information on toxicology, metabolism and dietary exposure presented in the paper and raised a number of questions along with suggestions for data that should be considered. However, overall, Members considered that EAs would not have adverse effects on maternal health at likely levels of exposure.

1.158 A statement will be prepared by the COT in 2023.

Raspberry Leaf tea in the maternal diet

1.159 As part of the current programme of work on the maternal diet, the Committee considered the use of herbal dietary supplements during pregnancy. These were supplements that were not officially recommended by the relevant authorities, but which were promoted by anecdotal evidence and unofficial sources as having various purported benefits. Raspberry leaf tea was identified as one of the supplements that should be considered in more detail.

1.160 Raspberry leaf was most commonly taken during pregnancy for its purported effects in stimulating and facilitating labour and in shortening its duration.

1.161 Members considered that it was not possible currently to derive a point of departure to be used in the risk assessment of raspberry leaf use during pregnancy, based on the data presented. There were numerous reasons for this.

1.162 It was agreed that a draft statement would be prepared in 2023 specifically cross-referencing the COT's previous work on some of the components of raspberry leaf, such as polyphenols.

Green tea catechins

1.163 The COT had been asked by the FSA to evaluate green tea catechins and the associated probable idiosyncratic hepatotoxicity. This was following a request from the Nutrition Labelling Composition and Standards (NLCS) Common Framework, on behalf of the UK to evaluate whether the conclusions of the 2018 EFSA opinion on the safety of green tea catechins were still applicable considering any new scientific data that may have become available since its adoption. This would enable the NLCS to consider the next steps for the risk management of these compounds.

1.164 The 2018 EFSA Opinion concluded that catechins (principally - epigallocatechin-3-gallate (EGCG), from infusions or in reconstituted drinks are generally considered safe. However, rare cases of liver injury have been reported after consumption of green tea infusions, most probably due to an idiosyncratic reaction. Based on the available data on the potential adverse effects of green tea catechins on the liver, there is evidence from interventional clinical trials that intake of doses equal to or above 800 mg EGCG/day taken as a food supplement has been shown to induce a statistically significant increase of serum transaminases in treated subjects compared to control.

1.165 A statement on green tea catechins will be published in 2023.

How the Committees evaluate the relevance and reliability of data when assessing a chemical of concern

1.166 The COT, COC and COM have continued to develop the joint non-technical statement on how the Committees evaluate the relevance and reliability of data when assessing a chemical of concern in 2022. An updated version was presented

to the COT in July. Further revisions are expected to be considered by correspondence across all three Committees in 2023.

An update of the COT position on aircraft cabin air

1.167 In 2007, the Committee on Toxicity (COT) published a statement on aircraft cabin air, having been asked by the Department for Transport (DfT) to undertake an independent scientific review of data submitted by the British Airline Pilots Association (BALPA) relating to organophosphate (OP) compounds, the cabin air environment, ill-health in aircraft crews and the possible relationship to smoke/fume events in aircraft, due to concerns about the possible effects on aircrew health of oil/hydraulic fluid smoke/fume contamination incidents in commercial aircraft (COT, 2007).

1.168 In 2013, DfT asked the COT to undertake an independent scientific review of the results of DfT-funded aircraft cabin environment research commissioned in response to recommendations made by COT in 2007, after which the COT issued a position statement on cabin air (COT, 2013).

1.169 The COT has now been asked by DfT to investigate any new data that have been published and to re-evaluate their previous views, and in particular consider the question “Is there evidence of exposure to chemical contaminants in cabin air that could have long-term health impacts, either from acute exposures or due to long-term low level exposures including mixtures, e.g. of volatile organic compounds (VOCs)?”.

1.170 In 2022, the Committee considered papers on an updated literature search on the potential health risks from organophosphate exposure in aircraft cabin air, an assessment of the concentrations of VOCs in aircraft cabin air compared with other modes of transport and other work environments, and a paper on carbon monoxide and carbon dioxide in aircraft cabin air.

1.171 Further papers will be considered in 2023, before the Committee publishes an updated position.

COT FSA Paving the way for a UK Roadmap: Development, Validation and Regulatory Acceptance of New Approach Methodologies (NAMs) in Chemical Risk Assessment – Development of a UK road map and Workshop Report

1.172 The FSA and COT are developing a UK roadmap towards acceptance and integration of New Approach Methodologies in chemical risk assessment, including predictive toxicology methods using computer modelling, into safety and risk assessments for regulatory decision making. The first draft of the road map was discussed in June 2021.

1.173 A 2-day workshop was then held in October 2021 with the intention of gaining insights from a variety of perspectives to help develop the COT FSA UK Roadmap.

1.174 The aim of the workshop was to receive insights, comments and ideas from a wide variety of stakeholders, industry, academia and government, on the roadmap. The idea was to develop it into a useful and engaging document that is of value to more than just the FSA and COT. The workshop addressed issues such as: what might be holding back the progress of NAMs being used in the regulatory space, including a range of areas such as socio-technical barriers, regulatory frameworks and current legislation.

1.175 Members were content with the first draft of the workshop report. Some suggestions on restructuring the introduction were made along with some minor edits.

1.176 The finalised report will be published next year. A third draft version of the roadmap will be published in 2023.

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Assurance of Joint Expert Group opinions

1.177 The Joint Expert Groups (JEGs) were established by the FSA to assess applications for the authorisations of regulated products that were previously authorised by the European Food Safety Authority (EFSA). The three JEGS were FCM JEG which covers food contact materials, AFFAJEG which has responsibility for animal feed and feed additives, and AEJEG which has responsibility for food

additives, enzymes and other regulated products. The COT provides support, challenge and assurance to the work of the three JEGS as set out below. In 2022, AFFA JEG was superseded by the reconstitution of the Advisory Committee on Animal Feeding stuffs (ACAF).

Draft Opinion on the extension of use of polyglycerol polyricinoleate

1.178 The COT considered a Risk Assessment prepared by the Joint Expert Group on Additives, Enzymes and other Regulated Products (AEJEG) regarding a n Application for the extension of use of PGPR in edible ices and emulsified sauces (RP217).

1.179 This item was reserved as it covers a draft AE JEG opinion on an application for the extension of use of the additive polyglycerol polyricinoleate, this is treated as draft policy.

1.180 A statement will be published in 2023.

Draft Opinion on the safety of the extension of use of mono- and di- glycerides (E471) for use as a surface treatment of fresh fruits and vegetables

1.181 The COT considered a Risk Assessment prepared by the AEJEG regarding an Application for the extension of use of mono- and di- glycerides for use as a surface treatment of fresh fruits and vegetables.

1.182 This item is currently reserved as it covers a draft AE JEG opinion on an application for the extension of use of the additive E471, this is treated as draft policy.

1.183 A statement will be published in 2023.

Evaluation of renewals of Smoke Flavourings authorisations

1.184 Smoke flavourings are covered by Retained EU Regulation 2065/2003 and therefore need to be authorised before they can be placed on the market in Great Britain (GB). Smoke flavouring primary product authorisations are applicant specific and are valid for 10 years. The current authorisations end in January 2024.

1.185 The FSA has received 8 applications requesting a renewal of the authorisation of smoke flavourings in June 2022, which will be evaluated by the AEJEG. The COT have been kept updated on the progress of these applications.

1.186 The AEJEG meetings for the evaluation of these Applications will commence in the first quarter of 2023.

1.187 This item was discussed as reserved business.

Presentations

UK legislation on Food Contact Materials – an overview – Presentation by FSA FCM policy team

1.188 In light of COT discussions on Biologically-Based Food Contact Materials such as bamboo composites and chitosan as well as anticipated items on ocean bound plastic (OBP) and the COT's remit to review the output of the Joint Expert Group on Food Contact Materials (FCM JEG), it was considered that an overview of the regulations covering food contact materials would be beneficial.

1.189 FSA policy colleagues provided a brief overview of the overarching food contact material legislation. This included a summary of the enforcing regulations for the UK, which are the Materials and Articles in Contact with Food Regulations 2012 (as amended). The regulations for Great Britain (England, Wales and Scotland) enforce retained Regulation 1935/2004 ("the framework regulation") and 10/2011 ("the plastics regulation"), with the current EU Regulations continuing to be applicable in Northern Ireland under the terms of the Northern Ireland Protocol.

1.190 All bio-based food contact materials need to meet the requirements under the retained framework regulation, including good manufacturing practice requirements. Depending on their composition some bio-based food contact materials are additionally required to adhere to the requirements under the retained plastics regulation. Finally, bio-based food contact materials are not regulated products in themselves but applications for such substances may need to be made should the business operator wish to use it in a material that falls under the scope of the plastics regulation.

1.191 Advanced materials may be categorised as active and intelligent materials and therefore would need to meet the additional requirements under retained Regulation 450/2009 ("the active & intelligent materials regulation"). Business

operators have a responsibility to ensure that they are aware of the individual components of a material or article and are adhering to the requirements of the relevant regulations. Should the individual components of a material or article not fall under the scope of the additional measures, the default is that it must meet the catch-all framework and good manufacturing requirements. However, the plastics regulation does include multi-component plastic containing materials.

1.192 The EU would be implementing (and since have in October 2022) a new recycled plastics regulation and also have new proposals for legislation on FCMs in general, with a consultation running until the end of January 2023. The FSA will consider appropriate options regarding the updating of retained legislation following the EU proposals. This will provide clarity to operators if they are placing material on the UK or EU markets or both. Environmental considerations are also being taken into account as are other legitimate factors. Ultimately however, the legislation has to ensure that products placed on the market are safe for consumers with no adverse health implications.

1.193 Following the presentation, the Committee discussed the practical implications of regulations for testing that needs to be carried out for a new bio-based material. It was noted that a number of steps would need to be adhered to by the business operator given that the material is unlikely to have been previously used in a food contact material scenario). If the material is expected to be used, for example, in multiple material types, different food contact applications or are multifunctional, business operators will need to ensure that they are carrying out appropriate due diligence. They are responsible for ensuring that final products have undergone the appropriate testing and are safe in expected use.

1.194 The Committee acknowledged that while not directly the topic of the discussion, in some situations, i.e. for non-food applications, the food contact regulations may not be entirely applicable for the product produced and therefore, a cross-cutting approach might be needed (examples such as medical devices and biocidal products).

1.195 There continues to be close collaboration between FCM policy at the FSA and other Government Departments, allowing the business operator to be signposted to the relevant Department.

PhD Student and Postdoctoral Fellow presentations

1.196 The FSA and COT have been considering New Approach Methodologies (NAMs) in order to understand the best scientific methodologies available for use in the risk assessment of chemicals, and to consider how these can be incorporated and accepted in a regulatory context.

1.197 In 2021, the FSA started funding a computational toxicology postdoctoral Fellow at the University of Birmingham and a PhD Student at King's College London as part of their Interdisciplinary Doctoral Program (LIDo-TOX AI). The Fellow and PhD student have been working alongside other Government Departments to understand how NAMs will improve indicative levels of safety in chemical risk assessment.

1.198 In addition, these new partnerships have helped with networking, research collaboration, training opportunities and other activities in this area. The Fellowship and studentship also compliment the work set out in the COT FSA UK Roadmap towards (see paragraph 1.169) using NAMs in chemical risk assessment.

1.199 The Postdoctoral Fellow and the PhD student prepared a yearly review and gave presentations to the Committee on their progress to date.

1.200 The Postdoctoral fellow presented two case studies. The first of these focused on the plasticiser di-2-ethylhexyl terephthalate (DEHTP). The main objective was to derive a health-based guidance value. Concentration-response data obtained from ToxCast studies, via the Chemicals Dashboard (US Environmental Protection Agency (EPA)), were used. The second case study had, as chemical of choice, a perfluorinated substance, perfluorooctanoic acid (PFOA). The main objective was to integrate an in silico workflow with transcriptomics data to derive a health-based guidance value for PFOA that could be compared with that previously recommended by EFSA. Transcriptomics data published by Health Canada were used as a data source from in vitro exposures of Human Liver Microtissues (a commercial preparation of spheroids comprising primary hepatocytes and Kupffer cells) to PFOA.

1.201 The PhD student presented on the hybrid Quantitative Structure Activity Relationship (QSAR) model of mutagenicity developed by the Kings College team, which is, on average, 78% accurate at predicting mutagenicity. The hybrid model consists of two constituent QSAR models which individually are approximately 70% accurate on average. The first QSAR model used molecular fingerprint-based similarity index calculations, whereas the second QSAR model used molecular fragmentation, to identify pro-mutagenic characteristics. Principal

component analysis (PCA) was successfully used to identify the key determinants of the predictions.

1.202 The COT Members were impressed with the progress to date and gave feedback to the fellow and PhD student.

Opportunities and outlook for UK food and Chemicals regulation post EU exit Workshop

1.203 The COT, UKHSA and FSA organised a workshop in July 2022 held in Liverpool on “Opportunities and outlook for UK food and Chemicals regulation post EU exit”.

1.204 The workshop was to build on the successful: Royal Society of Chemistry (RSC) Workshop of 2019 : Drivers and scope for a UK chemicals framework.

1.205 The 2019 RSC workshop examined where chemicals regulation might be in the post EU exit landscape in the UK and the opportunities that might be realised from that.

1.206 From the 2019 workshop a number of actions were suggested.

1.207 After three intervening years (2022), several global events have impacted the economy and regulation in the UK including the post EU exit environment. In light of these events, the COT considered it would be timely to have a second workshop to review what has been achieved and what still needs to be done to realise the full potential of EU exit.

1.208 The purpose of the workshop was to review the food and chemical regulatory landscape; its transfer to the UK; future UK development (REACH) and divergence (drivers and supporting science); identify challenges and opportunities to consider where new structures and investment are required to realise and address these.

1.209 A workshop report will follow in 2023.

Working Groups

SETE

Report of the Synthesis and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) of the Committee on Toxicity and the Committee on Carcinogenicity

1.210 The UK Committees on Toxicity (COT) and on Carcinogenicity (COC) regularly review epidemiological and toxicological evidence in their risk assessments. There is, therefore, a need for guidance on the approaches used by the Committees to integrate these evidence streams, both for scientific consistency and to ensure public transparency. To that end, the Committees established the Synthesising and Integration of Epidemiological and Toxicological Evidence Subgroup (SETE) to review and document current practice and provide applicable guidance.

1.211 SETE recognised that issues on which advice from the Committees is sought varies considerably and hence the guidance proposed should be sufficiently flexible to address this.

1.212 Scoping and problem formulation were identified as the crucial first step in the process. This ensures the right questions are asked, helps make the most efficient use of resources and identifies the most appropriate approaches to use in the assessment. An established system or guidance to assess the separate/different evidence streams should be followed where feasible. For both epidemiological and toxicological evidence, a prescriptive checklist or scoring approach is not recommended. However, identifying the strengths and weaknesses of studies is important. The decision-making process should be robust, transparent, evidence-based, defensible and documented, but equally importantly, it should be easy to use. Collaboration and ongoing dialogue between epidemiologists, exposure experts and toxicologists are strongly advised. Information on mode of action (MOA) can be invaluable for evidence integration as it underpins weight of evidence considerations by providing the mechanistic link between empirical observation and biological plausibility.

1.213 All lines of evidence should be considered, with no pre-existing hierarchy. One way to clearly depict the influence of the different lines of evidence on causality s via visual representation (Figure 1).

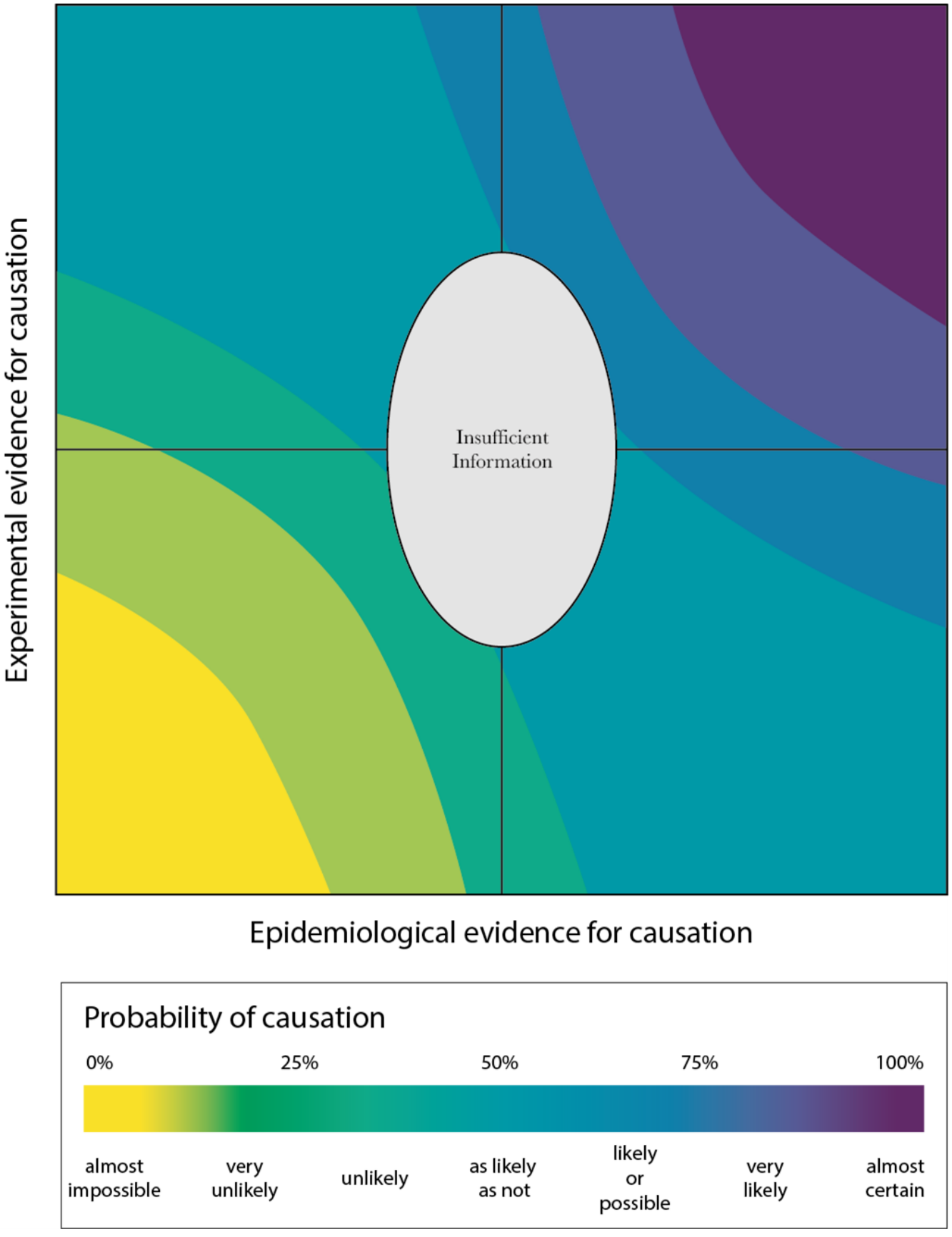

Figure 1 is an example for the visual representation of the likelihood of a causal relationship, considering both epidemiological and toxicological data. The diagram is a multicoloured oblong shape with 4 lined boxes within it. It has an axis and a white oval in the centre of the squares with text.

Figure 1: Example for the visual representation of the likelihood of a causal relationship, considering both epidemiological and toxicological data.

1.214 Decisions on whether there is sufficient information to reach a conclusion or whether a causal relationship in humans is more likely or unlikely can be reached based on where the causal relationship appears on a graph. It is important to begin with the initial estimate of causal relationship at the centre of the graph. Depending on whether the toxicological, mechanistic or epidemiological evidence assessed supports or discounts (or has no clear influence on) a conclusion of causality, placement on the graph is then moved accordingly, either in a positive or negative direction. The movement is influenced by several factors, including the strength or weakness of the evidence, any relative weighing given to epidemiological and toxicological studies and the uncertainties associated with the data. As more information is included in the process and/or becomes available, the placement of the toxicological and/or epidemiological evidence can be easily adjusted and the impact on any possible conclusion easily seen.

1.215 In contrast to other approaches, the above visualisation aims to provide a pictorial representation of the consensus views of a Committee on the influence of the different lines of evidence on causation, assessed by debate and agreement of scientific experts. In this way, it provides a more objective means of collating the views of the Committee and communicating the agreed conclusion of a Committee on the likelihood of causation.

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

1.217 The full SETE report and guidance document (Annex 1) can be found at SETE | Committee on Toxicity (food.gov.uk).

1.218 Please note, the guidance will be trialled by the COT for 2 years and then reviewed.

Joint SACN/COT Working Group on Plant Based Drinks

1.219 The Office of Health Improvement and Disparities (OHID) (previously Public Health England) and the FSA received an increasing number of enquiries regarding the use of plant-based drinks in the diets of infants and young children

aged 6 months to 5 years of age.

1.220 Current UK government advice regarding the use of plant-based drinks for infants and young children is that unsweetened calcium-fortified plant-based drinks, such as soya, oat and almond drinks, can be given to children from the age of 12 months as part of a healthy balanced diet; however, rice drinks should not be given due to the levels of arsenic in these products.

1.221 In 2021, the COT was asked to consider the potential risks posed by soya, almond and oat drinks consumed in the diets of these age groups. A COT Statement was published in 2021.

1.222 Overall, the Committee concluded that neither the safety of these drinks, nor the suitability of the current guidance, could be confirmed from a toxicological perspective. The Members agreed that, in addition to potential toxicological concerns, consideration of nutritional issues would also be required to assess whether it was necessary to issue additional advice on the consumption of plant-based drinks in children aged 6 months to 5 years of age. As a result, a joint SACN/COT Working Group was established in 2021, to consider the benefits and risks of plant-based drinks in diets across all life stages.

1.223 In 2022, a call for evidence was issued which aimed to seek evidence with regards to specific aspects of nutrition, safety and toxicity of plant-based drinks. Details on the call for information can be found at: Call for Evidence.

1.224 The Joint Working Group considered the information received in response to this call for evidence, the COT Opinions on plant-based drinks and cow’s milk as well as exposure information and utilised the Benefit-Risk Analysis for Foods (BRAFO) framework in order to compare the health risks and benefits of plant based drinks.

1.225 It is hoped that the report will be published in 2023.

Joint ACNFP/COT Working Group on Cannabidiol (CBD)

1.226 A joint Working Group has been established to review the data on cannabidiol (CBD) submitted as a part of the novel foods applications process.

1.227 The first meeting of the ACNFP/COT subcommittee was held in July and considered the toxicology datasets collated for CBD isolate applications and ultimately concluded that a list of toxicological uncertainties must be tackled before opinions on the safety of CBD isolates can be made.

1.228 The next meeting was held in September and the main topic of discussion was an in-depth review of the data on CBD isolates and synthetic CBD products. By using a refined but detailed table format, the Secretariat hopes to prompt further discussion amongst the subcommittee members. This will inform the next steps to support the review of dossiers in this group by the ACNFP.

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Emeritus Professor of Toxicology in the Faculty of Medicine at Imperial College London.

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Ms Jane Case

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Dr Caroline Harris PhD, CChem, FRSC

Practice Director and Principal Scientist, Exponent International Ltd. Term (Until March 2022).

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Dr Emily Hudson BSc (Hons) Mres

Dr David Kovacic

Declaration of members' interests during the period of this report

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

Dr Phil Botham

Personal Interest	**Employee:** Syngenta - Principal Science Advisor (part time).
Personal Interest	**Shareholder:** AstraZeneca, Regulatory Science Associates (Part, Time Consultant).
Personal Interest	**Membership:** British Toxicology Society, Society of Toxicology (USA), European Centre for Ecotoxicology and Toxicology of Chemicals Scientific Committee, European Crop Protection Association Toxicology Expert Group, Crop Life International Human Health Steering Team.
Non-Personal Interest	None.

Ms Jane Case

Personal Interest	**Employee:** Company Secretary of Muse Interiors, Stevens & Bolton LLP (as Jane Hughes).
Personal Interest	**Membership:** None.

Personal Interest	**Shareholder:** Standard Life Santander
Non-Personal Interest	None.

Dr Stella Cochrane

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

Dr James Coulson

Personal Interest	**Employee:** Cardiff University, Director of Medical, Scientific and Toxicology Consultancy Ltd.

Personal Interest	**Membership:** British Medical Association, British Pharmacology Society, British Toxicology Society National Trust, Royal College of Physicians of London.
Non-Personal Interest	None.

Dr René Crevel

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

Professor Thorhallur Ingi Halldorsson

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

Dr Caroline Harris

Personal Interest	**Employee:** Exponent International Ltd.
Personal Interest	**Membership:** International Union of Pure and Applied Chemistry.
Personal Interest	**Shareholder:** Exponent Inc.

Personal Interest		**Fellowships:** Royal Society of Chemistry.
Non-Personal Interest		**Membership:** Expert Committee on Pesticides.

Professor Gary Hutchison

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

Dr Sarah Judge

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

Non-Personal Interest	Research Funding.

Professor Gunter Kuhnle

Personal Interest	**Employee:** Professor of Nutrition and Food Science, University of Reading.
Non-Personal Interest	Research Funding.

Dr David Lovell

Personal Interest	**Employee:** Reader in Medical Statistics, St Georges Medical School, University of London.

Personal Interest	**Membership:** HESI GTTC – Biometrics Society, British Toxicology Society Genetics Society, Royal Society of Biology Laboratory Animal Science Association, Royal Statistical Society Statisticians in the Pharmaceutical Industry, United Kingdom Environment Mutagen Society (UKEMS), UK National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs), MRC EMINENT Scientific Review Board. **Also, private member of:** British Trust of Ornithologists (BTO) English Heritage, Liberty, Campaign of the Protection of Rural England (CPRE), Kew Gardens, Sandwich Bay Bird Observatory Trust (SBBOT), Chelsea Physic Garden, National Trust.

Personal Interest	**Shareholder:** National Grid, Pfizer, AstraZeneca (spouse shareholder), National Grid plc (spouse shareholder).
Non-Personal Interest	None.

Professor Shirley Price

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

Dr Mac Provan

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

Ms Juliet Rix

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

Dr Michael Routledge

nal Interest	**Employee:** Lecturer/Senior Lecturer/Associate Professor University of Leicester
Personal Interest	**Membership:** Member of working group, European Food Safety Authority, 2018-2019. Vice-President of UKEMS (UK Environmental Muta-Genesis Society).

Non-Personal Interest	None.

Dr Cheryl Scudamore

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

Dr Natalie Thatcher

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

Professor Mireille Toledano

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

Dr Simon Wilkinson

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

Professor Phillipe Wilson

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

Non-Personal Interest	None.

Professor Matthew Wright

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

Professor Maged Younes

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

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

Dr Silvia Gratz

Personal	**Interest**	**Employee:** Rowett Institute, University of Aberdeen.
Personal	**Interest**	**Membership:** The Nutrition Society (UK) The British Toxicology Society FSA Register of Specialists.
Non-Personal Interest		None

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

Annual Report 2022

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27. Annex 5 – 2022 - Glossary of Terms

Preface

Head and shoulders image of Professor Gareth Jenkins in front of a light-coloured background wearing a dark coloured shirt.

I am delighted to present this report on the work of the Committee on Mutagenicity (COM) during 2022.

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

The Committee also advises on important general principles and on new scientific work related to the assessment of mutagenic risk and makes recommendations on wider aspects of mutagenicity testing. The membership of the Committee,

declarations of their interests, agendas and minutes of meetings, and statements are all published on the internet at: Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment - GOV.UK (www.gov.uk).

In 2022, COM continued work discussing the genotoxicity of titanium dioxide (MUT/2022/05) following the updated opinion published by EFSA in 2021. This review of titanium dioxide will be continued and concluded in 2023/2024.

In 2022 COM, at the request of COC who were writing a paper on carcinogenicity biomarkers, discussed ‘genotoxicity biomarkers’ sections (MUT/2022/03) and contributed to the final COC Biomarkers paper.

COM also discussed the description of the process of chemical risk assessment from a lay perspective (MUT/2022/03) and we have now begun the process of generating lay summaries of COM decision papers (MUT/2022/13). I think it is a key priority to ensure that our work is presented in a way understandable to the lay person in the UK.

COM have made specific recommendation in 2022 on the mutagenic hazards and risks posed by a number of substances including; Acrylamide, novel can coatings, Bisphenol-A and hydroxyanthracene derivatives (HADs) used in foods.

The COM maintained its awareness of the implications of EU EXIT on its work and remained alert to the continuing uncertainty as to how the UK's regulatory environment and its relationships with international organisations will develop in 2023 and onwards.

I would specifically like to thank the COM secretariat for their exceptional support to the COM and to the IEH team for the excellent work they delivered in 2022. As always, I am grateful for the support of the individual members of the committee for their expert advice, the effort and time they put in and their support throughout the year.

Professor Gareth Jenkins- Chair

COT/COM/COC Annual Report 2022

Ongoing work - COM 2022

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COM guidance series update

Guidance statement the use of biomarkers in genotoxicity in risk assessment

2.1 At the request of the COC, the COM considered a revised version of the COC Guidance Statement G04 ‘The use of biomarkers in carcinogenic risk assessment’ at the COM March 2022 meeting (MUT/2022/03). Particular focus was given to the ‘DNA’ and ‘genotoxicity biomarkers’ sections, both of which had had been shortened in the current version of G04 as part of a document revision process.

2.2 It was agreed that COM would produce a guidance statement that provided a more comprehensive overview of these areas, which could then be referred to by the other Committees. A draft scoping document outlining the proposed content of guidance statement was presented to the COM at its meeting in June 2022 (MUT/2022/06).

2.3 Several modifications to the scoping document were suggested by members and these were incorporated into a first draft document presented at the COM October 2022 meeting (MUT/2022/11). Members considered that the focus of the COM document should be *in vivo* biomarkers of DNA damage, with greater distinction from the COC Guidance Statement G04. Work is ongoing to progress a second draft document.

Guidance on how the committees evaluate the relevance and reliability of data when assessing a chemical of concern

2.4 At the COM March 2022 meeting, the COM considered a draft document outlining the Committee evaluation process focussing on the relevance and reliability of data written specifically to inform the lay person (MUT/2022/03). This document evolved from a scoping paper on the topic of ‘biological relevance and statistical significance’, presented to the Joint COC/COM meeting in November 2020 (CC/MUT/2020/03) also attended by some COT members, which outlined some of the more relevant and significant work that has been published on this issue in recent years. It was agreed that two documents should be progressed. The first document should be aimed at the lay audience about the process used by the Committees to evaluate evidence and reach conclusions and a second document aimed at a more informed audience on statistical significance testing and consideration of biological relevance.

2.5 Paper MUT/2022/04 presented an updated version of the draft document, amended following comments from COM members at the March 2022 meeting. The draft document would also be discussed by COT and COC at their July 2022 meetings.

2.6 COM members asked for a small number of additional changes to be made prior to the document being evaluated by COC and COT. This included emphasising the public-facing role of the document.

Non-expert summaries for COM website

2.7 At the COM meeting in June 2022, it was agreed that the general public could benefit from the addition of non-expert summaries to the start of each COM guideline document.

2.8 A draft non-expert summary for the overarching COM guideline, 'Guidance on a strategy for genotoxicity testing of chemicals (MUT/2022/13) was presented at the COM October 2022 meeting. Members considered that some text could be removed, as this was available on the COM website, and a link provided to that website. In addition, it was recommended that links to the glossary should be utilised fully as this provided an immediate and understandable definition for readers. Specific comments on the paper were requested to be sent directly to the Secretariat so that the paper could be updated.

COM Evaluations - 2022

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EFSA assessment of the genotoxicity of acrylamide

2.9 Following a request by the European Commission (EC), the European Food Safety Authority (EFSA) published a statement on the assessment of recent publications on the genotoxicity of acrylamide (EFSA, 2022).

2.10 The request by the EC followed the publication of a review article by Eisenbrand (2020a) and its erratum (Eisenbrand, 2020b). However, as EFSA did not consider the review and erratum to be comprehensive, a literature search of the recent data on the genotoxicity and mode of action of acrylamide was also undertaken.

2.11 EFSA concluded that the majority of the new studies published since 2015 confirmed and extended the clastogenic properties of acrylamide/glycidamide. In addition to genotoxicity, non-genotoxic effects may contribute to the carcinogenicity of acrylamide. There was further substantial evidence for the genotoxicity of acrylamide mediated by the formation of its

metabolite glycidamide. Overall, the new studies evaluated extend the information assessed previously and support EFSA's conclusion on the risks to human health related to the presence of acrylamide in food. EFSA further considered the Margin of Exposure (MOE) approach to still be appropriate and concluded that an update of its 2015 opinion is currently not required.

2.12 The COM considered the recent EFSA assessment and agreed that the information/data considered in the assessment confirmed and strengthened most aspects of EFSA's previous opinion.

2.13 The review paper by Eisenbrand 2020 argued against a genotoxic mode of action for the carcinogenicity of acrylamide and that genotoxic effects were only seen above normal physiological levels of exposure. Members had reservations about the paper by Eisenbrand and considered that it had limitations. The COM agreed that exposure to acrylamide induced gene mutation and was clastogenic in mammalian cells. The genotoxic mode of action appeared to occur via CYP2E1 metabolism to the mutagenic and clastogenic metabolite glycidamide. The role of acrylamide itself was unclear. Members considered that the genotoxicity arising from acrylamide exposure may also involve the generation of reactive oxygen species (ROS) and oxidative damage.

2.14 Overall, the COM agreed with EFSA's conclusion that the MOE approach would still be appropriate.

Discussion paper on a coating in canned food packaging materials

2.15 This item was presented as a reserved item.

2.16 Members discussed the information provided to the Committee on a can coating as well as the assessment and discussions of the Joint Expert Group on Food Contact Materials (FCM JEG). Following the COMs assessment, the discussion paper was presented to the Committee on Toxicity, together with the discussions of the FCM JEG and COM. The work is ongoing, but a final assessment is expected in 2023.

Draft statement on the genotoxicity of hydroxyanthracene derivatives in food

2.17 The genotoxicity of hydroxyanthracene derivatives (HADs) used in foods had been discussed at the COM meeting in October 2021. Following a request from UK-wide Nutrition Labelling Composition and Standards (NLCS) policy group,

the UK Food Standards Agency (FSA) commissioned an independent view from the COM on the mutagenicity of HADs based on consideration of the European Food Safety Authority (EFSA) 2018 opinion on HADs and any additional new data that have become available.

2.18 This discussion of the COM was held in March 2022. At this meeting, COM Members were asked by the FSA Secretariat to consider whether they agree with the following overall conclusions of the EFSA ANS Panel, i.e. i) emodin, aloe-emodin, and dantron are genotoxic *in vitro*; ii) HADs should be considered as genotoxic *in vivo* unless there are specific data to the contrary (such as for rhein); iii) there is a safety concern for plant extracts containing HADs (although there is some uncertainty); and iv) it is not possible to provide advice on a daily intake of HADs that does not give rise to health concerns (for both the general population, and vulnerable subgroups of the population). Furthermore, the COM was asked to consider whether any of these conclusions would be affected by the results of the studies published since the 2018 EFSA opinion.

2.19 Overall, the COM agreed that that the available evidence indicates that emodin, aloe-emodin, and dantron are genotoxic *in vitro*, namely from Ames tests.

2.20 The COM agreed that the negative results from the *in vivo* bone marrow micronucleus assay are valid and concluded that there is reasonable evidence that there is no genotoxic effect or mechanism *in vivo*. Subsequently, a new *in vivo* genotoxicity study would not be helpful. The COM considered that the reported carcinogenic effects of HADs, including those seen in the comet assay of colon cells, are caused by the high levels of irritation, inflammation, and diarrhoea.

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

2.22 The Committee agreed that the studies published after 2018 are mostly negative *in vivo* data, which weaken the evidence that there is a genotoxic effect *in vivo*.

2.23 Following the COM consideration and conclusions, a draft statement was produced (MUT/2022/01) and Committee Members were asked to provide any comments on the structure and content of the draft statement. The COM were content with the draft statement, and this was agreed with no significant amendments.

Review of titanium dioxide genotoxicity

2.24 Following the publication of the European Food Safety Authority (EFSA) opinion on titanium dioxide in 2021, which concluded that titanium dioxide could no longer be considered to be ‘safe’ for use in food, the Food Standards Agency (FSA) initiated a review of the EFSA opinion.

2.25 The EFSA opinion was presented to the COM in June 2021 (MUT/2021/03) and to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) in July 2021 (TOX/2021/36). The COM had a number of concerns over the EFSA opinion on the genotoxicity of titanium dioxide. Due to this and following the advice of the COT the FSA initiated an independent evaluation of the safety of the use of titanium dioxide as a food additive.

2.26 In October 2021, paper MUT/2021/08 was presented to the COM, which summarised the available genotoxicity on titanium dioxide. Members considered that it was not possible to evaluate the genotoxicity of titanium dioxide at that stage. The COM suggested a sifting approach to the available genotoxicity should be adopted as a first step before evaluation. The Chair of the COM, a subgroup of the COM and the secretariat subsequently attended meetings to discuss and agree the criteria and methodology for sifting to identify suitable papers for the evaluation of titanium dioxide.

2.27 At the COM June 2022 meeting, paper MUT/2022/05 provided information and papers on approaches relating to the sifting and evaluation of the quality genotoxicity studies and evaluating data on nanomaterials. As an update since that meeting, members were informed that a sub-group of the COM had met to discuss the process to select relevant and appropriate studies to be reviewed by the committee. A proforma had been produced, which would be shared with members. This considered two levels, namely, whether the characteristics of the test material had been sufficiently described (e.g., micro or nano sized particles) and the quality and reliability of how the genotoxicity studies had been conducted.

Update on the COM review of the EFSA evaluation of bisphenol-a

2.28 The Food Standards Agency (FSA) provided an update on the EFSA consultation on its draft opinion proposing a lowering of the Tolerable Daily Intake (TDI) for bisphenol A.

2.29 EFSA published a consultation on its draft opinion, which closed on the 22nd February 2022. In response to this consultation the FSA requested that the Committee on toxicity of chemicals in food consumer products and the environment (COT) provide a view to EFSA. The COT had a number of concerns over the approach used by EFSA in its evaluation, which the COT considered made it difficult to assess the toxicity database as a whole and had a number of concerns relating to the studies used to derive the new EFSA proposed TDI. The COT had requested the opinion of COM members on the EFSA evaluation of the genotoxicity data on bisphenol A and thanked the COM for its contribution. COM members were generally content with the EFSA review of the genotoxicity data and agreed with the overall EFSA conclusion that DNA strand breaks, clastogenic and aneugenic effects seen in mammalian cells *in vitro* following exposure to bisphenol A were very likely due to oxidative stress related mode of genotoxicity and that bisphenol A was not mutagenic *in vivo*. The combined COT and COM comments had been submitted to EFSA.

2.30 Following the publication of the finalised EFSA opinion the FSA would need to consider whether it needed to be referred to the UK expert advisory committees again. It was considered unlikely that there would be a need to consult the COM further on the genotoxicity aspect and would more likely be referred to one of the other expert committees, such as the Committee on the carcinogenicity of chemicals in food consumer products and the environment (COC).

Horizon scanning: meetings and workshops - COM 2022

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2.31 A summary paper was presented outlining some of the current issues being discussed at a recent meeting and workshop covering issues that may be of interest to COM for future horizon scanning (MUT/2022/12). The first summary gave a brief overview of topics discussed at the UKEMS Next Generation

Sequencing Workshop, held in May 2022 in London. The second provided a summary of some sessions of the UK Environmental Mutagen Society (UKEMS) Annual Meeting, held in July 2022 in Harrogate.

2.32 A few suggestions were made by members during discussion of the paper. These included consideration of: iPS organoids as model systems (COM and COC); the use of genomics in toxicity testing strategies; and whether epigenetics should/can be incorporated into standard toxicity testing.

OECD guidelines - COM 2022

In this guide

2.33 Members were informed of a proposal from Norway to update OECD Test Guideline 489 on the in vivo alkaline comet assay to include the investigation of germ cells. Currently any modifications have not been sufficiently validated, but it was early stages for the OECD.

2.34 The COM also heard that the OECD Test Guideline 488 Transgenic rodent somatic and gene mutation assays had been updated and published.

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Chairman

Professor Gareth Jenkins

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

Members

Dr Carol Beevers

Regulatory Toxicology, Corteva Agriscience.

Amit Bhagwat

Lay Member.

Professor Shareen Doak

Professor of Genotoxicology & Cancer, Faculty of Health, Medicine and Life Science, Swansea University.

Dr Ann Doherty (From July 2022)

Head of Safety Innovation, Clinical Pharmacology and Safety Sciences, AstraZeneca.

Dr Paul Fowler

FSTox Consulting.

Dr Nathan Goldsmith (From September 2022)

Associate Member, Exponent.

Professor David Harrison MD DSc FRCPath FRCPEd FRCSEd

Professor of Pathology, University of St Andrews.

Dr George Johnson

Associate Professor, Swansea University Medical School.

Ms Julia Kenny

Nonclinical Safety Project Toxicologist, GSK.

Dr Andrew Povey

Reader in Molecular Epidemiology, University of Manchester.

Mr Paul Rawlinson (from July 2022)

Gentronix Ltd.

Mrs Madeleine Wang

Lay Member.

Secretariat

Dr Ovnair Sepai

PHE Scientific Secretary.

Dr D Gott BSc (Hons) PhD

FSA Scientific Secretary.

Mrs N Blowfield

Administrative Secretary.

Declaration of members interests during the period of this report

Professor Gareth Jenkins

Personal Interest	**Employer** Swansea University. **Honorary Contract** Swansea Bay University Health board.
Personal Interest	**Membership** President of United Kingdom Environment Mutagen Society (UKEMS) 2020-2023. British Association for Cancer Research. Senior Editor Mutagenesis (OUP), Editorial Board (and former editor 2013-2015) Mutation Research (Elsevier). President of the International Association of Environmental Mutagenesis and Genomics Societies (IAEMGS).

Non-Personal Interest	**Grants** National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (2018-2022). **Former grants** Health & Care Research Wales (2016-2020, 2014-2017. MRC/AstraZeneca PhD studentship (ITTP scheme) (2019-2023). Cancer Research Wales grants (2023-2026 and 2019-2023). External Examining roles (Bangor University DeMontfort University, University of Milan).

Dr Carol Beevers

Personal Interest	**Employee** Exponent International Ltd (up to 27 July 2021). Broughton Group (from 01 September 2021). Corteva Agriscience (from 01 September 2022).
Personal Interest	**Pension** Covance, Exponent, Broughton, Corteva Agriscience (from September 2022).

Personal Interest	**Shareholder** ITM Power, NIO Inc, Blackberry.
Personal Interest	**Membership** HESI GTTC (workgroup member). OECD (workgroup member). IWGT (work group chair). United Kingdom Environmental Mutagen Society (UKEMS).
Non-Personal Interest	None.

Mr Amit Bhagwat

Personal Interest	**Owner and Shareholder** Research and Consulting Business.
Non-Personal Interest	Bradford Teaching Hospitals NHS Foundation Trust - Public Governor (Rest of England & Wales). British Computer Society – the Chartered Institute for IT - Chair/Volunteer for Learned Events and Public Service Activities.

	Membership
Non-Personal Interest	Public Ambassador – NHS England subsidiary board related to Digital Urgent & Emergency Care (DUEC). Committee on Mutagenicity (COM). Prescribed Specialised Services Advisory Group, DHSC. Northern Ireland Practice and Education Council for Nursing and Midwifery (NIPEC).
	Contributor
Non-Personal Interest	Learned and professional development activities within the British Computer Society (chairing, committee and speaking responsibilities).
	Trustee
Non-Personal Interest	Myrovlytis Trust (funds research into rare diseases) – Chairing responsibility. Regional inclusive volunteering charity – Chairing responsibility.

Professor Shareen Doak

	Employee
Personal Interest	Swansea University.

Personal Interest	**Membership** United Kingdom Environmental Mutagen Society (UKEMS). Fellow of the Learned Society of Wales. Royal Society of Biology (FRSB). ILSI HESI (committee member). British Toxicology Society (BTS). Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medical Consumer Products (SAG-CS). Independent member of the Health & Safety Executive (HSE), Science Quality Assurance Group (SQAG). Commissioned by the Office for Product Safety and Standards (OPSS). Editor-in-Chief: Mutagenesis.
Non-Personal Interest	**Trustee** St David’s Medical Foundation (medical research & education charity). **PhD Studentship Grants** Unilever (2017 – 2020), AstraZeneca (2009 – 20160, Unilever (2010 -2017). **Research Grant** 2008 – 2010. Hoffman-LaRoche, Unilever.

Dr Ann Doherty (From July 2022).

	Employee AstraZeneca.
Personal Interest	**Pension** AstraZeneca. **Shareholder** AstraZeneca.
Personal Interest	**Membership** UK Environmental Mutagen Society (UKEMS), Committee member, ILSI HESI GTTC member, British Toxicology Society, MRC Toxicology Unit Review Board member.
Non-Personal Interest	None.

Dr Paul Fowler

	Pension
Personal Interest	Unilever (UK), Covance.
	Miscellaneous
Personal Interest	De Montfort University – External Examiner. FSTox Consulting – Director.

	Shareholder
Personal Interest	Unilever, Lloyds.
	Membership
Personal Interest	IGG (committee member), UKEMS (committee member), Rountable of Toxicology Consultants (RTC), British Toxicology Society (BTS), EEMGS (committee member), ILSI HESI GTTC member.
Non-Personal Interest	None

Dr Nathan Goldsmith (From September 2022).

Personal Interest	**Employee** Exponent International Ltd.
	Grants
Personal Interest	UKHSA (Potential exposure to carcinogens following e-cigarette use).
	Membership
Personal Interest	British Toxicology Society, (BTS).

Non-Personal Interest	None.

Professor David Harrison

	Employee University of St Andrews, UK, NuCana plc, UK.
Personal Interest	**Employee/Non-executive Director** LC Therapeutics Ltd, Benenox Ltd, UK – Non-executive Director (unpaid), PathAlba Ltd – Director (unpaid) – dormant.
Personal Interest	**Consultant** NHS Lothian – Honorary Consultant.
Personal Interest	**Miscellaneous** Cunningham Trust – (Medical Research Charity) Trustee, University of Edinburgh, UK – Honorary Professor, University of Glasgow, UK – Honorary Professor, University of Florida, Adjunct Professor, Viewbank Leuchars Ltd – Director (no salary).

Personal Interest	**Shareholder** VBL Ltd, UK, Ryboquin Ltd, UK, ILC Therapeutics Ltd.
Personal Interest	**Membership** Fellow Royal College of Pathologists, Fellow of Royal College of Physicians of Edinburgh, Fellow of Royal College of Surgeons of Edinburgh.
Non Personal Interest	**Miscellaneous** iCAIRD research consortium – Director (unpaid role), Pilgrim Care St Andrews (charity for the elderly) – Trustee (unpaid role). Visiopharm – Member, Scientific Advisory Board. EU Horizon 2020, Partner in KATY Award, grant support. Innovate UK/UKRI – Director of iCAIRD.

Dr George Johnson

Personal Interest	**Employee:** Swansea university. **Consultancy:** Fermenich, CEFIC, American Chemistry Council, Teva, Greenberg Traurig LLP, Osler, Hoskin & Harcourt LLP, Janssen, Medicines for Europe, Merck. **Director:** GTox ltd.
Personal Interest	**Membership** United Kingdom Environmental Mutagen Society (UKEMS), HESI GTTC chair), President of the European Environmental Mutagenesis and Genomics Society (EEMGS) 2019-2021, EMA expert member, IWGT, expert member, ICEM, committee member, British and European registered toxicologist.

Non-Personal Interest	**Relevant Grant Funding:** GSK, post-doctoral research funding – 2021-2022. nitrosamine research. SCIENSANO. MYCX-IT. 2020-ongoing. EMA. funding through Fraunhofer item. 2022-2023. HESI. fast fund. phd tuition fees. 2022-ongoing.

Ms Julia Kenny

Personal Interest	**Employee** GlaxoSmithKline/GSK
Personal Interest	**Shareholder** GSK, Haleon.
Personal Interest	**Pension** GlaxoSmithKline
Personal Interest	**Membership** UK Environmental Mutagen Society (UKEMS).
Non-Personal Interest	None

Dr Andrew Povey

Personal Interest	**Shareholder** Lloyds, Standard Life, Halifax, Santander (Partner Shareholder), Norwich Union (Partner Shareholder), Roadchef Topco Ltd (Partner Shareholder). **Miscellaneous** European Crop Protection Agency – Part of consortium awarded grant on exposure assessment.
Personal Interest	**Membership** UK Molecular Epidemiology Group (UK-MEG), UK Environmental Mutagen Society (UKEMS), American Association for Cancer Research (AACR), Molecular Epidemiology Group (MEG), British Association for Cancer Research (BACR).
Non-Personal Interest	**Miscellaneous** Departmental studentships funded by industrial and other bodies.

Mr Paul Rawlinson (From July 2022).

	Employee Gentronix Limited.
Personal Interest	**Pension** St James Place, Formerly Syngenta.
Personal Interest	**Membership** HESI GTTC (workgroup member), IGG (committee member), United Kingdom Environmental Mutagen Society (UKEMS).
Non-Personal Interest	None.

Ms Madeleine Wang

Personal Interest	None.
Non-Personal Interest	None.

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment Annual Report 2022

In this guide

Preface

Head and shoulders image of Professor David Harrison in front of a grey background wearing a white shirt with a blue and yellow striped tie.

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

The membership of the Committee, agendas and minutes of meetings, and statements are all published on the internet: Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment - GOV.UK (www.gov.uk).

In practice the work of the Committee is divided into three sections: (i) response to enquiries regarding specific chemicals or classes of chemicals; (ii) revision and updating of guideline documents that inform industry, regulators and public on what kinds of evidence help to determine the potential to cause cancer and how to evaluate them; (iii) review of underpinning science and recent technology to see if we can develop more appropriate, safe ways to assess the potential of chemicals to cause cancer, thereby increasing safety, reducing use of animals, increasing speed and reducing costs.

I am grateful to Members, Secretariat and other advisors and contributors, without all of whom the Committee could not operate effectively.

Professor David Harrison

COC Ongoing Topics - 2022

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Hydroxyanthracene derivatives

3.1 Following a request from UK-wide Nutrition Labelling Composition and Standards (NLCS) policy group, the UK Food Standards Agency (FSA) commissioned an independent view from the Committee on Mutagenicity (COM) on the mutagenicity of hydroxyanthracene derivates (HADs) based on consideration of the European Food Safety Authority (EFSA) 2018 opinion on HADs and any additional new data that have become available. The genotoxicity of HADs used in foods had been discussed at the COM meeting in October 2021 (see 2.17 above).

3.2 Overall, the COM agreed that the available evidence indicates that emodin, aloe-emodin, and dantron are genotoxic in vitro, namely from Ames tests. The COM agreed that the negative results from the in vivo bone marrow micronucleus assay are valid and concluded that there is reasonable evidence that there is no genotoxic effect or mechanism in vivo. Consequently, a new in vivo genotoxicity study would not be helpful. The COM considered that the reported carcinogenic effects of HADs, including those seen in the comet assay of colon cells, are caused by the high levels of irritation, inflammation, and diarrhoea. In March 2022 a discussion paper on the safety of HADs for use in food was brought for review by the COC for its opinion on the carcinogenic potential of HADs. The FSA requested that the COC review the carcinogenicity studies provided in the paper and evaluate the risk of HADs and whether a health-based guidance value (HBGV) could be derived from the information provided.

3.3 The COC agreed with the COM that HADs are not a genotoxic carcinogen in vivo. The committee suggested that while theoretically it would be possible to set an ADI, the data available was insufficient as a dose response has not been described. The COC indicated that a dose response was required in order to be able to identify a threshold or point of departure. The COC concluded that more information on the characterisation of HADs would be required for the Committee to discuss a possible HBGV and it would not be possible to set a HBGV for HADs as a single group as they are complex mixtures of different compounds that may have differing mechanisms of action. Therefore, more data would be required to make a decision as a blanket value could be misinterpreted.

3.4 Following a call to industry for new information and data, CRN UK were able to provide the FSA with a record of relevant journal articles that had not been considered in the original EFSA opinion. Following an assessment of the information provided, the Secretariat determined that one of the articles might address some of the issues raised by the Committee at the March 2022 meeting.

3.5 In July 2022 this additional article, which suggested a potential HBGV for HADs, was presented to the COC. Members indicated that as this HBGV was not based upon any new data and therefore, the value presented in the paper was based upon many different variables including different strains of animals used, different dosing regimens and various endpoints. The COC agreed that there was still insufficient data to conclude on an appropriate HBGV for HADs. It was noted that the likely levels of exposure seemed to be less than those that would be expected to cause a risk in humans, but this should be explored further with a detailed exposure analysis.

3.6 An interim position paper with the addition of dietary and dermal exposure assessment will be presented to the COC in 2023.

COT/COM/COC Annual Report 2022

COC Joint ongoing topics 2022

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Relevance and Reliability of Evidence

3.7 The COT, COC and COM have continued to develop the joint non-technical statement on how the Committees evaluate the relevance and reliability of data when assessing a chemical of concern in 2022. An updated version was presented to the COC in July 2022. Further revisions are expected to be considered by correspondence across all three Committees in 2023.

COC Workshop - 2022

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2. COT Preface - 2022
3. COT evaluations - 2022
4. Committee Procedures - 2022
5. Ongoing Work - COT 2022
6. Other Committee Activities Joint Expert Groups and Presentations -2022
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8. Committee on Mutagenicity of chemicals in Food, Consumer Products and the Environment Annual Report 2022
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10. COM Evaluations - 2022
11. Horizon scanning: meetings and workshops - COM 2022
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3.8 The COC held a workshop in November 2022 which aimed to determine what definitive steps can be undertaken to make progress towards improvement of the chemical risk assessment process and regulatory requirements for carcinogenicity, based on research undertaken over the last 10-20 years. The workshop considered issues in the context of pesticides, with different regulatory areas to be covered in future workshops.

3.9 Dr Susy Brescia (UK HSE) presented an outline of the status quo of the cancer assessment of pesticide active substances, identifying the limitations of the current paradigm and exploring some of the new approaches that are being developed. A second presentation was given by Dr Phil Botham (Syngenta Product Safety) which outlined a project being carried out by a working group of (mainly US) experts called the Rethinking Carcinogenicity Assessment for Agrochemicals Project (ReCAAP). This aims to propose a weight of evidence approach for waiving rodent cancer bioassays for the registration of food-use pesticides. The final presentation from Dr Richard Haworth (COC member) explored new approaches being taken for pharmaceuticals which evaluate whether a 2-year rat study is likely to add value to a human carcinogenicity risk assessment, and whether the assessment of pesticides can learn from these.

3.10 A number of key questions were then addressed in breakout discussion groups to answer the main theme questions:

- What opportunities are there to improve carcinogenic risk assessment in the UK?
- What is the future of the 2 year / lifetime bioassay?

3.11 A draft summary of the workshop will be presented to COC at the meeting in March 2023. Further development of the summary is ongoing.

Joint session - COC 2022

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3.12 COC and COM held a joint discussion session in March 2022, to which COT members were also invited.

3.13 Dr John Doe gave a presentation summarising the key points from the recent paper by Harrison and Doe ‘The modification of cancer risk by chemicals’ (Toxicology Research, Volume 10, Issue 4, August 2021, Pages 800–809). There was agreement that the model proposed by Harrison and Doe articulated the development of cancer very clearly and there was desire to consider its use in chemical risk assessments. Future aspects to address included quantification, accounting for chemical concentration effects, and ensuring appropriate communication of uncertainty and ambiguity.

3.14 This was followed by a presentation by Dr Lesley Rushton on the evidence for shift work acting as a modifying risk factor for cancer. This was

considered to exemplify why the impact of modifying factors for cancer risk should be evaluated, including considering other factors associated with them, for example obesity is associated with shift work and would also affect cancer risk/.

3.15 The session continued to provide a number of updates to COC and COM on the COT work on microplastics, the COM guidance on nanomaterials, the work of the FSA Joint Expert Groups, the OPSS Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products and the FSA computational toxicology fellowship and LiDO PhD studentship.

Horizon scanning - COC 2022

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3.16 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.

3.17 In 2022, the Committee continued to have a standing agenda item for each meeting on horizon scanning topics and to update the COC on upcoming topics for UK and international scientific advisory groups. A full horizon scanning discussion was held in November 2021 and the COC will review the priority topics from the subsequent horizon scanning discussions in 2023.

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

- Maintain a watching brief on factors affecting cancer susceptibility including shift work, stress and other lifestyle factors and how that might affect assessment of chemicals and carcinogenicity.
- Consider an update to guidance on assessment of nanomaterials, possibly as a joint activity across COC, COM and COT.
- Gain awareness of the potential effects of antibiotics and antivirals on the microbiome.
- Consider a joint discussion with COM on thresholds for in vivo mutagens and whether there is new information subsequent to the 2010 COM opinion.
- Endocrine disruption and the link with carcinogenicity, acknowledging that endocrine disruption is also within the COT remit.
- Impact of chemicals on potential for metastasis or progression of cancer, in particular with respect to the tumour microenvironment.
- Communication of cancer risk and how COC should be involved with this, especially with the move away from a yes/no decision on whether a

substance is a carcinogen, and ensuring consistency in describing risks, possibly starting with a landscape review of terminology across a number of Committees (FSA and UKHSA) and led by Lay Members.
- Ensuring appropriate considerations are made to acknowledging diversity in the population especially where there might be differences in risk between different groups.

Working Groups - COC 2022

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

3.19 The COT and COC set up a subgroup to review the approaches to synthesising epidemiological and toxicological evidence that are used in chemical risk assessments. More information is provided in the COT section 1.210.

Guidance statements - COC 2022

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3.20 The Committee continued development of the guidance statement series during 2022. Final revisions to the COC Guidance Statement (G04) ‘Use of Biomarkers in Carcinogenic Risk Assessment’ are ongoing and are expected to be completed in 2023.

2022 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

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In this guide

Chair

Professor David Harrison MD DSc FRCPath FRCPEd FRCSEd

Professor of Pathology, University of St Andrews.

Members

Mr Derek Bodey MA

Public Interest Representative.

Dr Gill Clare BSc PhD

Independent Consultant in Genetic Toxicology.

Dr Meera Cush

Senior Managing Consultant (Regulatory Toxicologist), Ramboll.

Dr Ruth Dempsey

Consultant: RD Science Speaks Consultancy, Sàrl.

Dr John Doe PhD

Research Fellow, Liverpool John Moore’s University.

Dr Richard Haworth MA VetMB DPhil FRCPath DipECVP DABT

Head of Pathology, Clinical Pharmacology & Safety Sciences, AstraZeneca.

Dr Ray Kemp BA MSc PhD MRTPI SIRM – To 30 June 2022

Public Interest Representative.

Professor Gareth Jenkins

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

Professor Neil Pearce BSc DipSci DipORS PhD DSc FRSNZ FMedSci FFPH

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

Dr Lesley Rushton OBE BA MSc PhD CStat HonFFOM (to 31st March 2022)

Emeritus Reader in Occupational Epidemiology, Imperial College London.

Dr Lesley Stanley MA PhD ERT FBTS

Consultant in Investigative Toxicology.

Professor Heather Wallace BSc (Hons) PhD FRCPath FBTS FRSC FRSB FBPS ERT (to 31st March 2022)

Professor in Biochemical Pharmacology and Toxicology, University of Aberdeen.

Secretariat

Miss B Gadeberg BSc (Hons) MSc ERT

UKHSA Scientific Secretary.

Dr D Gott BSc (Hons) PhD

FSA Scientific Secretary.

Ms Cath Mulholland BSc (Hons), ERT

FSA Scientific Secretary.

Mrs N Blowfield

Administrative Secretary.

Declaration of members interests during the period of this report

Professor David Harrison

	Employee University of St Andrews, UK, NuCana plc, UK.
Personal Interest	**Employee/Non-executive Director** ILC Therapeutics Ltd, Benenox Ltd, UK – Non-executive Director (unpaid), PathAlba Ltd – Director (unpaid) – dormant.

Personal Interest	**Consultant** NHS Lothian – Honorary Consultant.
Personal Interest	**Shareholder** VBL Ltd, UK, Ryboquin Ltd, UK, ILC Therapeutics Ltd.
Personal Interest	**Miscellaneous** Cunningham Trust – (Medical Resarch Charity) Trustee, University of Edinburgh, UK – Honorary Professor, University of Glasgow, UK – Honorary Professor, University of Florida, Adjunct Professor, Viewbank Leuchars Ltd – Director (no salary).
Personal Interest	**Membership** Fellow Royal College of Pathologists, Fellow of Royal College of Physicians of Edinburgh, Fellow of Royal College of Surgeons of Edinburgh.

Non Personal Interest	**Miscellaneous** iCAIRD research consortium – Director (unpaid role), Pilgrim Care St Andrews (charity for the elderly) –Trustee (unpaid role), Visiopharm – Member, Scientific Advisory Board. EU Horizon 2020, Partner in KATY Award, grant Support, Innovate UK/UKRI – Director of iCAIRD.

Mr Derek Bodey

Personal Interest	None.
Non-Personal Interest	None.

Dr Gill Clare

Personal Interest	**Pension** Shell Research Ltd, AstraZeneca.
Personal Interest	**Shareholder** AstraZeneca, Diageo, Marks and Spencer.
Personal Interest	**Consultant** Labcorp.

	Miscellaneous
Personal Interest	OPSS Register of Specialists from December 2020, OPSS Scientific Advisory Group from March 2021, Food Standards Agency (FSA) Joint Expert Group on Food Contact Materials (FCM-JEG) from May, 2019, FSA Joint Expert Group on Additives, Enzymes and other regulated products (co-opted), HSE REACH Independent Scientific Expert Pool from June 2021, Member of joint COT and COC Synthesis and Integration of Epidemiological and Toxicological Evidence sub-group, 2019 – 2021, University of Surrey visiting lecturer.
	Membership
Personal Interest	United Kingdom Environmental Mutagen Society (UKEMS), NIHR Academy.
Non-Personal Interest	None

Dr Meera Cush

	Employee
Personal Interest	Ramboll UK Limited, University of Surrey (Visiting Lecturer).

Personal Interest	**Membership** Royal Society of Biology.
Non-Personal Interest	None.

Dr Ruth Dempsey

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

Dr John Doe PhD

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

Dr Richard Haworth

Personal Interest	**Employee** AstraZeneca.
Personal Interest	**Shareholder** GlaxoSmithKline, Royal Dutch Shell (Spouse Shareholder), United Utilities (Spouse Shareholder).

	Membership
Personal Interest	British Society of Toxicological Pathology, European Society of Toxicological Pathology, Society of Toxicological Pathology.
Non-Personal Interest	None.

Dr Ray Kemp (To 30th June 2022).

	Director
Personal Interest	Rhodes-Kemp Law Ltd.
	Member
Personal Interest	Committee on Radioactive Waste, Management (CoRWM).
	Non-Executive Director
Personal Interest	Dept of Business, Energy and Industrial Strategy (BEIS).
	Independent Expert
Personal Interest	International Atomic Energy Agency – Mission to Fukushima Prefecture.
	Independent Expert
Personal Interest	Office for Rail and Road.
Personal Interest	Member - Committee on Medical Aspects of Radiation in the Environment (COMARE)

Personal Interest	**Member** Royal Town Planning Institute Specialist.
Personal Interest	**Member** Institute of Risk Management.
Non-Personal Interest	None.

Professor Gareth Jenkins

Personal Interest	**Employer** Swansea University, Honorary Contract, Swansea Bay University Health board.
Personal Interest	**Membership** President of United Kingdom Environment Mutagen Society (UKEMS) 2020 - 2023. Member British Association for Cancer Research Senior Editor Mutagenesis (OUP), Editorial Board (and former editor 2013-2015) Mutation Research (Elsevier). President of the International Association of Environmental Mutagenesis and Genomics Societies (IAEMGS).

Non-Personal Interest	**Grants** National Centre of Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (2018-2022). Former grants Health & Care Research Wales (2016-2020, 2014-2017. MRC/AstraZeneca PhD studentship (ITTP scheme) (2019-2023). Cancer Research Wales grants (2023-2026 and 2019-2023). External Examining roles (Bangor University. DeMontfort University, University of Milan).

Professor Neil Pearce

Personal Interest	None.
Non-Personal Interest	None.

Dr Lesley Stanley

Personal Interest	**Self-employed** Dr Lesley Stanley, Consultant in Investigative Toxicology.
Personal Interest	**Consultancy** School of Medicine, University of Dundee (2020 to date), Details of previous consultancy contracts available upon request.

Personal Interest	**Expert Appointments** REACH Independent Scientific Expert Pool, OPSS Register of Experts.
Personal Interest	**Honorary Appointment** Associate, School of Life Sciences, Edinburgh Napier University (Non-Stipendiary).
Personal Interest	**Investments** Investment Portfolio managed by Quilter Cheviot (joint with spouse), FundsNetwork Stocks and Shares ISA, Aviva Personal Pension Plan.
Personal Interest	**Ministry and Charities** Ordained Local Minister, Church of Scotland (non-stipendiary), Honorary Chaplain, University of Stirling (non-stipendiary) Supporter, Christian Aid **In Their Lifetime** programme and International Justice Mission.

Dr Lesley Rushton OBE BA MSc PhD Cstat HonFFOM (To 31st March 2022).

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

	Membership
Personal Interest	European Registered Toxicologist (ERT), Fellow of the British Toxicology Society (FBTS), Advisory Committee on Novel Foods and Processes (ACNFP).
Non-Personal Interest	None.

Professor Heather Wallace BSc Hons PhD FRCPath FBTS FRSC FRSB ERT
(To 31st March 2022).

Personal Interest	**Employee** University of Aberdeen.
Personal Interest	**Shareholder** Bank Santander SA, BT Group, NovaBiotics, Aviva.
Personal Interest	**Miscellaneous** EFSA – CONTAM Panel Cell ProTx – Director.

Personal Interest	**Membership** EUROTOX – Past President, British Toxicological Society (BTS), Medical Research Scotland – Chair and Trustee, Paediatric Medicines Expert Advisory Group – MHRA, Herbal Medicines Advisory Committee – MHRA.
Non-Personal Interest	None.

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To advise at the request of:

Food Standards Agency

Food Standards Scotland

Public Health England

Department of Health and Social Care

Other Government Departments and Agencies and those of the UK devolved Administrations.

1. To assess and advise on the toxic risk to man of substances which are:

a) used or proposed to be used as food additives or used in such a way that they might contaminate food through their use or natural occurrence in agriculture, including horticulture and veterinary practice or in the distribution, storage, preparation, processing or packaging of food.

b) used or proposed to be used or manufactured or produced in industry, agriculture, food storage or any other workplace.

c) used or proposed to be used as household goods or toilet goods and preparations.

d) used or proposed to be used as drugs, when advice is requested by the Medicines and Healthcare products Regulatory Agency.

e) used or proposed to be used or disposed of in such a way as to result in pollution of the environment.

2. To advise on important general principles or new scientific discoveries in connection with toxic risks, to co-ordinate with other bodies concerned with the assessment of toxic risks and to present recommendations for toxicity testing.

Annex 2 - 2022 - Code of Conduct for members of the COC/COM/COT

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Public service values

Members of the COC/COM/COT (hereafter referred to as “the Committee”) must at all times:

- observe the highest standards of impartiality, integrity and objectivity in relation to the advice they provide and to the management of their Committee.

- be accountable, through the Chair of the Food Standards Agency and the Chief Medical Officers, to Ministers, Parliament and the public for its activities and for the standard of advice it provides.

- in accordance with Government policy on openness, fully comply with the Freedom of Information Act 2000.

The Ministers of the sponsoring departments are answerable to Parliament for the policies and performance of the Committee, including the policy framework within which it operates.

Standards in Public Life

Members are expected to:

- comply with this Code, and ensure they understand their duties, rights and responsibilities, and that they are familiar with the function and role of their Committee and any relevant statements of Government policy. If necessary members should consider undertaking relevant training to assist them in carrying out their role.

- not misuse information gained in the course of their public service for personal gain or for political purpose, nor seek to use the opportunity of public service to promote their private interests or those of connected persons, firms, businesses or other organisations.

- not hold any paid or high profile unpaid posts in a political party, and not engage in specific political activities on matters directly affecting the work of the Committee. When engaging in other political activities, Committee members should be conscious of their public role and exercise proper discretion. These restrictions do not apply to MPs (in those cases where MPs are eligible to be appointed), to local councillors, or to Peers in relation to their conduct in the House of Lords.

- follow the Seven Principles of Public Life set out by the Committee on Standards in Public Life Committee on Standards in Public Life - GOV.UK (www.gov.uk)

Selflessness

Holders of public office should take decisions solely in terms of the public interest. They should not do so in order to gain financial or other material benefits for themselves, their family, or their friends.

Integrity

Holders of public office should not place themselves under any financial or other obligation to outside individuals or organisations that might influence them in the

performance of their official duties.

Objectivity

In carrying out public business, including making public appointments, awarding contracts, or recommending individuals for rewards and benefits, holders of public office should make choices on merit.

Accountability

Holders of public office are accountable for their decisions and actions to the public and must submit themselves to whatever scrutiny is appropriate to their office.

Openness

Holders of public office should be as open as possible about all the decisions and actions that they take. They should give reasons for their decisions and restrict information only when the wider public interest clearly demands.

Honesty

Holders of public office have a duty to declare any private interests relating to their public duties and to take steps to resolve any conflicts arising in a way that protects the public interests.

Leadership

Holders of public office should promote and support these principles by leadership and example.

These principles apply to all aspects of public life. The Committee has set them out here for the benefit of all who serve the public in any way.

Role of Members

Members have collective responsibility for the operation of their Committee. Members are appointed as individuals to fulfil the role of their respective Committees, not as representatives of their particular profession, employer or interest group and have a duty to act in the public interest. Members are appointed on a personal basis, even when they are members of stakeholder

groups and organisations. If a member declares an organisation’s view rather than a personal view they should make it clear at the time of declaring that view.

Members must:

- engage fully in collective consideration of the issues, taking account of the full range of relevant factors, including any guidance issued by the Food Standards Agency, Health Protection Agency and the Department of Health.

- undertake on appointment to comply with the Code of Practice for Scientific Advisory Committees.

- not divulge any commercially sensitive information, pre-publication or unpublished research data provided to the Committee.

- agree an annual report.

- ensure that an appropriate response is provided to complaints and other correspondence, if necessary with reference to the sponsor department.

- ensure that the Committee(s) does not exceed its powers or functions.

A member’s role on the Committee should not be limited by the expertise or viewpoint she or he was asked to bring to it. Any statement/report belongs to the whole Committee. Members should regard themselves free to question and comment on the information provided or the views expressed by any of the other members, even though the views or information provided do not relate to their own area of expertise.

If members believe the committee’s method of working is not rigorous or thorough enough, they have the right to ask that any remaining concerns they have be put on the record. Individual members should inform the Chair (or the Secretariat on his or her behalf) if they are invited to speak in public in their capacity as a Committee member. Communications between members and the Food Standards Agency (FSA) Board, CMOs and/or Ministers will generally be through the Chair except where the Chair has agreed that an individual member

should act on its behalf. Nevertheless, any member has the right of access to the FSA Board and/or the CMO on any matter that he or she believes raises important issues relating to his or her duties as a Committee member. In such cases the agreement of the rest of the Committee should normally be sought.

Committee appointments can be terminated early by either party, by giving 3 months' notice, in writing. Should the Committee be disbanded before the end of the period of appointment, appointments will terminate on dissolution.

In the event that a member is found guilty of grave misconduct their appointment will be terminated immediately, in the case of the COT by the Chair of the FSA. The Department of Health has delegated the powers for appointments to the COC and COM to the NHS Appointments Commission and it will terminate appointments in consultation with the PHE/DH.

Role of the Chair

The Chair has particular responsibility for providing effective leadership on the issues above. In addition, the Chair is responsible for:

- ensuring that the Committee meets at appropriate intervals,
- ensuring that the minutes of meetings accurately reflect proceedings and any reports to the FSA Board and/or Ministers accurately record the decisions taken,
- ensuring that where appropriate, the views of individual members have been recorded,
- representing the views of the Committee to the general public,
- ensuring that new members are briefed on appointment (and their training needs considered), and providing an assessment of their performance, on an annual basis or when members are considered for re-appointment to the Committee or for appointment to the board of some other public body,

- providing urgent advice to the FSA and HPA on issues within the remit of the Committee, in liaison with the Secretariat.

Role of the Deputy Chair

The Deputy Chair will assume the role of the Chair as described above if the Chair is not available.

Role of the Secretariat

The primary function of the Secretariat is to facilitate the business of the Committee. This includes supporting the Committee by arranging its meetings, assembling and analysing information, and recording conclusions. An important task is ensuring that proceedings of the Committee are properly documented and recorded. Minutes of all Committee meetings will be taken. These will accurately reflect the proceedings and discussions that take place and will be recorded on a non-attributable basis except where the views of one or more individual members need recording (for example, when declaring an interest).

The Secretariat is also a source of advice and guidance to members on procedures and processes. The Secretariat is drawn from staff of the Food Standards Agency and Public Health England. However, it is the responsibility of the Secretariat to be an impartial and disinterested reporter and at all times to respect the Committee’s independent role. The Secretariat is required to guard against introducing bias during the preparation of papers, during meetings, or in the reporting of the Committee’s deliberations. Current contact details for each of the Secretariats are shown on the back page of this report.

Role of the Assessor

Meetings of the Committee (and working groups) may be attended by Assessors. The Assessors are nominated by, and drawn from, the Agencies and Departments that sponsor the Committee, receive its advice, or have other relevant policy interests. Assessors are not members of the Committee and do not participate in Committee business in the manner of members.

The role of an Assessor is to keep their parent Department or Agency informed about the Committee’s work and act as a conduit for the exchange of information.

They do this by:

- advising the Committee on relevant policy developments and the implications of Committee proposals,
- informing the Committee work through the provision of information,
- being informed by the Committee on matters of mutual interest,
- sharing with the Secretariat the responsibility of ensuring that information is not needlessly withheld from the Committee. Assessors should make the Committee aware of the existence of any information that has been withheld from the Committee on the basis that it is exempt from disclosure under Freedom of Information legislation unless that legislation provides a basis for not doing so,
- ensuring that their parent Department or Agency is promptly informed of any matters which may require a response from Government.

Role of other Officials, Invited Experts and Contractors

Officials from Government Departments (not departmental assessors), Regulatory Agencies and Devolved Administrations may be called upon to advise the Committee on relevant developments in order to help the Committee formulate its advice. Invited experts and contractors may also bring particular technical expertise, which may be requested by the Committee on some occasions. In the event of an official, invited expert or contractor not being able to attend written submissions may be sent via the Secretariat.

Role of Observers

Members of the public and other interested parties may attend meetings as observers. However, they should not attempt to participate in Committee discussions. If an interested party wishes to provide information relevant to a topic for consideration by the Committee, they should be submitted in writing to

the Secretariat at least seven (7) working days before the meeting. The Secretariat will discuss with the Chair the most appropriate way to present the information to the committee and the Chair's decision will be final.

Observers who have submitted information in advance of the meeting may be invited to provide further explanation or to make brief comments at the discretion of the Chair. Observers and/or organisations must not interfere in the work of the Secretariat or input from invited experts, contractors, officials from Government Departments and Agencies in any way which, in the view of the Chair, constitutes harassment and/or might hinder the work of the Committee. Observers and/or organisations must allow other observers and other interested parties to attend items free from interference before, during and after a meeting.

Observers and/or organisations are required to respect the work of the Committee. The Committee's discussions represent the development of its view and any comments made in developing the agreed Committee view should not be attributed to individuals. Where a subject will be considered over several meetings, observers are asked to maintain the confidentiality of the discussion until an agreed Committee opinion is finalised. The Committee's conclusions are not finalised until completion of any necessary consultation and publication of a statement or report.

Under no circumstances will Observers be permitted to record Committee proceedings, on the basis that this might inhibit free discussion. The published minutes of the meeting would provide a record of the proceedings.

Failure to observe this code of conduct may lead to exclusion of individual observers and/or organisations from meetings of the Committee.

Communications and collaboration

Communications with the FSA Board, Chief Scientific Adviser and Executive

- The COT, COC and COM work in collaboration with several other Committees where the topics under consideration would benefit from expert advice from other Committees. These include, but are not limited to:
- The FSA’s Science Council; The Advisory Committee on Novel Foods and Processes (ACNFP); The Scientific Advisory Committee on Nutrition (SACN).
- Communications between the COT and the Board of the Food Standards Agency will generally be through the Chair except where the COT has agreed

that an individual member should act on its behalf. Nevertheless, any Member has the right of access to the Board of the Food Standards Agency on any matter that he or she believes raises important issues relating to his or her duties as a COT Member. In such cases the agreement of the rest of the Committee should normally be sought.
- Similarly, communications between the COT and the FSA Executive will generally be through the COT Secretariat although the COT Chair has the right of access to the FSA Chief Scientific Adviser and Deputy CSA at all times.
- Any member also has the right of access to the FSA Chief Scientific Adviser on any matter which he or she believes raises important issues relating to his or her duties as a member. In such cases the agreement of the COT Chair should normally be sought.

All observers and/or organisations are requested to read follow the Committees Openness policy (Annex 3).

Declaration of Members' Interests

Definitions

In this Code, 'the industry' means:

- Companies, partnerships or individuals who are involved with the production, manufacture, sale or supply of products subject to the following legislation.

General Food Regulations 2004,

The Food Safety Act 1990 (Amendment) Regulations 2004,

The Medicines Acts 1968 and 1971, 1981, 1986 & 2003,

The Food and Environmental Protection Act 1985,

The Consumer Protection Act 1987,

The Cosmetic (Safety) (Amendment) Regulations 2008,

Registration, Evaluation, Authorisation and Restriction of Chemicals (EC1970/2006),

- Trade associations representing companies involved with such products.

- Companies, partnerships or individuals who are directly concerned with research, development or marketing of a product which is being considered by the Committees on Toxicity, Mutagenicity, or Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.

- ‘the Secretariat’ means the Secretariat of the COC, COM and COT.

- ‘the Agency’ means either the Food Standards Agency or the Health Protection Agency.

- references to “member(s)” includes the Chair.

Different types of Interest

The following is intended as a guide to the kinds of interests which should be declared. Where members are uncertain as to whether an interest should be declared, they should seek guidance from the Secretariat or, where it may concern a particular product which is to be considered at a meeting, from the Chair at that meeting.

If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them.

However, neither the members nor the Secretariat are under any obligation to search out links of which they might reasonably not be aware. This Code suggests that interests of close family members are declared, members have in the past limited such declarations to personal partners, parents, children (minor and adult), brothers, sisters and the personal partners of any of these with the emphasis on disclosure only where the interest may or may be perceived (by a reasonable member of the public) to influence a members’ judgement.

The Secretariat is required to publish an up-to-date register of members’ interests, and these can be found on the relevant Committees website.

Personal Interests

A personal interest involves the member personally. The main examples are:

- Consultancies and/or direct employment: any consultancy, directorship, position in or work for industry which attracts regular or occasional payments in cash or kind.

- Fee-Paid Work: any work commissioned by industry for which the member is paid in cash or kind.

- Shareholdings: any shareholding in or other beneficial interest in shares of industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management.

- Membership or Affiliation: any membership role or affiliation that you or a close family member has to clubs or organisations with an interest or involvement in the work of the Agency.

Non-Personal Interests

A non-personal interest involves payment which benefits the organisation in which the member works but is not received by the member personally. The main examples are:

- Fellowships: the holding of a fellowship endowed by industry.

- Support by Industry: any payment, other support or sponsorship which does not convey any pecuniary or material benefit to a member personally, but which does benefit their position or organisation, e.g.

- A grant for the running of a unit or department for which the member is responsible.

- A grant or fellowship or other payment to sponsor a post or a member of staff or a post graduate research programme for which the member is

responsible. This does not include financial assistance for students.

- The commissioning of research or other work by, or advice from, staff who work in a unit for which the member is responsible.

Members are under no obligation to seek out knowledge of work done for, or on behalf of, the industry or other relevant bodies by departments in which they work, if they would not normally expect to be informed.

- Trusteeships: where a member is a trustee of a charity with investments in industry, the Secretariat can agree with the member a general declaration to cover this interest rather than draw up a detailed portfolio.

At meetings members are required to declare relevant interests and to state whether they are personal or non-personal interests and whether they are specific or nonspecific to the matter, product or substance under consideration.

Specific Interests

A member must declare a personal specific interest if they have at any time worked on a matter, product or substance under consideration and have personally received payment for that work, in any form.

A member must declare a non-personal specific interest if they are aware that the organisation in which they work has at any time worked on the matter, product or substance under consideration, but they have not personally received payment for that work, in any form.

Non-specific Interests

A member must declare a personal non-specific interest if they have a current personal interest in a company concerned with a matter, product or substance under consideration, which does not relate specifically to the matter, product or substance under discussion.

A member must declare a non-personal non-specific interest if they are aware that the organisation in which they work is currently receiving payment from the company concerned which does not relate specifically to the matter, product or substance under discussion.

If a member is aware that a substance, product or matter under consideration is or may become a competitor of a substance, product or matter manufactured, sold or supplied by a company in which the member has a current personal interest, they should declare their interest in the company marketing the rival product, substance or matter.

Handling conflicts of interests

The purpose of these provisions is to avoid any danger of Committee members being influenced, or appearing to be influenced, by their private interests in the exercise of their public duties. All members should declare any personal or business interest which may or may be perceived (by a reasonable member of the public) to, influence their judgement. A guide to the types of interest that should be declared is mentioned above.

Declaration of Interests to the Secretariat

Members are required to inform the Agency in writing prior to appoint of their current personal and non-personal interests, including the principal position(s) held. Members are not required to disclose the amount of any salary, fee, shareholding, grant etc. An interest is current if the member has an on-going financial involvement e.g., if he or she holds shares in industry, has a consultancy contract, or if they or the organisation for which they are responsible is in the process of carrying out work for the industry.

Following appointment members are asked to inform the Secretariat at the time of any change in their personal interests. However, the Secretariat will contact each member on an annual basis to update their declaration of interests. Changes in non-personal interests can be reported annually, and those involving less than £1000 from a particular company in the previous year need not be declared. The register of interests is kept up-to-date and open to the public via the website.

Declaration of Interest at Meetings

Members of the Committee are required to verbally declare any direct interests relating to salaried employment or consultancies, or those of close family 8 members in matters under discussion at each meeting, and if items are taken by correspondence between meetings. The declaration should note whether the interest is personal or nonpersonal, whether it is specific to the item under discussion, or non-specific and whether it is current or lapsed. Having fully

explained the nature of their interest the Chair will, decide whether and to what extent the member should participate in the discussion and determination of the issue, and it should be recorded in the minutes of the meeting.

Withdrawal from meetings

If a declaration of interest has been made and the Committee decides that the member should not participate in the discussion and should withdraw from the meeting (even if held in public) and it should be recorded in the minutes of the meeting. The Chair may first allow them to make a statement on the item under discussion.

Personal liability of Committee members

The Department of Health has a formal statement of indemnity for its advisory committee members, which includes the COC and COM, its guidance is taken from the Cabinet Office “Model Code of Practice for Board Members of Advisory Non-Departmental Public Bodies” and states that “Legal proceedings by a third party against individual board members of advisory bodies are very exceptional. A board member may be personally liable if he or she makes a fraudulent or negligent statement which result in a loss to a third party; or may commit a breach of confidence under common law or criminal offence under insider dealing legislation, if he or she misuses information gained through their position. However, the Government has indicated that individual board members who have acted honestly, reasonably, in good faith and without negligence will not have to meet out of their own personal resources any personal civil liability which is incurred in execution or purported execution of their board functions. Board members who need further advice should consult the sponsor department.”9 except where the person has acted recklessly.

The FSA has also drawn up a formal statement of indemnity for its advisory committee members.

Indemnity by the Food Standards Agency to Members of the

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

The Food Standards Agency hereby undertakes with the members (including the Chair) of the Committee on Toxicity of Chemicals in food, Consumer products and

the environment (COT) to indemnify them against all liability in respect of any action or claim which may be brought, or threatened to be brought, against them either individually or collectively by reason of or in connection with the performance of their duties as members, including all costs, charges and expenses which the Members may properly and reasonably suffer or incur in disputing any such action or claim.

The Members shall as soon as practicable notify the Food Standards Agency if any action or claim is brought or threatened to be brought against them in respect of which indemnity may be sought and if an action or claim is brought, the Food Standards Agency shall be entitled to take conduct of the defence, dispute, compromise or appeal of the action or claim and of any incidental negotiations relating to the action or claim.

The Food Standards Agency shall notify the Members as soon as practicable if it intends to so take conduct and the Members shall then provide to the Food Standards Agency such information and assistance as it shall reasonably request, subject to all out of pocket expenses properly and reasonably incurred by them being reasonably reimbursed. The Food Standards Agency shall, to the extent reasonable and practicable, consult with and keep the Members informed as and when reasonably requested by the Members in respect of any action or claim. If the Food Standards Agency does not so take conduct the Members shall keep the Food Standards Agency fully informed of the progress of the action or claim and any consequent legal proceedings and consult with the Food Standards Agency as and when required by the Food Standards Agency concerning the action or claim.

The indemnity shall not extend to any losses, claims, damages, costs, charges, expenses and any other liabilities:

- In respect of which the Members are indemnified by or through any defence organisation or insurers or,
- which may result from bad faith (including dishonesty), wilful default or recklessness on the part of the Members,
- which may result from any of the following circumstances:

1. any settlement made or compromise effected without the knowledge or consent of the Food Standards Agency on behalf of the Members of any action or claim brought, or threatened to be brought, against the Members.
2. Any admission by the Members of any liability or responsibility in respect of any action or claim brought, or threatened to be brought, against them.

3. Members taking action that they were aware, or ought reasonably to have been aware, might prejudice the successful defence of any action or claim, once the Members had become aware that such an action or claim had been brought or was likely to be brought.

Remuneration and Committee finance

In the financial year 2022/2023 the budget for the COT, excluding Secretariat resources was £100,539. Costs were met by the Food Standards Agency (FSA).

Committee members may claim a fee for Committee meetings:

COT Committee Chair £400 per day

COT Committee Member £300 per day

COT Members are able to claim for work undertaken between meetings at the above rates.

Different provisions apply to COC and COM Members. Details can be obtained from their respective Secretariats.

Review of fee rates

Fees in respect of the COT are set by the FSA and for COC and COM by the Department of Health and Social Care. The FSA will review and revise COT rates every 2 years with the intention that rates should rise in line with the recommendations of the Senior Salaries Review Board with regard to pay in the Senior Civil Service. The FSA will also take into account comparisons with rates paid in similar advisory bodies in the UK.

Travel and other expenses

Committee members are entitled to reimbursement of reasonable travel and subsistence expenses necessarily incurred on official committee business. Members must seek value for money and are encouraged to use the most cost effective and environmentally sustainable options for travel and accommodation.

Assurance

Where a risk assessment has been produced by Food Standards Agency, the Committee may occasionally be asked to assure this risk assessment. This will be published on the COT website once completed.

Urgent Advice

As set out above, part of the role of the Chair is to provide urgent advice to FSA and UKHSA on issues within the remit of the Committee, in liaison with the Secretariat. However, with the approval of the Chair, one or more COT Members may also provide such advice, particularly where they have relevant specialist knowledge. Similarly, with the approval of the Chair and in liaison with the Secretariat one or more COT Members may be asked to assure urgent advice prepared by the FSA or UKHSA.

Working Groups

The Committee may establish Working Groups to consider particular topics in depth or to make brief assessments of particular issues and advise the main Committee on the possible need for further action. Such Groups contain a number of Committee members (supplemented, as necessary, by external expertise in the particular subject being considered). A Committee Chair will play a leading role in deciding which Committee members should be invited to join such groups, which may meet on a number of occasions in a particular year. Committee members may claim an allowance for participating on a Working Group.

Terms and conditions of appointment

Appointments of members may be staggered so that only a proportion retire or are re-appointed each year, to help ensure continuity. COC and COM Chairs are ex officio members of each other’s Committees.)

COC and COM members are usually expected to attend 3 meetings in a year. COT members are expected to attend 7 meetings in a year. Members should allow appropriate preparation time. Meetings will usually be in London but an option for virtual attendance will be provided.

The COC/COM/COT Chair must also be available for a number of other activities including: attending, with the FSA Chief Scientist, the FSA Board’s annual discussion of the Agency’s science; engaging with the media on any high-profile relating to the Committee’s work, and discussion with the Agency Chief Scientist

and GACS Secretariat in planning and developing the Committee's work (including discussing and agreeing with the Agency's Chief Scientist a framework for providing assurance on the work of the Scientific Advisory Committees in providing advice to the Agency). It is expected that these additional activities might require 5-10 days input per year.

Feedback on performance

The COT Chair and members are asked to provide brief feedback on their experience on the committee each year to help the Agency ensure that the Committee operates effectively and identify any areas for improvement.

Committee members are normally appointed for a term of 3 years (a maximum 10 years/3 terms per member). The COT uses the feedback self-assessment form as one of the tools used to determine whether or not a committee member should be reappointed at the end of their (3 year) term.

Annex 3 – 2022 - Openness

In this guide

Introduction

1. The Committee on Toxicity (COT) and its sister committees the Committee on Mutagenicity (COM) and Committee on Carcinogenicity (COC) are non-statutory independent scientific advisory committees which advise the Chair of the Food Standards Agency and the Chief Medical Officers (for England, Scotland, Wales and Northern Ireland) and, through them, the Government on a wide range of matters concerning chemicals in food, consumer products and the environment.

2. The Government is committed to make the operation of scientific advisory committees such as the COT/COM/COC hereafter referred to as “the Committee” more open and to increase accountability. The Committee is aware that the disclosure of information that is of a confidential nature and is communicated in circumstances importing an obligation of confidence is subject to the common law of confidentiality. There are some circumstances making disclosure of confidential information lawful for example, where the individual to whom the information relates has consented; where disclosure is in the public interest; and where there is a legal duty to do so. However, guidance is set out in the Freedom of

Information Act 2000 which gives any person legal rights of access to information which is held by a public authority.

3. The Committee has agreed to hold open meetings as standard practice. Interest groups, consumer organisations etc can attend (subject to the appropriate procedures for handling commercially sensitive information and research not in the public domain, paragraphs 9-15 refer).

4. The Committee appoints lay/public interest member(s) to help to increase public scrutiny of Committee business.

5. The Committee has agreed to the publication of agendas, draft and finalised minutes, discussion papers and statements on the internet.

6. Statements will summarise all the relevant data, such as information regarding potential hazards/risks for human health in respect of the use of products and chemicals, and any recommendations for further research.

7. The Committee will be asked for an opinion based on the data available at the time of consideration. It is recognised that, for many chemicals, the toxicological information is incomplete and that recommendations for further research to address these gaps may form part of the Committee's advice.

8. The release of documents (papers, minutes and statements) where the Committee has agreed an opinion on the available unpublished data but where further additional information is required in order to finalise the Committee's conclusions, needs to be considered on a case-by case basis.

The relevant considerations include the likelihood that such additional data would alter the Committee's conclusion, any representations made by a company about, for example, commercial harm that early disclosure could cause and also the public interest in disclosure.

Procedures for handling commercially sensitive information and research data not in the public domain

Background

9. The Committee operates on a presumption of openness. However, it is recognised that the nature of the work will at times provide the Committee access

to information that is not in the public domain. Decisions on confidentiality will be exercised consistently with consideration to the Freedom of Information Act 2000 and Environmental Information Regulations 2004.

10. Where there is a need to discuss matters that cannot be put in the public domain the Committee may hold a discussion in “Reserved Business”. These items will be generally discussed either at the beginning or the end of an open meeting. It is expected that such cases will be infrequent and only in clearly justified circumstances. For the most part this comprises information which is commercially sensitive such as product formulations/specifications, methods of manufacture, and reports of toxicological investigations and company evaluations and safety assessment. It would also include pre-publication or unpublished research data.

11. “Reserved Business” items will be clearly indicated as such. The Committee will advise its reasons for withholding any information, and, if possible, an indication of when and where the information withheld may be published. Information subject to such restriction, including reserved sections of the minutes will be placed in the public domain as soon as practicable should the restrictions cease to apply at a later date.

12. Normal procedure is to publish a summary of the Committee's advice on their respective websites, in the Annual Report and where necessary to ask companies to release full copies of submitted reports for retention by the British Library at the completion of a review. Given the clear Ministerial commitment to the publication of detailed information regarding the activities of advisory committees, and in particular following the assessment of products which are already available to the general public, the Committee will publish statements via the Internet soon after they have been finalised.

13. Except in cases where there is legislation under which information has been submitted and which deals with disclosure and non-disclosure, the general principle of the common law duty of confidentiality will apply. This means that any information which is commercially sensitive, pre-publication or unpublished research data and has been obtained in circumstances importing a duty of confidence may not be disclosed unless consent has been given or there is an overriding public interest in disclosure (such as the prevention of harm to others).

14. The following procedure will be adopted which allows commercially sensitive information to be identified, assessed and appropriate statements to be

drafted and published on the basis of a prior mutual understanding with the companies. There is scope for companies to make representations also after submission of the information and prior to publication regarding the commercial sensitivity of data supplied and to comment on the text of statements which are to be published. However, companies would not have a right of veto in respect of such statements.

Procedures prior to committee consideration

Initial discussions

15. Upon referral to Committee the Secretariat will liaise with the relevant company supplying the product in the UK to:

- Clearly state the policy of Committee openness (summarised above).
- Identify and request the information needed by the Committee (e.g., test reports, publications etc).

Commercially sensitive information

- The company will be asked to clearly identify any commercially sensitive information and the reason for confidentiality.

Pre-publication and unpublished research data

17. The Committee and Secretariat will respect the confidentiality of authors of (unpublished or pre-publication) research data.

Handling confidential data

- The procedures by which the Committee will handle commercially sensitive information, pre-publication or unpublished research data and the public availability of papers, minutes, conclusions and statements where reference is made to such data will be discussed with the company or author prior to submission of papers to the Committee and is outlined in paragraphs 9-15 above. Companies will be informed that confidential annexes to Committee papers (e.g. where detailed information supplied in confidence such as individual patient information and full study reports of toxicological studies)

will not be disclosed but that other information will be disclosed unless agreed otherwise with an individual company.

- The following is a suggested list of information which may be disclosed in Committee documents (papers, minutes and statements). The list is not exhaustive and is presented as a guide:

a) name of product (or substance/chemical under consideration),

b) information on physico-chemical properties,

c) methods of rendering harmless,

d) a summary of the results and evaluation of the results of tests to establish harmlessness to humans,

e) methods of analysis,

f) first aid and medical treatment to be given in the case of injury to persons,

g) surveillance data (e.g. monitoring for levels in food, air, or water).

Procedures during and after Committee consideration

- The timing of release of Committee documents (papers, minutes and statements) where the item of business involved the consideration of confidential data would be subject to the general provisions outlined in paragraphs 9-15 above. Documents would not be released until the Committee statement is available.
- The most important outcome of the Committee consideration is likely to be the agreed statement. Companies will be given an opportunity to comment on the statement prior to publication and to make representations (for example, as to commercial sensitivities in the statement). The Chair would be asked to consider any comments provided, but companies would not be able to veto the publication of a statement or any part of it. Companies will continue to be asked to release full copies of submitted reports for retention by the British Library at the completion of a review.

Dissenting views

16. The Committee should not seek consensus at the risk of failing to recognise different views on a subject. Any significant diversity of opinion among the members of the Committee that cannot be resolved should be accurately

reflected in the minutes or report. Committee decisions should always include an explanation of where differences of opinion have arisen during discussions, specifically where there are unresolved issues and why conclusions have been reached. If however member(s) feel they cannot support the Committee conclusions they may declare a ‘minority report’ identifying which member(s) are making the minority report and setting out their position.

COC/COM/COT papers

17. Committee papers are available on the respective website. Papers will not include commercially sensitive documents, pre-publication, unpublished or material in the public domain. Where possible a cover page with weblinks (current at the time) will be provided.

Remuneration and Committee finance

18. In the financial year 2022/23 the budget for the COT, excluding Secretariat resources was £114,000. Costs were met by the Food Standards Agency (FSA).

Review of fee rates

19. Fees in respect of the COT are set by the FSA and for COC and COM by the Department of Health. The FSA will review and revise COT rates every 2 years with the intention that rates should rise in line with the recommendations of the Senior Salaries Review Board with regard to pay in the Senior Civil Service. The FSA will also take into account comparisons with rates paid in similar advisory bodies in the UK.

Travel and other expenses

20. Committee members are entitled to reimbursement of reasonable travel and subsistence expenses necessarily incurred on official committee business. Members must seek value for money and are encouraged to use the most cost effective and environmentally sustainable options for travel and accommodation.

Working Groups

21. The Committee may establish Working Groups to consider particular topics in depth or to make brief assessments of particular issues and advise the main

Committee on the possible need for further action. Such Groups contain a number of Committee members (supplemented, as necessary, by external expertise in the particular subject being considered). A Committee Chair will play a leading role in deciding which Committee members should be invited to join such groups, which may meet on a number of occasions in a particular year. Committee members may claim an allowance for participating on a Working Group.

Terms and conditions of appointment

22. Appointments of members may be staggered so that only a proportion retire or are re-appointed each year, to help ensure continuity. (Note: The COC/COM/COT Chairs are ex officio members of General Advisory Committee on Science (GACS) for the term of their appointment as the COC/COM/COT Chair. COC and COM Chairs are ex officio members of each other's Committees.)

23. COC and COM members are usually expected to attend 3 meetings in a year. COT members are expected to attend 7 meetings in a year. Members should allow appropriate preparation time. Meetings will usually be in London.

24. The COC/COM/COT Chair must also be available for a number of other activities including: attending, with the FSA Chief Scientist, the FSA Board's annual discussion of the Agency's science; engaging with the media on any high-profile relating to the Committee's work, and discussion with the Agency Chief Scientist and GACS Secretariat in planning and developing the Committee's work (including discussing and agreeing with the Agency's Chief Scientist a framework for providing assurance on the work of the Scientific Advisory Committees in providing advice to the Agency). It is expected that these additional activities might require 5-10 days input per year.

Feedback on performance

25. The COT Chair and members are asked to provide brief feedback on their experience on the committee each year to help the Agency ensure that the Committee operates effectively and identify any areas for improvement.

26. Committee members are normally appointed for a term of 3 years (a maximum 10 years/3 terms per member). The COT uses the feedback self-assessment form as one of the tools used to determine whether or not a committee member should be reappointed at the end of their (3 year) term.

4 – 2022 - Good Practice Agreement for Scientific Advisory Committees

In this guide

In this guide

Introduction

The Government Chief Scientific Adviser's Guidelines on the Use of Scientific and Engineering Advice in Policy Making set out the basic principles which government departments should follow in assembling and using scientific advice. The key elements are to:

- **Identify early** the issues which need scientific and engineering advice and where **public engagement** is appropriate.
- Draw on a **wide range of expert advice** sources, particularly when there is uncertainty.
- Adopt an **open and transparent approach** to the scientific advisory process and publish the evidence and analysis as soon as possible.
- **Explain publicly the reasons for policy decisions**, particularly when the decision appears to be inconsistent with scientific advice.
- **Work collectively** to ensure a joined-up approach throughout government to integrating scientific and engineering evidence and advice into policy making.

The Code of Practice for Scientific Advisory Committees and the Principles of Scientific Advice to Government provide more detailed guidance on the operation of Scientific Advisory Committees (SACs) and their relationship with their sponsor Departments.

The Food Standards Agency's Board adopted a **Science Checklist** in 2006 (updated in 2012) that makes explicit the points to be considered in the preparation of policy papers and proposals dealing with science-based issues, including those which draw on advice from the SACs.

These **Good Practice Guidelines** were drawn up in 2006 by the Chairs of the independent SACs that advise the FSA based on, and complementing, the Science Checklist. They were updated in 2012 in consultation with the General Advisory Committee on Science (GACS). (Note GACS has now been replaced by the FSA Science Council).

The Guidelines apply to the SACs that advise the FSA and for which the FSA is sole sponsor Department:

- Advisory Committee on Animal Feedingstuffs,
- Advisory Committee on Microbiological Safety of Food,
- Advisory Committee on Novel Foods and Processe,
- Science Council,
- Advisory Committee for Social Science (ACSS).

As well as those Committees, the FSA co-sponsors with the Department of Health and Social Care:

- Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment,
- Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment,
- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment.

For the SACs with a shared sponsorship the Guidelines apply formally to their advice to the FSA; they may opt to follow them also in advising other sponsor Departments.

All these committees share important characteristics. They are:

- Independent,
- work in an open and transparent way,
- are concerned with risk assessment and/or science governance, not with decisions about risk management.

The Guidelines relate primarily to the risk assessment process since this is the main purpose of most of the SACs. However, the SACs may, where appropriate, comment on risks associated with different risk management options, highlight any wider issues raised by their assessment that they feel should be considered (distinguishing clearly between issues on which the SAC has an expert capability and remit, and any other issues), or any evidence gaps and/or needs for research or analysis.

In addition, the Science Council and ACSS may advise the FSA on aspects of the governance of risk management, or on research that relates to risk management.

Twenty-nine principles of good practice have been developed. However, the different committees have different duties and discharge those duties in different ways. Therefore, not all the principles set out below will be applicable to all of the committees, all of the time.

The SACs have agreed to review their application of the principles annually and report this in their Annual Reports. Compliance with the Guidelines will also be covered in the annual self-assessments by Members and annual feedback meetings between each SAC Chair and the FSA Chief Scientist.

Principles

Defining the problem and the approach

The FSA will ensure that issues it asks an SAC to address are clearly defined and take account of stakeholder expectations in discussion with the SAC Secretariat and where necessary the SAC Chair. The SAC Chair will refer back to the FSA if discussion suggests that further iteration and discussion of the task is necessary.

Where an SAC proposes to initiate a piece of work the SAC Chair and Secretariat will discuss this with FSA to ensure the definition and rationale for the work and its expected use by the FSA are clear.

Seeking input

The Secretariat will ensure that stakeholders are consulted at appropriate points in the SAC’s considerations. It will consider with the FSA whether and how stakeholder views need to be taken into account in helping to identify the issue and frame the question for the committee.

Wherever possible, SAC discussions should be held in public.

The scope of literature searches made on behalf of the SAC will be clearly set out.

Steps will be taken to ensure that all available and relevant scientific evidence is rigorously considered by the committee, including consulting external/additional scientific experts who may know of relevant unpublished or pre-publication data.

Data from stakeholders will be considered and weighted according to quality by the SAC.

Consideration by the Secretariat and the Chair (and where appropriate the whole SAC) will be given to whether expertise in other disciplines will be needed.

Consideration will be given by the Secretariat or by the SAC, in discussion with the FSA, as to whether other SACs need to be consulted.

Validation

Study design, methods of measurement and the way that analysis of data has been carried out will be assessed by the SAC.

Data will be assessed by the committee in accordance with the relevant principles of good practice, e.g. qualitative social science data will be assessed with reference to guidance from the Government's Chief Social Researcher as set out in Quality in qualitative Evaluation: A Framework for Assessing Research Evidence or the Magenta Book

Formal statistical analyses will be included wherever appropriate. To support this, each SAC will have access to advice on quantitative analysis and modelling as needed.

When considering what evidence needs to be collected for assessment, the following points will be considered:

- the potential for the need for different data for different parts of the UK or the relevance to the UK situation for any data originating outside the UK.
- whether stakeholders can provide unpublished data.

The list of references will make it clear which references have been subject to external peer review, and which have been peer reviewed through evaluation by the Committee, and if relevant, any that have not been peer reviewed.

Uncertainty

When reporting outcomes, SACs will make explicit the level and type of uncertainty (both limitations on the quality of the available data and lack of knowledge) associated with their advice.

Any assumptions made by the SAC will be clearly spelled out, and, in reviews, previous assumptions will be challenged.

Data gaps will be identified and their impact on uncertainty assessed by the SAC.

An indication will be given by the SAC about whether the evidence base is changing or static, and if appropriate, how developments in the evidence base might affect key assumptions and conclusions.

Drawing conclusions

The SAC will be broad-minded, acknowledging where conflicting views exist and considering whether alternative interpretations fit the same evidence.

Where both risks and benefits have been considered, the committee will address each with the same rigour, as far as possible; it will make clear the degree of rigour and uncertainty, and any important constraints, in reporting its conclusions.

SAC decisions will include an explanation of where differences of opinion have arisen during discussions, specifically where there are unresolved issues, and why conclusions have been reached. If it is not possible to reach a consensus, a minority report may be appended to the main report, setting out the differences in interpretation and conclusions, and the reasons for these, and the names of those supporting the minority report.

The SAC's interpretation of results, recommended actions or advice will be consistent with the quantitative and/or qualitative evidence and the degree of uncertainty associated with it.

SACs will make recommendations about general issues that may have relevance for other committees.

Communicating the SACs' conclusions

Conclusions will be expressed by the SAC in clear, simple terms and use the minimum caveats consistent with accuracy.

It will be made clear by the SAC where assessments have been based on the work of other bodies and where the SAC has started afresh and there will be a clear statement of how the current conclusions compare with previous assessments.

The conclusions will be supported by a statement about their robustness and the extent to which judgement has had to be used.

As standard practice, the SAC secretariat will publish a full set of references (including the data used as the basis for risk assessment and other SAC opinions)

at as early a stage as possible to support openness and transparency of decision-making. Where this is not possible, reasons will be clearly set out, explained and a commitment made to future publication wherever possible.

The amount of material withheld by the SAC or FSA as being confidential will be kept to a minimum. Where it is not possible to release material, the reasons will be clearly set out, explained and a commitment made to future publication wherever possible.

Where proposals or papers being considered by the FSA Board rest on scientific evidence produced by a SAC, the Chair of the SAC (or a nominated expert member) will be invited to the table at the Open Board meetings at which the paper is discussed. To maintain appropriate separation of risk assessment and risk management processes, the role of the Chairs will be limited to providing an independent view and assurance on how their committee's advice has been reflected in the relevant policy proposals, and to answer Board Members' questions on the science. The Chairs may also, where appropriate, be invited to provide factual briefing to Board members about particular issues within their committees' remits, in advance of discussion at open Board meetings.

The SAC will seek (and FSA will provide) timely feedback on actions taken (or not taken) in response to the SAC's advice, and the rationale for these.

Annex 5 – 2022 - Glossary of Terms

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10. COM Evaluations - 2022
11. Horizon scanning: meetings and workshops - COM 2022
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13. 2022 Membership of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
14. Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment Annual Report 2022
15. COC Ongoing Topics - 2022
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23. Annex 1 - 2022 - Terms of Reference
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Numerical

3R’s principle: The 3Rs stand for Replacement, Reduction, Refinement. This is a strategy that is intended to reduce the number of animals used in experiments and to reduce animal experimentation overall; it also aims to mitigate the suffering and distress caused to the animals.

A

a priori: The formulation of an hypothesis based on theoretical considerations before undertaking an investigation or experiment.

Absolute risk (AR): is the probability or chance of an event. It is usually used for the number of events (such as a disease) that occurred in a group, divided by the number of people in that group.

Absorption (biological): Process of active or passive transport of a substance into an organism, in humans this is usually through the lungs, gastrointestinal tract or skin.

Acceptable daily intake (ADI): Estimate of the amount of a substance in food or drink, expressed on a bodyweight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk.

Acceptable risk: Probability of suffering disease or injury which is considered to be sufficiently small to be societally acceptable.

Acute: Short term, in relation to exposure or effect.

Acute reference dose (ARfD): Estimate of the amount of a substance in food or drink, expressed on a body weight basis that can be ingested in a period of 24 hours or less without appreciable health risk.

Acute toxicity: Adverse effects that occur over a short period of time (up to 14 days) immediately following a single exposure.

Adaptive response: The process whereby a cell or organism responds to a xenobiotic so that the cell or organism will survive in the new environment that contains the xenobiotic without impairment of function.

Adduct: A chemical grouping which is covalently bound (see covalent binding) to a large molecule such as DNA (qv) or protein.

Adductome: The totality of the adduct profile, usually to DNA, in an individual.

Adenoma: A benign neoplasm arising from a gland forming epithelial tissue such as colon, stomach or respiratory tract.

Adverse Outcome Pathway (AOP): A sequence of key events linking a molecular initiating event (MIE) to an adverse outcome through different levels of biological organisation. AOPs span multiple layers of biological organisation.

Adverse response: Change in morphology, physiology, biochemistry, growth, development or lifespan of an organism or its progeny which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other

environmental influences.

Aetiology: study of causation or origination.

Aggregate exposure: exposure to one chemical by all routes from all sources.

Ah receptor: The Ah (Aromatic hydrocarbon) receptor protein is a member of a group of regulatory sensor molecules. The identity of the natural endogenous chemicals which regulate the Ah receptor is unknown. Binding to the Ah receptor is an integral part of the toxicological mechanism of a range of chemicals, such as chlorinated dibenzodioxins and polychlorinated biphenyls.

Alkylating agents: Chemicals which leave an alkyl group covalently bound to biologically important molecules such as proteins and nucleic acids (see adduct). Many alkylating agents are mutagenic, carcinogenic and immunosuppressive.

Allele: Alternative form of a gene within the population.

Allergen: Substance capable of stimulating an allergic reaction.

Allergy: The adverse health effects that may result from the stimulation of a specific immune response.

Allergic reaction: an adverse reaction elicited by exposure to a previously sensitised individual to the relevant antigen.

Ames test: Also known as the bacterial reverse mutation assay. In vitro assay for bacterial gene mutations using strains of Salmonella typhimurium and Escherichia coli.

Androgen: The generic term for any natural or synthetic compound that can interact with and activate the androgen receptor. In mammals, androgens (for example, androstenedione and testosterone) are synthesised by the adrenal glands and the testes and promote development and maintenance of male secondary sexual characteristics.

Aneugen/aneugenic: (An agent) Inducing aneuploidy.

Aneuploidy: The circumstances in which the total number of chromosomes within a cell is not an exact multiple of the normal haploid (see 'polyploidy') number. Chromosomes may be lost or gained during cell division.

Apoptosis: A form of programmed, active cell death resulting in fragmentation of the cell into membrane-bound fragments (apoptotic bodies). These are usually

rapidly removed in vivo by engulfment by phagocytic cells. Apoptosis occurs normally during development but can be triggered abnormally by toxic stimuli.

As low as is reasonably achievable/ As low as is reasonably practicable (ALARA/ALARP): A risk management approach under which exposure to a substance or mixture is reduced to the lowest level that it is deemed to be reasonably achievable or practicable in particular circumstances or by available technological solutions.

B

Base pair (bp): Two complementary nucleotide bases in DNA joined together by hydrogen bonds.

Benchmark dose (BMD) modelling: An alternative quantitative approach to dose-response assessment using more of the data than the NOAEL process. This approach utilises mathematical models to fit all available data points and uses the best fitting model to interpolate an estimate of the dose (benchmark dose) that corresponds to a particular level of response (a benchmark response). A measure of uncertainty is also calculated, and the lower confidence limit on the benchmark dose is called the BMDL. The BMDL accounts for the uncertainty in the estimate of the dose-response that is due to characteristics of the experimental design such as sample size and biological variability. The BMDL can be used as the point of departure (see POD) for derivation of a health-based guidance value or a margin of exposure.

Benign tumour: Tumours showing a close morphological resemblance to their tissue of origin, growing in a slow expansile fashion and with a circumscribed form, usually encapsulated masses. They may stop growing and they may regress. Benign tumours do not infiltrate through local tissues, and they do not metastasise. They are rarely fatal.

Bias: An interference which at any stage of an investigation tends to produce results that depart systematically from the true values (to be distinguished from random error). The term does not necessarily carry an imputation of prejudice or any other subjective factor such as the experimenter's desire for a particular outcome.

Bioavailability: A term referring to the proportion of a substance which reaches the systemic circulation unchanged after a particular route of administration.

Bioinformatics: The science of informatics as applied to biological research. Informatics is the management and analysis of data using advanced computing techniques. Bioinformatics is particularly important as an adjunct to -omics research, because of the large amount of complex data this research generates.

Biological relevance: an effect considered by expert judgement as important and meaningful for human, animal, plant or environmental health. It therefore implies a change that may alter how decisions for a specific problem are taken.

Biomarker: Observable change (not necessarily pathological) in an organism, related to a specific exposure, effect or susceptibility.

Biomarker of effect: A measurable biochemical, physiologic, behavioural, or other alteration in an organism that, depending on the magnitude, can be recognised as associated with an established or possible health impairment or disease.

Biomarker of exposure: a chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in the human body indicative of exposure.

Biomarker of susceptibility: An indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific chemical substance.

Biomonitoring (human): the direct measurement of people's integrated exposure to toxic substances by measuring the substances, their metabolites or a biochemical change in human specimens, such as blood or urine.

Biomonitoring equivalent: an estimated concentration or range of concentrations of an environmental chemical in humans which is consistent with existing health-based guidance values such as the TDI or RfD/RfC. BEs provide a way of interpreting biomonitoring data in the context of these values.

Body burden: Total amount of a chemical present in an organism at a given time.

Bradford Hill considerations: Sir Austin Bradford Hill established a set of ‘principles’ (not be taken as ‘criteria’) that may be used to assist in the interpretation of associations reported from epidemiological studies:

Strength – The stronger the association the more likely it is causal. The COC has previously noted that the relative risks of <3 need careful assessment for effects

of bias or confounding.

Consistency – The association has been consistently identified by studies using different approaches and is also seen in different populations with exposure to the chemical under consideration.

Specificity – Limitation of the association to specific exposure groups or to specific types of disease increases likelihood that the association is causal.

Temporality – The association must demonstrate that exposure leads to disease. The relationship of time since first exposure, duration of exposure and time since last exposure are all important in assessing causality.

Biological gradient – If an association reveals a biological gradient or dose response curve, then this evidence is of particular importance in assessing causality.

Plausibility – Is there appropriate data to suggest a mechanism by which exposure could lead to concern? However, even if an observed association may be new to science or medicine it should not be dismissed.

Coherence – Cause and effect interpretation of data should not seriously conflict with generally known facts.

Experiment – Can the association be demonstrated experimentally? Evidence from experimental animals may assist in some cases. Evidence that removal of the exposure leads to a decrease in risk may be relevant.

Analogy – Have other closely related chemicals been associated with the disease?

Bronchial: Relating to the air passages conducting air from the trachea (windpipe) to the lungs.

C

Cancer: Synonym for a malignant neoplasm – that is, a tumour that grows progressively, invades local tissues and spreads to distant sites (see also tumour and metastasis).

Candidate gene: A gene that has been implicated in causing or contributing to the development of a particular disease.

Carcinogen: A causal agent that induces tumours. Carcinogens include external factors (chemicals, physical agents, viruses) and internal factors such as hormones. An important distinction can be drawn between **genotoxic** carcinogens which have been shown to damage DNA, and **nongenotoxic** carcinogens which act through other mechanisms. The activity of genotoxic carcinogens can often be predicted from their chemical structure - either of the parent compound or of active metabolites. Most chemical carcinogens exert their effects after prolonged exposure, show a dose-response relationship and tend to act on a limited range of susceptible target tissues. Carcinogens are sometimes species or sex-specific and the term should be qualified by the appropriate descriptive adjectives to aid clarity. Several different chemical and other carcinogens may interact, and constitutional factors (genetic susceptibility, hormonal status) may also contribute, emphasising the multifactorial nature of the carcinogenic process.

Carcinoma: Malignant tumour arising from epithelial cells lining, for example, the alimentary, respiratory and urogenital tracts and from epidermis, also from solid viscera such as the liver, pancreas, kidneys and some endocrine glands. (See also 'tumour').

Case-control study: (Synonyms - case comparison study, case referent study) A comparison is made of the proportion of cases who have been exposed to a particular hazard (e.g., a carcinogen) with the proportion of controls who have been exposed to the hazard.

Cell cycle (cell cycle arrest): The cell cycle is a series of events involving the growth, replication, and division of a eukaryotic cell. Cell cycle arrest: A regulatory process that halts progression through the cell cycle during one of the normal phases (G1, S, G2, M).

Cell transformation: The process by which a normal cell acquires the capacity for neoplastic growth. Complete transformation occurs in several stages both in vitro and in vivo. One step which has been identified in vitro is 'immortalisation' by which a cell acquires the ability to divide indefinitely in culture. Such cells do not have the capacity to form tumours in animals but can be induced to do so by extended passage in vitro, by treatment with chemicals, or by transfection with oncogene DNA. The transformed phenotype so generated is usually, but not always, associated with the ability of the cells to grow in soft agar and to form tumours when transplanted into animals. It should be noted that each of these stages of transformation can involve multiple events which may or may not be genetic. The order in which these events take place, if they occur at all, in vivo is

not known.

Cholinergic: A substance which is capable of producing, altering or releasing the neurotransmitter acetylcholine.

Chromosomal aberrations: Collective term of particular types of chromosome damage induced after exposure to exogenous chemical or physical agents which damage the DNA (see also aneugen, clastogen). Such numerical or structural chromosome changes tend to be those which are evident using light microscopy.

Chromosome: In simple prokaryotic organisms, such as bacteria and most viruses, the chromosome consists of a single circular molecule of DNA containing the entire genetic material of the cell. In eukaryotic cells, the chromosomes are thread-like structures, composed mainly of DNA and protein, which are present within the nuclei of every cell. They occur in pairs, the numbers varying from one to more than 100 per nucleus in different species. Normal somatic cells in humans have 23 pairs of chromosomes, each consisting of linear sequences of DNA which are known as genes.

Chronic effect: Consequence which develops slowly and has a long-lasting course (often but not always irreversible).

Chronic exposure: Continued exposures occurring over an extended period of time, or a significant fraction of the life-time of a human or test animal.

Clastogen: An agent that produces chromosome breaks and other structural aberrations such as translocations. Clastogens may be viruses or physical agents as well as chemicals. Clastogenic events play an important part in the development of some tumours (clastogenicity).

Clearance: Volume of blood or plasma, or mass of an organ, effectively cleared of a substance by elimination (metabolism and excretion) in a given time interval. Total clearance is the sum of the clearances for each eliminating organ or tissue.

Clone: A term which is applied to genes, cells, or entire organisms which are derived from - and are genetically identical to - a single common ancestor gene, cell, or organism, respectively. Cloning of genes and cells to create many copies in the laboratory is a common procedure essential for biomedical research.

Coding regions: those parts of the DNA that contain the information needed to form proteins. Other parts of the DNA may have non-coding functions (e.g., start-stop, pointing or timer functions) or as yet unresolved functions or maybe even

‘noise’.

Codon: a set of three nucleotide bases in a DNA or RNA sequence, which together code for a specific amino acid.

Cohort: A defined population that continues to exist through a period of time, e.g., a group of individuals who had a specific occupation.

Cohort study: (Synonyms - follow-up, longitudinal study) The study of a group of people defined at a particular point in time (the cohort), who have particular characteristics in common, such as a particular exposure. They are then observed over a period of time for the occurrence of disease. The rate at which the disease develops in the cohort is compared with the rate in a comparison population, in which the characteristics (e.g., exposure) are absent.

Combined exposure: exposure to multiple chemicals by a single or multiple routes at the same or different times.

Comet assay: A genotoxicity assay in which DNA strand breaks in an individual cell are measured using single-cell gel electrophoresis. Cell DNA fragments assume a "comet with tail" formation on electrophoresis and are detected with an image analysis system. Alkaline assay conditions facilitate sensitive detection of double-strand and single-strand damage, as well as alkali-labile sites. Modifications to standard methodology enable detection of types of DNA damage, e.g., DNA-DNA or DNA-protein cross-links and base-oxidation.

Complementary DNA (cDNA): cDNA is DNA that is synthesised in the laboratory from mRNA by reverse transcription. A cDNA is so-called because its sequence is the complement of the original mRNA sequence.

Confounding variable: (synonym - confounder) A confounding variable is a factor that is independently associated with both an intervention or exposure and the outcome of interest. Failure to account for this will distort the observed measure of association in the statistical analysis. For example, in observational studies, cigarette smoking is a confounding variable with respect to an association between alcohol consumption and heart disease because it is a risk factor for heart disease and is associated with alcohol consumption but is not a consequence of alcohol consumption. Similarly, if people in the experimental group of a controlled trial are younger than those in the control group, age could act as a potential confounder and make it difficult to ascertain whether a lower risk of death in one group is due to the intervention or the difference in ages.

Confounding may also occur in experimental studies, where in a feed trial, unpalatability might result in reduced food consumption and weight loss, rather than weight loss occurring through toxicity.

Congeners: Related compounds varying in chemical structure that often, but not always, share biological properties.

Continuous Data: Quantitative data that can be measured and has an infinite number of possible values within a selected range.

Copy number variants (CNVs): Alterations in the DNA of a genome that results in the cell having an abnormal number of copies of one or more sections of the DNA. CNVs correspond to relatively large regions of the genome that have been deleted (fewer than the normal number) or duplicated (more than the normal number) on certain chromosomes.

Covalent binding: Chemical bonding formed by the sharing of an electron pair between two atoms. Molecules are combinations of atoms bound together by covalent bonds (see adduct).

Critical effect size (CES): The magnitude of the adverse effect selected at which to determine the dose to serve as a point of departure in assessing the risk from exposure to a chemical. This term is often used synonymously with Benchmark Response (BMR). Choice of CES includes both statistical and toxicological considerations.

Cumulative exposure: exposure to multiple chemicals on the basis of grouping them on some common characteristic, such as mode of action, adverse effect, or inclusion in a product formulation.

P450 (CYP): An extensive family of haem-containing proteins involved in enzymic oxidation of a wide range of endogenous and xenobiotic substances and their conversion to forms that may be more easily excreted. In some cases, the metabolites produced may be chemically reactive and have increased toxicity. In other cases, the substances may be natural precursors of hormones (e.g., steroids).

Cytogenetic: Concerning chromosomes, their origin, structure and function.

D

(DNA) Deletion: A type of mutation where there is a loss of DNA (nucleotide base pairs) from the genome. Deletions may range in size from a single nucleotide to an entire chromosome. Such deletions may be harmless, may result in disease, or may in rare cases be beneficial.

Deoxyribonucleic acid (DNA): The carrier of genetic information for all living organisms except the group of RNA viruses. Each of the 46 chromosomes in normal human somatic cells consists of 2 strands of DNA containing an estimated 50 - 250 million nucleotides, specific sequences of which make up genes. DNA itself is composed of two interwound chains of linked nucleotides.

DNA damage: Injuries to DNA that introduce deviations from its normal, chemical structure and which may, if left unrepaired, result in a mutation or a block of DNA replication. These deviations can occur naturally or may be caused by environmental physical or chemical agents.

DNA methylation: A reversible biochemical modification of DNA more or less universally present in organisms from bacteria to humans. Methyl groups can be enzymatically added to or removed from cytosine (C). It is associated with silencing of DNA sequences.

DNA probe: A piece of single-stranded DNA, typically labelled so that it can be detected (for example, a radioactive or fluorescent label can be used), which can single out and bind with another specific piece of DNA. DNA probes can be used to determine which sequences are present in a given length of DNA or which genes are present in a sample of DNA.

DNA repair: Processes that repair potentially damaging changes in DNA, including those induced by chemical mutagens (see mutagen.) Through the action of enzymes, individual DNA bases may be replaced, or part of a strand of DNA may be replaced, using its opposite, paired strand as a template. These processes may themselves be prone to error and result in potentially deleterious changes.

DNA repair genes: Genes which code for proteins that repair damage in DNA sequences.

DNA damage response (DDR): Cells respond to the perception of DNA damage by arresting cell-cycle progression and attempting repair: collectively these actions are known as the DNA-damage response (DDR).

DNA sequencing: process by which the sequence of nucleotides along a strand of DNA is determined. Where either the whole genome or the exome (the region which encodes proteins) is sequenced this is referred to as whole genome/exome sequencing (WGS/WES).

Dominant lethal mutation: A dominant mutation (i.e., where mutation of a single allele is sufficient to cause a change in phenotype) that causes death of an early embryo.

Dopaminergic: Releasing or involving dopamine as a neurotransmitter.

Dose: Total amount of a substance administered to, taken or absorbed by an organism. May be qualified such as external dose, absorbed dose.

Dose-response relationship: how an effect caused by a chemical changes as the dose of the chemical changes, after a certain exposure time.

E

Endocrine active substance (EAS): A substance that can interact or interfere with the endocrine system.

Endocrine disrupter (ED): An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny or (sub)populations.

Endonuclease: An enzyme that cleaves its nucleic acid substrate at internal sites in the nucleotide sequence.

Enterohepatic circulation: Cyclical process involving intestinal re-absorption of a substance that has been excreted through bile followed by transfer back to the liver, making it available for biliary excretion again.

Epidemiology: Study of factors determining the causes, frequency, distribution, and control of diseases in a human population.

Epigenetics: The study of heritable changes in gene function that occur without a change in the sequence of nuclear DNA and the processes involved in the unfolding development of an organism.

Epigenetic age: An estimate of biological age based on changes in epigenetic marks at particular locations along the genome.

Epigenetic drift: Divergence of the epigenome as a function of age due to stochastic changes in epigenetic marks.

Epigenetic marks: Features not directly governed by the genetic code, which include methylation of DNA and covalent modification of histone proteins. The latter may be tagged with methyl, acetyl, ubiquitin, phosphate, poly(ADP)ribose and other biochemical groups. These groups and their particular pattern of protein modification (e.g., mono-, bi-, tri-methylated at different amino acids and combinations of amino acids) modify the function of the tagged proteins and influence the way genes are expressed.

Epigenome: The comprehensive collection of genome-wide epigenetic phenomena, including DNA-methylation patterns, chromatin modifications, and non-coding RNA.

Epigenomic reprogramming: Resetting epigenetic marks so they resemble those of other cells from earlier developmental stages. This is of particular relevance for germline cells after the fusion of gametes when the genome is brought back into a "zero-state" of gene expression.

Epithelium: The tissue covering the outer surface of the body, the mucous membranes and cavities of the body.

Erythema: Reddening of the skin due to congestion of blood or increased blood flow in the skin.

Estrogen: Sex hormone or other substance capable of developing and maintaining female characteristics of the body (note UK spelling is oestrogen).

Exogenous: Arising outside the body.

Exposure Assessment: Process of measuring or estimating concentration or intensity, duration and frequency of exposure to an agent. The exposure could be via the environment, consumer products or the diet, or due to occupation.

F

Fetotoxic: Causing toxic, potentially lethal effects to the developing fetus.

Fibrosarcoma: A malignant tumour arising from connective tissue (see 'tumour').

First Pass Metabolism: rapid uptake and metabolism of an agent by the intestine or the liver, immediately after enteric absorption and before it reaches the systemic circulation.

Fluorescence In-Situ Hybridisation (FISH): A technique that allows individual chromosomes and their centromeres to be visualised in cells.

Forestomach: (See glandular stomach).

Free Radicals: any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital. Many radicals are unstable and highly reactive.

Full gene sequence: the complete order of bases in a gene. This order determines which protein a gene will produce.

G

Gavage: Administration of a liquid via a stomach tube, commonly used as a dosing method in toxicity studies.

Gene: The functional unit of inheritance: a specific sequence of nucleotides along the DNA molecule, forming part of a chromosome.

Gene expression: The process by which the information in a gene is used to create proteins or polypeptides.

Gene families: Groups of closely related genes that make similar products.

Gene mutation: A permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

Gene product: The protein or polypeptide coded for by a gene.

Genetic engineering: Altering the genetic material of cells or organisms in order to make them capable of making new substances or performing new functions.

Genetic polymorphism: a variation in germ-line DNA sequence among individuals, groups, or populations (e.g., a genetic polymorphism might give rise

to blue eyes versus brown eyes, or population level differences in metabolic capacity). Genetic polymorphisms may be the result of chance processes or may have been induced by external agents (such as viruses or radiation). Generally, changes in DNA sequence which have been confirmed to be caused by external agents are called “mutations” rather than “polymorphisms”.

Genetic predisposition: susceptibility to a disease which is related to a polymorphism, which may or may not result in actual development of the disease.

Genetically modified organism (GMO): An organism which has had genetic material inserted into or removed from its cells.

Genome: All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.

Genomic DNA: The basic chromosome set consisting of a species-specific number of linkage groups and the genes contained therein.

Genomic imprinting: The phenomenon whereby a small subset of all the genes in our genome are expressed according to their parent of origin.

Genomics: The study of genes and their function.

Genotoxic: A chemical or physical agent which has the ability to induce mutations or so-called indicator effects which are mechanistically associated with the formation of mutations (e.g., induction of DNA modifications, DNA repair, or recombination). All mutagenic substances are genotoxic but not vice versa.

Genotype: The particular genetic pattern seen in the DNA of an individual. “Genotype” is generally used to refer to the particular pair of alleles that an individual possesses at a certain location in the genome. Compare this with phenotype.

Germ cells: Cells that give rise to the gametes of an organism that reproduces sexually. The cells undergo mitotic and meiotic cell division in the gonads followed by cellular differentiation into mature gametes, either oocytes or sperm.

Glandular stomach: The stomach in rodents consists of two separate regions – the forestomach and the glandular stomach. Only the glandular stomach is directly comparable to the human stomach.

H

Half-life: In the context of toxicokinetics, this is the time in which the concentration of a substance in vivo will be reduced by 50%, assuming a first order elimination process.

Hazard: Set of inherent properties of a substance, mixture of substances or a process involving substances that make it capable of causing adverse effects to organisms or the environment.

Health based guidance value (HBGV): A value indicating the amount of chemical in food that a person can consume on a regular basis usually over a lifetime without any significant risk to health.

Hepatic: Pertaining to the liver.

Hepatocyte: The principal cell type in the liver, possessing many metabolising enzymes (see 'metabolic activation').

Heterozygous: having two different forms (alleles) of a gene that controls a particular characteristic, one inherited from each parent, and therefore able to pass on either form.

Histone methylation: The modification of certain amino acids in a histone protein by the addition of methyl groups.

Histone modification: Covalent post-translational modifications to histone proteins including methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation, which regulate gene expression. The modifications made to histones can impact gene expression by altering chromatin structure.

Histone tails: A structural aspect of histones that are major targets for post-translational modifications of histones (see Histone modifications).

Hodgkin's lymphoma: Cancer of the lymphatic system.

Homeostatic: Any self-regulation process by which biological systems tend to maintain stability while adjusting to conditions that are optimal for survival.

Horizon scanning: The systematic examination of potential threats, opportunities and likely future developments, which are at the margins of current thinking and planning. Horizon scanning may explore novel and unexpected issues, as well as persistent problems and trends. Overall, horizon scanning is intended to improve the robustness of policies and the evidence base.

Hypoxanthine-guanine Phosphoribosyltransferase **(HPRT) assay:**

This assay uses cultured mammalian somatic cells to detect mutagenic agents. The principle of the method relies on the fact that mutations (caused by mutagens) destroy the functionality or the HPRT gene or protein, which is detected by using a toxic analogue. The HPRT-mutants are viable colonies that can be scored.

Hypoxanthine-guanine Phosphoribosyltransferase **(HPRT) gene:**

A protein coding gene. This transferase allows cells to recycle purines, a building block of DNA and RNA.

Hypermethylation: Increase in the methylation of cytosine-guanosine base pairs in regulatory regions of DNA.

Hyperplasia: An increase in the size of an organ or tissue due to an increase in the number of cells through cell division.

Hypertrophy: An increase in the size of an organ or tissue due to an increase in the volume of individual cells within it.

Hypomethylation: The loss of the methyl group in 5-methylcytosine nucleotides in DNA. Hypomethylation can be used to describe the unmethylated state of specific nucleotides or as a general phenomenon affecting large parts of the genome.

I

Idiosyncrasy: Specific (and usually unexplained) reaction of an individual to e.g., a chemical exposure to which most other individuals do not react at all. General allergic reactions do not fall into this category.

In silico: a term used to describe a computerised analysis of the structure of a chemical to assess its potential hazard.

In situ hybridisation (ISH): Use of a DNA or RNA probe to detect the presence of the complementary DNA sequence in cloned bacterial or cultured eukaryotic cells.

In vitro: A Latin term used to describe studies of biological material outside the living animal or plant (literally “in glass”).

In vivo: A Latin term used to describe studies in living animals or plants (literally “in life”).

Incidence: Number of discrete events, for example new cases of illness occurring during a given period in a specific population.

(Enzyme) Inducing agent: A chemical which, when administered to an animal, causes an increase in the expression of a particular enzyme. For example, chlorinated dibenzodioxins are inducing agents which act via the Ah-receptor (qv) to induce P450 (qv) CYP1A1.

Intraperitoneal: Within the abdominal cavity.

Isomer: Isomers are two or more chemical compounds with the same molecular formula but having different properties owing to a different arrangement of atoms within the molecule.

K

Key event: An empirically observable precursor step that is itself a necessary element of an AOP or MOA. A key event is a necessary, though usually not a sufficient, step in a process that results in an adverse outcome.

kilobase (kb): A length of DNA equal to 1000 nucleotides.

Knockout animals: Genetically engineered animals in which one or more genes, usually present and active in the normal animal, have been eliminated or inactivated.

L

LC50/LD50: The concentration or dose that causes death in 50% of a group of experimental animals to which it is administered. It can be used to assess the acute toxicity of a compound but is being superseded by more refined methods.

Less than lifetime (LTL) exposure: any exposure that is not continuous daily exposure, for example, short-term, intermediate or intermittent, or a combination of these.

Leukaemia: A group of neoplastic disorders (see tumour) affecting blood-forming elements in the bone marrow, characterised by uncontrolled proliferation and disordered differentiation or maturation. Examples include the lymphocytic leukaemia’s which develop from lymphoid cells and the myeloid leukaemia’s which are derived from myeloid cells (producing red blood cells, mainly in bone marrow).

Ligand: A molecule which binds to an allosteric binding site in a protein, such as a receptor.

Lipids: Fats, substances containing a fatty acid and soluble in alcohols or ether, but insoluble in water.

Lipophilic: 'Lipid liking' - a substance which has a tendency to partition into fatty materials.

Lowest observed adverse effect level (LOAEL): The lowest administered dose at which a statistically significant adverse effect, relative to that of the control, has been observed. Also given as LOEL when no ‘adverse’ effects are seen.

Lymphocyte: A type of white blood cell that plays central roles in adaptive immune responses.

Lymphoma: Malignant tumours arising from lymphoid tissues. They are usually

multifocal, involving lymph nodes, spleen, thymus and sometimes bone marrow, and other sites outside the anatomically defined lymphoid system. (See also 'tumour').

M

Malformations: The inheritance of an abnormal or anomalous formation of tissues and organs often referred to as a deformity.

Malignant tumour (synonym: cancer): A tumour (qv) composed of increasingly abnormal cells in term of their form and function. Some well differentiated examples still retain characteristics of their tissues of origin but these are progressively lost in moderately and poorly differentiated malignancies. Most malignant tumours grow rapidly, spread progressively through adjacent tissues and metastasise to distant sites.

Margin of exposure (MOE) approach: A methodology that allows the comparison of the risks posed by substances when it is not possible or not appropriate to establish a HBGV. This would include substances that are genotoxic and carcinogenic, and contaminants for which there is insufficient information to establish a Tolerable Daily Intake The MOE approach uses a reference point (or POD), often taken from an animal study, corresponding to a dose that causes no or a low response (for example the NAOEL, LOAEL, BMDL10).

This reference point is then compared with various exposure estimates in humans. The lower the MOE, the greater the concern. The MOE considered to be of low or negligible concern is context specific. In general, for substances that are genotoxic and carcinogenic, and MOE of >10,000, when based on a reference point from an animal study, would be considered of low concern. For a non-genotoxic, non-carcinogenic contaminant, an MOE of > 100 would be considered of negligible concern.

Margin of safety (MOS) approach: A methodology used to assess relative risk when there is exceedance of a HBGV. The MOS is expressed as the ratio of the HBGV to measured or estimated exposure. The lower the MOS is below 1, the greater the concern.

Maximum tolerated dose: The MTD for a long-term study of carcinogenicity is a dose that produces minimal signs of toxicity on repeated administration, meaning no more than a 10% weight decrement, as compared to the appropriate control groups; and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span.

Mechanism of action: an understanding of the molecular basis for an effect and its detailed description, so causation can be established in molecular terms.

Meiosis: The process of cell division in sexually reproducing organisms that reduces the number of chromosomes in reproductive cells from diploid to haploid leading to the production of gametes in animals and spores in plants. During the first meiotic division there is homologue pairing, efficient intergenic recombination between homologues during pairing, and the suppression of sister chromatid separation. S phase is absent at the start of the second meiotic division. Thus, the outcome of meiosis should be four genetically unique haploid cells.

Messenger RNA (mRNA): The DNA of a gene is transcribed (see transcription) into mRNA molecules, which then serve as a template for the synthesis of proteins.

Meta-analysis: In the context of epidemiology, a statistical analysis of the results from independent studies, which aims to produce a single estimate of an effect.

Metabolic activation: Metabolism of a compound leading to an increase in its activity, whether beneficial (e.g., activation of a pro-drug) or deleterious (e.g.,

activation to a toxic metabolite).

Metabolic activation system: A cell-free preparation (e.g., from the livers of rats pre-treated with an inducing agent (qv)) added to in vitro tests to mimic the metabolic activation typical of mammals.

Metabolism: Chemical modification of a compound by enzymes within the body, for example by reactions such as hydroxylation (see P450), epoxidation or conjugation. Metabolism may result in activation, inactivation, change in activity, accumulation or excretion of the compound.

Metabolite: Product formed by metabolism of a compound.

Metabolomics: The measurement of the amounts (concentrations) and locations of all metabolites in a cell.

Metabonomics: Metabonomics is a subset of metabolomics and is defined as the quantitative measurement of the multiparametric metabolic responses of living systems to pathophysiological stimuli or genetic modification.

Metaphase: Stage of cell division (mitosis and meiosis) during which the chromosomes are arranged on the equator of the nuclear spindle (the collection of microtubule filaments which are responsible for the movement of chromosomes during cell division). As the chromosomes are most easily examined in metaphase, cells are arrested at this stage for microscopical examination for chromosomal aberrations (qv) - known as metaphase analysis.

Metastasis: The process whereby malignant cells become detached from the primary tumour mass, disseminate (mainly in the blood stream or in lymph vessels) and seed out in distant sites where they form secondary or metastatic tumours. Such tumours tend to develop at specific sites and their anatomical distribution is often characteristic, i.e., it is non-random.

Microbiome (Human): Human microbiome is the full array of microorganisms (the microbiota) that live on and in humans and, more specifically, the collection of microbial genomes that contribute to the broader genetic portrait, or metagenome, of a human. Often a subset of the microbiome is the subject of interest, for example the intestinal or dermal microbiome.

Micronuclei: Whole or fragmented chromosomes that fail to segregate normally during cell division and may be lost from the main nuclei but remain in the body of the cell forming micronuclei. Centromere positive micronuclei contain DNA

and/or protein material derived from the centromere. The presence of centromere positive micronuclei following exposure to chemicals in vitro or in vivo can be used to evaluate the aneugenic potential of chemicals.

Minimal risk level: defined in this document as an estimate of daily human exposure to a chemical, identified by expert judgement, that is likely to be associated with a negligible risk of carcinogenic effect over a specified duration of exposure (usually a lifetime).

Mitogen: A stimulus which provokes cell division in somatic cells.

Mitosis: The process in cell division in somatic cells by which the nucleus divides, typically consisting of four stages, prophase, metaphase, anaphase, and telophase, and normally resulting in two new nuclei, each of which contains a complete copy of the parental chromosomes. The outcome of mitosis should be two genetically identical diploid cells.

Mode of Action: a biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data. It describes key cytological and biochemical events, i.e., those that are both measurable and necessary to the observed outcome, in a logical framework. It contrasts with mechanism of action.

Mode of genotoxic a**ction (MoGA):** The mode of action of a genotoxicant refers to the underlying events involved in the process whereby the chemical induces genotoxic effects. In order for a specific mode of action to be supported there needs to be evidence from robust mechanistic data to establish a biologically plausible explanation. Mode of genotoxic action should be distinguished from the term mechanism of action. The latter relates to having sufficient understanding of the molecular basis of the chemical genotoxicity to establish causality. Thus, mechanism of action is at the other end of a continuum from little or no evidence of mode of genotoxic action to scientific proof of mechanism of action.

Molecular initiating event (MIE): the initial point of chemical/stressor interaction at the molecular level within the organism that results in a perturbation that starts the AOP.

Mouse lymphoma assay: An in vitro assay for gene mutation in mammalian cells using a mouse lymphoma cell line L5178Y, which is heterozygous for the gene (carries only one functional allele rather than a pair) for the enzyme thymidine kinase (TK+/-). Mutation of that single gene is measured by resistance

to toxic trifluorothymidine. Mutant cells produce two forms of colony - large, which represent mutations within the gene and small, which represent large genetic changes in the chromosome such as chromosome aberrations. Thus, this assay can provide additional information about the type of mutation which has occurred if colony size is scored.

Mucosal: Regarding the mucosa or mucous membranes, consisting of epithelium containing glands secreting mucus, with underlying layers of connective tissue and muscle.

Multigenerational effects: Effect seen in exposed generations, including those that may have been exposed in utero, as offspring or gametes. For effects in unexposed generations see ‘Transgenerational effects’.

Murine: Often taken to mean “of the mouse”, but strictly speaking means of the Family Muridae which includes rats and squirrels.

Mutagen: is a physical or chemical agent that changes the genetic information (usually DNA) of an organism that can be inherited by daughter cells.

Mutation: A permanent change in the amount or structure of the genetic material in an organism or cell, which can result in a change in phenotypic characteristics. The alteration may involve a single gene, a block of genes, or a whole chromosome. Mutations involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Changes involving whole chromosomes may be numerical or structural. A mutation in the germ cells of sexually reproducing organisms may be transmitted to the offspring, whereas a mutation that occurs in somatic cells may be transferred only to descendent daughter cells.

Mutational signatures: Mutational signatures are characteristic profiles of mutation types arising from specific mutagenesis processes such as DNA replication infidelity, exogenous and endogenous genotoxins exposures, defective DNA repair pathways and DNA enzymatic editing.

Mycotoxin: Toxic compound produced by a fungus.

Nanomaterial: A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.

N

Neoplasia: the abnormal proliferation of benign or malignant cells.

Neoplasm: See 'tumour'.

Neoplastic: Abnormal cells, the growth of which is more rapid that that of other cells of the same tissue type.

Neural tube defect (NTD): Is a birth defect in which an opening in the spine or cranium remains from early in human development.

Neurobehavioural: Of behaviour determined by the nervous system.

Neurotransmitter: A chemical that is released from a nerve cell which thereby transmits an impulse from a nerve cell to another nerve, muscle, organ, or other tissue. A neurotransmitter is a messenger of neurologic information from one cell to another.

No observed adverse effect level (NOAEL): The highest administered dose at which no statistically significant adverse effect has been observed in comparison to the control. Also given as NOEL when no ‘adverse’ effects are seen.

Non-Hodgkin lymphomas: (NHLs) are a diverse group of hematologic cancers which encompass any lymphoma other than Hodgkin’s Lymphoma.

No observed genotoxic effect level (NOGEL): This is the highest experimental dose level where no statistically significant increase in the genotoxic effect measured in the study is identified.

Nucleic acid: One of the family of molecules which includes the DNA and RNA molecules. Nucleic acids were so named because they were originally discovered within the nucleus of cells, but they have since been found to exist outside the nucleus as well.

Nucleosome: A repeating subunit of DNA packaging consisting of DNA wound in sequence around histone proteins.

Nucleotide: the "building block" of nucleic acids, such as the DNA molecule. A nucleotide consists of a nucleoside attached a phosphate group. A nucleoside comprises one of four bases - adenine, guanine, cytosine, or thymine - attached to a sugar group. In DNA the sugar group is deoxyribose, while in RNA (a DNA-related molecule which helps to translate genetic information into proteins), the

sugar group is ribose, and the base uracil substitutes for thymine. Each group of three nucleotides in a gene is known as a codon. A nucleic acid is a long chain of nucleotides joined together, and therefore is sometimes referred to as a "polynucleotide."

Null allele: Mutations that result in absence of gene product or a non-functional product.

Null hypothesis: type of conjecture used in statistical tests, which are formal methods of reaching conclusions or making decisions on the basis of data. In toxicology, a common null hypothesis is that there is no effect of treatment with a substance. Statistical testing may enable a conclusion that this is most likely incorrect, i.e., the null hypothesis is rejected with a stated probability of error, or it is not possible to reach a conclusion. It is not possible by conventional statistical testing to prove the null hypothesis is most likely correct, i.e., that there is no effect. This is the axiomatic difficulty of “proving a negative”.

O

Odds ratio (OR): The odds of disease in an exposed group divided by the odds of disease in an unexposed group.

Oedema: Excessive accumulation of fluid in body tissues.

Oligonucleotide: A molecule made up of a small number of nucleotides, typically fewer than 25.

‘Omics’ technologies: A scientific subdiscipline that combines the technologies of genomics and bioinformatics to identify and characterise mechanisms of action of known and suspected toxicants. The collective term ‘omics’ refers to the genomic (DNA sequence analysis) and post-genomic (e.g., transcriptomics, proteomics, metabolomics, epigenomics) technologies that are used for the characterisation and quantitation of pools of biological molecules (e.g. DNA, mRNAs, proteins, metabolites), and the exploration of their roles, relationships and actions within an organism.

Oncogene: A gene which is associated with the development of cancer (see proto-oncogene).

P

Pharmacodynamics: The process of interaction of drugs with target sites and the subsequent reactions leading to the desired biological effects (see toxicodynamics).

Pharmacokinetics: Description of the fate of drugs in the body, including a mathematical account of their absorption, distribution, metabolism and excretion (see toxicokinetics).

Pharmacogenomics: The science of understanding the correlation between an individual patient's genetic make-up (genotype) and their response to drug treatment. Some drugs work well in some patient populations and not as well in others. Studying the genetic basis of patient response to therapeutics allows drug developers and medical practitioners to design and use therapeutic treatments more effectively.

Phenotype: The observable physical, biochemical and physiological characteristics of a cell, tissue, organ or individual, as determined by its genotype and the environment in which it develops.

Phenotypic change: A change in the observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.

Physiologically based pharmacokinetic (PBPK) model: A mathematical model which is used to predict the absorption, distribution, metabolism and excretion of a chemical substance in humans.

Phytoestrogen: Any plant substance or metabolite that can mimic or modulate the actions of endogenous oestrogens, usually by binding to oestrogen receptors, and which can therefore induce biological responses.

Pig-A gene mutation assay: An assay which utilises the Pig-A gene which codes for one subunit of a glycosylphosphatidyl inositol anchor protein. Loss of function arising from Pig-A mutations can readily be assessed using straightforward immunochemistry and flow cytometric methods, thus making it useful to measure gene mutations induced by chemicals or radiation.

Plasmid: A structure composed of DNA that is separate from the cell's genome (qv). In bacteria, plasmids confer a variety of traits and can be exchanged between individuals, even those of different species. Plasmids can be constructed and manipulated in the laboratory to deliver specific genetic sequences into a cell.

Point of departure: a dose associated with a defined level of effect, which can be determined empirically or by modelling dose-response data from experimental studies, from which a health-based guidance value can be established, or which can be used for a margin of exposure assessment. Examples include a BMDL, NOAEL or LOAEL.

Polymer: A very large molecule comprising a chain of many similar or identical molecular sub units (monomers) joined together (polymerised). An example is the polymer glycogen, formed from linked molecules of the monomer glucose.

Polymerase chain reaction (PCR): A method for creating millions of copies of a particular segment of DNA. PCR can be used to amplify the amount of a particular DNA sequence until there are enough copies available to be detected.

Polymorphism: (see genetic polymorphism)

^{32}P postlabelling assay: An experimental method designed to measure low levels of DNA adducts induced by chemical treatment. It involves labelling of adducted nucelosides from digested DNA with ^{32}P and their quantification following chromatographic separation.

Prevalence: The number of discrete cases, for example of a disease, that are present in a population at a given time.

Primer: Short pre-existing polynucleotide chain to which new deoxyribonucleotides can be added by DNA polymerase.

Primordial germ cells: Highly specialised cells that are precursors of gametes, which, following meiosis, develop as haploid sperm and eggs that generate a new organism upon fertilisation.

Proteomics: The analysis of the entire protein complement of a cell, tissue, or organism under a specific, defined set of conditions.

Proto-oncogene: One of a group of normal genes that are concerned with the control of cellular proliferation and differentiation. They can be activated in various ways to forms (oncogenes) which are closely associated with one or more steps in carcinogenesis. Activating agents include chemicals and viruses. The process of proto-oncogene activation is thought to play an important part at several stages in the development of tumours.

Q

Quantal Data: When the response for an individual unit (well, animal etc) is a binary value, such as alive / dead, or response / no response, the data are treated as quantal. The responses are assumed to follow a binomial distribution within each dose group. This assumption is required for the calculations of confidence intervals and the p values resulting from statistical tests.

R

ras oncogene: The Ras protein family are a class of protein called small GTPase and have important roles in cell signalling. The ras gene is the most common oncogene involved in human cancer - mutations that permanently activate ras are found in 20-25% of all human tumours and up to 90% in certain types of cancer (e.g., pancreatic cancer).

Receptor: A small, discrete protein in the cell membrane or within the cell with which specific molecules interact to initiate a change in the working of a cell.

Recombinant DNA: DNA molecules that have been created by combining DNA from more than one source.

Reference nutrient intake (RNI): An amount of the nutrient that is sufficient, or more than sufficient, to ensure adequate nutrient function for most (usually at least 97%) people in a group. If the average intake of a group is at the RNI, then the risk of deficiency in the group is very small.

Regulatory gene: A gene which controls the protein-synthesising activity of other genes.

Relative potency factor (RPF): The toxic potency of a substance expressed relative to that of an index chemical to enable cumulative risk assessment (*qv)*. The RPF is similar to the TEF (*qv*) but is used when the information on common MIEs, toxicokinetics and outcomes of the members of an assessment group is less reliable than that required for application of the TEF approach.

Relative risk: A measure of the association between exposure and outcome. The rate of disease in the exposed population divided by the rate of disease among the unexposed population in a cohort study or a population-based case control study. A relative risk of 2 means that the exposed group has twice the disease risk compared to the unexposed group.

Reporter gene: A gene that encodes an easily assayed product that is coupled to the upstream sequence of another gene and transfected (qv) into cells. The

reporter gene can then be used to see which factors activate response elements in the upstream region of the gene of interest.

Risk: Probability that a harmful event (death, injury or loss) arising from exposure to a chemical or physical agent may occur under specific conditions.

Risk assessment: process of evaluating a potential hazard, likelihood of suffering, or any adverse effects from certain human activities. Comprised of the four aspects, hazard identification, hazard characterisation, exposure assessment and risk characterisation. Can be carried out retrospectively or prospectively.

Risk management: process designed to identify, contain, reduce, or eliminate the potential for harm to the human population; usually concerned with the delivery system and site rather than performance.

Ribonucleic acid (RNA): a molecule similar to DNA, in that it is a nucleic acid comprised of a chain of nucleotides. However, unlike DNA, RNA exists as a single-stranded chain. RNA has various biological roles in coding, decoding, regulation and expression of genes.

S

Sarcoma: cancer that arises from transformed cells of mesenchymal (connective tissue) origin.

Serotonergic: Denoting a nerve ending that releases and or stimulated by serotonin.

Signal induction pathway: The molecular pathways that signal (i.e., turn on or off) biochemical pathways or biological functions (e.g., biochemical pathways leading to nerve conduction).

Single nucleotide polymorphism (SNP): DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. For example, a SNP might change the DNA sequence A***A***GGCTAA to A***T***GGCTAA.

Strand breaks: Relating to DNA, a single strand break occurs when there is a break in double-stranded DNA in which only one of the two strands has been cleaved; the two strands have not separated from each other. Double strand breaks occur when both strands in the double helix are severed and are particularly hazardous to the cell because they can lead to genome rearrangements.

Sister chromatid exchange (SCE): Exchange of genetic material between two subunits of a replicated chromosome.

Somatic cells: Any biological cell that forms part of the body of an organism, excluding reproductive cells and undifferentiated stem cells.

Stakeholder: A person or organisation representing the interests and opinions of a group with an interest in the outcome of (for example) a review or policy decision.

Statistical significance: a conclusion drawn when, after carrying out a statistical test of the null hypothesis of no effect, the hypothesis is considered unlikely to be true. The criterion for the decision is often a probability (p) value, chosen to be, but not necessarily, $p<0.05$.

Stem cell: an unspecialized cell capable of perpetuating itself through cell division and having the potential to give rise to differentiated cells with specialized functions.

Suppressor gene: A gene which helps to reverse the effects of damage to an individual's genetic material, typically these are effects which might lead to uncontrolled cell growth (as would occur in cancer). A suppressor gene may, for example, code for a protein which checks genes for misspellings, and/or which triggers a cell's self-destruction if too much DNA damage has occurred.

Systematic review: A formalised review that has been prepared using a documented systematic approach to minimising biases and random errors.

Systems biology: The computational and mathematical analysis and modelling of complex biological systems.

Systems toxicology: The integration of classical toxicology with quantitative analysis of large networks of molecular and functional changes occurring across multiple levels of biological organisation.

T

T25: the dose eliciting a 25% increase in the incidence of a specific tumour above the background level.

TD50: For any particular sex, strain, species and set of experimental conditions, the TD50 is the dose rate (in mg/kg body weight/day) that, if administered

chronically for a standard period - the "standard lifespan" of the species-will halve the mortality-corrected estimate of the probability of remaining tumourless throughout that period.

Teratogen: A substance that can cause congenital malformations (structural defects) in a developing fetus following maternal exposure.

Testicular dysgenesis syndrome (TDS): The hypothesis that maldevelopment (dysgenesis) of the fetal testis results from hormonal or other malfunctions of the testicular somatic cells which in turn predispose a male to the disorders that comprise the TDS, i.e., congenital malformations (cryptorchidism and hypospadias) in babies and testis cancer and low sperm counts in young men.

Threshold: the level of dose or exposure below which there is no effect above that in the control group or population. There are several different uses of the term threshold, for example observable threshold, biological threshold, population threshold.

Threshold of toxicological concern (TTC): a pragmatic, scientifically valid methodology to prioritise substances of unknown toxicity found in food for further evaluation. It is used when there are limited chemical-specific toxicity data and can be used for substances with or without structural alerts for genotoxicity and for cancer and non-cancer endpoints.

Tolerable daily intake (TDI): An estimate of the amount of contaminant, expressed on a body weight basis (e.g., mg/kg bodyweight), that can be ingested daily over a lifetime without appreciable health risk. The term is preferred for substances that are unintentionally present.

Tolerable upper level (TUL): The highest level of nutrient that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the TUL, the risk of adverse effects increases.

Toxic equivalency factor (TEF): A measure of relative toxicological potency of a chemical compared to a well characterised reference compound. TEFs can be used to sum the toxicological potency of a mixture of chemicals which are all members of the same chemical class, having common structural, toxicological and biochemical properties. TEF systems have been published for the chlorinated dibenzodioxins, dibenzofurans and dioxin-like polychlorinated biphenyls, and for polycyclic aromatic hydrocarbons.

Total toxic equivalent (TEQ): Is a method of comparing the total relative toxicological potency within a sample. It is calculated as the sum of the products of the concentration of each congener multiplied by the toxic equivalency factor (TEF).

Toxicodynamics: The process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

Toxicogenic: producing or capable of producing toxins, e.g., a fungal strain.

Toxicokinetics: The description of the fate of potentially toxic chemicals in the body, including a mathematical account of their absorption, distribution, metabolism and excretion, particularly at doses that are toxic. (see pharmacokinetics)

Transcription: the process during which the information in a piece of DNA (qv) is used to construct an mRNA (qv) molecule.

Transcriptomics: Techniques used to identify mRNA from actively transcribed genes.

Transgenerational effects: Effects seen in generations that have not been exposed, either directly to the substance under consideration or indirectly as offspring or gametes via parental exposure. For effects in exposed populations, see ‘multigenerational effects’.

Transfer RNA (tRNA): RNA molecules which bond with amino acids and transfer them to ribosomes, where protein synthesis is completed.

Transfection: A process by which exogenous genetic material (DNA or RNA) is introduced into a cell with the object of altering the phenotype or genotype of the cell.

Transgenic: Genetically modified to contain genetic material from another species (see also genetically modified organism).

Transgenic animal models: Animals which have extra (exogenous) fragments of DNA incorporated into their genomes. This may include reporter genes to assess in-vivo effects such as mutagenicity in transgenic mice containing a recoverable bacterial gene (lacZ or lac I). Other transgenic animals may have alterations of specific genes believed to be involved in disease processes (e.g., cancer). For example, strains of mice have been bred which carry an inactivated copy of the p53 tumour suppressor gene, or an activated form of the ras

oncogene which may enhance their susceptibility of the mice to certain types of carcinogenic chemicals.

Translation: In molecular biology, the process during which the information in mRNA molecules is used to construct proteins.

Tumour (Synonym - neoplasm): A mass of abnormal, disorganised cells, arising from pre-existing tissue, which are characterised by excessive and uncoordinated proliferation and by abnormal differentiation. Benign tumours show a close morphological resemblance to their tissue of origin; grow in a slow expansile fashion; and form circumscribed and (usually) encapsulated masses. They may stop growing and they may regress. Benign tumours do not infiltrate through local tissues, and they do not metastasise (qv). They are rarely fatal. Malignant tumours (synonym - cancer) resemble their parent tissues less closely and are composed of increasingly abnormal cells in terms of their form and function. Well differentiated examples still retain recognisable features of their tissue of origin, but these characteristics are progressively lost in moderately and poorly differentiated malignancies: undifferentiated or anaplastic tumours are composed of cells which resemble no known normal tissue. Most malignant tumours grow rapidly, spread progressively through adjacent tissues and metastasise to distant sites. Tumours are conventionally classified according to the anatomical site of the primary tumour and its microscopical appearance, rather than by cause. Benign tumours may evolve to the corresponding malignant tumours; examples involve the adenoma → carcinoma sequence in the large bowel in humans, and the papilloma → carcinoma sequence in mouse skin.

Tumour initiation: A term originally used to describe and explain observations made in laboratory models of multistage carcinogenesis, principally involving repeated applications of chemicals to the skin of mice. Initiation, in such contexts, was the first step whereby small numbers of cells were irreversibly changed or initiated. Subsequent, separate events (see tumour promotion) resulted in the development of tumours. It is now recognised that these early, irreversible heritable changes in initiated cells were due to genotoxic damage, usually in the form of somatic mutations and the initiators used in these experimental models can be regarded as genotoxic carcinogens.

Tumour microenvironment: This is a complex system of many cell types, including cancer cells, fibroblasts, endothelial cells, leukocytes and antigen-presenting cells, together with connective tissue. The microenvironment is integral in determining the functionality, physiology and spread (metastasis) of cancer.

Tumour promotion: Originally used, like ‘tumour initiation’ to describe events in multistage carcinogenesis in experimental animals. In that context, promotion is regarded as the protracted process whereby initiated cells undergo clonal expansion to form overt tumours. The mechanisms of clonal expansion are diverse, but include direct stimulation of cell proliferation, repeated cycles of cell damage and cell regeneration and release of cells from normal growth-controlling mechanisms. Initiating and promoting agents were originally regarded as separate categories, but the distinction between them is becoming increasingly hard to sustain. The various modes of promotion are non-genotoxic, but it is incorrect to conclude that ‘non-genotoxic carcinogen’ and ‘promoter’ are synonymous.

U

Uncertainty factor: Value used in extrapolation from a reference point (or POD), determined in experimental animals, to humans (assuming that humans may be more sensitive) or from a sub-population of individuals to the general population: for example, a value applied to the NOAEL to establish an ADI or TDI. The value depends on the size and type of population to be protected and the quality of the toxicological information available.

Unscheduled DNA synthesis (UDS): DNA synthesis that occurs at some stage in the cell cycle other than the S period (the normal or 'scheduled' DNA synthesis period), in response to DNA damage. It is usually associated with DNA repair.

V

Volume of distribution: Apparent volume of fluid required to contain the total amount of a substance in the body at the same concentration as that present in the plasma, assuming equilibrium has been attained.

W

Weight of evidence: This approach uses a combination of several independent sources of evidence (e.g., toxicological or genotoxicity data) to arrive at a conclusion regarding potential hazard (such as mutagenicity).

WHO-TEQs: The system of Toxic Equivalency Factors (TEFs) used in the UK and a number of other countries to express the concentrations of the less toxic dioxin-like compounds (16 PCDDs/PCDFs and 12 PCBs) as a concentration equivalent to

the most toxic dioxin 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is that set by the World Health Organisation (WHO), and the resulting overall concentrations are referred to as WHO-TEQs (Total toxic equivalents) (see also Toxic Equivalency Factor).

X

Xenobiotic: A chemical foreign to the biologic system.

Xenoandrogen: A ‘foreign’ compound with androgenic activity (see androgen).

Xenoestrogen: A 'foreign' compound with oestrogenic activity (see oestrogen).

Organisational abbreviations

COC: Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment: is an independent scientific committee that provides advice the government and government agencies on whether substances are likely to cause cancer.

COM: Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment: is an independent scientific committee that assesses and advises the government and government agencies on mutagenic risks to humans.

COT Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment: is an independent scientific committee that provides advice to the government and government agencies on matters concerning the toxicity of chemicals.

EFSA European Food Safety Authority:

Expert Group on Vitamins and Minerals (EVM): An independent UK expert advisory committee which was asked to advise on safe levels of intakes of vitamins and minerals in food supplements and fortified foods.