Committee on Toxicity

Committee on Carcinogenicity

Committee on Mutagenicity

Annual Report 2020

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

Annual Report 2020

Contents

About the Committees

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

The aim of these reports is to provide a brief background to the Committees' decisions. Those seeking further information on a particular subject can obtain relevant references from the Committee's administrative secretary or from the internet sites listed below.

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

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

The Committees' procedures for openness include the publication of agendas, finalised minutes, agreed conclusions and statements. These are published on the internet at the following addresses:
COT: http://cot.food.gov.uk
COC: https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food- consumer-products-and-the-environment-coc
COM: https://www.gov.uk/government/organisations/committee-on-mutagenicity-of-chemicals-in- food-consumer-products-and-the-environment

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

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

Preface

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

[To be added]

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COT evaluations

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

Background

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

What are E(N)NDS?

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

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

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

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

1.6 In the UK, the maximum strength of nicotine in e-liquid that is permitted for sale under the Tobacco and Related Products Regulations[1] is 20 mg/mL, but some countries allow the sale of products containing higher levels, for example double this strength. This may affect how the different studies are interpreted in the context of likely UK use. ENNDS products are regulated under the General Product Safety Regulations[2].

[1] http://www.legislation.gov.uk/uksi/2016/507/contents
[2] http://www.legislation.gov.uk/uksi/2005/1803/contents/made

Scope of the COT review

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

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

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

Committee discussion

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

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

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

1.13 Data indicated that E(N)NDS use might increase the likelihood of users experiencing symptoms of irritation, including a burning sensation in the throat, nose, or eyes. In addition, it is possible that vaping may increase respiratory symptoms in people with respiratory disease or conditions, and adverse cardiovascular symptoms in people with cardiovascular disease. Such effects can also occur in those smoke conventional cigarettes.

1.14 The Committee was concerned about the possibility of harm to health from the flavouring ingredients, often approved food flavouring agents, used in e-liquids when heated and inhaled. This is because these substances may result in health effects after inhalation that do not occur when consumed in food. There was insufficient information to assess this risk. The Committee has therefore proposed the types of information that would be useful for assessment of the risk of inhalation of flavouring agents used in E(N)NDS[3].

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

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

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

Overall conclusions

1.18 Overall, the COT concluded:

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

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

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

[3] https://cot.food.gov.uk/sites/default/files/frameworkforriskassessingflavourings_0.pdf

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

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

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

The full COT statement can be found here:
https://cot.food.gov.uk/sites/default/files/2020-09/COT%20E%28N%29NDS%20statement%202020-04.pdf

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

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

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

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

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

1.23 Consequently, a framework for the risk assessment of flavouring compounds has been developed, this provides a number of steps designed as a set of principles to guide the risk assessment process for a flavouring compound in E(N)NDS.

The full COT statement can be found here:

https://cot.food.gov.uk/sites/default/files/2020-08/frameworkforriskassessingflavourings_0_madeaccessibleinadobepro_to%20be%20uploaded_.pdf

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

1.24 The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked by the Scientific Advisory Committee on Nutrition (SACN) to review the risk of toxicity from chemicals in the diets of infants (aged 0 to 12 months) and young children (age 1 to 5 years). The aim of the reviews was to identify and appraise new evidence that had emerged since the Government's recommendations on complementary and young child feeding were formulated and to determine whether the current advice should be revised.

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

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

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

1.28 The COT has further evaluated the information provided by EFSA on perfluorooctanesulfonic acid and perfluorooctanoic acid in 2018 and perfluoroalkyl substances (PFASs) in 2020 and on dioxins and dioxin-like compounds in 2020. It is anticipated that a statement on PFASs will be published in 2021. Due to the uncertainties and inconsistencies in the description and evaluation of the key studies in EFSAs assessment of dioxins the COT could not agree with the revised tolerable weekly intake (TWI) and recommended undertaking a review of the evidence base on dioxin to derive a health-based guidance value (HBGV). The COT is awaiting the final publication by EFSA on bisphenol A and phthalates before deciding if a full re-evaluation of its current advice is required.

The overarching COT statement can be found here.

https://cot.food.gov.uk/sites/default/files/2020-09/Overarching%20statement%20contaminants%20in%20infants%20and%20young%20children.pdf

The addendum to the overarching COT statement can be found here.

https://cot.food.gov.uk/sites/default/files/2020-08/Addendum%20to%20the%20Overarching%20statement%200-

5%20year%20old%20%28002%29_accessibleinadobepro_to%20be%20uploaded_.pdf

Position paper on CBD in food products

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

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

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

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

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

1.34 Further discussion took place in January 2020, when the Secretariat had been able to obtain, examine and discuss some of the recent clinical and non-clinical data on the medicinal form of CBD, reviews and assessment reports of which were now publicly available online (with thanks to the cooperation of GW Pharmaceuticals (the manufacturers of Epidiolex®). This data was from the pharmaceutical grade CBD in its purest form *i.e.* >98% CBD; however, other commercially available CBD products, as might be used in novel foods, may be less pure and might contain other cannabinoids, which would have their own toxicological effects, as well as potentially interacting with CBD itself and hence might affect the adverse effects of CBD. It is important to note that few data are available on these related substances.

1.35 Even with this new data, COT Members agreed that there was still insufficient data to

undertake a provisional risk assessment as it was not possible to determine a reliable point of departure such as a NOAEL. However, some general conclusions could be drawn that applied to CBD as a novel food.

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

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

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

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

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

1.40 The FSA put out consumer guidance in February 2020 on the safety of CBD in CBD food products which drew on the views of the COT.

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

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

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

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

The full COT statement can be found here:

https://cot.food.gov.uk/sites/default/files/2020-08/cbdpositionpaper290720_accessibleinadobepro.pdf

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

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

1.46 The discussion paper was presented to the Committee, who decided that a full Statement should follow. The Statement was prepared and progressed and through Committee meetings in 2019. It was published in 2020 and below is a summary

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

1.48 Many of the bacteria are beneficial, digesting food and producing essential substances that humans cannot, but sometimes they can cause disease. The microbiota interact chemically with cells lining the gut to prevent inflammation and

the absorption of toxins. The gut bacteria and the immune system work together to prevent invasion by pathogens. Food and the general environment contain chemicals (such as pesticides and heavy metals) that may kill some types of organisms and allowing others to grow more than usual. This effect is called dysbiosis. However, some changes can also occur in diseases such as Crohn's disease, naturally as animals and people age, and with diet, and they may not in all cases be directly associated with any harm to the host.

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

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

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

1.52 Studies have been carried out to test the effects of chemicals on the bacteria found in humans grown in vitro or have looked at the bacteria in samples of faeces from people exposed to, or treated with, a particular chemical or drug.

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

- A "model" made up of known bacteria is not the same as a whole natural bacterial community, so not all possible effects would be seen and some of the effects may not occur in the whole community;
- Some bacteria cannot be cultured outside the body because they need precise conditions or are "fed" by other species
- Not all of the types of bacteria in the gut come out in the faeces
- It is difficult to decide whether changes seen in a disease are a cause or an effect of the disease, or of any medication taken to treat that disease.

- It is also difficult to determine if a change seen after exposure to a drug or some other substance is an effect that would cause harm to the host of the bacteria or whether the bacteria have just adjusted to its presence.

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

Risk assessment

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

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

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

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

The potential risks of exposure from microplastics

1.59 The potential risks from microplastic exposure was identified as a topic that should consider through horizon scanning. Following review of the literature, it was decided that nanoplastics should also be included. An initial scoping paper was presented to the COT in October 2019 since when the topic and additional information have been discussed several times by the Committee with a view to producing an overarching statement.

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

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

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

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

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

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

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

a) a comprehensive assessment of micro- and nanoplastics and contaminant concentrations in seafood species different food types (*e.g*. seafood, edible meat tissue and offal, vegetables, fruit, drinks *etc*.) and matrices (*i.e*. air, soil, food and water) and the impact of the effect that cooking may have on the desorption and subsequent bioavailability of contaminants/leachants, in order to better understand the implications for human health.

b) Consideration of the potential degradation of novel/emerging plastic-based materials on the market such as biobased plastics (*e.g*. bamboo ware, polylactic acid, chitin *etc*.) and other advanced polymer matrix composite materials into micro- and nanoplastics during use and end-of-life should be taken into account when considering the potential risks of exposure to such materials, as it is unclear how much they already contribute to microplastic exposure.

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

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

1.67 Future sub-statements will consider in detail the potential toxicological risks of exposure from microplastics *via* the oral and inhalation routes to provide supplementary material in support of this overarching statement. This could include a review of the potential risks from oral exposure of microplastics, and a review of the potential risks of microplastics *via* the inhalation route to be produced jointly with the Committee of Medical Effects of Air Pollutants (COMEAP) Secretariat at Public Health England. The need for additional reviews of other significant routes of exposure will also be considered.

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

WRAP study on potatoes and acrylamide

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

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

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

1.72 Members discussed the conclusions of the study and it was noted that there would be no potential health issues (relating to acrylamide formation) if a consumer decided not to store potatoes in the fridge.

Statement on the potential risks of combined exposure to mycotoxins

1.73 The potential risks from combined exposure to mycotoxins was identified as a topic that the COT should consider during horizon scanning. Discussions took place at several meetings during 2020. A planned statement will bring together the

conclusions from these discussions and list the research recommended by the COT.

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

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

1.76 Furthermore, the availability of relevant food consumption data is scarce, and the development of multi-analyte methods is still not yet fully applied as standard. The management of left-censored exposure data, the use of probabilistic models and a multi-biomarker approach should be consistent and have a well-defined approach. The Committee noted that there was a lack of UK data, particularly in biomonitoring; however, there are a number of studies ongoing. Although the UK will not be collecting new data for mycotoxins under the Human Biomonitoring for the European Union (HBM4EU) initiative. However, in the future, more data could be obtained through Health Protection Research Units. Such research was considered to be a priority by the COT.

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

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

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

1.79 As part of the work on the maternal diet (see paragraph 1.126) the COT was asked to consider the potential effects that excess iodine intake may have during preconception, pregnancy and lactation.

1.80 Iodine is an essential component of thyroid hormones which are important in growth and development. It is found in foods such as fish and seafoods as well as fortified products and food supplements. Seaweed is a very rich source of iodine and may

lead to high levels of consumption in some consumers.

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

1.82 Overall, members agreed that while there were no concerns in the general population, exposure to excess iodine in high seaweed consumers could pose a potential risk to maternal health. It was concluded that the currently available data was not sufficient to enable a risk benefit assessment to be performed. The final statement will be published in due course.

COT assurance

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

1.83 Due to the manner by which soybean and other grains, such as wheat, are grown, harvested, stored and transported, adventitious contamination of wheat flour with soya is known to occur. Soybeans and products thereof are recognised as causing allergies and are included on the Regulation (EU) 1169/2011 annex II list of declarable allergens[4].

1.84 In 2014, the FSA recommended an action level of 236 mg/kg be applied by UK Flour Millers for soya protein in wheat flour, based on due diligence sampling data at the time and the conclusions from a 2013 published paper from Remington et al[5]. Subsequently, more data became available on the dose-response relationship for soya protein allergy, along with further soya contamination data and therefore, the FSA conducted an updated risk assessment to guide risk management actions.

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

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

b) The current application of a set action level at the raw ingredient supply level may be hindering effective communication of risk through the supply chain and the ultimate decision on the necessity to communicate risk to

[4] European Parliament, Council of the European Union. 2011. Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers.

[5] Remington BC, Taylor SL, Marx DB, Petersen BJ, Baumert JL. 2013. Soy in wheat - Contamination levels and food allergy risk assessment. Food and Chemical Toxicology. 62:485-491.

the final consumer via a precautionary allergen statement, e.g. 'may contain'.

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

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

Committee procedures

Revision of the COT Terms of Reference and Code of Practice

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

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

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

Exploring Dose Response Workshop Report

1.89 Advances in biology, computer science and other related fields are paving the way for major improvements in how environmental and public health risks posed by potentially toxic chemicals are evaluated. The combined advances in discovery and clinical sciences, data science and technology have resulted in toxicity testing which has reached a pivotal transformation point known as part of the 4th industrial revolution (4IR). One of the major recent scientific advancements is the development of alternative toxicity testing and computer modelling strategies for the evaluation of hazard and exposure.

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

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

PBPK for Regulators Workshop

1.92 As a follow-up to the Exploring Dose Response Workshop delivered in March 2020 where the Tox21 approach[6] and novel approach methodologies (NAMs) for use in chemical risk assessment were discussed and explored; a workshop that focused on physiologically based pharmacokinetic (PBPK) modelling was held in December 2020.

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

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

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

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

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

- Any lessons learnt from authoritative bodies or industry.

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

EFSA consultations

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

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

1.97 Ochratoxin A (OTA) is a mycotoxin produced by several fungal species and human exposure occurs through the consumption of contaminated food products, such as cereals and cereal products, beans, pulses, cocoa products, nuts, spices, dried fruit, coffee, wine, beer and grape juice and in kidney, liver and blood from farm animals, where it occurs by transfer from animal feed. The most sensitive and crucial effects of OTA are on the kidneys; the extent of the kidney damage is dose- and time-dependent as OTA accumulates in the kidneys. At high concentrations, OTA induces kidney tumours in rodents.

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

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

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

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

1.101 In the draft opinion, the EFSA CONTAM panel assessed 27 perfluoroalkyl substances (PFASs). They decided to use a mixtures approach and had established a Tolerable Weekly Intake (TWI) for the sum of four PFAS (perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS)). These are currently the PFASs which

contribute most to the levels observed in human serum, they share toxicokinetic properties in humans and show similar toxicological profiles.

1.102 EFSA decided to base their PFASs assessment on the effects on the immune system, specifically on a decrease in vaccination response. A no observed adverse effect concentration (NOAEC) of 31.9 ng/mL was taken from the Abraham *et al.* (2020) study for the sum of the four PFASs. Pharmacologically-based pharmacokinetic (PBPK) modelling was then used, taking into account 12 months of breastfeeding by the mother, to calculate an estimated intake by the mother of 1.16 ng/kg bw per day for the sum of the four PFASs. This value was multiplied by 7 to calculate the TWI (1.16 x 7 = 8 ng/kg bw per week).

1.103 The COT noted the measuring at different time points, after vaccination, in the Abraham *et al.* (2020)[7] and Grandjean *et al*. (2012)[8] studies (1 and 5 and 7.5 years, respectively) could be an explanation for the difference in potency between the compounds. It was unclear whether there is a correlation between 1, 5 and 7.5 years. For children that were breastfed the impact of the mother's transfer of PFASs will be in the first year. Therefore, the data from the first year may not be as robust as data in the 5-7.5 years age groups. The COT suggested that preference should be given to using the data from the older children.

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

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

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

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

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[7] Abraham K, Mielke H, Fromme H, Volkel W, Menzel J, Peiser M, Zepp F, Willich SN and Weikert C. (2020). Internal exposure to perfluoroalkyl substances (PFASs) and biological marker in 101 healthy one-year old children: Associations between levels of perfluorooctanoic acid (PFOA) and vaccine response. *Archives of Toxicology*, 94(6): 2131-2147. Available at: https://pubmed.ncbi.nlm.nih.gov/32227269/

[8] Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P and Heilmann C. (2012). Serum Vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA.* **307:** 391-397. doi: 10.1001/jama.2011.2034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22274686

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

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

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

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

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

1.112 Glycoalkaloids are a group of nitrogen-containing compounds which are naturally produced by the Solanaceae plant family. This family includes popular vegetables such as tomatoes and potatoes. The main role of glycoalkaloids are to protect against pest attacks and pathogens. Acute toxic effects such as vomiting, diarrhoea and abdominal pain have been observed following ingestion of potato glycoalkaloids.

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

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

1.115 Overall, the Committee Members concluded that, as the greening of potatoes (where

glycoalkaloid levels are highest), can be seen and therefore removed, the health risks from potato glycoalkaloid consumption can be minimised. It was noted that the current FSA advice was to remove green, sprouting or damaged areas of potato prior to consumption. Therefore, no health concerns were highlighted.

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

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

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

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

1.119 It was noted that EFSA had not referenced the Haber et al., (2017)[9] paper that the COT had used in its 2018 statement on nickel in the infant diet. The Haber paper had used the same studies as EFSA (2015) but had used a more relevant endpoint as the basis for calculating a toddler toxicity reference value (TRV) for repeat exposures to nickel. The TRV calculated (20 µg/kg bw/day) was similar to the TDI established by EFSA in its recent update (13 µg/kg bw/day).

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

1.121 The Committee agreed with the HBGVs established by EFSA

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

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

1.123 The Committee was invited to provide any comments it wished to be submitted to

[9] Haber LT, Bates HK, Allen BC, Vincent MJ, Oller AR. (2017). Derivation of an oral toxicity reference value for nickel. Regul Toxicol Pharmacol. 87 Suppl 1:S1-S18.

EFSA on the draft EFSA opinion.

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

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

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

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

1.128 The Committee was unable to follow and understand EFSAs decision making process to apply the NOAEL/LOAEL approach; especially given the previous push by EFSA to apply BMD modelling and the minimal difference in the calculated chronic human intake from the previous (BMD) and current (NOAEL/LOAEL) approach. However, based on the NOAEL/LOAEL approach, the COT agreed with EFSAs additional uncertainty factor of 3 for the extrapolation from a LOAEL to a NOAEL and that an MOE of 24 would not be of concern.

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

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

1.130 The Committee was invited to provide any comments it wished to be submitted to WHO on the draft revision of chapter 5 of the revised Environmental Health Criteria

240 (EHC 240) publication on the "principles and methods for the risk assessment of chemicals in food, a guidance document that was released by the World Health Organisation for public consultation.

1.131 The Committee noted potential discrepancies between the descriptions of the benchmark dose approach in the draft and by the Environmental Protection Agency were addressed. Comparisons were made between the flow chart presented and that used by EFSA; preference for the flow chart used by EFSA was expressed.

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

Working Groups

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

1.133 The COT and COC set up a subgroup to review the approaches to synthesising epidemiological and toxicological evidence that are used in chemical risk assessments. While data integration is already applied in the work of the Committees, there is a general feeling that there is no explicit explanation of the procedure used and that there also was scope for improvement in the Committees' approaches. The terms of reference are to provide an output which will combine current practice and guidance and that will be applicable and realistic.

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

Horizon scanning

1.135 New topics suggested included that of residues in human pharmaceuticals in food, developments in dietary exposure assessment and evaluation of the exposome.

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

1.137 The Committee had been asked to consider alternatives to plastic packaging; particularly those from plant materials (see paragraph??).

1.138 The Committee also discussed potential ideas for research including looking at blood levels of chemicals in relation to levels in breast milk and monitoring and undertaking a dietary survey of plant-based milks to support the ongoing Committee work in this area.

Ongoing work

Hepatotoxicity of turmeric supplements

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

acute emetic effects, and Ochratoxin A (OTA), which is a genotoxic carcinogen, were evaluated.

1.155 The main challenge in the assessment of the safety of these drinks was the lack of information regarding dietary intakes for infants and young children following dairy-free or plant-based diets. Organisations providing advice on providing a balanced diet for vegan children under 5 were used to identify appropriate portion sizes and consumption frequency to develop representative intake scenarios for children following dairy-free or plant-based diets. These were then used to calculate daily intake figures for different age groups in order to calculate exposure to the chemicals of concern in the different drinks. The need for consumption information for people following plant-based diets more generally was also highlighted by the Committee as the popularity of these diets is increasing and information on realistic dietary intakes would help inform future risk assessments on similar issues.

1.156 Overall the Committee concluded that for soya drinks, it was concluded that the intakes of phytoestrogens from consumption of soya drinks in children aged 6 months to 5 years of age was less than the previously estimated maximum intake of 9.5 mg/kw bw per day in infants aged 0 to 6 months, who were consuming soya-based infant formula to ensure adequate nutrition, where medically necessary; hence there was less potential concern. Members agreed that, in addition to potential toxicological concerns, consideration of nutritional issues would also be required to assess whether it was necessary to issue additional advice on the consumption of soya-based drinks in children aged 6 months to 5 years of age.

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

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

Alternatives to Plastic Packaging

1.159 Due to the adverse environmental impacts of fossil-based plastics, and owing to a large proportion of total plastic being used in packaging, there are various initiatives to reduce the amount of conventional plastic used within packaging. As a result of government initiatives around the world, and in conjunction with pressure from consumers, recent years have therefore seen a major global increase in the development and use of biobased materials for food contact applications.

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

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

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

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

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

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

Less than lifetime exposure

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

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

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

refine the risk assessment. The COT will consider further how to approach bioaccumulative chemicals.

1.169 The COT considered that “less than lifetime” is not exactly the correct term for what is variable exposure over a lifetime.

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

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

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

1.172 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.

1.173 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.

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

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

Herbal Supplements Used in Pregnancy

1.176 As part of the SACN work (see paragraph ?? above), on nutrition and maternal health, the Committee considered commonly recommended herbal supplements used during pregnancy to identify priority compounds for further review.

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

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

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

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

Dioxins and Dioxin-like PCB's

1.181 The Committee reviewed the EFSA opinion on "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food" in 2019 and 2010. They focussed on the derivation of the revised tolerable weekly intake (TWI) of 2 pg TEQ/kg bw/week and subsequently considered its implications for risk management.

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

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

1.184 Any reduction in the current HBGV would take decades to reduce dioxin exposure in the population, due to the properties of dioxins, especially the long half-life in humans. The current COT TDI was based on the most sensitive endpoint in the animal studies and is intended to protect the most sensitive population group, hence it would also be protective for all population groups. Thus, while the re-assessment of dioxin was a necessary and important piece of work going forward the COT does not consider it necessary in the meantime to alter its current advice on dioxins.

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

1.185 The nicotine present in ENDS products has predominantly been in the free base form. However, some more recent products contain organic acids in the e-liquid,

leading to the presence of a proportion of the nicotine in the protonated form, as a salt. Nicotine salts are less volatile than freebase nicotine and are reported to produce a less harsh experience during inhalation. Members considered the presence of nicotine salts in ENDS products and the pharmacokinetics of nicotine when inhaled in the salt form.

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

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

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

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

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

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

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

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Declaration of members interests during the period of this report

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