Ongoing Work - COT 2022

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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.