COT Ongoing Work 2021

In this guide

The COT risk assessment of substances in the diet of women in preconception, pregnancy and up to 24 months post-partum

Background

1.130 The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its 2011 reports 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' and the 2018 report 'Feeding in the first year of life". In the latter report, the impact of breastfeeding on maternal health was also considered. 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. 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. Accordingly, the COT were asked to contribute to this project.

Prioritisation of xenobiotics

1.131 Following discussion of the prioritisation papers on substances to be considered for risk assessment, the Committee agreed that some substances were of sufficient concern to be allotted individual papers and others could be grouped together into an overarching Statement.

1.132 The substances for which individual papers were requested are:

- Vitamin D, iodine, caffeine, vitamin A, ginger, ochratoxin a, fumonisins, zearalenone, citrinin, ergot alkaloids, phytoestrogens, lead, mercury. cadmium, arsenic, selenium, acrylamide, oily fish, raspberry leaf and echinacea.

1.133 Substances to be included in an overarching statement are:

- Aflatoxins, nivalenol, deoxynivalenol, T2 & HT2, patulin, vitamin E, vitamin C, camomile, peppermint, evening primrose oil, dandelion, camomile, resveratrol, heterocyclic amines, legacy pesticides, non-dioxin-like PCBs and alcohol.

1.134 Other substances that may be reviewed include dioxins, bisphenol A and fusarenon-X, some of which are awaiting the opinions of other advisory bodies. The Committee may choose to add additional substances to the list or change the approach to substances on the list as the work progresses.

Alcohol and the maternal diet: The 2016 Chief Medical Officers report

1.134 The Committee considered whether alcohol should be considered as one of the xenobiotics being considered in the review of the maternal diet. Although alcohol *per se* was not within the SACN remit it could be considered as a wider health issue.

As the database for the potential effects of alcohol in pregnancy was extensive, Members considered the most recent UK Government recommendations and the data on which they had been based in order to establish whether further work in this area would be of value.

1.135 The UK Government suggests that women who are pregnant or trying to become pregnant should avoid alcohol altogether. This advice, which is given on, for example, the NHS website, is based on recommendations from the “Low Risk Drinking Guidelines produced by the UK Chief Medical Officers (CMO) in 2016”. These recommendations were based on the findings of a number of systematic reviews and meta-analyses. The results of these studies were largely inconclusive with respect to the effects of low levels of alcohol exposure and methodological flaws in the studies were noted. A number of additional systematic reviews and meta-analyses have been published covering the same end points considered in the CMO report, but as previously, the results for low levels of exposure were inconclusive and methodological failings were noted.

1.136 The COM reviewed alcohol in 2005 and concluded that there was no clear evidence for a risk from (low) alcohol consumption during pregnancy, but they were not able to fully exclude a risk. The COM further concluded that alcohol itself was probably not genotoxic, however the breakdown product acetaldehyde most

likely was. Overall, the COM was unclear what other chemicals may be present in alcoholic beverages that might cause an effect.

1.137 Alcohol is produced endogenously, and metabolic enzymes have been proven to be extremely effective at preventing cellular damage in the body and aiding the elimination of alcohol. Hence, the biological mechanism would need to be taken into account when considering the available epidemiology and it is possible there is a threshold for the effects of alcohol.

1.138 The CMO report is thorough and the approach and conclusions on alcohol in pregnancy are reasonable, given the data considered in the report. The evidence is not strong enough to completely rule out some risk from low levels of alcohol exposure in pregnancy. As the data published since 2011 do not greatly add to the CMO report on the clarity of the issue and given the work and resources involved, a further review would be unlikely to change the current advice to women. Members therefore agreed not to take this review further.

Ongoing topics in maternal diet

Vitamin D

1.139 The Committee assessed if exposure to excess intake of vitamin D from various sources (including UV radiation, dietary sources, and supplements) would pose a risk to maternal health.

1.140 The relationship between oral vitamin D intake and serum levels is unclear due to many uncertainties such as season, time of day, amount of skin exposed, skin pigmentation and use of SPF sunscreen. However, exposure from UV radiation is considered unlikely to result in vitamin D toxicity due to inbuilt mechanisms in the skin where pre-vitamin D3 reaches a maximum concentration in the skin within a few hours after UVB radiation exposure. Other uncertainties in the assessment is the use of data from non-pregnant women of child-bearing age (i.e., 16-49 years) to construct the exposure assessment in pregnant women, since the diet of the latter may vary.

1.141 Higher strength vitamin D supplements are likely to be the biggest contributor to vitamin D exposure, and consumption of these supplements alone is sufficient to result in exceedance of the TUL of 100 µg/day. The diet alone without consumption of vitamin D containing supplements is unlikely to be a cause of concern, and consumption of both dietary sources of vitamin D and higher strength vitamin D supplements are likely to result in exposure levels

greater than the TUL of 100 µg/day.

1.142 A statement setting out the Committee’s assessment of vitamin D will be published in 2022.

Cadmium

1.143 The COT discussed a review of the literature on cadmium in the maternal diet and requested additional information, with particular regard to maternal dietary intake and the implications for subpopulations where consumption of certain food groups might be higher.

1.144 As smoking is a significant source of cadmium, information on cigarette smoke and vaping should be included also considering bystander/passive smokers. Further information on metallothionein and the role it plays in the body and the placenta was also requested.

1.145 The Committee will continue to work on cadmium during 2022.

Vitamin A

1.146 Vitamin A (retinol) is essential for the health of adults, children and developing foetuses, although both deficiency and excess lead to toxicity, particularly developmental malformation in the fetus.

1.147 Dietary retinol comes pre-formed from animal derived foods such as liver or liver products or is converted from carotenoids such as β-carotene which form the colouring matter in vegetables such as carrots and peppers. Retinol is absorbed with dietary fats, bound to plasma proteins and stored in the liver. Retinol is oxidised in the tissues to retinal, which is essential for vision, and then to retinoic acid, which is essential for fetal development and other functions.

1.148 In many countries, the issue for maternal health is deficiency but in richer nations adequate dietary levels are normally met. A tolerable upper limit (UL) of 3000 µg retinol/day has been set by EFSA as a level unlikely to cause developmental malformations but there is uncertainty about the actual level that may be associated with toxicity. However, pregnant women are advised not to consume foods such as liver or supplements such as cod liver oil which may cause them to exceed the UL.

1.149 Oral and topical retinoid-based products are used to treat severe acne, often in young women who may become pregnant and although the risks are

disputed, their use is not recommended in pregnancy. Recent evidence suggests that an association between retinoid acne treatment and depression may be ill-founded, but uncertainties still exist.

1.150 Few if any ill effects have been ascribed to taking supplements containing β-carotene.

1.151 A statement setting out the Committee's assessment of vitamin A will be published in 2022.

Ginger and ginger supplements

1.152 As part of the current programme of work on the maternal diet, the Committee considered the use of dietary supplements during pregnancy to identify those that might need reviewing. These are supplements that are not officially recommended but which are promoted by anecdotal evidence and unofficial sources as having various purported benefits. It was agreed that ginger should be considered in further detail.

1.153 The Committee considered the potential effects of ginger and 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 drugs as well as data on potential exposure.

1.154 As it is commonly believed that ginger suppresses morning sickness, pregnant women may be using the supplements for this purpose. Whilst ginger consumption in the diet is not considered to be of concern due to the long history of safe use for culinary purposes, however, problems could arise from consumption of more concentrated products such as the various forms of supplements.

1.155 There are limited human data, and these are not strongly indicative of any toxicological concern but there are some indications of possible adverse effects and numerous uncertainties. Ginger did not appear to be systemically toxic but did appear to have reprotoxic effects at high doses in animal studies. Ginger is thought to affect prostaglandin function which may be relevant to this.

1.156 It is not possible to determine a point of departure to use in the risk assessment of ginger. While there is some equivocal evidence for the possible effect of ginger on reproduction, it is not possible to characterise it based on the data available. There is no clear indication that ginger is detrimental to consumers.

1.157 The potential for contamination of ginger with heavy metals and/or mycotoxins cannot be excluded.

1.158 A statement setting out the views of the Committee on will be published in 2022.

Iodine

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

1.160 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.

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

1.162 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.

1.163 The final statement setting out the Committee’s views on iodine will be published in 2022.

NAMs Roadmap

1.164 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 can be 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 the 4th industrial revolution (4IR). One of the major recent scientific advancements is the development of New Approach Methodologies (NAMs) including high throughput screening, omics and in silico computer modelling strategies such as Artificial Intelligence and machine learning for the evaluation of hazard and exposure. This also supports the Replacement, Reduction and Refinement (3Rs)

approach.

1.165 The future of the safety assessment of chemicals in food depends on adaptability and flexibility in utilising the best scientific methodologies and strategies available to respond to the accelerating developments in science and technology.

1.166 NAMs are gaining traction as a systematic approach to support informed decision making in chemical risk assessment. Integration of these technologies as part of the FSA chemical risk assessment process will be fundamental in the future in the future of human safety assessments to protect consumers.

1.167 The Food Standards Agency (FSA) responds to food incidents and it is important that robust risk assessments on the safety of a chemical can be provided.

However, sometimes there is very little, or no, toxicological information for a given chemical. For such chemicals, the use of NAMs could provide a more indicative level of risk and therefore greater confidence can be provided for them as well as less uncertainty that individual compounds can be assessed.

1.168 In order to achieve this, the FSA and COT are developing a UK roadmap towards acceptance and integration of NAMs, including predictive toxicology methods using computer modelling, into safety and risk assessments for regulatory decision making.

1.169 During 2020, Members discussed the latest draft version of the roadmap The Committee endorse the roadmap and a supporting workshop, and congratulate the FSA for taking the lead in this area. Developing the roadmap will involve engaging with other government departments and regulatory bodies.

The potential health risks of bamboo bio-composite food contact materials

1.170 Advice on biobased food contact materials (BBFCMs) has been increasingly requested from the Food Standards Agency (FSA) so it was therefore considered timely for the Committee to review the available toxicological information on BBFCMs.

1.171 It was agreed that a health risk assessment should be conducted for bamboo composites based on its potential hazards.

1.172 The migration of formaldehyde and melamine from bamboo composite cups is a potential concern to human health and it would therefore be appropriate to conduct a full risk assessment once UK data are available.

1.173 As obtaining the data and providing a full risk assessment will require time, the COT agreed to publish an interim position paper to set out their concerns and allow for risk management action.

1.174 The interim position paper will be finalised and published in 2022.

Chitin and chitosan in food packaging materials

1.175 The FSA is currently assessing whether there are any risks to health posed by bio-based food contact materials (BBFCMs). One of the first materials to be reviewed was including that containing chitin or chitosan.

1.176 Chitin and chitosan can be derived from fungi or from shellfish. Therefore there are potential concerns for individuals who are allergic to shellfish, but only limited data are available.

1.177 The risk of allergenicity from these BBFCMs appears to be low. However, before the potential risks to human health can be fully assessed, 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.

1.178 Further information on chitin or chitosan derived from fungi is also needed.

1.179 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.

1.180 A second draft statement on this work will be presented to the COT in 2022.

PBPK Workshop

1.181 The FSA and the COT held a “PBPK for Regulators” workshop in December 2020 in a multidisciplinary setting with delegates from regulatory agencies, government bodies, academia and industry. The workshop provided a platform to enable expert discussions on the application of PBPK to human health risk assessment in a regulatory context.

1.182 The presentations covered current applications of PBPK modelling: in the agrochemical industry for *in vitro* to *in vivo* extrapolation (IVIVE); pharmaceutical industry for drug absorption related issues (e.g. the effect of food on drug absorption) and drug-drug interaction studies, as well as dose extrapolations to special populations (*e.g.* those with a specific disease state, paediatric/geriatric age groups, and different ethnicities); environmental chemical risk assessment fields; an overview of the current regulatory guidance; and a PBPK model demonstration. This enabled attendees to consider the wide potential and fit for purpose of application of PBPK modelling in these fields. Attendees further considered the applicability of PBPK models in the context of future food safety assessment, for refining exposure assessments of chemicals with narrow margins of exposure and/or to fill data gaps from more traditional approaches (i.e., data from animal testing).

1.183 The overall conclusions from the workshop proceedings were as follows:

- PBPK modelling tools are applicable in the explored areas of use, and there is some expertise available for their utilisation.
- PBPK modelling offers opportunities from which to address questions for compounds that are otherwise not solvable.
- Widespread acceptance amongst regulatory bodies appears to be limited by lack of available in-house expertise.
- Familiarisation using real world case studies would help in developing more experts in the field and increasing acceptance.
- In a regulatory context, establishing fitness for purpose for the use of PBPK models requires multi-partite discussion and harmonised guidance.
- PBPK modelling is part of the wider “new approach methodologies” for risk assessment.

1.143 A summary of proceedings from this workshop will be published in due course.

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

1.144 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 (see paragraph 1.30).

1.145 As noted elsewhere, following on from the assessment of plant based drinks a joint SACN/COT Working Group has been established to bring together the nutritional and toxicological aspects of plant based drinks.

1.146 The main comparator for plant-based drinks should be cow’s milk and to enable comparison, the potential chemical constituents and contaminants within cows’ milk should be reviewed. These included veterinary medicine residues, pesticide residues, nitrate and nitrite, bisphenol A, phthalates, dioxins and dioxin-like biphenyls, non-dioxin-like polychlorinated biphenyls, polycyclic aromatic hydrocarbons, selected isoflavones, 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.

1.147 The Committee concluded that there were no health concerns arising from the consumption of cow’s milk associated with the compounds noted above.

1.148 A statement covering the Committee’s views on the safety of milk will be published in due course.

Interim Position paper on Titanium Dioxide

1.149 Following the discussions by both COT and COM a draft interim position paper on titanium dioxide, capturing the outcomes of the discussions from the two Committees and outlining the next steps was prepared. The Interim Position Paper will be published in due course.