TOX/2021/24

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Discussion paper for the prioritisation of dietary components and xenobiotics for future papers on their effects on maternal health – Part 2

Introduction

1. 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.

2. 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.

3. 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. This subject was initially discussed during the horizon scanning item at the January 2020 meeting with a scoping paper being presented to the Committee in July 2020. This included background information on a provisional list of chemicals proposed by SACN. It was noted that the provisional list of chemicals was subject to change following discussion by COT who would be guiding the toxicological risk assessment process: candidate chemicals or chemical classes can be added or removed as the COT considered appropriate. The list was brought back to the COT with additional information in September 2020[1]. Following a discussion at the COT meeting in September 2020, it was agreed that papers on a number of components should be prioritised and to this end, papers on iodine, vitamin D and dietary supplements have been or will be presented to the Committee. The remaining list of compounds were to be triaged on the basis of toxicity and exposure. The current paper presents information intended to aid this process.

4. A paper submitted to the Committee in February covered chemical entities of biological origin. The list of remaining chemical and food entities for consideration is: **heavy metals (including arsenic), selenium, heterocyclic amines, acrylamide, dioxins and dioxin-like PCBs, non-dioxin-like PCBs, bisphenol A, legacy pesticides and components of oily fish**.

[1] COT Contribution to SACN review of nutrition and maternal health: proposed scope of work and timetable. Available at: https://cot.food.gov.uk/sites/default/files/2020-09/TOX-2020-%2045%20%20Maternal%20diet%20scoping%20paper_0.pdf

5. For ease of comparison, the health-based guidance values for the substances considered and the upper bound 95th percentile exposure values are tabulated in Table 4, at the end of the text of this paper.

Heavy metals

6. The heavy metals lead (Pb), cadmium (Cd), mercury (Hg) and the metalloid arsenic (As) are assessed below. The Committee may decide whether this should constitute the exhaustive list or whether other metals should be added.

Lead

7. Lead is found as a natural constituent of the environment, but also as an anthropogenic contaminant, arising from its historic use in water pipes, paints and petrol. EFSA published an opinion on lead in the diet in 2010.

Toxicity

8. The EFSA CONTAM Panel identified cardiovascular effects and nephrotoxicity in adults as potential critical adverse effects of lead on which to base the risk assessment and derived BMDL values for these effects. Lead-associated neurotoxicity was found to affect central information processing, especially for visuospatial organisation and short-term verbal memory, to cause psychiatric symptoms and to impair manual dexterity. There is considerable evidence demonstrating that the developing brain is more vulnerable to the neurotoxicity of lead than the mature brain.

9. The BMDLs derived from blood lead levels in µg/L were: for effects on systolic blood pressure $BMDL_{01}$, 36 (1.50 µg/kg bodyweight (bw) per day); effects on prevalence of chronic kidney disease $BMDL_{10}$, 15 (0.63 µg/kg bw per day). The CONTAM Panel concluded that the current Joint Expert Committee on Food Additives (JECFA) Provisional Tolerable Weekly Intake (PTWI) of 25 µg/kg bw per week was regarded as no longer appropriate as there was no evidence for a threshold for critical lead-induced effects and the margins of exposures were such that the possibility of an effect from lead in some consumers, could not be excluded.

10. Disha *et al* (2019, from abstract) collected venous blood from 44 Taiwanese women and analysed lead levels by atomic absorption spectrometry. They found a strong correlation between blood lead levels and blood pressure in women suffering from pre-eclampsia, but not in healthy women. The mean blood lead level was 3.42 ± 2.18 mg/dL in preeclamptic women, which was significantly higher ($p = 0.0132$) than that in healthy women (2.38 ± 2.43 mg/dL).

11. Yazbeck *et al* (2009) also found an association between blood lead concentration and blood pressure in women with pre-eclampsia. Age, parity, weight gain, alcohol, smoking habits, and calcium supplementation were comparable between hypertensive and non-hypertensive women. Lead levels were significantly higher in hypertensive (mean ± SD, 2.2 ± 1.4 µg/dL) than in normotensive patients (1.9 ± 1.2 µg/dL; $p = 0.02$). Adjustment for potential confounders did not eliminate

the significant association between blood lead levels and the risk of hypertension (adjusted odds ratio = 3.3; 95% confidence interval, 1.1–9.7).

Exposure

12. EFSA stated that in average adult consumers, lead dietary exposure ranges from 0.36 to 1.24 and up to 2.43 µg/kg bw per day in high consumers in Europe. The available evidence showed that for women of child-bearing age and vegetarians, dietary exposure was no different from that of the general adult population. The total dietary exposures to lead (µg/kg bw per day) for average (Mean) and 95th percentile (P95) in 459 females aged between 20 and 40 years in Great Britain in 2010 were 0.44 (mean lower bound (LB)), 0.92 (mean upper bound (UB)), 0.72 (95^{th} percentile LB) and 1.49 (95^{th} percentile UB).

Cadmium

13. Cadmium is found widely in the environment and is released from anthropogenic sources. In the bodies of animals and humans it can cause damage to the kidneys, primarily to the proximal tubule of the nephron. and to the bones by displacement of calcium. The International Agency for Research on Cancer (IARC) has reviewed cadmium and cadmium compounds multiple times, most recently in 2012, and has classified them as human carcinogens that cause cancers of the lung, prostate and paranasal sinuses after inhalation (IARC, 2012). Cadmium indirectly induces oxidative stress, which causes damage to membranes, DNA and proteins. Oxidative stress may also form part of the mechanism of kidney and bone damage as well as cadmium-induced carcinogenesis (Nair *et al*., 2013).

Toxicity

14. EFSA published an Opinion on cadmium in food and feed in 2009. In this publication, EFSA derived a PTWI of 2.5 mg/kg bw/week, based on a one-compartment toxicokinetic model. JECFA published a statement on cadmium in 2010 and, using the same studies as EFSA, derived a Provisional Tolerable Monthly Intake (PTMI) of 25 mg/kg bw per month, also based on a one-compartment toxicokinetic model. In a 2011 report, EFSA considered the discrepancy between these two HBGVs but concluded that its own evaluation was correct. The COT used the EFSA PTWI in their assessment of cadmium in the infant diet (COT, 2018).

15. Sengupta *et al* (2015) reviewed the effects of metals including cadmium on female reproduction. The authors reported that there were few data on the effects of cadmium on human female reproductive function. However, they pointed to work by Sipowicz *et al* (1995), who found that Cd ions alone inhibited the contraction of strips of uterine tissue from post-partum women but at low concentrations (10^{-9} to 10^{-8}M), Cd enhanced the contractions induced by Ca^{2+} ions and oxytocin. In addition, a paper by Paksy *et al* (1997) showed that Cd reduced the FSH-stimulated production in cells cultured from ovarian follicular aspirates of 41 women undergoing in vitro fertilization (IVF), though the lowest concentration that had this effect was 35 times that found in the ovary of a female smoker.

Exposure

16. EFSA published an Opinion on dietary exposure to cadmium in 2012. They estimated a middle bound overall weekly average cadmium intake of 2.04 µg/kg bw and a potential 95th percentile at 3.66 µg/kg bw. Individual dietary exposure ranged between a weekly minimum LB average of 1.15 to a maximum UB average of 7.84 µg/kg bw and a minimum lower bound 95th percentile of 2.01 and a maximum upper bound 95th percentile of 12.1 µg/kg bw. Large contributions to the overall intake were made by grains and grain products (26.9 % by weight), vegetables and vegetable products (16.0%) and starchy roots and tubers (13.2%). Of these, potatoes (13.2%), bread and rolls (11.7%), fine bakery wares (5.1%), chocolate products (4.3%), leafy vegetables (3.9%) and water molluscs (3.2%) contributed the most to cadmium dietary exposure across age groups. These data confirmed that children and adults at the 95th percentile exposure could exceed health-based guidance values.

17. JECFA is currently requesting submission of new data on cadmium fin all food sources, but particularly in chocolates and cocoa products, from over the last 10 years. In particular: levels and patterns of human exposure to cadmium from all food sources (particularly chocolates and cocoa products); food consumption patterns; including different age/population groups; and biomarkers of exposure. An updated dietary exposure assessment to cadmium from all food sources is planned to be included for discussion at the 91st meeting of JECFA, scheduled in early 2021.

Arsenic (As)

18. Arsenic is a metalloid present at low concentrations in the environment and occurs in elemental inorganic (iAs such as As(III) and As(V)) and carbon-associated organic forms. such as arsenobetaine and different arsenosugars (most common in seafood) and (methylarsonate, methylarsenite and dimethylarsinate (DMA)).

Toxicity

19. Inorganic arsenic (iAs), is more toxic (and As(III) > As(V)) than organic arsenic compounds. IARC has classified iAs and iAs compounds, including arsenic trioxide, arsenite and arsenate, as ‘carcinogenic to humans’ (Group 1) (IARC, 2012). Evidence of carcinogenicity of organic forms including dimethylarsinic acid and arsenobetaine was less adequate (designated Group 2A and Group 3 respectively).

20. In 2009, the EFSA CONTAM Panel concluded that the PTWI of 15 µg/kg b.w. was no longer appropriate as and established a $BMDL_{01}$ between 0.3 and 8 µg/kg bw per day for an increased risk of cancer of the lung, skin and bladder, as well as skin lesions (EFSA CONTAM Panel, 2009). In 2010 JECFA withdrew its PTWI of 15 µg/kg bw and, based on epidemiological studies, instead identified a $BMDL_{0.5}$ for lung cancer of 3.0 µg/kg b.w. per day (2-7 µg/kg bw per day based on the range of estimated total dietary exposure) (WHO, 2011).

21. Ashley-Martin *et al* (2018) assessed associations between speciated As and gestational diabetes mellitus (GDM). Concentrations of speciated As [(inorganic

(trivalent, pentavalent)), methylated arsenic species metabolites dimethylarsinic acid (DMA)), and organic (arsenobetaine)] were measured in first trimester urine samples from 1243 Canadian women, 4% of whom met the diagnostic criteria for GDM. Compared to women in the lowest tertile of DMA (<1.49 µg As/L), women with concentrations exceeding 3.52 µg As/L (3rd tertile) experienced an increased risk of GDM (aOR = 3.86; 95% CI: 1.18, 12.57) (p-value for trend across tertiles = 0.04). When restricted to women carrying male infants, the magnitude of this association increased (aOR 3rd tertile = 4.71; 95% CI: 1.05, 21.10). The authors concluded that there was a positive relation between DMA and GDM and the possible differences in risk by fetal sex required further investigation.

22. Using the Edinburgh Postpartum Depression scale, Valdés *et al* (2017) found that the score for Chilean women older than 25 years without a history of depression was associated with lower urinary inorganic arsenic. The adjusted coefficient for the total urinary natural logarithm of inorganic arsenic in multiple linear regressions was -2.51 (95% CI: -4.54, -0.48; P-value=0.02). For women older than 25 years old with a history of depression, this value was 2.09 (95% CI: -0.90, 5.08; P-value=0.16).

23. Salmeri *et al* (2020) performed a systematic review and meta-analysis to provide a comprehensive overview of published evidence on the association between As and gestational diabetes mellitus. The data from 9 studies from various countries indicated a link between inorganic and organic arsenic, as determined in various bodily matrices (blood, urine, toenails) and exposure from drinking water and gestational diabetes, but the authors pointed out large heterogeneity in the studies (water> blood> urine) and the need for further work in the area to increase confidence in causation.

Exposure

24. EFSA (2014) used their Comprehensive European Food Consumption Database to estimate chronic dietary exposure to iAs using 28 surveys from 17 European countries. Mean dietary exposure among the adult population ranged from 0.09 to 0.38 µg/kg bw per day, and 95th percentile dietary exposure estimates ranged from 0.14 to 0.64 µg/kg bw per day. The main contributor to dietary exposure to iAs was non-rice grain-based processed products, particularly wheat bread and rolls. Other foods that were important contributors to iAs exposure were rice, milk and drinking water.

Mercury

25. The three chemical forms of mercury are (i) elemental mercury (Hg0), (ii) inorganic mercury (mercurous (Hg+) and mercuric (Hg2+)) cations and (iii) organic mercury (e.g. methylmercury). In its elemental form, mercury is the only metal that is liquid at room temperature and is the prevalent form in the atmosphere. Inorganic mercury is used in batteries, fungicides, antiseptics or disinfectants. Organic mercury, that is mercury covalently bound to carbon, has been used as fungicides and in pharmaceutical products such as thiomersal and is the most common form in the food chain (EFSA 2012, corrected version, 2018).

Toxicity

26. In 2003, JECFA reviewed the provisional tolerable weekly intake (PTWI) for methylmercury and established a revised PTWI of 1.6 µg/kg body weight (bw). Neurodevelopment was considered to be the most sensitive health outcome and development in utero the most sensitive period of exposure. Calculation of the PTWI was based on an average benchmark dose level or no-observed-effect level (BMDL or NOEL) of 14 mg/kg (14 µg/g) for mercury in maternal hair in the studies of neurodevelopmental effects in cohorts of children from the Faroe Islands and the Seychelles.

27. In 2010, JECFA reviewed the PTWI for total mercury. The Committee considered kidney weight changes, to be the critical endpoint and derived a BMDL10 for relative kidney weight increase in male rats of 0.11 mg mercuric chloride/kg bw/d, corresponding to 0.06 mg/kg bw/d as mercury. After application of a 100-fold uncertainty factor, the Committee established a PTWI for inorganic mercury of 4 µg/kg bw.

28. Orr *et al* (2018) gavage dosed pregnant and non-pregnant female Wistar rats with three non-toxic doses of $CH_3[^{203}Hg]$ on gestational days (GD) 10, 15, and 19. Non-pregnant rats were gavaged at the same time intervals. On GD 20, samples of kidney and blood were gamma counted. Blood and kidney levels of radioactive Hg appeared to be lower in pregnant animals compared with non-pregnant ones and the authors suggested that this was due to pregnancy-induced increase in blood volume and because of placental circulation. Thus, the toxic burden to the female appeared reduced, but potentially at the expense of the fetus.

Exposure

29. There is UK Government advice outlined on the NHS website regarding restricting the consumption of oily and predatory fish for girls, women who are considering becoming pregnant or may become pregnant one day, and pregnant or breast feeding women. This is partially to mitigate maternal exposure to mercury and potential damage to the developing fetal nervous system. The link to this advice is provided in the section on oily fish in this paper (paragraph 94).

30. In the UK Total Dietary Survey (TDS) (Rose *et al*, 2010), total mercury was detected in the 'Offal' (4 µg/kg), and 'Other vegetables' food groups (0.7 µg/kg); the concentration was below the LODs (0.5 - 3 µg/kg depending on food group) in all other categories apart from fish and seafood. Also, in the UK, mercury was detected at concentrations at or above the LOD (0.2 –1.0 µg/kg depending on sample weight taken) in only about one quarter of the samples in a wide range of commercial weaning foods and formulae, usually in those containing fish (FSA, 2006). The mean mercury concentration was 1 µg/kg, slightly lower than the mean value from a previous survey where the mean was 3 µg/kg (FSA, 2003).

31. EFSA (2012) found that in the 15 surveys available that reported food consumption for adults (>18 to 65 years old) covering a total of 30,788 survey participants, the MB mean methylmercury dietary exposure varied between 0.07

and 1.08 µg/kg bw per week, with a median of 0.24 µg/kg bw per week, The 95th percentile ranged between 0.51 and 3.04 µg/kg bw per week, with a median of 1.13 µg/kg bw per week.

32. Dietary exposure of women of child-bearing age did not differ appreciably from dietary exposure of the general adult population.

Heterocyclic amines

33. Heterocyclic and aromatic amines are products of cooking, mostly at high temperatures found largely, but not exclusively, in meat products. Many have been placed in Category 1 as human carcinogens by IARC.

34. HCAs are formed as a result of reactions between amino acids and creatine when meat is exposed to cooking temperatures above 150°C. HCAs were found to be genotoxic in both *in vivo* and *in vitro* tests and carcinogenic to rats and mice (Aeschbacher, 1991; Carthew *et al,* 2010). Four types of HCAs are formed during cooking. These include 2-amino, 3-methylimidazo[4,5-f]quinolone (IQ), 2-Amino-3,4-dimethylimidazo[4,5-f]quinolone (MeIQ), 2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-Amino-1-methyl-6-phenylimiazo[4,5-b]pyridine (PhiP). PhiP has been shown to cause cancer of the colon and mammary glands in a dose dependant manner in rat studies. PhIP can also be transferred from mothers to their offspring via breastmilk (Bellamri et al, 2018).

35. Carthew et al (2010) estimated a $BMDL_{10}$ of 2.71 mg/kg/day for the association of PhIP with colon tumours in rodents, and of 0.48 mg/kg/day for prostate tumours. Assuming a 70 kg adult body weight, these amounts correspond to 189,700,000 ng/day and 33,600,000 ng/day of PhIP, and the upper 95% CrI estimate of the mean daily exposure to PhIP was 635 ng/day. The $BMDL_{10}$ of MeIQx as derived from an in vitro assessment on human colon epithelial cells was found to be 8.8µM (Zhang et al., 2017).

36. Naga *et* al (2002) found that when pregnant ICR mice were dosed orally with the mutagenic heterocyclic amine 9-(4'-Aminophenyl)-9H-pyrido [3,4-b] indole (aminophenylnorharman, APNH) at 0, 0.625, 1.25, 2.5 or 5 mg/kg/day on gestational days (GD) 6 to 15, maternal death occurred at 5 mg/kg/day and the overall health of dams deteriorated at doses of 2.5 mg/kg/day and above. Liver and kidney lesions were observed in dams treated with APNH at 2.5 or 5 mg/kg/day. Increased preimplantation loss was observed at 5 mg/kg/day and post-implantation loss was observed at 2.5 mg/kg/day and above. Fetal body weight was decreased by APNH in a dose-dependent manner. The frequency of fetal cleft palate increased significantly in the group treated with APNH at 2.5 mg/kg/ day compared to the controls, which the authors suggested arose from the adverse effect of APNH on the maternal environment during organogenesis, but there were no significant increases in skeletally malformed fetuses in any APNH-treated group. The frequency of lumbar ribs was increased dose dependently.

37. Single doses of APNH were also given at 0, 5, 10, or 20 mg/kg on GD 12 only. The overall health of dams did not deteriorate following the single dose. Post-

implantation loss was observed at 20 mg/kg. However, there were no fetuses with cleft palate even when APNH was given at 20 mg/kg.

Exposure

38. Pouzou *et al* (2018) assessed dietary exposure to two HCAs iPHiP and MeIQx) in America from consumption of a range of meats that had been cooked in different ways. Irrespective of the type of meat involved, frying produced the greatest exposure in ng/day to both HCAs (317 and 50.7 ng/day respectively).

39. Carthew *et al* (2010) found a mean Margin of Exposure (MOE) for PHiP of approximately 400,000 and a 95th percentile MOE of approximately 100,000. The EFSA Scientific Committee concluded that for substances that are both genotoxic and carcinogenic, an MOE of 10 000 or higher, based on a $BMDL_{10}$ from an animal study, and taking into account overall uncertainties in the interpretation, would be of low concern from a public health point of view.

40. Zhang *et al* (2017) found a mean MOE for MeIQx of approximately 10,000 and a 95th percentile of approximately 2500. This is smaller than the MOE of 10,000 that is regarded as of low concern for genotoxic carcinogens.

Bisphenol A (BPA)

41. Bisphenol A (BPA) is used as a monomer in the manufacture of polycarbonates and epoxy resins and as an additive in plastics. Polycarbonates are used in food contact materials such as reusable beverage bottles, infant feeding bottles, tableware (plates and mugs) and storage containers. Epoxy resins are used in protective linings for food and beverage cans and vats.

42. In 2015, the EFSA CEF panel published an Opinion on the risks to public health associated with bisphenol A (BPA) exposure. Exposure was assessed for various groups of the human population in three different ways: (1) external (by diet, drinking water, inhalation, and dermal contact with cosmetics and thermal paper); (2) internal exposure to total BPA (absorbed dose of BPA, sum of conjugated and unconjugated BPA); and (3) aggregated (from diet, dust, cosmetics and thermal paper), expressed as oral human equivalent dose (HED) referring to unconjugated BPA only. An updated EFSA opinion on BPA is in preparation and will be published in due course.

Toxicity

43. BPA has been found to increase kidney and liver weights in parental animals and in all the generations of rats and mice examined in multi-generation studies. EFSA (2015) noted that only limited conclusions could be drawn from human studies on the likelihood of associations between BPA exposure during pregnancy and disturbed fetal growth, or maternal and infant decreased thyroid function. In several multi-generation studies no effects were observed over a dose range of 3 μg/kg bw per day to at least 50 mg/kg bw per day.

44. A $BMDL_{10}$ of 8,960 µg/kg bw per day was calculated for increases in the mean relative kidney weight in a two generation toxicity study in mice. No $BMDL_{10}$ could be calculated for increases in cellular proliferation in the mammary gland that has been reported in several species. The $BMDL_{10}$ was converted to a Human Equivalent Dose (HED) of 609 µg/kg bw per day. The CEF Panel applied a total uncertainty factor of 150 (for inter- and intra-species differences and uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects) to establish a temporary (t-)TDI of 4 µg/kg bw per day.

Exposure

45. EFSA (2015) found that women of childbearing age had dietary exposures to BPA that were comparable to men of the same age (up to 0.388 µg/kg bw per day).

46. By comparing this t-TDI with the exposure estimates, the CEF Panel concluded that there was no health concern for any age group from dietary exposure and low health concern from aggregated exposure. The CEF Panel noted considerable uncertainty in the exposure estimates for non-dietary sources, whilst the uncertainty around dietary estimates was relatively low.

Acrylamide

47. Acrylamide is a low molecular weight compound that is created in a variety of foods, largely those rich in starch and low in moisture, especially potato products, coffee and coffee substitutes during the production process at above 120^{o}C. Until 2002, acrylamide was regarded as an industrial chemical used for the production of polyacrylamide products such as water filters and gels for laboratory use.

Toxicity

48. In 2015, the EFSA CONTAM Panel identified four possible critical endpoints for acrylamide toxicity, *viz* neurotoxicity, effects on male reproduction, developmental toxicity, and carcinogenicity. There is more evidence for acrylamide toxicity and genotoxicity from experimental animal studies than from human exposure, which seems to be accounted for largely by CYP-mediated epoxidation of the parent compound to glycidamide, which is known to form DNA adducts. Rat and mouse studies have shown some signs of developmental toxicity (skeletal changes, impaired body weight gain, changes in the central nervous system, and neurobehavioural effects) at exposure levels that, in some cases, are also associated with maternal toxicity. The lowest NOAEL reported for developmental toxicity was 1.0 mg/kg b.w. per day from studies in rats exposed gestationally and neonatally.

49. Wei et al., 2014 administered acrylamide to female mice in drinking water at doses of 0, 20 or 40 mg/kg bw per day for 30 consecutive days. This led to significant reduction in body weights, uteri and ovary weights and the number of corpora lutea. There was a dose-related decrease in the proportion of primordial follicles and increase in the proportion of antral follicles in the ovaries of treated mice. The proportion of primary follicles was increased at the low dose, but not the high dose relative to the group. Immunohistochemistry showed that nitric oxide

synthase (NOS) signalling was involved in follicular development and atresia. Total NOS, intracellular (i)NOS and extracellular (e)NOS activities were significantly increased with increasing doses of acrylamide. Serum progesterone concentrations were dose-dependently significantly reduced, but 17β-estradiol concentrations were unchanged. In an *in vitro* study, the viability of mouse ovary granulosa cells was reduced in a dose-dependent manner by exposure for 48 hours to acrylamide at 0, 0.5 and 5 mM.

50. The CONTAM Panel selected $BMDL_{10}$ values of 0.43 mg/kg bw per day for peripheral neuropathy in rats and of 0.17 mg/kg bw per day for neoplastic effects in mice from studies reported in the literature. The lowest range of $BMDL_{10}$s was found for total mammary tumours from the study by Johnson et al. (1986), ranging from 0.30 to 0.46 mg/kg b.w. per day.

Exposure

51. The CONTAM Panel calculated MOE values for the neurotoxic effects of acrylamide ranging from 1,075 (minimum (LB) to 226 (maximum UB) for the mean exposure, and from 717 (minimum LB) to 126 (maximum UB) for the 95th percentile exposure estimates across surveys and age groups). The Panel concluded that the current levels of dietary exposure to acrylamide are not of concern with respect to non-neoplastic effects. However, although the epidemiological associations have not demonstrated acrylamide to be a human carcinogen, the MOEs indicate a concern for neoplastic effects based on animal evidence.

52. For the neoplastic effects of acrylamide, mean MOEs for the estimates of human dietary exposure ranged from 425 (minimum LB) to 89 (maximum UB), and 95th percentile MOEs from 283 (minimum LB) to 50 (maximum UB). Since the MOEs were all substantially lower than 10 000, the CONTAM Panel concluded that although the available human studies had not shown conclusively that acrylamide was a human carcinogen, there was a concern with respect to neoplastic effects.

Dioxins and dioxin-like PCBs

53. Polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are two groups of tricyclic planar compounds that are formed by combustion of organochlorine compounds or of non-chlorine compounds in the presence of chlorine. Of these, 75 PCDD and 135 PCDF “congeners” have been found, with structures varying in the number of chlorine atoms and their positions in the rings. Only17 of these are relatively persistent in animals and humans and therefore considered relevant. (EFSA 2018)

Toxicity

54. Dioxins have a range of toxic effects on cells and animals and 2,3,7,8-tetrachlorodibenzyl dioxin (TCDD) is regarded as the most toxic of the group. The toxicities of other congeners are related to that of TCDD by Toxic Equivalency Factors (TEFs) The toxicity of mixtures of dioxins and dioxin-like PCBs are quantified

by the product of the concentration of each congener in the mixture and a TEF to yield a Toxic Equivalent (TEQ) value. (Van den Berg et *al*, 2006).

55. The COT evaluated dioxins and dioxin-like PCBs in 2001. The COT agreed with the evaluation of the EU Scientific Committee on Food (SCF) that in 2000 recommended a temporary tolerable weekly intake (t-TWI of 7 pg WHO-TEQ/kg bw. SCF re-evaluated this t-TWI based on rat studies which investigated only reproductive effects only on male offspring. Applying an overall uncertainty factor of 10 to the Lowest Observed Adverse Effect Dose (LOAEL) derived from estimated human daily intakes (EHDI) the SCF concluded that 14 pg/kg bw per week should be considered as a tolerable intake for 2,3,7,8-TCDD.

56. In 2010, the COT published a report on halogenated dioxins and biphenyls in food and concluded that these derivatives only contributed a very minor amount to the total level of dioxin TEQs in the diet and hence their presence was not a major concern for health.

57. JECFA (2002) "…considered adverse effects on the reproductive tracts of prenatally-exposed male rats to be the critical endpoint for risk assessment. The maternal LOEL and NOEL values of 25 ng/kg bw and 13 ng/kg bw, respectively, from the pivotal studies were converted to equivalent human monthly intake (EHMI) values of 630 pg/kg & 330 pg/kg by addition of 3 ng/kg bw to account for background body burden levels and calculation of the equivalent human body burdens at steady-state, based on assumed 1st-order kinetics at low-doses, 50% oral absorption & systemic half-life in humans of 7.6 years. To the EHMI values, the Committee applied total safety factors of 9.6 and 3.2, respectively, to account for intraspecies variation (3.2) & use of a LOEL instead of a NOEL (3). From the resultant range of PTMIs of 40–100 pg/kg bw per month, the Committee chose the mid-point, 70 pg/kg bw per month, as the PTMI to be applied to intake of PCDDs, PCDFs and coplanar PCBs expressed as TEFs."

58. The best-known study of the effects of dioxins on humans is the Seveso Women's Health Study (Eskenazi et al, 2000). After the industrial accident in Seveso, Italy in 1979, when an explosion caused the release of dioxins into the surrounding area, blood samples were taken from the exposed population and the reproductive health of exposed females who were, or who became of child-bearing age over the following 20 years, was followed. Wesselink et al (2014) followed up the initial findings and found no association between TCDD estimated at pregnancy and spontaneous abortion, fetal growth, or gestational length. However, there was a non-significant inverse association between maternal serum concentrations from 1979 and birthweight and this association was stronger among the first post-explosion births, but was still non-significant.

59. EFSA (2018) considered recent studies on female reproductive health, mainly among dioxin-exposed women from Seveso, and decided that there was insufficient evidence of effects on the incidence of endometriosis, pubertal development, menstrual cycle characteristics, ovarian function, time to pregnancy, uterine leiomyoma, or age at menopause.

60. EFSA (2018) used toxicokinetic modelling to estimate that the exposure of adolescents and adults should be less than 0.25 pg WHO-TEQ/kg bw/ day. The CONTAM panel established a TWI of 2 pg TEQ/kg bw /week. This was based on the critical effect of sperm concentrations that were inversely associated with serum concentration of TCDD, PCDD-TEQ and PCDD/F-TEQ in a study of Russian children whose parents had been exposed to dioxins (mainly TCDD) during manufacture of trichlorophenol and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) (Ryan et al, 2002).

61. The COT has recently (2021) produced a position paper on dioxins, addressing the seven-fold reduction in the TWI proposed by EFSA. The Committee concluded that EFSA's estimation was based upon weak data sets and provided little justification for such a reduction in the HBGV, the current value of 14 pg TEQ/kg bw /week having previously been shown to afford protection to the developing fetus. The European Commission (EC) has not yet adopted EFSA's new TWI due to ongoing work at the international level to review the basis and values of the WHO toxic equivalent factors (TEFs). The review of the TEFs and a finalised assessment by the EC are not expected until 2022, at the earliest.

Exposure

62. Consumption data from European countries by EFSA (2018) showed that the mean and 95th percentile intakes of total TEQ by adolescents and adults, was between 2.1 and 10.5 pg TEQ/ kg bw/week and thus could represent a considerable exceedance of the TWI. For the age groups of Other Children, Adolescents, Adults and Elderly the main contributors were 'Fatty fish' (up to 56% contribution), 'Unspecified fish meat' (up to 53.4% contribution), 'Cheese' (up to 21.8% contribution) and 'Livestock meat' (up to 33.8% contribution).The COT reviewed the draft EFSA opinion and agreed with the selection of the critical endpoint for the establishment of an HBGV and accepted that if possible, human data should be used for this purpose but was unable to conclude this was robust (COT, 2018).

Non-dioxin-like (NDL) PCBs

63. Some PCBs do not share the same toxic endpoints as the dioxins and have different effects, for example oestrogenic and anti-oestrogenic effects, and are therefore regarded as a separate group of persistent organic chemicals that are present in the environment and food.

64. The COT concluded in 1997 that any carcinogenesis caused by PCBs in animal studies was likely to be due to a "non-genotoxic" mechanism and accepted the advice of the COM and COC that it would be prudent to assume that all PCB congeners are potential human carcinogens. The Committee noted that preliminary work indicated that current human body burdens of PCBs may be affecting thyroid hormone levels. Further work was thought to be needed to develop an approach to assessing the health risks of the non-coplanar PCB congeners, but it was felt unlikely that there was a health risk from current intakes of PCBs from food. PCBs were likely to persist as contaminants of the environment for many years and the Committee recommended that levels in food and in human milk should continue to be monitored at regular intervals to confirm that the downward trend continued.

Otherwise a further review would be recommended to determine how human exposure could be reduced.

65. EFSA published a scientific opinion on non-dioxin-like PCBs in feed and food in 2005 concluding that "no health-based guidance value for humans can be established for NDL-PCB because simultaneous exposure to NDL-PCB and dioxin-like compounds hampers the interpretation of the results of the toxicological and epidemiological studies, and the database on effects of individual NDL-PCB congeners is rather limited. There are however indications that subtle developmental effects, being caused by NDL-PCB, DL-PCB, or polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans alone, or in combination, may occur at maternal body burdens that are only slightly higher than those expected from the average daily intake in European countries. Because some individuals and some European (sub)-populations may be exposed to considerably higher average intakes, a continued effort to lower the levels of NDL-PCB in food is warranted." The developmental effects reported for non-dioxin like PCBS are described below.

66. In two-generation studies, rats were exposed via the diet to a mixture of PCBs termed Aroclor 1254 at 0, 0.06, 0.32, 1.5, or 7.6 mg/kg bw/ day or another mixture called Aroclor 1260 at 0, 0.39, 1.5, or 7.4 mg/kg bw/day. Aroclor 1254 caused significantly reduced litter sizes at 7.6 mg/kg b.w. per day in the F1a generation and at 1.5 mg/kg b.w. per day in the F1b, F2a, and F2b generations. No effects were found for Aroclor 1260.

67. Reduced conception rates have been seen in female monkeys exposed for 2 months to 0.8 mg of the mixture Aroclor 1248 /kg b.w. per day. Increased menstrual duration and bleeding was observed in monkeys exposed to this mixture in the diet at >0.1 mg/kg b.w. per day from before conception and throughout pregnancy, with reduced conception rates at 0.2 mg/kg bw/ day. In Rhesus monkeys given oral capsule doses of Aroclor 1254 at 0, 0.005, 0.02, 0.04, or 0.08 mg/kg bw/day for up to 72 months, conception rates were significantly ($p<0.05$) reduced at 0.02 mg/kg b.w. per day and higher. Foetal mortality was significantly ($p<0.05$) increased at 0.08 mg/kg bw/day, and marginally ($p=0.077$) increased at 0.02 mg/kg b.w. per day. Dose-related early abortions were reported in female monkeys fed a diet that provided 0.1 or 0.2 mg/kg b.w. per day Aroclor 1248 for 15 months.

68. Taylor et al (2007, from abstract) found changes in the sex ratio of children for mothers who had measurable levels of PCBs in their blood before they became pregnant. Higher levels of estrogenic PCBs correlated with a preponderance of male, offspring and higher levels of anti-estrogenic PCBs correlated with higher numbers of female offspring. However, Rocheleau et al (2011) did not find such a relationship.

69. In an epidemiological study, Cohn et al (2012) tested the hypothesis that polychlorinated biphenyls (PCBs) measured during the early postpartum period could predict increased risk of maternal breast cancer diagnosed before age 50. They found strong breast cancer associations with three PCB congeners: PCB 167 and PCB 187 were associated with a lower risk whereas PCB 203 was associated with a sixfold increased risk of breast cancer. The net association of PCB exposure was nearly a threefold increase in risk among women with a higher proportion of PCB 203 in relation to the sum of PCBs 167 and 187. Postpartum PCB exposure

was deemed likely to represent pregnancy exposure, and could predict increased risk for early breast cancer depending on the mixture that represented internal dose.

70. JECFA last evaluated the non-dioxin-like PCBs in 2015. Six of these (PCB 28, PCB 52, PCB 101, PCB 138, PCB 153 and PCB 180) are often called “indicator PCBs”. The Committee focused on the six indicator PCBs, as there were sufficient data (toxicological, biomonitoring, occurrence and dietary exposure) available for review. National and international estimates of dietary exposure to the sum of the six indicator PCBs ranged, for mean exposure, from <1 to 82 ng/kg bw per day and, for high percentile exposure, from <1 to 163 ng/kg bw per day. None of the available studies on the six indicator PCBs was suitable for derivation of health-based guidance values or for assessment so a comparative approach using the minimal effect doses was used to estimate MOEs to provide guidance on human health risk. Because the MOEs are based on minimal effect doses, they were considered to give some assurance that dietary exposures to were unlikely to be of health concern for adults and children, based on the available data.

71. Zhang et al (2018, from abstract) found that plasma levels of PCBs, particularly PCB52, in a cohort of Chinese women in the first trimester of pregnancy were associated with a greater risk of developing gestational type 2 diabetes mellitus later in pregnancy (measured by oral glucose tolerance test at 24 – 28 weeks).

Legacy pesticides

72. Since 2009, 16 new Persistent Organic Pollutants have been added to the Stockholm Convention database. These include the pesticides α–, β– and γ–hexachlorocyclohexane (α–HCH, β–HCH and γ-HCH or lindane). The acute mechanism of action of these compounds is binding at the $GABA_A$ site in the gamma aminobutyric acid (GABA) chloride ionophore complex, inhibiting the flow of chloride ions into the nerves and leading to prolonged nervous excitation.

73. Included on the Stockholm list are also chlordecone, pentachlorophenol (with its salts and esters) and endosulfan and its isomers.

Hexachlorocyclohexanes

Toxicity

74. In their statement on hexachlorocyclohexanes in the infant diet (2014), COT agreed with the approach taken by EFSA to derive a TDI of 0.04 µg/kg bw for γ-HCH, based on the LOAEL from the study on lymphocyte proliferation in female mice by Meera et al. (1992, cited by EFSA, 2005). For α–HCH the COT concluded that, because its toxicity had not been well characterised, the available information was insufficient to propose a TDI, and therefore applied an MOE approach using the NOAEL of 0.1 mg/kg bw/day for hepatotoxicity as a reference point. This was supported by the findings on tumour promotion in the studies cited by EFSA (2005). The COT also applied an MOE approach for β-HCH using the LOAEL of 0.18 mg/kg bw/day based on centrilobular hypertrophy as a reference point.

75. Llop *et al* (2017) found that women in the third tertile for β-HCH in serum samples taken during the first trimester of pregnancy had lower total serum T3. The interactions between the thyroid deiodinase gene SNP DIO1 rs2235544 and β-HCH were statistically significant. There was a strong inverse association between β-HCH and freeT4 among women with CC deiodinase genotype.

Exposure

76. EFSA (2020) performed chronic exposure assessments on a range of pesticides using consumption data from the PRIMo database and found that oral intakes for γ-HCH (lindane) ranged from 0.003 to 1.7% (LB -UB) of the ADI (0.005 mg/kg bw/day). For α–HCH and β-HCH, which do not have ADI values, intakes were estimate as $2 \times 10^{-9} – 2 \times 10^{-5}$ and $1 \times 10^{-7} – 2 \times 10^{-5}$ mg/kg bw/day (LB – UB) respectively. Medina-Pastor P, and Triacchini G. (2020)

Organochlorine pesticides

Toxicity

77. Yin *et al* (2020) found that higher plasma levels of organochlorine pesticides (OCPs) were associated with increased odds of higher plasma homocysteine after adjustment for potential confounding factors. Positive correlations were observed between plasma β-HCH and plasma homocysteine concentrations ($r = 0.172$, $p = 0.002$), which may have implications for defects of the placenta, Chaudhry *et al* (2019). Maternal plasma homocysteine concentration was significantly associated with an increased risk of both the composite outcome of any placenta-mediated complication ($p = 0.0007$), SGA ($p = 0.0010$), severe SGA, and marginally with severe preeclampsia, but not preeclampsia, placental abruption and pregnancy loss. An increase in homocysteine concentration significantly increased the odds of any placenta-mediated complication.

78. The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) derived an acute reference dose (ARfD) for chlordecone of 10 μg/kg bw and an acceptable daily intake (ADI) of 0.5 μg/kg bw/ day.

79. In 1993, Health Canada derived a TDI for pentachlorobenzene of 5 μg/kg bw/ day. This was derived from a LOAEL of 5.2 mg/kg bw/ day based on minimal to moderate centrilobular hepatocellular hypertrophy and occasional necrosis of hypertrophied hepatocytes (considered to be secondary to the hypertrophy).

Exposure

80. Using the Pesticide Residues Intake Model (PRIMo), EFSA (2020) concluded that the short- and long-term intake of chlordecone residues at the level of the proposed MRLs for animal products was not expected to exceed the toxicological reference values derived by the French authorities.

81. Junqué *et al* (2020) found that the concentrations of organochlorine compounds (OCs), including pentachlorobenzene, hexachlorobenzene (HCB), hexachlorocyclohexanes (α-, β-, γ- and δ-HCH), polychlorobiphenyls (PCBs 28, 52, 101, 118, 138, 153 and 180), DDT and metabolites, in maternal serum samples collected at the first trimester of pregnancy, at delivery and in umbilical cord from a cohort of Spanish mother-newborn pairs (n = 50), were generally low. There was a small but statistically significant increase in maternal venous OCs between the first trimester and delivery. HCB, β-HCH and the PCB congeners in cord blood were significantly correlated with their concentrations in maternal venous blood. 4,4'-DDT showed maternal-cord blood correlated with the low metabolic capacity of newborns for OC metabolism. Older maternal age correlated with maternal venous OC concentrations, and higher body mass index correlated with higher 4,4'-DDE concentrations in maternal venous blood and cord blood. In some cases, highest concentrations were found in the women with highest education level and most affluent social class. OC concentrations in the population of the same geographic area and age range had decreased between since 2002

Endosulfan

82. Endosulfan is a non-systemic organochlorine insecticide that was developed in the 1950s for the control of sucking, chewing and boring insects and mites on a very wide range of agricultural crops, such as *inter alia* fruit, potatoes, cucurbits, tea, coffee, cereals, oilseed crops, sugar cane and mushrooms, It is also used to control home and garden pests. Endosulfan is less lipophilic than other similar pesticides (for example aldrin and dieldrin) and therefore has a lower propensity to bioaccumulate and biomagnify. (EFSA 2005, updated 2006)

Toxicity

83. The Joint FAO/WHO Meeting on Pesticide Residues (JMPR, FAO/WHO, 1998) established an ADI of 0 - 0.006 mg/kg bw for technical endosulfan on the basis of the NOAEL of 0.6 mg/kg bw/day in the two-year dietary study of toxicity in rats and a safety factor of 100. The ADI was supported by similar NOAEL values in the 78-week dietary study of toxicity in mice (NOAEL of 0.58 mg/kg bw.day), a one-year dietary study of toxicity in dogs (NOAEL of 0.8 mg/kg bw/day), and a study of developmental toxicity in rats (NOAEL of 1.5 mg/kg bw/day).

84. In their Statement of 2014, COT concluded that the concentrations of endosulfan in food were unlikely to pose a health risk to infants based on the ADI of 6 µg/kg bw established by JMPR. Reduced body weight and pathological findings in the kidney and lymph nodes were observed at higher doses. JMPR also established an acute reference dose (ARfD) of 20 µg/kg bw/day based on a NOAEL of 2000 µg/kg bw/day in a 90-day study of neurotoxicity in rats, with a safety factor of 100.

85. Bérenger *et al* (2020) found an association between decreased body length of infants at birth and β-endosulfan concentration in the hair of mothers in a cohort of 311 French women, from whom samples were taken after they had given birth. The authors suggested that the results should be interpreted cautiously, until they were replicated or verified by further epidemiological or mechanistic studies.

86. There are very few papers concerning toxicity in pregnant women or women of childbearing age but Singh (2007) indicated that there are additive effects of this insecticide in co-exposure to the mycotoxin citrinin on the reproductive health of experimental Wistar rats. Oral dosing of a combination of citrinin (10 mg/kg feed) and endosulfan (1 mg/kg bw) led to a greater frequency of histopathological changes than did each treatment alone. Observations included engorged vasculature, vacuolar degeneration and karyomegaly in liver; congestion, tubular degeneration and cast formation in kidneys; vascular changes and hemosiderosis in uterus and lymphocytic depletion and apoptosis in the lymphoid organs were recorded in the animals of the toxin treated groups. Fetal reabsorptions were also greater in the combined treatment group than in the individual treatments or controls.

Exposure

87. A total diet study performed between 1993 and 1996 in Canada found an average daily dietary intake for total endosulfan of 0.024 mg/kg bw. (Health Canada, 2003)

88. Ruprich et al (1995) reported a median dietary intake of 0.015 µg/kg bw/day for the sum of α-, β-endosulfan and endosulfan sulphate in the Czech Republic in 1994.

Oily Fish

89. Oily fish are defined as fish species with oil in soft tissues and in the coelomic cavity around the gut. Their fillets may contain up to 30% oil, although this figure varies both within and between species. Examples of oily fish include small fish such as sardines, herring and anchovies, and other larger fish such as salmon, trout, tuna, swordfish and mackerel (FSA, 2004). Contrary to earlier advice, fresh or canned tuna are no longer classified as oily fish (NHS, 2021).

90. Internet searches reveal many papers that concentrate on the presence in oily fish of environmental contaminants, such as mercury and dioxins and how toxicity is potentially mitigated by the polyunsaturated fatty acids (PUFAs) that comprise the fish oil. Combined risk-benefit considerations were addressed in a joint COT/SACN report in 2004 but are outside the scope of this paper.

91. The joint COT/SACN report (2004) provided advice on fish consumption for all adults from the point of view of environmental toxins. The report also gives the concentration of organic pollutants and heavy metals in a variety of fish types, including some oily fish.

92. The UK Government recommends that no more than 2 portions of oily fish should be consumed by girls, women who are considering becoming pregnant or may become pregnant one day, and pregnant or breast feeding women (NHS, 2021).

93. The FSA Exposure Assessment Team has provided the following information on the consumption of oily fish by women of childbearing age (16 – 49 years)

Table 1. Estimation of chronic consumption data for oily fish by women of aged 16 – 49 years (Bates *et al*, 2014, 2016, 2020, Roberts *et al* 2018).

Number of consumers	g/kg bw/day*		Respondents in population
	Mean	97.5th percentile	
311	0.38	1.3	1874

*rounded to 2 SF
**based on salmon, mackerel, herring and sardines.

The mercury content of the fish upon which the above table is based are given as (mg/kg): salmon, 0.022; mackerel (Atlantic), 0.050, herring, 0.084; sardines, 0.013. Using the value for herring as the most conservative value, intake of mercury from the above consumption figures would be as shown in Table 2.

Table 2. Estimation of mercury intake from oily fish by women of aged 16 – 49 years.

Number of consumers	mg/kg bw/day		% (PTWI/7)* (mean, 97.5)
	Mean	97.5th percentile	
311	0.03	0.11	14, 48

*In the section on mercury (above), the PTWI by JECFA for methyl mercury is 1.6 mg/kg bw/week, equivalent to 1.6/7 =0.23 mg/kg bw/day.
Mercury Levels in Commercial Fish and Shellfish (1990-2010) Archived2015-05-03 at the Wayback Machine U.S. Food and Drug Administration. Accessed 8 January 2012.

Persistent organic pollutants in oily fish

94. The Woods Hole Oceanographic Institute and the Bergen Marine Research Cluster reported that in Northeast Atlantic mackerel (NEA) "…concentrations of POPs in NEA in general were low and well below the EU's maximum levels for dioxins and dl-PCBs (3.5 ng TE/kg ww for sum dioxins and 6,5 ng TE/kg ww for sum dioxins and dl-PCBs), and PCB6 (70 µg/kg ww). There were geographical differences, with significantly higher concentrations of dioxins and dl-PCBs in the Skagerrak (1.6 ± 1.2 ng TEQ/kg ww) than in the North Sea (0.89 ± 0.63 ng TEQ/kg ww), the Norwegian Sea (0.95 ± 0.61 ng TEQ/kg ww) and the area west of Scotland (0.87 ± 0.61 ng TEQ/kg ww). In the Skagerrak, one of the 60 fish analysed in the baseline study were above the EU's maximum levels for sum dioxins and dl-PCB." Note: ww = wet weight

Taking the North Sea as the principal source of oily fish for the UK

Table 3. Estimation of dioxin and dioxin-like PCB intake from oily fish by women of aged 16 – 49 years.

Number of consumers	pg TEQ/kg bw/day		% (TWI/7)* (mean, 97.5)
	Mean	97.5th percentile	
311	0.34	1.2	17, 60

*In the section on dioxins and dioxin-like PCBs (above), the TWI is 14 pg/kg bw/week, equivalent to 14/7 =2 pg/kg bw/day.

95. Thus overall, for women of childbearing age, neither the mean or 97.5th percentile consumption level would be a cause for concern with respect to methyl mercury intake. This is also the case applying the current TWI of 14 pg TEQ/ kg bw/ week for the dioxins and dioxin-like PCBs.

Selenium

96. Selenium is a trace element and Group 16 non-metal that is naturally present in many foods, added to others, and available as a dietary supplement. Selenium, which is nutritionally essential for humans, is a constituent of more than two dozen selenoproteins that play critical roles in reproduction, thyroid hormone metabolism, DNA synthesis, and protection from oxidative damage and infection.

97. The UK Government recommends selenium intakes of 75 µg/d for men (19-64) and 60 µg/d for women (NHS 2021) to be acquired through the diet. It currently recommends those who take supplements that “taking 350 µg or less a day of selenium supplements is unlikely to cause any harm”.

Toxicity

98. Selenium toxicity can occur with acute or chronic ingestion of excess selenium. Symptoms of selenium toxicity include nausea; vomiting; nail discoloration, brittleness and loss; hair loss; fatigue; irritability; and foul breath odour (often described as “garlic breath”). Severe and even fatal toxicity from selenium has been known, but only in extremely high doses. In conditions such as pre-eclampsia there appears to be more risk associated with low blood levels of Se than with high levels (see, for example, Ghaemi *et al* 2013).

99. Wells *et al* (2011) studied the relationship between selenium and maternal blood pressure among 270 deliveries using umbilical cord serum as a proxy for maternal exposure levels. A biphasic response was seen. When selenium was <70 µg/L, increasing selenium levels were related to a non-statistically significant decrease in blood pressure but at 70 – 90 µg/L, a 1-µg/L increase was related to a 0.37 mmHg (95% confidence interval (CI): 0.005, 0.73) change in systolic and a 0.35 mmHg (0.07, 0.64) change in diastolic blood pressure. There were very few

selenium values >90 µg/L. The authors concluded that this u-shaped relationship between selenium and blood pressure was consistent with a dual role of selenium as an essential micronutrient that is nonetheless a toxicant at higher concentrations; but further study was needed.

100. Ferm *et* al (1990) found embryo toxicity of selenium compounds in hamsters but at levels that caused maternal toxicity. Malformations, mainly encephaloceles, were noted with oral and intravenous selenite and selenate but were associated with maternal toxicity manifested by inanition and weight loss. Fetal body weights and lengths were reduced in a dose-dependent manner with the inorganic forms. Single oral doses of selenomethionine above 77 mmol/kg induced similar malformations but not when the dose was delivered orally over four days nor by minipump over several days. Fetal body weights and lengths were decreased by selenomethionine in a dose-dependent manner. Maternal toxicity was pronounced with the higher doses of selenomethionine.

101. Selenium and its compounds have been classified by IARC as Group 3: unclassifiable as to its carcinogenicity to humans, although the American Cancer Society classifies selenium sulphide as “reasonably anticipated to be a human carcinogen”

102. In 2000, the Scientific Committee on Food (SCF) established an UL for selenium of 300 µg/day for adults, including pregnant and lactating women. This was based on a NOAEL of 850 µg/day for clinical selenosis (and application of an uncertainty factor of 3. The NOAEL was based on the absence of clinical signs in individuals with selenium levels below 1000 µg/L

Exposure

103. The Exposure Assessment Team have provided the following data for selenium consumption by women of childbearing age:

97,5th percentile chronic intake (UB) = 2.3 µg/kg bw/ day (144 µg/person/ day)
97,5th percentile acute intake (UB) = 3.1 µg/kg bw/ day (194 µg/person/ day)

Summary

104. To aid in assessment of the chemical described in this paper, a summary table is provided below, comprising the HBGV for each substance and estimated exposure via the diet.

Table 4 Comparison of reported exposure of adults to substances of interest with their health-based guidance values. Exposures are upper bounds of 97.5th percentiles of exposure

Compound	HBGV μg/kg bw/day (endpoint)	Authority	Exposure μg/kg bw/day	% HBGV	Maternal effect
Lead	1.5 (Systolic blood pressure) 0.63 (renal damage)	EFSA	1.49	99 240	Blood pressure increases in women with pre-eclampsia
Cadmium	2.5 (kidney damage)	EFSA	12.1	480	Reduction in FSH levels. In vitro effects on uterine contraction
Arsenic	0.3 (lung cancer)	EFSA	0.64	210	Gestational Diabetes Mellitus
Mercury	1.6 (Me Hg)(neurodevelopmental effects) 4 (total) mg/kg bw/week (kidney weight change)	JECFA	3.04 mg/kg bw/week	190	Kidney effect leading to increased fetal exposure. Neurodevelopmental effects in utero
Heterocyclic Amines (PhIP)	480 (Prostate cancer $BMDL_{10}$)	Carthew *et al* (2010)	0.635	760(MOE)	Mammary gland tumours
MeIQX	8.8 (growth of human colon epithelial cells)	Zhang (2017)		10,000 (mean MOE) 2500 (97.5^{th} MOE)	
APNH	-	-		-	Pre and post implantation loss, reduced fetal weight, cleft palate.
Bisphenol A	4 (Increase in mouse kidney weight)	EFSA	0.388	10	Thyroid function
Acrylamide	430 (neuropathy)	EFSA		126	Mammary gland tumours

	170 (cancer)			(MOEs) 50	
Dioxins & dioxin-like PCBs	2 x 10^{-6} (male reproduction)	EFSA	1.05 x 10^{-5}	530	Suspected low birthweight of offspring
Non-dioxin-like PCBs	None derived		0.16		Breast cancer, GDM, reduced conception rate
Hexacyclochlorohexanes	0.04(Lymphocyte proliferation)	EFSA	0.085	1210	Thyroid hormone depletion
Organo chlorines	10 (ARfD) 0.5 (ADI) (chlordecone 0.5 (pentachlorobenzene	ANSES Health Canada		Within HBGVs (EFSA)	Placenta complications and pre-eclampsia
Endosulfan	6 Developmental toxicity *inter alia*	JMPR	0.024	0.4	Uterine haemosiderosis
Oily fish Methyl Mercury	230 In utero neuro development)	JMPR	30 (mean) 110 (97.5th)	13, 48	Neurodevelopmental effects in utero
Dioxins	2 pgTEQ/kg bw/day	EFSA	1.2 pgTEQ/kg bw/day	60	Reproductive effects in male offspring
Selenium	4.3 (300 mg/day for a 70 kg adult)	EFSA	3.1 (acute) 2.3 (chronic)	65 48	Possible increased blood pressure in childbirth

Discussion

105. This paper presents a triage of the toxicity and exposure to extrinsic substances and contaminants with regard to their possible effects on maternal health. Oily fish is presented here because it is subject to contamination, particularly with mercury and dioxins. Some substances described above have better data regarding maternal health than others. Whether the effects seen are significant for human health and in particular maternal health requires more and more robust data. Members are requested to consider the questions below.

Questions for the Committee

106. The Committee are asked to consider:

1 Which of the above substances should be taken forward to risk assessment?
2 Which of the substances taken forward to risk assessment should have separate papers and which can be covered by an overarching Statement?
3 Does the Committee have any other comments on this paper?

Secretariat

2021

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