TOX/2020/53

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

Testing the COC guidance on less than lifetime exposure

Introduction

1. At the March 2020 meeting the Committee considered a set of principles produced by the Committee on Carcinogenicity (COC) on considering less than lifetime exposure to genotoxic and non-genotoxic carcinogens. The COT had previously expressed interest in this topic at the joint COT, COC and COM meeting in October 2017, and the COT was asked to consider the applicability of the principles developed by the COC to less than lifetime (LTL) exposures for other endpoints which are considered by the COT.

2. The COT discussed the extent to which it had addressed LTL exposures to date. Examples were carcinogenic risks to infants exposed for short periods and life stage-specific risks such as caffeine consumption during pregnancy. The COT considered that it would be useful to test the COC set of principles using cases from past COT work.

The COC principles

3. The set of COC principles is attached at Annex A. The first step is to define the exposed population groups and to define the LTL exposure scenario under consideration. Some life stages may have greater susceptibility, e.g. pregnant women, infants, children or the elderly, which may need to be taken into account in the assessment of risk.

4. At the March meeting, the COT noted that in the principles, LTL exposure to non-genotoxic carcinogens is compared to the health-based guidance value (HBGV) for long-term exposure in the first instance. If this is exceeded, then consideration should be given to refining the exposure assessment, using a short-term HBGV or considering a Haber's rule-based approach.

5. Haber's rule states that the incidence and/or severity of a toxic effect depends on the total exposure over time, i.e. exposure concentration rate (c) times the duration time (t) of exposure ($c \times t$). The COC principles indicate that, in the case of non-genotoxic carcinogens, application of a Haber's rule-based approach may be particularly appropriate if the chemical

bioaccumulates and/or if the chemical needs to have a prolonged effect for carcinogenicity to occur.

6. At the March 2020 meeting, the COT noted that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) meetings on veterinary medicine residues have also been considering LTL exposure. JECFA has started to link the exposure assessment with the toxicological profile of the substances. They consider, for example, whether a point of departure (POD) for developmental toxicity is close to the POD from a chronic toxicity study which has been used to establish the ADI, and whether the POD for a shorter-term, typically 90-day, study is close to that for a chronic study. However, JECFA uses the same HBGV for all exposure scenarios other than acute.

Test cases

7. Two examples have been selected from the COT's recent programme on the risks from chemicals in the diets of infants and young children: cadmium and fumonisins. These were selected because less than lifetime exceedances of chronic HBGVs were identified.

Cadmium in the diet of infants aged 0-12 months and children aged 1 to 5 years

8. The COT published a statement on the risks from cadmium in the diet of infants and young children in 2018 (COT, 2018). The below is based on the information in the statement and its key references but is taken through the various steps of the COC principles.

Step 1: What is the LTL scenario being assessed for risk?

Step 1A: Define the exposed population(s)

9. All of the population is exposed to cadmium via the diet and additional sources. However, this work was conducted as part of a review of the science underpinning Government advice on feeding infants and young children in order to determine whether the advice should be revised. Therefore, the interest was in a) risks from dietary exposure as an infant and b) risks from dietary exposure as a young child. Infants were considered to be ages 0 to <12 months and young children considered were ages 12 months to <60 months (5 years).

Step 1B: Define the exposure scenario

10. The exposure scenario is total exposure through food, water and other significant environmental sources (e.g. air, dust, soil) to cadmium as an infant (age 0 to <12 months) and as a young child (age 12 months to <60 months). However, this is in the context that exposure to cadmium will continue beyond these ages, though presumably at lower levels on a per kg bodyweight basis.

11. The COT statement identified that food is the major source of exposure for infants and young children, with drinking water, air, soil and dust making only a minor contribution to total exposure. The food groups contributing the most to exposure were miscellaneous cereals, bread and potatoes.

12. The COT statement presented dietary exposure assessments for cadmium in the diets of infants and young children. These are discussed further below under Step 3.

Step 2: What is the potential carcinogenic hazard(s) being assessed?

Step 2A: Characterisation of the carcinogen(s) of concern - consideration of a non-genotoxic MOA.

Step 2B: Characterisation of the carcinogen(s) of concern - consideration of a genotoxic MOA

13. In the COC guidelines this step is regarding the assessment of the carcinogenic hazard, including the mode of action for carcinogenicity. To apply this to the COT's work on non-carcinogens, this step can be interpreted as hazard identification and characterisation (although cadmium may also be carcinogenic). Some of the considerations under Step 2a (for non-genotoxic carcinogens) on pages 5-6 of the COC principles are also applicable to non-carcinogens if modified slightly as follows:

- Have toxicokinetic properties been defined, including the potential for rapid metabolism or accumulation to occur

- Are dose-response relationships available for the various endpoints

- Whether the endpoint used as the basis for the chronic HBGV is the most applicable endpoint for the LTL exposure(s) being assessed

- Are the dose route, duration and intermittency of the studies used to generate hazard data relevant to the LTL scenario being considered

- The availability of suitable human data from occupational or epidemiology studies which can be used to derive an HBGV

- Has a dose-response relationship (in humans or animals) being defined for the endpoint on which an HBGV might be based

- Have cumulative exposure effects been assessed either in human or animal studies

- Potency, particularly when the time to the adverse effect occurring is known to be rapid

- Whether there is evidence for reversibility of changes following cessation of exposure

14. Cadmium has a long biological half-life, estimated to be between 10 and 30 years in humans (EFSA, 2009). Studies of distribution in animals show that the highest level of accumulation is in the liver and kidneys. Following prolonged exposure durations, the concentrations in the kidneys exceed those in the liver, except at very high exposure levels. In autopsy studies in humans exposed to low-normal levels of cadmium, approximately 50% of the total body burden is found in the kidneys, 15% in the liver, and only a small part in the skeleton (EFSA, 2009).

15. Adverse effects that cadmium is associated with include renal damage, particularly to the proximal tubular cells in the kidney, where it accumulates over time and can lead to renal dysfunction; and skeletal effects such as low bone mineral density, osteoporosis and risk of fractures. Cadmium is also classified by IARC as carcinogenic to humans (group 1) based on cancers of lung cancer and limited evidence of liver, kidney and prostate cancer. This was based on high cadmium exposures of workers exposed by inhalation. More recent studies on exposure to cadmium in the general population have reported associations with bladder, breast, endometrial and prostate cancers.

16. EFSA (2009) noted that the earliest effect of cadmium is renal tubular damage and established a TWI on that basis, though they noted that data on adverse skeletal effects should also be considered more in the risk assessment once more data are available. JECFA has also established a PTMI for cadmium on the basis of renal tubule effects.

Step 3: Assessment of risk
Step 3A: Risk assessment of non-genotoxic (threshold) carcinogens

17. Step 3A appears the most appropriate for threshold non-carcinogenic effects, as opposed to step 3B, which is for genotoxic carcinogens.

18. The COC principles state that step 3A involves establishing a HBGV for lifetime exposure in the first instance and comparing an assessment of LTL exposure to this. Alternatively, if the data are inadequate to establish an HBGV a margin of exposure (MOE) should be calculated. The principles note that use of an HGBV or MOE based on long-term toxicity studies may be considered precautionary when applied to short duration LTL scenarios.

19. The COT statement used the EFSA TWI in its risk assessment of cadmium, after considering the difference between the EFSA and JECFA evaluations. The TWI was based on urinary β2-microglobulin as a marker for kidney damage. A $BMDL_5$ of 4 µg U-Cd/g creatinine was calculated from human studies. A chemical-specific adjustment factor of 3.9 was applied to account for interindividual variation of urinary cadmium within the studied populations, resulting in a level of 1 µg U-Cd/g creatinine. A one-compartment model was fitted to a large dataset based on non-smoking Swedish women aged 58-70 years to estimate the relationship between dietary cadmium exposure and urinary cadmium concentration. It was concluded order to remain below 1 µg Cd/g creatinine in urine in 95 % of the population by age

50, the average daily dietary cadmium intake should not exceed 0.36 µg Cd/kg bw, corresponding to a weekly dietary intake of 2.52 µg Cd/kg bw. The TWI was therefore established at 2.5 µg/kg bw.

20. Tables 1-7 below are copied from the COT statement, and express estimated dietary exposures for different age groups of infants and young children as percentages of the TWI.

Table 1: Risk characterisation of cadmium intake from exclusive breastfeeding in 0 to 6-month old infants, with breast milk. Intakes are expressed as percentages of the EFSA TWI (2.5 µg/kg bw/week)

Cadmium concentration (µg/L)	**Average consumer (800 mL/day) Age 0 to <4 months**	**Average consumer (800 mL/day) Age 4 to <6 months**	**High consumer (1200 mL/day) Age 0 to <4 months**	**High consumer (1200 mL/day) Age 4 to <6 months**
Mean 0.4	15*	11	23	17
Max 1.2	46	34	68	52

*Values are % of EFSA TWI
Values rounded to 2 significant figures (SF)

Table 2: Estimated cadmium intake relative to TWI from breast milk in 4 to 18 month old infants only partly fed breast milk

Breast milk consumption	**4 to <6 months**	**6 to <9 months**	**9 to <12 months**	**12 to <15 months**	**15 to <18 months**
Mean@0.4 mg Cd/L	10*	7.6	4.2	3.4	2.8
97.5th percentile @0.4 mg Cd/L	17	19	13	8.4	5.9
Mean@1.2 mg Cd/L	31	23	13	10	8.4
97.5th percentile @1.2 mg Cd/L	52	56	39	25	18

*Values are % of EFSA TWI
Values rounded to 2 SF

Table 3: Estimated dietary intake of cadmium relative to TWI from exclusive feeding on infant formulae for 0 to 6 month olds

Infant formula	**Age 0 to <4 months** **Average consumer (800 mL/day)**	**Age 0 to <4 months** **High level consumer (1200 mL/day)**	**Age 4 to <6 months** **Average consumer (800 mL/day)**	**Age 0 to <4 months** **High level consumer (1200 mL/day)**
Ready-to-Feed [a]	0-8.4*	0-11	0-5.6	0-8.4
Dry Powder [b, c]	17-22	25-34	14-17	20-25
Dry Powder [c] + TDS water of <1.2 µg/L [d]	53-62	84-92	42-45	64-70
Dry Powder [c] + median water of 0.04 µg/L [d]	20-25	28-36	17-20	22-28
Dry Powder [c] + 97.5th percentile water of 0.4 µg/L [d]	31-36	45-53	28-31	34-39

*Values are % of EFSA TWI
Values rounded to 2 SF
[a] Exposure based on first milk infant formula using LB to UB cadmium concentrations of 0-0.2 µg/L
[b] Exposure does not include the contribution from water
[c] Exposure based on first milk infant formula using LB to UB cadmium concentrations of 3-4 µg/kg
[d] Calculated assuming reconstituted formula comprises 85% water

Table 4: Estimated Intake of cadmium from infant formulae, commercial infant foods and other foods for 4 to 12-month olds relative to TWI

Food	**4 to <6 months** **Mean**	**4 to <6 months** **97.5th**	**6 to <9 months** **Mean**	**6 to <9 months** **97.5th**	**9 to <12 months** **Mean**	**9 to <12 months** **97.5th**
Infant formula	0.11-3.9*	1.4-7.8	0.14-3.4	0.36-7.6	0.14-2.5	1.5-5.3
Commercial infant foods	15	64	22-23	81-84	21-22	90-92

Other foods	17	87	39	130	56	150
Total (excl. water)	34-36	130	62-64	150	76-78	170

*Values are % of EFSA TWI
Values rounded to 2 SF
Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

Table 5: Estimated dietary intake of cadmium from infant formulae, commercial infant foods and other foods in children aged 12 to 18 months relative to TWI

Food	**12 to <15 months Mean**	**12 to <15 months 97.5th**	**15 to <18 months Mean**	**15 to <18 months 97.5th**
Infant formula	0 – 11*	0-6	0.6	0-2.8
Commercial infant foods	11	59-62	5.6	39
Other Foods	62-64	150	67-70	150
Total (excl. water)	73-76	160	73-76	150

*Values are % of EFSA TWI
Values rounded to 2 SF
Determined from a distribution of consumption of any combination of categories rather than by summation of the respective individual 97.5th percentile consumption value for each of the three food categories

Table 6: Estimated dietary intake of cadmium based on the total diet study (TDS) data in children aged 12 to 18 months, relative to the TWI, taking into account the contribution from of UK water containing the highest median and 97.5th percentile concentrations of cadmium

Cadmium concentration in the water	**12 to <15 months Mean**	**12 to <15 months 97.5th**	**15 to <18 months Mean**	**15 to <18 months 97.5th**
0.04 µg/L[a]	81-140*	170-260	90-150	170-250
0.4 µg/L[b]	81-140	170-260	90-150	170-250

*Values are % of EFSA TWI
Values rounded to 2 SF

[a] Highest median concentration in UK drinking water. [b] Highest 97.5th percentile concentration in UK drinking water

Table 7: Estimated dietary intake of cadmium based on the TDS data in children aged 18 months to 5 years, relative to the HBGV, taking into account the contribution from of UK water containing the highest median and 97.5th percentile concentrations of cadmium

Cadmium concentration in the water	**18 to <24 months** **Mean**	**18 to <24 months** **97.5th**	**24 to <60 months** **Mean**	**24 to <60 months** **97.5th**
0.04 µg/L[a]	95-170*	160-260	90-150	150-220
0.4 µg/L[b]	95-170	160-260	90-150	150-220

*Values are % of EFSA TWI
Values rounded to 2 SF
[a] Highest median concentration in UK drinking water. [b] Highest 97.5th percentile concentration in UK drinking water

21. The COT statement also estimated exposures from air, dust and soil. As noted above in paragraph 11, above, these were minor sources of exposure and were not aggregated with dietary exposures in the COT statement. For the purposes of this exercise the intakes from air, dust and soil will not be considered. However, the intakes estimated in the COT statement were up to 7.8% of the TWI for dust, up to 1.6% of the TWI for soil and up to 3.6% of the TWI for air.

22. Thus, exceedances of the TWI were estimated in high consumers aged for 4 months on, and possibly in mean consumers from 12 months on.

23. The COT statement concluded that the exceedances were small in magnitude and would not be expected to remain at these levels over the decades of bioaccumulative exposure considered by EFSA in setting the HBGV. The Committee concluded that this was therefore not a major cause for concern. However, considering the cumulative nature of cadmium toxicity, efforts to minimise the levels of this metal in the environment should continue.

24. The COC principles state that if the chronic HBGV is exceeded, then refinement of the assessment should be undertaken through consideration of:

- Whether a refined exposure assessment can be carried out
- The contribution of the LTL exposure to chronic background exposure (e.g. in terms of body burden or cumulative exposure)
- Whether the results from a shorter-term study are a more appropriate basis for risk assessment of the scenario being considered.

25. Considering that estimated exposures based on lower bounds still exceed the TWI for high level consumers, a significant refinement of the

dietary exposure assessment does not appear possible. Biomonitoring of urinary cadmium concentrations may be the most refined basis for an exposure assessment but at ages 50 and above given that the basis of the TWI is based on urine concentrations being below 1 µg Cd/g creatinine in 95 % of the population at age 50.

26. Since the adverse effects of cadmium, primarily renal and skeletal, are related to its bioaccumulation over many years, LTL exposures of infants and young children are perhaps best considered in the context of their contributions to body burdens or total exposure over a particular prolonged period of time.

27. The TWI is based on urinary cadmium concentrations at age 50 years. Thus, it might be considered that dietary exposure should be averaged over at least the first 50 years of life.

28. The COT statement does not contain exposure estimated for cadmium from 5 years of age and above. Therefore, new exposure data have been generated for these higher ages using data from the same TDS and consumption data from years 1-8 of the rolling National Diet and Nutrition Survey (NDNS), as shown in Table 8 and 9, below.

Table 8: Estimated dietary intake of cadmium based on the TDS data in people aged 5-<50 years or 5 years plus

Age (years)	**Mean (µg/kg bw/week)**	**97.5th (µg/kg bw/week)**
5 - <50	0.98-1.7	2.3-3.6
5+	0.91-1.6	2.1-3.3

Table 9: Estimated dietary intake of cadmium based on the TDS data in people aged 5-<50 years or 5 years plus, relative to the TWI

Age (years)	**Mean**	**97.5th**
5 - <50	39-68*	92-140
5+	36-64	84-130

*Values are % of EFSA TWI

29. Thus, possible small exceedances of the TWI are also identified in these age groups but only at the upper bound estimates of the 97.5th percentile exposures.

30. To estimate average dietary exposure over the first 50 years of life, the number of months in each age range was taken into account. 0-<4 months (duration 4 months) is 0.67% of 50 years (600 months), the 2 month age range of 4-<6 months is 0.33%, the 3 month age range of 6-<9 months is 0.5% and so on so that 9-<12 months is 0.5%, 12-<15 months is 0.5%, 15-18 months is 0.5%, 18-<24 months is 1%, 24-<60 months is 6%, and the remaining 5 years to <50 years is 90%.

31. Since some of the exposure assessments overlap ages for infants and young children depending on the data used or the dietary sources, choices needed to be made on which exposure estimates to use. The following assessment is based on exclusive breast feeding for 0-<4 months; consumption of infant formula, commercial infant foods and other foods for ages 4-<6 months, 6-<9 months and 9-<12 months, and using estimates based on the TDS for ages 12 months on. Estimated exposure assessments for breastmilk had been conducted using both a mean and maximum reported concentration; the maximum concentration has been used here though this choice should only make a small difference to the estimates of long term exposure. Table 10 presents the estimated exposures averaged over the first 50 years of life.

Table 10: Estimated weekly dietary intake of cadmium averaged over first 50 years of age, and compared to the TWI

	Mean	**97.5th**
Intake (µg/kg bw/week)	1.1-1.9	2.4-3.8
% TWI	44-76	96-150

32. These estimated exposures are only a little higher than the estimated exposures for ages 5-<50. They indicate a possible small exceedance of the TWI at the 97.5th percentile. One limitation of the approach is that it assumes that a high level consumer of cadmium remains a high level consumer for most of their life and thus the 97.5th estimates may be overestimates.

33. Table 11 presents the exposures averaged over a lifetime. Although the oldest individuals in the NDNS are older than 80 years of age, for the purposes of determining the fractions of life spent at the different ages a lifespan of 80 years has been assumed. Thus, the four month of age 0-4 months is 0.42% of 80 years (960 months), 4-<6 months is 0.21%, 6-<9 months is 0.31%, 9-<12 months is 0.31%, 12-<15 months is 0.31%, 15-<18 months is 0.31%, 18-<24 months is 0.63%, 24-<60 months is 3.8%, and the remaining 5 years to <80 years is 94%. The same consumption data were used as before.

Table 11: Estimated weekly dietary intake of cadmium averaged over life, and compared to the TWI

	Mean	**97.5th**
Intake (µg/kg bw/week)	0.99-1.7	2.2-3.4
% TWI	40-68	88-140

34. These estimated exposures are only a little higher than the estimated exposures for ages 5 years plus. They indicate a possible small exceedance of the TWI at the 97.5th percentile. As stated previously, one limitation of the approach is that it assumed that a high level consumer of cadmium remains a high level consumer for most of their life and thus the 97.5th estimates may be overestimates. Overall, it appears that dietary exposures over a lifetime are likely to be around the level of the TWI in high level consumers.

35. These dietary exposure assessments do not take into account smoking. EFSA (2009) noted that smoking can contribute the same level of internal exposure to cadmium as the diet. Thus, smokers would exceed the TWI. It is interesting to consider how smoking as an adult should be factored into a risk assessment of cadmium in the diets of infants and young children. However, the risk assessment of cadmium in the diets of infants and young children was conducted to inform Government advice, and the Government advises against smoking. Furthermore, it is clear that dietary cadmium exposure as an infant or young child makes a minor contribution to dietary exposure averaged over a lifetime or the first 50 years of life.

36. The COT will wish to consider the appropriateness of the approaches taken here of averaging exposure over the first 50 years of life or over a lifetime, and whether this assessment would change the conclusions reached in the COT statement on cadmium in the infant diet.

Fumonisins in the diet of infants aged 0 to 12 months and children aged 1-5 years

37. The COT considered fumonisins in the diet of infants and young children in 2019 and its conclusions were published in the addendum to the overarching statement on the potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years published in 2020 (COT, 2020). The below is based on the information in working papers presented to the COT and the statement and their key references but is taken through the various steps of the COC principles.

Step 1: What is the LTL scenario being assessed for risk?

Step 1A: Define the exposed population(s)

38. Fumonisins are a type B trichothecene mycotoxin produced by several Fusarium species. Some fumonisin sub-types can also be produced by Aspergillus niger. They are found as contaminants in several food commodities such as maize, rice, corn and other cereals, peanuts, fruits (grapes and mangoes), dried fruits, green coffee beans and onions. All of the population is exposed to fumonisins in the diet. However, this work was conducted as part of a review of the science underpinning Government advice on feeding infants and young children in order to determine whether the advice should be revised. Therefore, the interest was in a) risks from dietary exposure as an infant and b) risks from dietary exposure as a young child. Infants were considered to be ages 0 to <12 months and young children considered were ages 12 months to <60 months (5 years).

Step 1B: Define the exposure scenario

39. The exposure scenario is infants ages 0 to <12 months and young children ages 12 months to <60 months (5 years) exposed to fumonisins in the diet. Dietary sources include breast milk, infant formula, foods specifically for infants and other foods. Exposure to fumonisins in the diet will be life-long but the particular interest here was to assess risks to infants and young children as part of a review of the science underpinning Government advice on feeding infants and young children in order to determine whether the advice should be revised. There are no other sources of exposure.

Step 2: What is the potential carcinogenic hazard(s) being assessed?

Step 2A: Characterisation of the carcinogen(s) of concern - consideration of a non-genotoxic MOA.

Step 2B: Characterisation of the carcinogen(s) of concern - consideration of a genotoxic MOA

40. The fumonisins are not genotoxic carcinogens. They may be non-genotoxic carcinogens, amongst other adverse effects. As for the cadmium test case, the considerations under Step 2A (for non-genotoxic carcinogens) on pages 5-6 of the COC principles are also applicable to non-carcinogenic effects if the wording is modified slightly as follows:

- Have toxicokinetic properties been defined, including the potential for rapid metabolism or accumulation to occur

- Are dose-response relationships available for the various endpoints

- Whether the endpoint used as the basis for the chronic HBGV is the most applicable endpoint for the LTL exposure(s) being assessed

- Are the dose route, duration and intermittency of the studies used to generate hazard data relevant to the LTL scenario being considered

- The availability of suitable human data from occupational or epidemiology studies which can be used to derive an HBGV

- Has a dose-response relationship (in humans or animals) being defined for the endpoint on which an HBGV might be based

- Have cumulative exposure effects been assessed either in human or animal studies

- Potency, particularly when the time to the adverse effect occurring is known to be rapid

- Whether there is evidence for reversibility of changes following cessation of exposure

41. According to information in the COT scoping paper, fumonisins are poorly absorbed from the gastrointestinal tract after oral exposure (<4%). Once in the circulatory system, they have a half-life of ~4 hours. Following absorption, small amounts of fumonisins are distributed to virtually all organs, particularly the kidney and liver. Ester metabolites are hydrolysed into two tricarballylic acid moieties, and the amino group is acetalised. The metabolites are rapidly excreted mainly in the bile (>=90% of the parent), which results in low plasma, tissue and urinary concentrations.

42. Thus, in contrast to cadmium, fumonisins are rapidly metabolised and eliminated and do not bioaccumulate.

43. Toxicology studies have mostly tested fumonisin FB_1 but FB_{2-4} are considered to have similar toxicological profiles and potencies based on more limited in vitro and in vivo data (EFSA, 2018). In repeat dose studies in rats and mice, liver and kidney toxicity are observed primarily. Liver effects include apoptosis, necrosis, proliferation, regeneration and hyperplasia of the bile duct. Kidney effects include increases in free sphingoid bases (which are caused by disruption to sphingolipid metabolism), apoptosis and cell regeneration in the renal tubules of the outer medulla. Upon chronic exposure liver and kidney tumours are observed. FB_1 is not DNA reactive but is clastogenic via induction of oxidative stress.

44. Embryotoxicity was observed in rats, mice and rabbits but only at dose levels causing maternal toxicity, while in Syrian hamsters embryotoxicity was also seen in the absence of maternal toxicity. There were some indications that FB_1 causes neural tube defects in sensitive mouse strains.

45. EFSA established a TDI on the basis of liver effects in a 26 week study in wild type (p53 +/+) and transgenic (p53 +/-) mice. Benchmark dose modelling was performed on liver apoptosis and induction of megalocytic hepatocytes using the combined data for both strains. EFSA calculated a

$BMDL_{10}$ based on model averaging of 0.1 mg/kg bw/day of FB_1 for induction of megalocytic hepatocytes and applied an uncertainty factor of 100 to establish a TDI of 1 µg/kg bw/day. FB_{2-4} were included with FB_1 in the TDI based on in vitro and in vivo evidence indicating similar adverse effects.

46. JECFA also established a PMTDI, also based on induction of megalocytic hepatocytes in the 26 week mouse study (WHO, 2012). However, JECFA estimated a range of $BMDL_{10}$s of 0.165-1.178 mg/kg bw/day. JECFA took the lowest BMDL10 of 0.165 mg/kg bw/day, applied an uncertainty factor of 100 and rounded to 1 significant figure to establish a PMTDI of 2 µg/kg bw/day. The higher JECFA PMTDI than the EFSA TDI is due to differences in the BMD modelling.

47. The toxicological data include a shorter term study in mice. Howard et al. (2002) conducted a 28-day study in female mice of FB_1 with doses ranging from 0 to 22.9 mg/kg bw per day. Centrilobular apoptosis, hypertrophy and other microscopic changes indicative of liver toxicity were reported at 11.5 mg/kg bw per day. JECFA concluded that the NOAEL was 2.2 mg/kg bw/day (WHO, 2012). JECFA conducted benchmark dose modelling on the results of this study for hepatic apoptosis and hepatocyte hypertrophy. The lowest $BMDL_{10}$ calculated was 673 µg/kg bw/day, based on hepatocyte hypertrophy (the range of $BMDL_{10}$s from the different models was 673-3939 µg/kg bw/day; model averaging was not used at that time).

Step 3: Assessment of risk
Step 3A: Risk assessment of non-genotoxic (threshold) carcinogens

48. Step 3B, risk assessment for genotoxic carcinogens, would not apply here, so step 3A is followed for all non-genotoxic effects.

49. Step 3A involves initially establishing a HBGV for lifetime exposure in the first instance and comparing an assessment of LTL exposure to this. Alternatively, if the data are inadequate to establish an HBGV a margin of exposure (MOE) should be calculated. The principles note that use of an HGBV or MOE based on long-term toxicity studies may be considered precautionary when applied to short duration LTL scenarios.

50. The COT evaluation compared dietary exposures to both the EFSA TDI and the JECFA PMTDI, both of which were based on a 26 week study in mice.

51. The dietary exposure assessments from the COT evaluation (COT, 2019) are copied in Tables 12-15, below:

Table 12: Estimated exposures to fumonisins (µg/kg bw/day) from infant formulae for 6 to 12-month olds from using consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013).

Food	**6 to <9 months Mean**	**6 to <9 months 97.5th**	**9 to <12 months Mean**	**9 to <12 months 97.5th**
Infant formula [a] (median level)	0-0.023	0-0.042	0-0.018	0-0.035
Infant formula [b] (maximum level)	0-1.7	0-3.0	0-1.3	0-2.5

[a] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 2.5 (upper-bound) µg/kg
[b] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 179 (upper-bound) µg/kg

Table 13: Estimated exposures to fumonisins (µg/kg bw/day) from infant formulae in children aged 12 to 18 months from using consumption data from the DNSIYC (DH, 2013).

Food	**12 to <15 months Mean**	**12 to <15 months 97.5th**	**15 to <18 months Mean**	**15 to <18 months 97.5th**
Infant formula [a] (median level)	0-0.013	0-0.029	0-0.012	0-0.023
Infant formula [b] (maximum level)	0-0.96	0-2.1	0-0.83	0-1.6

[a] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 2.5 (upper-bound) µg/kg
[b] Exposure based on dry infant formula using fumonisins concentrations of 0 (lower-bound) and 179 (upper-bound) µg/kg

Table 14: Estimated fumonisin chronic exposures from the TDS in infants and young children aged 4 to 15 months (µg/kg bw/day).

Fumo-nisin	4 to <6 months Mean	4 to <6 months 97.5th percentile	6 to <9 months Mean	6 to <9 months 97.5th percentile	9 to <12 months Mean	9 to <12 months 97.5th percentile	12 to 15 months Mean	12 to 15 months 97.5th percentile
B1	0.000-0.0079	0.000-0.032	0.000-0.030	0.0011-0.11	0.000-0.052	0.0008 9-0.13	0.000-0.071	0.0014-0.16
B2	0.000-0.0068	0.000-0.026	0.000-0.027	0.000-0.10	0.000-0.048	0.000-0.13	0.000-0.067	0.000-0.15
B3	0.000-0.0063	0.000-0.025	0.000-0.024	0.000-0.088	0.000-0.042	0.000-0.11	0.000-0.058	0.000-0.13
Total	**0.000-0.021**	**0.000-0.083**	**0.000-0.082**	**0.0011-0.30**	**0.000-0.14**	**0.0008 9-0.37**	**0.000-0.20**	**0.0014-0.44**

Values rounded to 2 significant figures (SF)

Table 15: Estimated fumonisin chronic exposures from the TDS in infants and young children aged 15 to 60 months (µg/kg bw/day).

Fumo-nisin	15 to 18 months Mean	15 to 18 months 97.5th percentile	15 to 18 months Mean	15 to 18 months 97.5th percentile	24 to 60 months Mean	24 to 60 months 97.5th percentile
B1	0.000-0.083	0.0015-0.19	0.000-0.089	0.0020-0.15	0.000-0.080	0.0014-0.15
B2	0.000-0.078	0.000-0.17	0.000-0.085	0.000-0.150	0.000-0.077	0.000-0.14
B3	0.000-0.068	0.000-0.16	0.000-0.073	0.000-0.13	0.000-0.066	0.000-0.13
Total	**0.000-0.23**	**0.0015-0.52**	**0.000-0.25**	**0.0020-0.43**	**0.000-0.22**	**0.0014-0.42**

Values rounded to 2 SF

52. Thus, the 97.5th percentile exposure estimates for 6 to <9 months old infants consuming infant formula with fumonisins present at the maximum concentration of 179 µg/kg exceeded both the EFSA TDI (1 µg/kg bw/day) and JECFA PMTDI (2 µg/kg bw/day), at 3.0 µg/kg bw/day. The COT concluded as follows: "However, exposure to infant formulae is considered short when compared to a lifetime. In addition, the German data (Zimmer et al., 2008) on which the assessment was based may not accurately reflect the levels of fumonisins in infant formulae in today's market. While the data were the only ones available to the COT at the time, the authors of the study noted that the concentrations reported have been declining and only one manufacturer was contributing to the high concentrations observed. The COT concluded that occasional exceedances are unlikely to result in adverse toxicological effects as the HBGVs were based on repeat-dose effects."

53. For the purposes of this exercise testing the principles for assessing the risks from LTL exposure it will be assumed that the concentrations in infant formula do accurately reflect the concentrations in the current UK market. Potential exceedances of the EFSA TWI were also identified in high consumers in the 9-<12 month and 12-<15 month age groups consuming infant formula containing the highest concentration. However, these did not greatly exceed the JECFA PMTDI. The EFSA TDI and JECFA PMTDI are based on the same data and are only different due to differences in the BMD modelling. The period of 6-<9 months, at which intakes could be up to 300% of the EFSA TDI and 150% of the JECFA PMTDI is a period of 3 months.

54. The COC principles state that if the long HBGV is exceeded then consideration should be given to refining the exposure assessment, or consideration should be given to using a short-term HBGV or consideration should be given to a Haber's rule based approach.

55. The TDI and PMTDI are based on liver effects in a 26-week mouse study. This is a reasonably chronic study in mice, though it is not a lifetime. As discussed under Step 2B above, results are also available from a 28-day study in mice. Although Howard et al. (2002) conducted histopathological analysis of the liver and other organs was performed, the occurrence of

megalocytic hepatocytes was not reported. However, hepatocellular hypertrophy, hepatocellular apoptosis, hepatocellular cytoplasmic vacuolisation, Kupffer cell hyperplasia and macrophage pigmentation were. As stated above, JECFA conducted benchmark dose modelling on the results of this study for hepatic apoptosis and hepatocyte hypertrophy. The lowest $BMDL_{10}$ calculated was 673 µg/kg bw/day, based on hepatocyte hypertrophy (the range of $BMDL_{10}$s from the different models was 673-3939 µg/kg bw/day; model averaging was not used at that time).

56. If an uncertainty factor of 100 were applied, and the resulting short-term HBGV be rounded to one significant figure, then a short-term HBGV based on the $BMDL_{10}$ of 673 µg/kg bw/day would be 7 µg/kg bw/day.

57. The highest estimated intake, based on the maximum concentration in infant formula and consumption at the 97.5th percentile by infants aged 6-<9 months is 3 µg/kg bw/day, which is about 40% of this short-term HBGV.

58. In the 9-<12 month group, the highest estimated intake, based on the maximum concentration in infant formula and consumption at the 97.5th percentile, is 2.5 µg/kg bw/day, also exceeding both the EFSA TDI of 1 µg/kg bw/day and JECFA PMTDI of 2 µg/kg bw/day. This is 36% of the proposed short-term HBGV.

59. While estimated intakes in infants aged 6-<9 months and 9-<12 months are within the proposed short-term HBGV, estimated intakes for ages 12 months on which are based on the TDS (Tables 14 and 15) are well within both the EFSA TDI and JECFA PMTDI and thus intakes over the long term will be within these lifetime HBGVs.

60. Thus, is appears that there is no concern. The COT will wish to consider whether it agrees with this approach for fumonisins and the conclusion.

Other examples relevant to the COT's work

61. One other example from the COT's work on chemicals in the diets of infants and young children is nickel (COT, 2018b). In the COT's 2018 Statement on nickel in the diet on infants and young children, the COT did not use the TDI established by EFSA in 2015 of 2.8 µg/kg bw. Instead, the COT considered a higher TDI of 20 µg/kg bw/day to be applicable to infants and young children. In this case, the reason for the difference was that the EFSA TDI was based on post-implantation loss in a reproductive toxicity study, which was not considered relevant to infants and young children. The higher TDI was based on a NOAEL for effects on body weight in the F1 generation of a two-generation study in rats, which was considered to reflect the prepubescent population; in addition, the same NOAEL had been reported in a chronic study. Thus, in this case the COT did not establish a shorter-term HBGV as such, but rather one that was specific to the population group being considered.

62. Vitamin A (preformed vitamin A, i.e. retinol and retinyl esters) is an example where there is a chronic health-based guidance value for which short-term exceedance may also be of concern by a specific population subgroup (women in early pregnancy). In its consideration of vitamin A in the diet of young children, the COT applied the tolerable upper intake level (UL) established by the former Scientific Committee on Food (SCF) (COT, 2017). This was based on teratogenicity but also considered by the SCF to be protective of hepatotoxicity since it is 2.5 times lower than the lowest daily intake associated with hepatotoxicity during chronic intake (EFSA, 2006). Thus, the same HBGV is applicable to long term exposure by the general population but short-term exceedance by a particular population subgroup (women in early pregnancy) would also be of concern. However, this is addressed in the COC principles in that under Step 1 – define the exposed population – it is noted that some life stages may have greater susceptibility following exposure, which needs to be taken into account in Step 3.

63. Caffeine is an example of a chemical for which the guidance value is lower for a specific subgroup of the population (pregnant women, 200 mg/day) than for non-pregnant adults (300 mg/day). Short-term exceedance of the guidance value for pregnant women would be of concern, whereas the higher guidance value for the general population is based on possible increased risk of cardiovascular disease and is applicable to longer term exposure.

Discussion

64. The COC principles on less than lifetime exposure have been trialled using two cases from the COT's recent work on chemicals in the diets of infants and young children, cadmium and fumonisins. Exceedances of the long term HBGVs had been identified. The COC principles indicate that approaches that may be taken to refining less than lifetime risk assessments include using a Haber's rule based approach or establishing a short-term HBGV. The Haber's rule based approach is further described in the COC principles as the contribution of the LTL exposure to chronic background exposure (e.g. in terms of body burden or cumulative exposure).

65. The adverse effects of cadmium relate to its bioaccumulation over many years and so a Haber's rule based approach has been trialled in this paper, averaging exposure over a relevant timeframe. The COT will wish to consider whether the it agrees with how this approach has been applied. The COT's Statement on cadmium in the diet of infants and young children concluded that exceedances of the TWI by infants and young children were small in magnitude and would not be expected to remain at these levels over the decades of bioaccumulative exposure considered by EFSA in setting the HBGV. The Committee concluded that this was therefore not a major cause for concern. However, considering the cumulative nature of cadmium toxicity, efforts to minimise the levels of this metal in the environment should continue. This assessment has shown that intakes averaged over the first 50 years or

more of life are around the level of the TWI at the 97.5th percentiles, with the upper bound estimates being slightly above the TWI.

66. The fumonisins are rapidly metabolised and excreted and so the alternative approach of establishing a short-term HBGV has been taken. The COT's Statement on fumonisins in the diet of infants and young children concluded that short term exceedances of the EFSA TDI and JECFA PMTDI, primarily for 6 to <9 months old infants consuming infant formula with fumonisins present at the maximum concentration exceedances were unlikely to result in adverse toxicological effects as the HBGVs were based on repeat-dose effects. This assessment has shown the LTL exceedances of the TDI and PMTDI to be well within a proposed short-term HBGV.

67. Another example from the COT's previous work is nickel. The TDI was based on post-implantation loss in a reproductive toxicity study. The COT considered this not-relevant to infants and young children and established a higher HBGV for infants and young children, which was based on effects on body weight and chronic toxicity. Thus, this higher HBGV was not a shorter term HBGV but one more relevant to the population group under consideration. This is not a scenario that is reflected in the COC principles given their focus on carcinogenicity.

68. Finally, there are examples from the COT's past work where HBGVs are based on developmental toxicity, and short term exceedances by pregnant women would be of concern. The COC principles do reflect that some age groups and life stages may have greater susceptibility, which may need to be taken into account in the assessment of risk. If COT principles were to be produced, they might expand on this.

Questions on which the views of the Committee are sought

69. Members are invited to consider the following questions.

i). Do Members agree that the test cases for cadmium and nickel have appropriately followed the COC principles on less than lifetime exposure?

ii). Would following the COC principles have changed the conclusions previously drawn by the COT on cadmium and fumonisins in the diets of infants and young children?

iii). Should COT-specific principles on less than lifetime exposure be produced based on the COC principles?

iv). Do Members have any other comments?

Secretariat
October 2020

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TOX/2020/XX ANNEX A

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

Testing the COC guidance on less than lifetime exposure

COC (2019). COC set of principles for consideration of risk due to less than lifetime exposure. COC Guidance Statement G09 – version V1.0

Note: The contents of this Annex will not be included in the version of the paper published on the COT website. However, the COC principles can be found online at https://www.gov.uk/government/publications/less-than-lifetime-exposure-principles-for-consideration-of-risk

Secretariat
October 2020