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

Scoping paper on the potential risks from polycyclic aromatic hydrocarbons (PAHs) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

Introduction

1. PAHs (polycyclic aromatic hydrocarbons) are organic compounds characterised by the presence of 2 or more fused aromatic rings, many of which are known carcinogens. Although naphthalene, with 2 fused rings, would technically be part of this group of compounds it is usually not regarded as a member. PAHs are common products of combustion and are widely distributed in the environment as the result of vehicle exhaust and industrial processes and in the diet in cooked food and cooking by-products such as oils vaporised from frying pans and smoke from barbecues. Production of PAHs by cooking is greater when fat expressed from the food drips directly onto the heating element or hot coals.

2. The diet is a significant source of PAHs for non-smokers, but cigarette smoke makes the major contribution to the intake for smokers. Second-hand or “side-stream” smoke is known to contain a higher concentration of PAHs than mainstream smoke and thus may contribute to the intake of non-smokers (EFSA 2008).

3. EFSA (2008) addressed PAHs in food. Considering the enormous number of possible members in the group, they concluded that although benzo[a]pyrene (BaP) alone has been used as a marker for PAHs, the presence of a mixture of BaP, benz[a]anthracene (BaA), benzo[b]fluoranthene (BbF) and ChR, designated PAH4, gave a better measure for risk assessment purposes.

4. Infant formula are the major sources of PAH exposure to young infants. Breast milk data in the literature are given as μg/kg fat but intake is of whole milk. Maternal intake and hence milk concentrations vary with location (urban or rural), season (Summer or Winter) (Pulkrabova *et al*, 2016) and smoking status (Zanieri *et al,* 2007)

Absorption, distribution, metabolism and excretion

5. PAHs may be absorbed via ingestion in food, inhalation and by dermal contact. The magnitude of absorption appears to be oral >> dermal >> inhalation (Lao *et al* 2018, from abstract).

6. Absorption in the digestive tract depends upon bioaccessibility, the proportion of the PAH content of food that is released when the food is eaten and the amount and type of PAH in question. PAH uptake in the gut depends upon fat absorption in the presence of bile to produce micelles. PAHs appear to follow the longer chain (>10

carbons) fatty acids into the lymphatic system rather than the shorter chain (2 – 10 carbons) into the portal vein (Harris *et al*, 2013).

7. The PAHs are not intrinsically genotoxic but require oxidation by the CYP enzymes 1A1, 1A2, 1B1 and 3A4 to various diols, quinones and epoxides which become electrophilic compounds able to form DNA adducts that can lead to mutagenesis and carcinogenesis (Xue and Warshawsky, 2005). PAHs induce the CYPs by binding to and activating the aryl hydrocarbon receptor (AhR) (EFSA 2008). Cellular oxidative stress mechanisms are also induced (Murphy *et al*, 2008). CYP1A1, 1A2 and 1B1 appear also to be involved in detoxification of BaP (Shi *et al*, 2010, Nebert *et al* 2013).

8. Levels of PAH metabolites peak within the first hour following ingestion and then slowly decline, reaching pre-ingestion levels by about 24 hours. (Li *et al*, 2012)

Toxicity

9. Short term PAH exposure appears to cause eye and skin irritation, nausea and vomiting and local inflammation but since PAHs occur as mixtures that may also include other non-PAH components, it is difficult to ascertain that the PAHs are the causative agents of these effects (Kim *et al* 2013).

Carcinogenicity

10. Exposure to PAHs has been associated with increased risk of cancer of various tissues including the breast (White *et* al, 2016), oesophagus (Roshandel *et al*, 2012), gastrointestinal tract (Diggs *et al*, 2011) and lung (Moorthy *et al* (2015).

11. Not all PAHs are equally carcinogenic, and BaP is not always present or prevalent in carcinogenic mixtures of PAHs. IARC has classified BaP as in Group1 (carcinogenic to humans, 2012), and BaA, BbF and ChR as in Group 2B (possible human carcinogens, 2010).

https://monographs.iarc.fr/wp-content/uploads/2018/09/ClassificationsAlphaOrder.pdf

Health Based Guidance Values (HBGVs)

12. EFSA (2008) used the US EPA BMD software (BMDS) to derive $BMDL_{10}$ values for BaP and PAH4 of 0.070 mg/kg bodyweight (bw)/day (70 μg/kg bw/day) and 0.340 mg/kg bw/day (340 μg/kg bw/day) respectively. In this paper, where possible, intakes of both BaP and PAH4 will be compared with their EFSA $BMDL_{10}$ values but where either only BaP data are given, or where the PAHs are not given individual values but regarded as a group of > 4, BaP is considered alone.

Breast milk

13. No data on UK milk were found. For the purposes of this paper, the data of Santonicola *et al* (2017) were used in exposure and risk assessment since they gave the highest European values for BaP (0.81μg/kg fat) and PAH4 (2.77 μg/kg fat).

14. Breast milk is estimated to consist of 4,1% fat (Finglas *et al* 2015). Exposures to BaP in whole milk ranged from 0.0034 to 0.0068 μg/kg bw/ day and for PAH4 from 0.012 to 0.023 μg/kg bw/ day for average (800 ml/day) and high-level (1200 ml/day) consumers. The most exposed group is the 0 - <4-month-old high level consumers.

15. All the MOEs were greater than 10,000, indicating that they were unlikely to be of concern for genotoxic carcinogens

Infant formula

16. A FSA survey performed in 2003 – 4 (White *et al*, 2004) is the latest UK data source on PAHs in infant formula, and gave mean values of BaP and PAH4 in 96 samples of infant formulae of 0.047 and 0.358 μg/kg respectively.

17. Exposures to BaP ranged from 0.0050 to 0.010 μg/kg bw/ day and for PAH4 from 0.037 to 0.073 μg/kg bw/ day. As for breast milk, the most exposed group is the 0 - <4-month-old high level consumers.

18. For BaP the MOEs for the average consumer are greater than 10,000, indicating that they are unlikely to be of concern for genotoxic carcinogens. However, BaP in the high-level consumers and all the intakes of PAH4 are lower than 10,000 which may represent a concern for human health.

19. However, the European Medicines Agency and International Council for the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) have both recently published guidance on the risk assessment of shorter than lifetime exposure to genotoxic and/or mutagenic substances (links below). Both groups state that, for short exposures, higher limits (i.e. lower MOEs) can be set as levels of low concern for health. Therefore, since the low MOE values from infant formula cover only a short period of an individual's lifetime and the values for food (see below) are calculated to be much higher, these low values are unlikely to contribute significantly to overall risk. COC are currently drafting guidance on less than lifetime exposure.
https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-guideline-limits-genotoxic-impurities_en.pdf
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_31Mar2017.pdf

Food

20. The highest upper bound 97.5th percentile exposure to BaP was 8.8 μg/kg bw/ day in the 4 - < 6-month-old group and for PAH4 24 μg/kg bw/ day in the 15 - <18-month-old group.

21. All MOEs are greater than 10,000, indicating these are unlikely to be a concern for health, except for the upper-bound 97.5th percentile intakes of BaP for the 4 to <6 and 6 to <9-month age groups (8000 and 8300 respectively). For the groups in question, although this level of intake is undesirable, the MOEs are still fairly high, the numbers of infants involved will be small and, as stated above for infant formula exposure, at this level only takes place for a short period of life, these are still unlikely to be of concern.

Environmental

Air

22. Data from the DEFRA interactive map of the BaP concentration in UK air shows that most of the country in 2017 was exposed to <0.1 ng BaP/m^3, with urban areas reaching a range of 0.2 – 0.4 ng BaP/m^3. The only exception to this was an area near Port Talbot in Wales, where there was a measurement of > 1.0 ng BaP/m^3.

https://uk-air.defra.gov.uk/data/gis-mapping

23. Air exposures were at most 0.75 ng/kg bw/day in the 12 to <15-month-old group at the highest air concentration of 1.0 ng/m^3. This gives a MOE of 93,000, which represents a low concern for health.

Soil

24. Potential exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to BaP and PAH4 in soil were calculated assuming ingestion of 30 or 50 mg/day, respectively (US EPA, 2011a). Younger infants, who are less able to move around and come into contact with soil, are likely to consume less soil than children of these age groups.

25. Data on BaP in urban and Principal Domain (non-urban) soils are shown in Appendix1. For Principal Domain soils, both the median (0.037 mg/kg) and the conservative Normal Background Concentration (NBC, the upper 95% confidence level of the 95th percentile measurement, 0.5 mg/kg), give MOE values greater than 10,000 (410,000 to 610,000 and 31,000 to 45,000 respectively). For the urban soils, while the median value of gives MOE values of 56,000 to 84,000 and is thus unlikely to be of concern for health, the NBC value gives values ranging from 4,200 to 6,300 across the age ranges and thus may represent a risk to children living in such areas. However, given that these are high consumers, the conservative nature of the NBC and that this will only occur over a limited portion of their lifetime, these values are still unlikely to be a concern for health in most places.

Dust

26. Ma and Harrad (2015) reviewed the data on PAHs in indoor air, settled house dust and diet. Only one paper on UK house dust was reported, giving a concentration

in particles <62 μm in diameter of 345 μg/kg for BaP and 5095 μg/kg for ΣPAH (excluding naphthalene).

27. Potential exposures of UK infants aged 6 to 12 months and young children aged 1 to 5 years to PAHs in dust were calculated assuming ingestion of 30 or 60 mg/day, respectively (US EPA, 2011a). The exposure of children aged 6 months to 5 years to BaP ranges from 0.0011 to 0.0016 μg/kg bw/day. These values give daily MOEs of 43,000 to 65,000 and so would not be expected to be a risk to the health in these age groups.

Conclusions

28. The concentrations of BaP and PAH4 in human breast milk and food in general give rise to intakes that have margins of exposure of greater than 10,000 when compared with the respective $BMDL_{10}$ values which, for a genotoxic carcinogen represents a low level of concern.

29. Where MOEs are below 10,000, they are mostly in infant formula, which would be a major constituent of the diet for only a short period of an individual's life and would not be expected to contribute significantly to overall lifetime exposure.

30. Levels estimated to be ingested in soil and dust and inhaled in air are also > 10,000 and thus do not represent a concern for health, except in the areas of highest contamination, where MOEs of <10,000 for soil, but this risk is mitigated by the short period of like over which high exposure takes place.

Secretariat

June 2019

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Appendix 1: Urban and Principal Domain UK soil concentrations of benzo[a]pyrene (mg/kg)

Taken from Defra. 2012. Technical Guidance Sheet on normal levels of contaminants in English soils: Benzo(a)pyrene – supplementary information. Technical Guidance Sheet No. TGS04s, July 2012. *Department for Environment, Food and Rural Affairs (Defra)*, Soils R&D Project SP1008.

	Urban Domain			Principal Domain		
Percentile	lower	middle	upper	lower	middle	upper
50	0.18	0.27	0.43	0.031	0.037	0.042
55	0.21	0.32	0.50	0.038	0.044	0.051
60	0.25	0.38	0.58	0.045	0.053	0.061
65	0.29	0.44	0.68	0.054	0.064	0.075
70	0.34	0.53	0.81	0.067	0.078	0.092
75	0.41	0.64	0.99	0.082	0.10	0.11
80	0.50	0.79	1.2	0.10	0.12	0.15
85	0.62	1.0	1.6	0.13	0.16	0.20
90	0.81	1.4	2.2	0.19	0.23	0.29
95	1.2	2.2	3.6	0.31	0.39	0.50