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

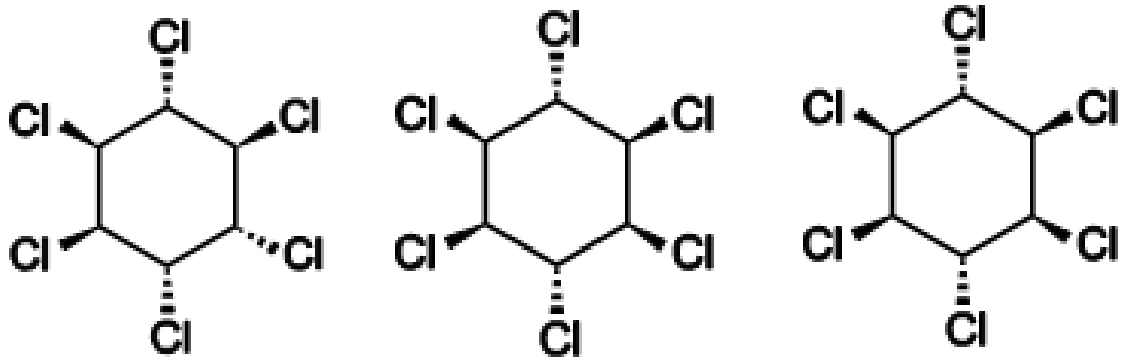
Review of the potential risks from α-, β- and γ-hexachlorocyclohexanes in the diet of children aged 1-5 years

Introduction

1. A previous COT statement (COT, 2014) gave an overview of potential risks from occurrence of, α-, β- and γ-hexachlorocyclohexanes (HCHs) in the infant diet. This current statement will provide an updated overview, focusing on children aged 1-5 years, addressing any changes to health-based guidance values (HBGVs), new exposure and toxicity data.

Background

2. The chemical structures of α-, β-, and γ-HCH are shown in Figure 1. Due to their lipophilic properties and persistence in the environment, β-HCH, and to a lesser extent, α-HCH and γ-HCH, bioaccumulate and biomagnify in the food chain. They are distributed globally, with transfer from warmer to colder regions through evaporation and condensation (EFSA, 2005).



α-HCH (CAS 319-84-6) β -HCH (CAS 319-84-6) γ -HCH (CAS 319-84-6)

Figure 1. Chemical structures of α-, β-, and γ-HCH

3. HCHs have been used as pesticides. The term “lindane” has been commonly used for HCH mixtures used as pesticides in which γ-HCH was >99% of total HCH, and throughout this statement the term is used only with that meaning (elsewhere “lindane”, has sometimes also been used as a synonym for γ-HCH).

4. Pesticidal use of products in which γ-HCH made up less than 99.0 % of all HCHs was banned in the EU by Council Directive 79/117/EEC of 21 December 1978. Authorisation for use of lindane as a pesticide in the EU was withdrawn by Commission Decision 2000/801/EC of 20 December 2000. This action was taken primarily because of concerns about its safety for operators, the fate and behaviour of γ-HCH in the environment and effects on non-target organisms.

5. The maximum levels of pesticides that are currently permitted in the EU in foods sold for infants are set out in Directive 2006/141/EC on infant formula and follow-on formula, and Directive 2006/125/EC on processed cereal foods and baby foods for infants and young children. The maximum permitted levels in other food products are described in Directive 2005/396/EC. A general maximum residue level (MRL) (0.01 mg/kg) is applicable 'by default' in all cases where an MRL has not been set specifically for a product or product type. This default applies to HCHs in infant and follow-on formula and in processed cereal foods and baby foods for infants and young children. As regards other food products for human consumption, several different MRLs apply depending on the HCH isomer and the food commodity in question, although for most, the default MRL applies. MRLs range from 0.004 to 0.2 mg/kg for α-HCH, from 0.003 to 0.1 mg/kg for β-HCH, and from 0.001 to 1 mg/kg for γ-HCH (Directive 2013/212/EC).

γ-HCH

6. The gamma isomer (γ-HCH) is considered first in this statement, because more extensive toxicological data are available for the compound, and there is some scope for extrapolation to the alpha and beta isomers.

Toxicity of γ-HCH

7. The previous COT statement discussed observations of neurotoxicity and renal toxicity in several animal studies and concluded that evidence of renal toxicity in rats was irrelevant to humans (COT, 2014). However, effects of paraesthesia of the face and extremities, headaches, vertigo, abnormal EEG patterns, seizures and convulsions have been reported in humans occupationally exposed to γ-HCH (ATSDR, 2005). Additionally, there are two case reports showing renal toxicity and hepatoxicity after γ-HCH exposure. A 30-year-old male farmer who ingested 50 mL of γ-HCH developed acute intrinsic renal failure with increased blood urea and creatinine, reduced urine output and acute fulminate hepatic failure. The pathophysiology of this case is unknown, but no other substance abuse was reported in this individual (Paul *et al*., 2013). In another case report, a 62-year-old male with 12 years occupational exposure to γ-HCH gas developed liver cirrhosis (EbrahimiDaryani *et al*., 2008).

8. Other findings noted in the previous statement include immunological toxicity and endocrine disruption potential in animal studies. More recent findings have indicated altered immunological function of human lymphocytes treated with γ-HCH (Michałowicz *et al*., 2013). As well as increases in luteinizing hormone and follicle stimulating hormone alongside decreased testosterone in men occupationally exposed to γ-HCH (ATSDR, 2005). Negative correlations (r = −0.500) between γ-

HCH and Insulin-like growth factor 1 levels in females has also been noted (Bapayeva *et al*., 2016).

9. The association between lindane and endometriosis remains inconclusive and there is inconsistency in reports of γ-HCH's reproductive toxicity. Epidemiology studies not reported in the prior statement identified a 2.53-fold increased risk of neural tube defects compared to controls (Ren *et al*., 2011). Also, strong negative associations were found between γ-HCH and sperm counts in infertile patients with reduced sperm motility, although these effects were not significant in fertile men (Khan *et al*., 2010).

10. The COT previously agreed that γ-HCH is unlikely to be a human liver carcinogen and there is weak epidemiological evidence of associations between γ-HCH and non-Hodgkin lymphoma (NHL) (COT, 2014). However, the International Agency for Research on Cancer (IARC) stated there was sufficient evidence in humans for the carcinogenicity of γ-HCH for NHL after review of several studies. The IARC then categorised γ-HCH as "carcinogenic to humans" (Group 1) (IARC, 2015). Since the IARC evaluation, a prospective study identified a non-significant increased risk of NHL from lindane use in females (Louis *et al*., 2017). Furthermore, the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) concluded that γ-HCH does not have in vivo oestrogenic activity (COC, 2004). As for prostate cancer, only one study in the previous COT statement reported a positive exposure relationship (Mills and Yang, 2003). Since then later studies have identified significantly higher mean levels of γ-HCH in blood of prostate cancer patients compared to controls (Kumar *et al*., 2010 study; Pi *et al*., 2016).

11. Differing findings on the association between γ-HCH and Parkinson's disease (PD) were formerly reported by (COT, 2014). More recently, a case control study found non-significant increased risks of PD from γ-HCH exposure in participants whose residence were within 0-1000m of crop cultivation. Additionally, exposure to participants in the year 1990 and onwards was found to significantly increase the risk of PD (Brouwer *et al*., 2017).

Health-based guidance values (HBGVs)

12. HBGVs are presented in Table 1, the previous evaluation (COT, 2014) used the tolerable daily intake (TDI) value of 0.04 µg/kg bw based on the LOAEL from the study by Meera *et al*. (1992).

Table 1. ADIs, TDIs and RfD proposed for γ-HCH.

Source of HBGV	HBGV (µg/kg bw/day)	Critical effect and species NOAEL/LOAEL in mg/kg bw/day	Uncertainty factor	Study selected to derive HBGV
Health Canada (1992), cited in EFSA (2005)	Group TDI 0.3 for all HCH		Unkno wn	
RIVM (2001)	TDI 0.04	Immunotoxicity in female rats LOAEL 0.012	300	Meera et al., 1992
JMPR (FAO/WHO, 2002)	ADI 5	Decreased survival, liver and spleen effects in rats NOAEL 0.47	100	Amyes, 1990
JMPR (FAO/WHO, 2002)	ARfD 60	Increased fore-limb grip strength and decreased grooming behaviour NOEL 6	100	
Health Canada (2010)	ADI 0.5	Decreased survival, liver and spleen effects in rats NOAEL 0.47	1000	Amyes, 1990
Integral Consulting (2011c)	RfD 0.01	Immunotoxicity in female rats LOAEL 0.012	1,000	Meera et al., 1992

Sources of γ-HCH and occurrence levels

Breast Milk

14. The previous COT statement (COT, 2014) reflects the most recent data on γ-HCH in human breast milk in UK populations, where γ-HCH was detected in breast milk at mean and maximum concentrations of 0.8 and 7.7 µg/kg milk fat Kalantzi *et al*., 2004).

Infant formula

15. Infant formulae are included in the UK national monitoring programme for pesticide residues in food, which is overseen by the Expert Committee on Pesticide Residues in Food (PRiF). Infant formulae were last surveyed between January and February 2014 and γ-HCH was not detected at or above the reporting limit[1] of 0.01 mg/kg, i.e. the current MRL (PRiF, 2014a).

16. Recent monitoring of the wider UK food supply in July to September 2018 did not identify γ-HCH in retail samples of milk at or above the reporting limit of 0.002 mg/kg, indicating that levels in infant formula produced from cows' milk produced in the UK are likely to be well below 0.01 mg/kg (PRiF, 2018c). Soya milk, soya tofu and soya pieces have not been included in the UK pesticide monitoring programme since 2006, where the previous statement (COT, 2014) reported that γ-HCH was undetected at its reporting limit of 0.002 mg/kg and is likely to be well below 0.01 mg/kg.

[1] The reporting limit is the lowest calibrated level employed during analysis to detect residues. The reporting limit may vary slightly from laboratory to laboratory depending on the equipment available and operating procedures used.

17. In 2016 60% of infant food (including infant formulae) was imported to the UK is from Ireland (AHDB, 2017). The previous statement (COT, 2014) includes the most recent data on γ-HCH reported in a survey by the Food Safety Authority of Ireland in 2004; γ-HCH was not detected at a limit of quantification (LOQ) of 0.001 mg/kg for reconstituted formula. Also, γ-HCH was also not detected above the LOD of 0.0007 mg/kg for cows' milk in an Irish total diet study conducted during 2001-2005.

Complementary food

18. Animal based infant foods containing meat, fish, eggs and cheese were last surveyed by PRiF between January and September 2014 (PRiF, 2014b). γ-HCH was not identified in the infant food samples at or above reporting limits of 0.01 mg/kg.

19. Cereal based infant foods were last surveyed between January and February 2013 and fruit and vegetable based infant foods were last surveyed between February and March 2013. γ-HCH was undetected in either of these infant foods at or above their reporting limits of 0.01 mg/kg (PRiF, 2013).

20. Recent monitoring of the wider UK food supply between January and September 2018 did not identify γ-HCH to be over its reporting limits ranging from 0.01 mg/kg for most commodities such as fruits, vegetables and cereals to 0.002 mg/kg in meats, milk, cheese and eggs. Collectively there were 2,329 samples for a range of commodities surveyed and γ-HCH did not exceed its MRL of 0.01 mg/kg in any (PRiF, 2018a, b, c).

21. The health and safety executive (HSE) have supplied the following data from their database regarding the presence of γ-HCH in various foods. In 2006 one sample of chorizo from Spain and one sample salami from Switzerland γ-HCH was found at concentrations of 0.006 and 0.005 mg/kg respectively (HSE, 2019).

22. An EFSA report analysed pesticide occurrence data obtained from 30 reporting countries (including the UK) in 2017. The analysis included 88,247 samples from 12 food products (oranges, pears, kiwi fruits, cauliflowers, onions, carrots, potatoes, beans (dried), rye grain, husked rice grain, poultry fat and sheep fat). The results showed that γ-HCH was quantified below or equal to its MRL (0.01 mg/kg) in 0.59% of samples of animal origin (poultry fat and sheep). Only one sheep fat sample from Spain (accounting for 0.3% of all samples) exceeded the MRL for γ-HCH (EFSA, 2019).

Exposure

Breast Milk

23. Estimates of γ-HCH exposure from breast milk were based on the mean concentration (0.8 µg/kg milk fat, 0.028 µg/kg whole milk) from the most recent UK study (Kalantzi *et al*., 2004). It was assumed that the fat content of breast milk was

3.5% (COT, 2014). Table 2**Error! Reference source not found.** presents the exposure of γ-HCH from breast milk to children aged (12 to 15 months).

Table 2. Chronic consumption of Breastmilk and γ-HCH exposure to UK infants and Young children (DH, 2013)

	Consumption of breast milk (g/kg bw/day)		**Exposure of γ-HCH (µg/kg bw/day)**	
Age group (months)	**Mean**	**97.5th Percentile**	**Mean**	**97.5th Percentile**
12 to 15	29	75	0.00082	0.0021
15 to 18	25	52	0.000709	0.0015

Infant formula

24. An exposure assessment for γ-HCH in infant formula and cow's milk was not performed, as γ-HCH could not be detected at or above many of the reporting limits/LOQs described in paragraphs (15-16).

Complementary foods

25. The latest pesticide residues in food report by JMPR (FAO/WHO, 2002) that included review of γ-HCH was published in 2015. As lindane is no longer used as a pesticide the JMPR considered monitoring data, and based on these, advised on the setting of extraneous maximum residue limits (EMRLs) and conducted dietary risk assessments. MRLs, supervised trials median residue levels (STMRs) and highest residue levels (HRs) previously estimated by the JMPR from supervised field trials in 2003, when lindane was used as a pesticide, were either maintained or lowered based on decreases in residue levels shown by the monitoring data. For example, in the case of poultry and mammalian meats, monitoring data from various European countries, India and the USA showed that residues had declined 10-fold, and therefore the JMPR recommended an EMRL 10-fold lower than the previous MRL and also reduced the STMR and HR 10-fold for use in dietary risk assessments of chronic and acute exposure, respectively. In the case of cereal grains, the JMPR recommended the EMRL be the same as the existing MRL and therefore the same STMR and HR were used in the dietary risk assessments as previously estimated by the JMPR from field trials.

26. For the GEMS/food cluster diet; G07 (which includes the UK) (WHO, 2012), JMPR estimated γ-HCH intakes of various population groups, including children aged 6 years and under. These intakes were calculated for a range of commodities based on estimated STMR values ranging from 0.00002 – 0.005 mg/kg (
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31. Table 3) (FAO/WHO, 2015).

Table 3. Estimated intake values of γ-HCH for GEMS/food cluster diet; G07

Commodity	STMR (mg/kg)	Estimated intake (µg/person/day)
Cereal grains, raw (incl processed	0.005	1.73
MEAT FROM MAMMALS other than marine mammals, raw (incl prepared meat) -80% as muscle	0.00007	0.01
MEAT FROM MAMMALS other than marine mammals, raw (incl prepared meat) - 20% as fat	0.0005	0.01
Edible offal (mammalian), raw	0.00002	0.00
Milks, raw or skimmed (incl. dairy products)	0.00003	0.01
Poultry meat, raw (incl prepared) - 90% as muscle	0.0006	0.04
Poultry meat, raw (incl prepared) - 10% as fat	0.0008	0.01
Eggs, raw, (incl dried)	0.0007	0.02
Total intake (µg)/person/day)		**1.8**

32. The Food Standards Agency's (FSAs) exposure assessment team have also provided estimated γ-HCH intakes for the commodities listed above, using consumption data of 1.5 to 5 year olds from the National Diet and Nutrition Survey (NDNS) results (

33. Table *4*). The highest dietary exposures are estimated for cereal grains, although these exposure estimates are likely to be conservative, as the STMR values used were estimated from field trials of lindane use when lindane was used as a pesticide. The JMPR recommended the same EMRL be set for γ-HCH in cereal grains as the existing MRL and therefore used the same STMR and HR as estimated previously from field trials in the exposure assessment. However, based on the monitoring data from European countries the JMPR concluded that at least 99.8% of residues will be below the EMRL with 99% confidence, so the STMR, which is half of the EMRL, might be an overestimate of the current average residue level in cereals.

Table 4. Estimated intake values of γ-HCH in children aged 1.5 to 5 years using NDNS consumption data Years 1-8 (Bates et al., 2014; Bates et al., 2016) and estimated STMR values by JMPR (FAO/WHO, 2015)

Commodity	**STMR (mg/kg)**	**Consumption (g/person/day)**		**Estimated intake (µg/person/day)**	
		Mean	**97.5th percentile**	**Mean**	**97.5th percentile**
Cereal grains, raw (incl processed	0.005	68	129	0.34	0.65
MEAT FROM MAMMALS other than marine mammals, raw (incl prepared meat) -80% as muscle	0.00007	38	103	0.0027	0.0072
MEAT FROM MAMMALS other than marine mammals, raw (incl prepared meat) - 20% as fat	0.0005	10	26	0.005	0.013
Edible offal (mammalian), raw	0.00002	12	38	0.00024	0.00076
Milks, raw or skimmed (incl. dairy products)	0.00003	295	782	0.0089	0.024
Poultry meat, raw (incl prepared) - 90% as muscle	0.0006	14	46	0.0084	0.028
Poultry meat, raw (incl prepared) - 10% as fat	0.0008	2	5	0.0016	0.004
Eggs, raw, (incl dried)	0.0007	19	57	0.013	0.04
Total intake (µg)/person/day)				**0.38**	**0.77**

Risk characterisation

34. Estimated mean and 97.5th percentile intakes for breast milk are below the ADI (5 µg/kg bw) and TDI (0.04 µg/kg bw) (FAO/WHO, 2002) (Table 1) and are therefore not of toxicological concern to children aged 12 to 18 months.

35. Results from long and short-term dietary risk assessments performed by JMPR indicate that consumption of commodities presented in (

36. Table 3) are not of toxicological concern to various population groups. JMPR reported an international estimated daily intake (IEDI) of γ-HCH to be 0-1% of the ADI (0-0.005 mg/kg bw/day), based on 17 GEMS/Food cluster diets. The specific estimated daily intake (EDI) for the G07 cluster diet was 0.6% of the ADI. Additionally, none of the commodities analysed exceeded the ARfD (0.06mg/kg); majority of the commodities were 0% of the ARfD) (FAO/WHO, 2015).

37. Results from a long-term dietary exposure assessment by EFSA showed γ-HCH to be 4.5% and 0.002% of its ADI (0.005 mg/kg bw/day) in the upper and lower bound scenario respectively, suggesting that long-term intake of residues from food of animal and plant origin described in paragraph 21 are unlikely to be a cause for concern to European consumers (EFSA, 2019).

38. Estimated mean and 97.5th percentile intakes for all commodities were below the ADI (5 µg/kg bw) and all commodities except cereal grains were either at or

below the TDI (0.04 µg/kg bw) (FAO/WHO, 2002) (Table 1).Estimated intakes of cereal grains exceeded the TDI by 8.5 and 16 fold in mean and 97.5th percentile exposure groups respectively (

39. Table *4*). Given that this is a conservative assessment as previously explained, intakes values are likely to be overestimates, implying effects on health of 1-5-year olds are unlikely.

α-HCH

Toxicity of α-HCH

40. The previous COT statement reported evidence of immunosuppression, hepatoxicity (liver hypertrophy), neurotoxicity (stimulation of the nervous system and inhibition of gamma-aminobutyric acid-mediated chloride ion uptake) in animal studies. As for reproductive toxicity no evidence was previously reported, although potential reproductive toxicity was noted in a study that identified significantly higher levels of α-HCH in maternal and cord blood in the small for gestational age cases compared to control cases (Chand *et al*., 2016).

41. Evidence of α-HCH's genotoxicity has been inconclusive, with findings of non-genotoxic mechanism of tumorigenicity and negative Ames test results. Other studies reported increases in micronuclei and DNA breakage compared to controls. A more recent study identified α-HCH as a non-genotoxic agent (Ennaceur, 2016). With regards to carcinogenicity, it was concluded that α-HCH is likely to be a non-genotoxic liver carcinogen in rodents with a MOA not relevant to humans.

Health-based guidance values (HBGVs)

42. The COT previously agreed that none of the HBGVs identified in literature were to be used for risk characterisation, as the human relevance of the critical effects used to derive the HBGVs were questionable, and the toxicity of α-HCH is not well characterised. Although, a NOEL of 0.1 mg/kg was used as part of the risk characterisation, which has been cited in earlier and recent EFSA publications (EFSA, 2005, 2019).

Sources of α-HCH

Breast milk

43. The previous statement (COT, 2014) reflects the most recent data on α-HCH in human breast milk in UK populations; α-HCH was not detected at an LOD of 0.01 mg/kg milk fat in samples collected between 2001 and 2002.

Infant formula

44. Infant formulae are included in the UK national monitoring programme for pesticide residues in food, which is overseen by the PRiF. Infant formula was last surveyed between January and February 2014; α-HCH was not detected at or above the reporting limit of 0.01 mg/kg, i.e. the current MRL (PRiF, 2014a).

45. Recent monitoring of the wider UK food supply in July to September 2018 did not identified α-HCH in retail samples of milk at or above their reporting limit of

0.02 mg/kg, indicating that levels in infant formula produced from cows' milk produced in the UK are likely to be well below 0.01 mg/kg (PRiF, 2018c). Soya milk, soya tofu and soya pieces have not been included in the UK pesticide monitoring programme since 2006, where the previous statement (COT, 2014) reported α-HCH was undetected at its reporting limit of 0.002 mg/kg and is likely to be well below 0.01 mg/kg.

46. As previously mentioned much of the infant formula consumed in the UK is imported from Ireland. The previous COT statement includes the most recent survey data on α-HCH reported by the Food Safety Authority of Ireland in 2004; α-HCH was not recorded with LOQs of 0.001 mg/kg for reconstituted formula and 0.007 mg/kg for cows' milk (COT,2014).

Complementary foods

47. Animal based infant foods containing meat, fish, eggs and cheese were last surveyed by PRiF between January and September 2014 (PRiF, 2014b). α-HCH was not identified in the infant food samples at or above their reporting limits of 0.01 mg/kg.

48. The presence of α-HCH in cereal and vegetable based infant foods is unknown as in the most recent survey (PRiF, 2013) and in earlier surveys α-HCH was not examined in these infant food samples.

49. Recent monitoring of the wider UK food supply between January and September 2018 did not identify α-HCH to be over its reporting limits ranging from 0.01 mg/kg for most commodities such as fruits, vegetables and cereals to 0.002 mg/kg in meats, milk, cheese and eggs. Collectively there were 2,329 samples for a range of commodities surveyed and α-HCH did not exceed its MRL of 0.01 mg/kg in any (PRiF, 2018a, b, c).

50. A survey by the Safety Authority of Ireland in 2006 included 19 samples of vegetable/meat based infant foods, 13 samples of fruit-based infant food and 11 cereal-based infant foods. α-HCH was not detected in any samples at a LOQ of 0.001 mg/kg (FSA Ireland, 2006).

51. The HSE have informed that from 2008 onwards there were no positive results for α-HCH in baby/infant food in their database (HSE, 2019).

52. In an EFSA report (paragraph 21) presenting results on pesticide residues in food samples taken from various reporting countries (including the UK) in 2017. It was found that α-HCH was quantified below or equal to its MRL (0.01 mg/kg) in 0.9% of samples of animal origin (poultry fat and sheep) (EFSA, 2019).

Exposure

Breast milk

53. An exposure assessment for α-HCH in breast milk was not performed, as it was not detected at the LOD of 0.01 mg/kg fat and is therefore considered unquantifiable (Woolridge *et al*., 2004).

Infant formula

54. An exposure assessment for α-HCH in infant formula and cow's milk was not performed, as it could not be detected at or above many of the reporting limits/LOQs described in paragraphs (48-49) and is therefore considered unquantifiable.

Complementary foods

55. An exposure assessment for α-HCH in complementary food was not performed as the 2015 pesticide residues in food report by JMPR described in (paragraph 25) did not include α-HCH. Furthermore, α-HCH could not be detected at or above the reporting limits/ LOQs in the surveys described in paragraphs (51-53). Other data provided in an EFSA report (paragraph 21 and 55) reporting food samples containing of α-HCH are insufficient to conduct a meaningful exposure assessment.

Risk characterisation

50. α-HCH was not detected in breast and cow's milk at a LOD of 0.01 and 0.007 mg/kg respectively. Infant formula, also did not contain α-HCH at or above the LOD of 0.001 mg/kg for reconstituted formula, implying α-HCH is present at levels below the NOAEL of 0.1 mg/kg (paragraph 46) and is not of toxicological concern to children aged 15-18 months.

51. As for complementary food α-HCH was present in a variety of foods below a reporting limit of 0.01 mg/kg and LOQ of 0.001 mg/kg, both of which are below the NOAEL of 0.1mg/kg and is therefore unlikely to be toxicological concern to children aged 1-5 years old.

β-HCH

Toxicity of β-HCH

52. The previous statement (COT, 2014) presented findings of hepatoxicity (increased liver weight, hyalinization and CYP induction) and a toxic effect in the thymus, testes and ovaries in animal studies. There are no recent epidemiological findings of hepatoxicity in humans, and with regards to endocrine disrupting potential there has been conflicting findings on the association of β-HCH and endometriosis.

53. Other results from animal studies reported evidence of neurotoxicity (ataxia and reduced nerve tail conduction velocity) and associations between β-HCH and PD in humans were considered inconclusive (COT, 2014).

54. Reproductive effects of infertility were previously reported in animal studies and it was also concluded that β-HCH is not mutagenic (COT, 2014). With regards to carcinogenicity, the COT determined that findings of β-HCH causing liver tumours in

rodents was via non-genotoxic mechanisms and is irrelevant to humans. Other conclusions were that evidence of associations between β-HCH and NHL are inconsistent, and studies showed no evidence of increased risk of breast cancer.

Health-based guidance values

55. In the previous evaluation none the HBGVs identified in literature were used as the human relevance of the critical effects used to derive the HBGVs were questionable and the toxicity of β-HCH is not well characterised (COT, 2014). Alternatively, a margin of exposure (MOE) approach was used and will be used in this current evaluation. The previous evaluation used a LOAEL of 0.18 mg/kg based on centrilobular hypertrophy as a reference point. In a recent EFSA publication a NOAEL of 0.1 mg/kg for β-HCH was cited in earlier and recent EFSA publications (EFSA, 2005, 2019).

Sources of β-HCH

56. The Kalantzi *et al*., 2004 study remains the most recent source of UK data on β-HCH in breast milk, where β-HCH was detected in breast milk and mean and maximum levels of 15 and 1500 µg/kg milk fat found in samples collected between 2001 and 2003

Infant formula

57. Infant formulae are included in the UK national monitoring programme for pesticide residues in food, which is overseen by PRiF. Infant formula was last surveyed between January and February 2014; β-HCH was not detected at or above the reporting limit of 0.01 mg/kg, i.e. the current MRL (PRiF, 2014a).

58. Recent monitoring of the wider UK food supply in July to September 2018 did not identified β-HCH in retail samples of milk at or above their reporting limit of 0.002mg/kg, indicating that levels in infant formula produced from cows' milk produced in the UK are likely to be well below 0.01 mg/kg (PRiF, 2018c). Soya milk, soya tofu and soya pieces have not been included in the UK pesticide monitoring programme since 2006, where the previous statement (COT, 2014) reported β-HCH was undetected at its reporting limit of 0.002 mg/kg and is likely to be well below 0.01 mg/kg.

59. As previously mentioned much of the infant formula consumed in the UK is imported from Ireland. The previous COT statement includes the most recent data on β-HCH reported in a survey by the Food Safety Authority of Ireland in 2004. β-HCH was not detected at a LOQ of 0.001 mg/kg for reconstituted formula or above the LOD of 0.0007 mg/kg for cow's milk in an Irish total diet study conducted during 2001-2005 (COT,2014).

Complementary food

60. Animal based infant foods containing meat, fish, eggs and cheese were last surveyed by PRiF between January and September 2014 (PRiF, 2014b). β-HCH was

not identified in the infant food samples at or above their reporting limits of 0.01 mg/kg.

61. Presence of β-HCH in cereal and vegetable based infant foods is unknown, as in the most recent survey (PRiF, 2013) and in earlier surveys β-HCH was not examined in these infant food samples.

62. Recent monitoring of the wider UK food supply between January and September 2018, where 2,329 samples were surveyed, β-HCH was not identified to be over its reporting limits ranging from 0.01 mg/kg for most commodities such as fruits, vegetables and cereals to 0.002 mg/kg in meats, milk, cheese and eggs. Collectively, there were 2,329 samples for a range of commodities surveyed and β-HCH did not exceed its MRL of 0.01 mg/kg in any (PRiF, 2018a, b, c).

63. The HSE have supplied the following data regarding the presence of β-HCH in various foods. In 2008 one sample of whitebait from Bulgaria at 0.01 mg/kg and in 2015 one sample of feta cheese from Greece at 0.005 mg/kg (HSE, 2019).

64. In an EFSA report (paragraph 21) presenting results on pesticide residues in food samples taken from various reporting countries (including the UK) in 2017. It was found that β-HCH was quantified below or equal to its MRL (0.01 mg/kg) in 1.2% of samples of animal origin (poultry fat and sheep) (EFSA, 2019).

Exposure

Breast milk

65. Estimates of exposure from breast milk were based on the mean concentration of 15 µg/kg milk fat (equivalent to 0.525 µg/kg whole milk) from the most recent UK study Kalantzi et al., 2004. It was assumed that the fat content of breast milk was 3.5%). Table 5**Error! Reference source not found.** presents the exposure of β-HCH from breast milk to children aged (12 to 15 months).

Table 5. Chronic consumption of Breastmilk and β-HCH exposure to UK infants and Young children (DH, 2013)

Age group (months)	**Consumption of breast milk (g/kg bw/day)**		**Exposure of β-HCH (µg/kg bw/day)**	
	Mean	**97.5th Percentile**	**Mean**	**97.5th Percentile**
12 to 15	29	75	0.015	0.039
15 to 18	25.3	51.8	0.013	0.027

Infant formula

66. An exposure assessment for β-HCH in infant formula and cow's milk was not performed, as β-HCH could not be detected at or above many of the reporting limits/LOQs described in paragraphs (57-58).

Complementary food

67. An exposure assessment for β-HCH in complementary food was not performed as the 2015 pesticide residues in food report by JMPR described in (paragraph 25) did not include β-HCH. Furthermore, β-HCH could not be detected at or above the reporting limits/LOQs described in paragraphs (60-61).

Risk characterisation

68. The MOEs calculated for potential maximum exposures to β-HCH were calculated with a NOAEL of 0.1mg/kg and are show in Table 6.

Table 6. MOEs calculated from comparison of potential exposures from breast milk in children aged 12 to 18 months to β-HCH with the reference point of 0.1 mg/kg bw/day.

Consumption group	**Age**	
	12-15 months	**15-18 months**
Mean	>6600	>7600
97.5th percentile	>2500	>3700

69. The MOEs for children aged 12-18 months in the mean consumption group ranged from >6,000 to 7,600 and >2500 to >4700 for children in the 97.5th percentile consumption group. These MOEs do indicate toxicological concern for breastfed children.

Overall Conclusions

70. Dietary exposure of γ-HCH in children aged 1-5 years is unlikely to be of toxicological concern as all dietary exposure estimates were in line with HBGVs, with the exception of cereal grains. Although, this is likely to be an overestimate as explained in (paragraph 32). As for α-HCH, its dietary concentrations were lower than many of its reporting limits, implying exposure is insignificant and not toxicological concern. Finally, β-HCH had large MOE values for breast milk indicating risk of appreciable health effects are very low, additionally its presence in infant formula and complementary food were lower than its reporting limits further indicating risk of appreciable health effects to be low. Ultimately, HCHs are no longer used and levels of exposure are expected to decrease over time.

Questions to be asked to the committee

i) Do the committee consider it sufficient to include the key points (i.e HBGVs, exposure, conclusions) in the addendum, or wish to request a full

discussion paper on the potential risk from α-, β and γ-HCH in the diet of children aged 1 to 5?

ii) Do the committee agree that exposures to α-, β and γ-HCH in the diet are not of toxicological concern to 1 to 5-year olds?

iii) Do members have any other comments?

Secretariat
October 2019

Abbreviations

ADI	Acceptable daily intake
ARfD	Acute reference dose
bw	Body weight
COC	Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
COT	Committee on Toxicology, Consumer Products and the Environment
CYP	Cytochrome P450
DH	Department of Health
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
EDI	Estimated daily intake
EEG	Electroencephalogram
EFSA	European Food Safety Authority
EMRL	Extraneous maximum residue limits
FAO	Food and Agricultural Organisation of the United Nations
FSA	Food Standards Agency
GEMS	Global Environment Monitoring System
HBGV	Health based guidance value
HCH	Hexachlorocyclohexane
HR	Highest residue
HSE	Health and safety executive
IARC	International Agency for Research on Cancer
IEDI	International estimated daily intake
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	Lowest observed adverse effect level
LOD	Limit of detection
LOQ	Limit of quantification
MOE	Margin of exposure
MRL	Maximum residue limit
NDNS	National Diet and Nutrition Survey

NHL	Non-Hodgkin Lymphoma

NOAEL	No observed adverse effect level
PD	Parkinson's disease
PRiF	Expert Committee on Pesticide Residues in Food
RfD	Reference Dose
RIVM	Rijksinsituut Voor Volksgezondheid En Milieu
STMR	Supervised trials median residue
TDI	Tolerable daily intake
WHO	World Health Organisation

References

Agriculture and Horticulture Development Board (AHDB). (2017). Infant milk Formula – the opportunity for import displacement. https://dairy.ahdb.org.uk/news/news-articles/august-2017/infant-milk-formula-%E2%80%93-the-opportunity-for-import-displacement/#.XUmF42zsZr0 (Accessed 06 August 2019)

Amyes, SJ. (1990). Lindane: Combined oncogenicity and toxicity study by dietary administration to Wistar rats for 104 weeks. Unpublished report No. 90/CIL002/0839 from Life Science Research Ltd, Suffolk, England. Submitted to WHO by CIEL, Brussels, Belgium (cited in FAO/WHO, 2002).

ATSDR. (2005). Toxicological profile for alpha-, beta-, gamma-, and delta-hexachlorocyclohexane. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Bapayeva, G., Issayeva, R., Zhumadilova, A., Nurkasimova, R., Kulbayeva, S. and Tleuzhan, R. (2016). Organochlorine pesticides and female puberty in South Kazakhstan. *Reproductive Toxicology*. 65:67-75.

Bates B, Cox L, Nicholson S, Page P, Prentice A, Steer T, Swan G (2016). National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014). https://www.gov.uk/government/statistics/ndns-results-from-years-5-and-6-combined

Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, Swan G (2014). National Diet and Nutrition Survey (NDNS): results from Years 1 to 4 (combined) of the rolling programme for 2008 and 2009 to 2011 and 2012. https://www.gov.uk/government/statistics/national-diet-and-nutrition-survey-results-from-years-1-to-4-combined-of-the-rolling-programme-for-2008-and-2009-to-2011-and-2012

Brouwer, M., Huss, A., van der Mark, M., Nijssen, P.C., Mulleners, W.M., Sas, A.M., Van Laar, T., de Snoo, G.R., Kromhout, H. and Vermeulen, R.C. (2017). Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands. *Environment international*. 107:100-110.

Chand, S., Mustafa, M.D., Banerjee, B.D. and Guleria, K. (2014). CYP17A1 gene polymorphisms and environmental exposure to organochlorine pesticides contribute to the risk of small for gestational age. European Journal of Obstetrics & Gynecology and *Reproductive Biology*. 180:100-105.

Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC). (2004). Breast cancer risk and exposure to organochlorine insecticides: consideration of the epidemiology data on dieldrin, DDT and certain hexachlorocyclohexane isomers. Statement COC/04/S3. http://www.iacoc.org.uk/statements/coc04s3full.pdf.

Committee on toxicity of chemicals in food, consumer products and the environment (COT) (2014). COT statement on the potential risks from α-, β- and γ-hexachlorocyclohexanes in the infant diet. https://cot.food.gov.uk/sites/default/files/cot/cotstatmhchs.pdf

DH (2013). Diet and Nutrition Survey of Infants and Young Children (DNSIYC), 2011. Available at: http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

EbrahimiDaryani, N., Keramati, M., EbrahimiDaryani, N. and Bashashati, M. (2008). Lindane-Induced Hepatotoxicity in Human: Report of a Rare Case. *Govaresh*.13(1):58-59.

European Food Safety Authority (EFSA) (2005). Opinion of the Scientific panel on Contaminants in the Food Chain on a request from the Commission related to gamma-HCH and other hexachlorocyclohexanes as undesirable substances in animal feed. *The EFSA Journal*. 250, 1 – 39

European Food Safety Authority (EFSA). (2016). Scientific support for preparing an EU position in the 48th Session of the Codex Committee on Pesticide Residues (CCPR). *EFSA Journal.* 14(8).https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4571

Ennaceur, S. (2017). Study of the genotoxic and cytotoxic effects of the α-, β-, and γ-Hexachlorocyclohexane isomers in human lymphocyte cells using the cytokinesis-block micronucleus assay. *Drug and chemical toxicology*. 40(1):85-89.

European Food Safety Authority (EFSA). (2019). The 2017 European Union report on pesticide residues in food. *EFSA Journal*. 17(6),p.e05743.https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2019.5743

Expert Committee on Pesticide Residues in Food (PRiF). (2013). Pesticide Residues Monitoring Programme for Quarter 1 2013. https://webarchive.nationalarchives.gov.uk/20151023234404/http://www.pesticides.gov.uk/Resources/CRD/PRiF/Documents/Results%20and%20Reports/2013/2013%20Q1%20Final.pdf

Expert Committee on Pesticide Residues in Food (PRiF). (2014a). Pesticides residues monitoring Programme for Monitoring Programme for Quarter 1 2014. https://webarchive.nationalarchives.gov.uk/20151023185219/http://www.pesticides.gov.uk/Resources/CRD/PRiF/Documents/Results%20and%20Reports/2014/Q1%202014%20%20FINAL.pdf

Expert Committee on Pesticide Residues in Food (PRiF). (2014b). Pesticides residues monitoring Programme for Monitoring Programme for Quarter 3 2014. https://webarchive.nationalarchives.gov.uk/20151023185139/http://www.pesticides.gov.uk/Resources/CRD/PRiF/Documents/Results%20and%20Reports/2014/Q3%202014%20FINAL.pdf

Expert Committee on Pesticide Residues in Food (PRiF). (2015). Pesticides residues monitoring Programme for Monitoring Programme for Quarter 1 2015

https://webarchive.nationalarchives.gov.uk/20151023185610/http://www.pesticides.gov.uk/Resources/CRD/PRiF/Documents/Results%20and%20Reports/2015/Q1%202015%20FINAL.pdf

Expert Committee on Pesticide Residues in Food (PRiF). (2018a). Report on the pesticide residues monitoring programme: Quarter 1 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/738311/pesticide-residues-quarter1-2018-report.pdf

Expert Committee on Pesticide Residues in Food (PRiF). (2018b). Report on the pesticide residues monitoring programme: Quarter 2 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/762243/pesticide-residues-quarter2-2018-report.pdf

Expert Committee on Pesticide Residues in Food (PRiF). (2018c). Report on the pesticide residues monitoring programme: Quarter 3 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784337/pesticide-residues-quarter3-2018-report.pdf

Food and Agriculture Organization/World Health Organization (FAO/WHO). (2002). Pesticide residues in food, Lindane, pp 181-186. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. Rome, Italy 16-25 September 2002.

Food and Agriculture Organization/World Health Organization (FAO/WHO). (2015) Pesticide Residues Report. FAO plant production and protection paper 223.http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report2015/web_JMPR_2015_Report_Draft_Nov_21v2.pdf.

Food Safety Authority of Ireland. (2004). Report on surveillance of infant food for pesticide residues. http://www.fsai.ie/uploadedfiles/pesticide_residues_infant.pdf

Food Safety Authority of Ireland. (2006). Report on surveillance of infant food for pesticide residues. https://www.fsai.ie/uploadedFiles/infant_food_pesticides.pdf

Health and safety executive (HSE). (2019). HCHS/HSE Data. Email

International Agency for Research on Cancer. (2015). DDT, lindane and 2,4-D. *IARC Monographs On the evaluation of carcingoeni c risk to humans.*113.https://monographs.iarc.fr/wp-content/uploads/2018/07/mono113.pdf.

Kalantzi OI, Martin FL, Thomas GO, Alcock RE, Tang HR, Drury SC, Carmichael PL, Nicholson JK, Jones KC. (2004). Different levels of polybrominated diphenyl ethers (PBDEs) and chlorinated compounds in breast milk from two U.K. Regions. *Environ Health Perspect*. 112(10):1085-91.

Khan, F.H., Ganesan, P. and Kumar, S. (2010). Y Chromosome microdeletion and altered sperm quality in human males with high concentration of seminal hexachlorocyclohexane (HCH). *Chemosphere*. 80(9):972-977.

Kumar, V., Yadav, C.S., Singh, S., Goel, S., Ahmed, R.S., Gupta, S., Grover, R.K. and Banerjee, B.D. (2010). CYP 1A1 polymorphism and organochlorine pesticides levels in the etiology of prostate cancer. *Chemosphere.* 81(4):464-468.

Louis, L.M., Lerro, C.C., Friesen, M.C., Andreotti, G., Koutros, S., Sandler, D.P., Blair, A., Robson, M.G. and Freeman, L.E.B. (2017). A prospective study of cancer risk among Agricultural Health Study farm spouses associated with personal use of organochlorine insecticides. *Environmental Health*, 16(1):95.

Meera P, Rao PR, Shanker R, Tripathi 0. (1992). Immunomodulatory effects of γHCH (lindane) in mice. *Immunopharmacol Immunotoxicol* 14: 261-282.

Michałowicz, J., Mokra, K., Rosiak, K., Sicińska, P. and Bukowska, B. (2013). Chlorobenzenes, lindane and dieldrin induce apoptotic alterations in human peripheral blood lymphocytes (in vitro study). *Environmental toxicology and pharmacology*, *36*(3):979-988.

Mills PK, Yang R. (2003). Prostate cancer risk in California farm workers. *JOEM*.45(3):249-258.

Paul, R., Talukdar, A., Bhattacharya, R. and Santra, G., 2013. γ-Benzene hexachloride poisoning leading to acute hepatorenal decompensation. *Case Reports*, *2013*, p.bcr2013009851.

Pi, N., Chia, S.E., Ong, C.N. and Kelly, B.C. (2016). Associations of serum organohalogen levels and prostate cancer risk: Results from a case–control study in Singapore. *Chemosphere*. 144:1505-1512.

Ren, A., Qiu, X., Jin, L., Ma, J., Li, Z., Zhang, L., Zhu, H., Finnell, R.H. and Zhu, T. (2011). Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects. *Proceedings of the National Academy of Sciences*. 108(31):12770-12775.

Roberts, C., Steer, T., Maplethorpe, N., Cox, L., Meadows, S., Nicholson, S., Page, P. and Swan, G. (2018). National Diet and Nutrition Survey: results from years 7 and 8 (combined) of the Rolling Programme (2014/2015–2015/2016). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/699241/NDNS_results_years_7_and_8.pdf

WHO (World Health Organisation). (2012). GEMS/Food Consumption Cluster Diets. Map and List. Available from: http://www.who.int/foodsafety/chem/Global_GEMS_CLUSTERS_2012.jpg?ua=1. and http://www.who.int/foodsafety/chem/cluster_diets_2012.pdf?ua=1&ua=1. (Accessed 06 August 2019)