TOX/2013/04

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

Review of potential risks of α-, β- and γ-hexachlorocyclohexanes in the infant diet

Introduction

1. The Committee on Toxicity (COT) has been asked to provide advice on toxicity of chemicals in the infant diet, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. An initial paper (TOX/2012/3), highlighting some of the areas requiring consideration was discussed by the COT in February, 2012. The COT concluded that persistent organic pollutants included in the Stockholm convention since 2009, i.e. α- and β-hexachlorocyclohexane, lindane (γ-hexachlorocyclohexane), chlordecone, pentachlorobenzene, perfluoro octane sulfonic acid salts and perfluoro octane sulfonic fluoride, technical endosulfan and its related isomers, required further evaluation. This discussion paper provides a summary of the available toxicological information on α-, β- and γ-hexachlorocyclohexanes (HCHs). It also provides estimates of exposure via breast milk, infant formula, infant foods and water.

2. There are currently no Government recommendations on complementary and young child feeding that relate to HCHs.

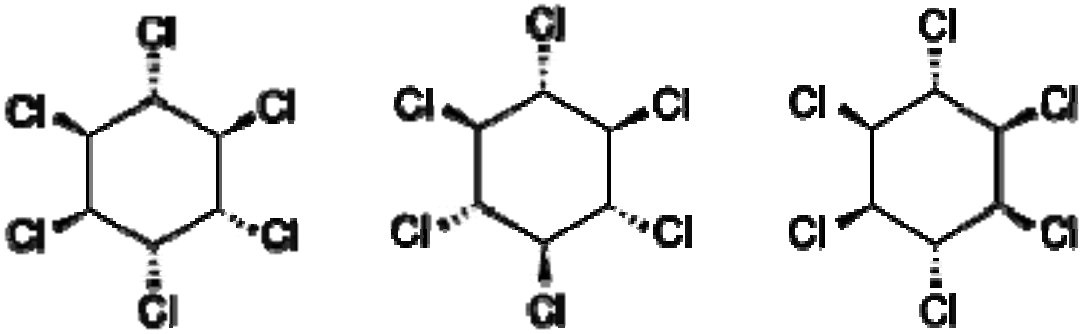
3. Lindane (γ-HCH) has been evaluated by the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO) (WHO-IPCS, 1991) and by the Joint Food and Agriculture Organization (FAO)/WHO Meeting on Pesticide Residues (JMPR) (FAO/WHO, 2002). In addition, α- and β-HCH have been reviewed by IPCS (WHO-IPCS, 1992). The European Food Safety Authority (EFSA) has published an opinion on γ-HCH and other HCHs as contaminants in animal feed (EFSA, 2005). On behalf of Syngenta Crop Protection and Stauffer Management Company, Integral Consulting recently reviewed the toxicity of α-, β- and γ-HCH and proposed reference doses (RfDs), (Integral Consulting, 2011a, b, c).

Identity

4. HCHs are organochlorines and encompass a group of eight isomers; α-, β-, δ-, ε-, ζ-, η-, θ- and γ-HCH. Technical-grade HCH consists of approximately 60–70% α-HCH, 5–12% β-HCH, 10– 15% γ-HCH, 6–10% δ-HCH, and 3–4% ε-HCH (Kutz et al. 1991). This review focuses on α- β- and γ-HCH since these are listed as persistent organic pollutants in the Stockholm convention. Their structures are presented in Figure 1.

Figure 1. Chemical structure for α-, β-, and γ-HCH

α-HCH (CAS 319-84-6) β-HCH (CAS 319-85-7) γ-HCH (CAS 58-89-9)



5. The term “lindane” commonly refers to pesticidal products that contain >99% γ-HCH, although it has also been used colloquially as a synonym for γ-HCH. In this discussion paper the term “lindane” is used when referring to the product, and γ-HCH is used when referring to the chemical. Lindane has been used for topical insecticide treatment in humans and animals. It has been estimated that for each ton of lindane produced, around 6-10 tons of other isomers, were generated (Stockholm Convention, 2009).

6. Because of their lipophilic properties and persistence in the environment, β-HCH, followed by α-HCH and to a lesser extent γ-HCH bioaccumulate and biomagnify in the food chain. Their semivolatility allows them to be transported long-range and undertake “cold condensation”, thus increased levels are usually found in water in colder regions. The long-range atmospheric transport has resulted in global distribution especially of the most stable isomers α- and β-HCH (EFSA, 2005).

7. Pesticidal use of HCH products that contained less than 99.0 % γ-HCH was banned in the EU by Council Directive 79/117/EEC of 21 December 1978. The authorization for lindane use as a pesticide was withdrawn in the EU by Commission Decision 2000/801/EC of 20 December 2000. This action was taken primarily due to concerns with regard to its safety, in particular for operator exposure, the fate and behaviour of lindane in the environment and effects on non-target organisms.

8. There are no current Marketing Authorisations (product licences) in the UK for any medicines containing lindane as the active ingredient (Medicines and Healthcare products Regulatory Agency, personal communication, 2013). However, it is still used in other countries. For example, shampoos with lindane for medical purposes are approved by the US Food and Drug Agency (USFDA) and are marketed in the US. Lindane is typically used at 1 % concentration (Reynolds, 1996). USFDA suggests their use as a second-line medication for patients with scabies and lice who have failed or cannot tolerate first-line therapies (USFDA, 2007).

Hazard identification and characterisation

Toxicokinetics

9. The information on toxicokinetics summarised below is based on the reviews of the IPCS on α- and β-HCH (WHO-IPCS, 1992) and on lindane by JMPR (FAO/WHO, 2002). The relevant sections of those reviews are included in Annex A Part A, Annex A Part B and Annex B respectively. In general, the data are very limited for α- and β-HCH, whereas more information is available for lindane. Searches of the scientific literature have identified few studies published since these reviews were written. These are summarised below where relevant.

Absorption

10. From the limited available data it appears that α- and β-HCH are almost completely absorbed from the gastrointestinal tract (WHO-IPCS, 1992, see Annex A page 43 and 97). Similarly, γ-HCH is rapidly and extensively absorbed in mice and rats after oral dosing (FAO/WHO, 2002, see Annex B pages 118 to 123).

11. Absorption of lindane through skin was examined using human volunteers and was confirmed with different solvents such as white spirit and alcohol (Dick et al., 1997).

Distribution

11. Following absorption α- and β-HCH are predominantly distributed to the liver, kidney, brain, muscle and adipose tissue with marked accumulation in the fat. β-HCH is reported to pass the blood-brain barrier less readily than other HCH isomers. Transplacental and lactational transfer also occur (WHO-IPCS, 1992, see Annex A pages 43 to 44 and 97 to 98).

12. γ-HCH is extensively distributed throughout the body of rodents. In mice and rat, results from several studies showed similar distribution patterns with radiolabel detected in fat, brain, kidney, muscle, liver and ovary tissue after administration of lindane in the diet. The highest concentration is found in adipose tissue (FAO/WHO, 2002, see Annex B pages 118 to 123).

Metabolism

13. Metabolism of HCHs involves dechlorination. The major phase I metabolite of α- HCH is 2,4,6- trichlorophenol, with lesser amounts of 1,2,4-, 2,3,4- and 2,4,5-trichlorophenol, 2,3,4,5- and 2,3,4,6-tetrachlorophenols and 1,3,4,5,6-pentachlorocyclohex-1-ene. A glutathione conjugate has also been reported (WHO-IPCS, 1992, see Annex A pages 44 to 45)

14. β-HCH is also metabolised predominantly to 2,4,6- trichlorophenol, but with fewer other chlorophenols having been reported. Conjugation is reported to be mainly with glucuronide or sulphate (WHO-IPCS, 1992, see Annex A pages 99 to 100).

15. The metabolism of γ-HCH is extensive in mammals, involving stepwise dehydrogenation, dechlorination and dehydrochlorination, which may be followed by conjugation with sulphate or glucuronide. Cytochrome P450 (CYP) appears to be involved in the phase I metabolism. The predominant metabolite is again 2,4,6-trichlorophenol, with other varying amounts of other chlorophenols produced, depending on species. Figure 1 in Annex B shows the proposed metabolic pathways of γ-HCH (FAO/WHO, 2002). EFSA noted that 70 metabolites of γ-HCH have been identified in animals and humans, including (in no particular order) pentachlorophenol, 2,3,4,6- and 2,3,5,6-tetrachlorophenol and 2,4,6-trichlorophenol, tetrachlorophenols, 2,3,4,5,6-pentachlorobenzene and pentachlorocyclohexene and conjugates with glutathione, glucuronide and sulphate. (EFSA, 2005).

Excretion

16. After intraperitoneal injection to rats, 40-80% of α-HCH was excreted in the urine and 5-20% in the faeces. The half-life for clearance from the fat was reported to be 6.9 days in female rats and 1.6 days in male rats. The half-life for elimination from the brain of female rats was reported to be 6 days (WHO-IPCS, 1992, see Annex A page 43).

17. In rats, 70% of β-HCH is eliminated within 28 days, one third of this being excreted in the urine as metabolites, suggesting that faecal excretion is more important for β-HCH than for α-HCH. A 2-stage process has been reported for elimination of β-HCH in mice, the half-life for the first stage being 2.5 days and that for the second stage being 18 days. The half-life for clearance from blood in rats (sex not specified) was 1 month, and the half-life for clearance from fat was 14 days in male rats and 28 days in female rats. A half-life of 22 days for clearance from "internal organs" and 20 days for the brain were reported in female rats. (WHO-IPCS, 1992, see Annex A page 97).

18. The elimination of β-HCH in humans was investigated by Jung et al., (1997) in a group of 40 former workers of a lindane-producing plant by analyzing at least 2 blood specimens (3 specimens in 3 workers) from different time points. Assuming a first-order kinetic model for excretion, the median half-life of β-HCH was 7.2 years calculated by concentrations in whole blood and 7.6 years calculated by concentrations in extractable lipids. In univariate analyses an influence of age, percent body fat, and liver disease on clearance was observed. All factors showed a positive correlation with half-life. The data support the assumption of first-order kinetics.

19. Breast milk is a route of excretion of β-HCH in lactating women. Waliszewski et al. (2009) determined the concentration of organochlorine pesticide levels in human breast milk samples from the 4th to the 30th day postpartum. Milk samples were taken from forty participants who had lived a minimum of 5 years in Veracruz (Mexico) prior to admittance for delivery. The β-HCH residues presented as mean and standard deviation (SD) in the breast milk samples decreased during lactation from 95 (60) on the 4^{th} day to 66 (45) μg/kg on the 30^{th} day.

20. Urine is the major route of excretion of metabolites, with a smaller proportion in the faeces. The half-life of γ-HCH in rats was estimated to be 3–5 days,

approximately 80% of the administered dose being excreted within 8 days (FAO/WHO, 2002, see Annex B pages 124 to 128).

Induction of drug metabolising enzymes

21. α-HCH has been reported to induce glutathione-S-transferase (Puatanachokchai et al., 2006). A dose and time-dependent increase in the levels of CYP2B, 2C, 2E and 3A has been observed in rats exposed to α-HCH for 6 weeks at 6 to 50 mg/kg bw/day 2 weeks after exposure to the tumour initiator diethylnitrosamine (Masuda et al, 2001; Puatanachokchai et al., 2006).

22. Scientific literature has given little attention to the effects of β-HCH on drug metabolising enzymes. It has been suggested that this might be due to their lack of relevance in the mode of action required by β-HCH to exert its effects (Integral Consulting, 2011b).

23. γ-HCH has been reported to induce several drug-metabolising enzymes including glutathione-S-transferase and UDP-glucuronosyl transferase, but inhibit others such as epoxide hydrolase (FAO/WHO, 2002, see Annex B pages 124 to 128). Parmar et al. (2003) reported dose-dependent increased levels of CYP 1A1/1A2, 2B1/2B2 and 2E1 enzymes in the liver and brain of rats dosed with γ-HCH at 2.5 mg/kg bw per day or more for 21 days.

Toxicity of HCHs

24. Reviews of α-, β- and γ-HCH were carried out by Integral Consulting in 2011 aiming to establish RfDs. The US Environmental Protection Agency (USEPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) reviews of HCH toxicity (ATSDR, 2005; USEPA, 2001) were used as a starting point. Integral Consulting also included other relevant studies until 2011. The reviews prepared by Integral Consulting on α-, β- and γ-HCH are provided in Annex C, D and E respectively. Additional searches in the scientific literature have been carried out until the present time.

25. The available toxicological data indicate that HCHs can exhibit neurotoxicity, immunotoxicity, hepatoxicity, carcinogenicity and reproductive toxicity. α- and γ-HCH exhibit renal toxicity in rats that is considered not to be relevant to human risk assessment since it is a consequence of accumulation of α-2micro-globulin, a protein that is not found in humans (Integral Consulting, 2011a; FAO/WHO, 2002).

Acute toxicity

26. Oral LD50 values for α-HCH and β-HCH are in the region of 1000 - 4000 and 1500 to > 16,000 mg/kg b.w. respectively in rats and mice. Signs of toxicity were mainly related to stimulation of the nervous system (WHO-IPCS, 1992, see Annex A pages 47 and 101). For γ-HCH oral LD50 values are 56 to 250 mg/kg bw in mice and 140–190 mg/kg bw in rats (FAO/WHO, 2002, see Annex B pages 129 to133).

Repeat dose toxicity

27. Hepatotoxicity has been reported for all three HCH isomers in many studies. Those identified as pivotal by other reviews are described below.

28. In a 90-day study, rats given 0, 2, 10, 50 or 250 mg α-HCH/kg diet showed growth depression at the highest dose (equivalent to 12.5 mg α-HCH/kg b.w./day). Liver hypertrophy was seen at a dose of 10 mg/kg diet (equivalent to 0.5 mg/kg b.w./day). The NOAEL was 2 mg α-HCH/kg diet (equivalent to 0.1 mg/kg b.w./day). Signs of immunosuppression (reduced levels of immunoglobulins) were seen at 2.5 mg α-HCH/kg b.w./day (Kuiper et al., 1985; cited in EFSA, 2005).

29. The oral toxicity of β-HCH was investigated in a 13-week study in rats with doses of 0, 2, 10, 50, or 250 mg/kg feed. Liver effects (increased weight, centrilobular hypertrophy, and proliferation of smooth endoplasmic reticulum or increased activity of microsomal enzymes) were observed in all dose groups. Effects on the thymus, testes and ovaries, and severe morbidity were observed in the highest dose group (Van Velsen et al., 1986a). This study was identified by Integral Consulting (2011b) as the pivotal study for proposing an RfD, and a LOAEL of 0.18 mg/kg bw per day for hyalinization of centrilobular cells was identified.

30. Hepatocellular hypertrophy was observed in a number of studies of γ-HCH in mice, rats and rabbits. In a 2-year study of toxicity and carcinogenicity in rats, the NOAEL was 10 ppm in the diet (equal to 0.47 mg/kg bw per day) on the basis of increased liver weight, hepatocellular hypertrophy, increased spleen weight and deaths at 100 ppm (equal to 4.7 mg/kg bw per day (Amyes et al., 1990) (FAO/WHO, 2002).

Neurotoxicity

31. α-HCH has been reported to inhibit GABA-mediated chloride ion uptake in mouse brain, which is considered to play a primary role in its action on the central nervous system (CNS) (WHO-IPCS, 1992 Annex A page 57). However information on the dose response relationship for neurotoxicity following oral exposure are not available.

32. β-HCH has been observed in acute and semi-chronic studies to induce ataxia in rats with a NOAEL of 5 mg/kg b.w. per day and 19 mg/kg bw per day in mice. Other effects such as reduced tail nerve conduction velocity have been reported at higher concentrations (WHO-IPCS, 1992 Annex A page 109).

33. There are a large number of studies on neurotoxicity of γ-HCH, which have been evaluated by JMPR (FAO/WHO, 2002). With a single exposure in rats, a NOAEL at 6 mg/kg bw was reported on the basis of increased fore-limb grip strength and decreased grooming behaviour. In a 90-day study of neurotoxicity in rats, the NOAEL for males was 7.1 mg/kg bw per day on the basis of hypersensitivity to touch and hunched posture. In a study of developmental neurotoxicity in rats, the NOAEL for maternal toxicity after 25 days of exposure *ad libitum* was 4.2 mg/kg bw per day on the basis of decreased body weight, decreased food consumption and increased reactivity to handling. .

Immunotoxicity

34. A study by Van Velsen et al., (1986a) on rats exposed through diet to β-HCH for 13 weeks reported a number of immunological effects with a NOAEL at 4.5 and 3.3 mg/kg bw/day for males and females respectively. The described effects were significantly decreased levels of red and white blood cells in conjunction with increased extramedullar haematopoiesis in the spleen and hypertrophy of the thymus and adrenal gland. Lower NOAELs at 0.89 and 0.66 mg/kg bw/day were reported for relative increased weight in spleen and thymus.

35. Based on a study in which mice were given γ-HCH at 0, 10, 40 or 160 mg/kg in the diet for 39 weeks to examine the effects on the total number of leukocytes and on the relative proportion of lymphocyte populations, JMPR concluded that γ-HCH is not immunotoxic (FAO/WHO, 2002; see Annex B page151).

36. A study by Meera et al., (1992) investigated a number of different immunological endpoints in female rats exposed for 24 weeks to γ-HCH with a 97 % purity. Lymphocyte transformation and haemolytic plaque forming cell assay was observed at 0.012 mg/kg bw per day, the lowest dose tested. The lymphocyte proliferation response to concanavalin A increased up to 8 weeks with a later decrease after 12 weeks. An increase in the plaque forming assay number up to 8 weeks was followed by suppression up to 24 weeks. Other effects were reported at higher doses such as necrosis of thymus, lymph nodes and spleen.

Reproductive toxicity

37. No information is available on reproductive toxicity and α-HCH in the IPCS and Integral Consulting reports. Additional searches in the scientific literature did not find studies evaluating reproductive effects of α-HCH.

38. In a 2 generation-study, rats in the F0 generation were fed β-HCH (> 98%) for 13 weeks. Almost complete infertility was reported in the F1 generation with a NOAEL of 0.02 mg/kg bw/day (van Velsen, 1986b in PhD Thesis, cited in IPCS-WHO, 1992, Annex A pages 104 to 105). A later publication by Van Velsen et al, (1986a) reported endocrine effects in the parental generation. In females, decreased body weight and increased weight of the adrenal gland and uterus with a NOAEL of 0.13 mg/kg bw per day were observed. Atrophy of the testes, reduced size of seminiferous tubules and lower number of Leydig cells were observed in males with a NOAEL of 3.3 mg/kg bw per day (Integral Consulting, 2011b, Annex D Table 8)

39. There are a large number of studies that have investigated the reproductive toxicity of γ-HCH. The outcomes are diverse and occasionally inconsistent between studies. In rats, effects such as delayed vaginal opening, decreased ovary weight and decreased number of fetuses have been reported. In F1, the effects observed were decreased weight and viability of pups and increased spleen weight. Semi-chronic studies in mink ranging from 12 to 17 weeks exposure at 1 mg/kg day induced effects such as reduced litter size (F2), reduced testis size (F3), reduced mating receptivity and increased embryo loss. Endocrine effects have also been

investigated in a number of studies. The most prominent effects are a decrease in the levels of thyroid hormones and modulation of luteinizing and follicle-stimulating hormone which are likely to be related with the alteration of oestrous cycle as reported by some studies (Integral Consulting, 2011c, Annex E Table 8).

40. In an extended two-generation reproduction study (Matsuura et al., 2005), rats were exposed to γ-HCH at 0, 10, 60 and 300 ppm diet for 10 weeks before and through mating until terminal necropsy (males); and through mating, gestation, lactation until F1 weaning at post partum day 21 (females); the F1 were treated in the same manner as F0 animals after weaning at postpartum day 21. Findings in all generations included decreased body weight gain, increased liver weights and centrilobular hypertrophy and induction of hepatic drug metabolising enzymes, Reproductive effects included lack of nursing and retrieval behaviour, possibly due to effects on the nervous system, but no effects on oestrus cycle, spermatogenesis, mating, fertility, pregnancy or parturition. No changes were found in endpoints for endocrine disrupting activity. In the males of the low dose group (equal to an average of 0.56 mg/kg bw/day) the relative liver weight was statistically significantly higher than control, but without clear dose-dependency. Other effects were observed at the high, and in some instances also in the mid dose group. Overall, the results of this study indicate a NOAEL of 0.56 mg/kg bw/day F0 males and 0.6 mg/kg bw/day (average of pre-mating and gestation period) in F0 females.

Genotoxicity

41. α-HCH was not mutagenic in the Ames test in *Salmonella typhymurium* or in a reverse mutation assay in *Escherichia coli* and *Saccharomyces cerevisiae*. Positive results have been obtained for induction of DNA binding *in vitro* and *in vivo*, DNA fragmentation *in vitro* and chromosome alterations *in vivo* (Integral Consulting 2011a, see Annex C Table 3).

42. β-HCH was not mutagenic in the Ames test in *Salmonella typhymurium* (WHO-IPCS, 1992). It was negative in the spot test in *Bacillus subtilis* and for DNA binding *in vitro,* but positive for DNA fragmentation *in vitro* in human MCF-7 breast carcinoma cells (Integral Consulting 2011b, see Annex D Table 3).

43. Data on genotoxicity of γ-HCH are inconsistent. γ-HCH was positive in the Ames test in *Salmonella typhymurium* and negative in the hypoxanthine-guanyl phosphoribosyl transferase (HPRT) assay with Chinese hamster ovary (CHO) cells. Tests for DNA binding were weakly positive *in vivo* as well as *in vitro*. Mixed outcomes with positives and negatives were obtained in a variety of assays for DNA breakage (Comet assay), fragmentation (micronucleus), repair (unscheduled DNA synthesis) and sister chromatid exchange *in vitro* as well as *in vivo* (Integral Consulting, 2011c, see Annex E Table 3). JMPR concluded that genotoxicity was found only at cytotoxic concentrations or in the presence of lindane precipitate and that lindane is not genotoxic (FAO/WHO, 2002).

Carcinogenicity

44. α-HCH has been shown to cause benign and malignant liver tumours in multiple mouse strains and in rats, with rats being less sensitive than mice. Results obtained from initiation-promotion studies for α-HCH support the role of α-HCH as a tumor promoter. In initiation-promotion studies, formation of preneoplastic hepatic foci has been used as a marker for carcinogenic potential (Integral Consulting, 2011a). Masuda et al, (2001) gave male rats a single injection of diethylnitrosamine, followed by partial hepatectomy, and then α-HCH at 0.01 – 500 mg/kg in the diet for 6 weeks. Dose-dependent increases were reported in the number of altered hepatic foci at 0.5 – 500 mg/kg with a NOAEL of 0.1 mg/kg diet, equivalent to about 0.01 mg/kg bw per day.

45. A number of studies of carcinogenicity have been reported for β-HCH in rats and mice. While there are limitations in several of them, they do not indicate that β-HCH is carcinogenic (Integral Consulting, 2011b; see Annex D Tables 2 and 5).

46. An extensive number of studies have investigated the effects of γ-HCH in carcinogenicity (Integral Consulting 2011c; see Annex E Table 2). It did not induce a carcinogenic response in rats or dogs, but increased incidences of adenomas and carcinomas of the liver were observed in agouti and pseudoagouti mice at a dose of 23 mg/kg bw per day in a study of the role of genetic background in the latency and incidence of tumorigenesis (Wolff et al., 1987). No tumours were observed in black mice in this study nor in any other strain of mice. In another study, a slightly increased incidence of lung adenomas was observed in female mice at the highest dose (21 mg/kg bw per day); however, there was a limited dose–response relationship and this tumour is common in the strain of mice used, the incidence (27%) only slightly exceeding that in other control groups (19%) (USEPA, 2001). In the absence of genotoxicity and on the basis of the weight of the evidence from the studies of carcinogenicity, JMPR concluded that lindane is not likely to pose a carcinogenic risk to humans (FAO/WHO, 2002).

Observations in humans

47. The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluated whether exposure to organochlorine insecticides including β-HCH and lindane was associated with an increased risk of breast cancer in 2004 (COC, 2004). The COT concluded:

β-HCH. "*β-HCH should be regarded as having weak in vivo oestrogenic activity. There is evidence from investigations undertaken in the UK for a decline in β-HCH concentrations in human fat samples after 1982/3. The available epidemiological studies do not suggest any evidence for an association between β-HCH and increased risk of breast cancer. Overall the available data do not suggest that environmental exposure to β-HCH is a cause for concern as a risk factor for human breast cancer".*

Lindane. *"Lindane (γ-HCH) does not have any in vivo oestrogenic activity. It is not approved for use as a pesticide in the U.K. Exposure is likely to be negligible. The Committee have previously concluded that there is no biological rationale for including lindane in any epidemiology studies on risk of breast cancer. The Committee concluded there is no reason to undertake any further reviews of the association of this chemical with increased risk of breast cancer".*

48. A number of relevant studies have been identified after the COC statement, these have been collated in the reports carried out by Integral Consulting (2011a, b, c). No relevant studies have been identified subsequent to the publication of the Integral Consulting reports.

49. One study investigated a possible association between α-HCH body burden and cancer (Mathur et al., 2002). In this study, 135 breast cancer patients and 50 females without cancer filled out questionnaires and were evaluated for their body burden of pesticides through blood testing. α-HCH blood levels were significantly higher in breast cancer patients, 41–50 years of age, compared to women of the same age without the disease. Integral Consulting (2011a) highlighted that the study did not account for confounders such as presence of other organochlorine pesticides and body fat levels (a parameter associated with breast cancer risk and body burden of lipohilic chemicals).

50. A potential association of β-HCH with non-Hodgkins lymphoma has also received attention (Integral Consulting, 2011b, Annex D Table 1). Two investigations did not find any association between β-HCH body burden and diagnose of non-Hodgkin lymphoma (Cantor et al, 2003; Cocco et al, 2008). The investigation by Spinelli et al, (2007) found a weak association. The study by Quintana et al, (2004) reported a positive association. The cited studies had limitations mostly related to limited information on potential confounders but also variability in the analytical sample results. Other investigations have evaluated the potential association of β-HCH to the incidence of endometrial cancer (Sturgeon et al., 1998) and risk of testicular germ cell cancer (McGlynn et al., 2008). Both studies concluded a lack of association.

51. Potential associations between β-HCH body burden and neurotoxicity have been investigated. Neurotoxicity was reviewed in one study which found higher levels of β-HCH in subjects diagnosed with Parkinson's disease than in controls (Richardson et al, 2009). However, the study had limitations such as small sample size and the fact that a considerable number of diagnosed subjects did not present detectable levels of β-HCH.

52. Several investigations on the potential associations between γ-HCH body burden and breast cancer have been published after the COC statement (paragraph 47) (Integral Consulting, 2011c; see Annex E Table 1). A study by Mills et al. (2006) reported no association after evaluation of a database with a total of 23,513 women of Hispanic origin diagnosed with breast cancer in California during the years 1988-1999. Muir et al. (2004) evaluated information relating to all cases of female breast

cancer (age ≥45 years at diagnosis), resident and diagnosed in Lincolnshire and Leicestershire in the period 1989 to 1991, obtained from the Trent Cancer Registry. The authors reported a positive association in rural wards in Leicestershire in contrast to wards in Lincolnshire. The slope coefficient (confidence intervals) was 0.31* (0.05–0.57) and R^2 was 0.11* with a significant p value ≤ 0.05. No clear explanation for such an outcome was provided by the authors. The study presented limitations such as confounders not controlled for, aggregated data, limited study design and inaccurate exposure assessment amongst others.

53. Potential associations between γ-HCH body burden and non-Hodgkins lymphoma and prostate cancer have been investigated (Integral Consulting, 2011c, see Annex E Table 1). Weak positive associations were found in two studies investigating potential association to non-Hodgkin lymphoma (Blair et al, 1998; McDuffie et al, 2001) whilst increased odd ratios were reported in another two studies (Lee et al, 2004; Rafnsson et al, 2006). The studies presented limitations such as confounding factors not controlled for and unspecific measure of exposure amongst others. A study by Mills et al, (2003) found association between γ-HCH and prostate cancer; however, the study presented limitations such as unknown exposure levels of the subjects prior to the study and inaccurate exposure metrics.

54. γ-HCH body burden and adverse effects in neurological and reproductive endpoints have been investigated in a number of studies. No significant associations were found in the studies evaluating neurological endpoints (Fleming et al, 1994; Corrigan et al, 2000; Firestone et al, 2005; Hancock et al, 2008). A study by Pierik et al, (2007) reported a non-significant increased incidence of undescended testes. An investigation in vitro on human sperm exposed to γ-HCH resulted in no disruptive effects to the sperm functions. This outcome led the authors to suggest that environmentally relevant concentrations of γ-HCH in humans may not be positively correlated with adverse testicular effects (Pflieger-Bruss et al, 2006).

Allergy

55. No studies have been found in the scientific literature associating α-, β- and lindane to incidence of allergy, atopic disease or hypersensitivity.

Health-based guidance values (HBGV)

56. Table 1 summarises the tolerable/acceptable daily intakes (TDI or ADI) and RfDs that have been established or proposed for HCH isomers.

Table 1 TDIs, ADI and RfDs established for HCH isomers.

Isomer	Source of HBGV	HBGV	Study selected to derive HBGV
α-HCH	Integral Consulting (2011a)	RfD 0.3 µg/kg bw/ day	Masuda et al, 2001
	Slooff and Matthijsen, (1988) confirmed by RIVM (2001)	TDI 1 µg/kg bw/day	Not identified
	Health Canada (1992), cited in EFSA (2005)	Group TDI 0.3 µg/kg bw/day	Not identified
β-HCH	Integral Consulting (2011b)	RfD 0.06 µg/kg day	Van Velsen et al, 1986a
	Slooff and Matthijsen, (1988) confirmed by RIVM (2001)	TDI 0.02 µg/kg bw/day	Van Velsen et al, 1986b
	Health Canada (1992), cited in EFSA (2005)	Group TDI 0.3 µg/kg bw/day	Not identified
γ-HCH	Integral Consulting (2011c)	RfD 0.01 µg/kg day	Meera et al., 1992
	RIVM (2001)	TDI 0.04µg/kg bw/day	Meera et al., 1992
	Health Canada (1992), cited in EFSA (2005)	Group TDI 0.3 µg/kg bw/day	Not identified
	JMPR (FAO/WHO, 2002)	ADI 5 µg/kg bw/day	Amyes et al., 1990

57. The RfD for α-HCH proposed by Integral Consulting (2011a) was based on the study of Masuda et al, (2001) on promotion of hepatocarcinogenicity in male rats (paragraph 44). The NOAEL was 0.1 mg/kg day. An uncertainty factor (UF) of 300 (10 each to account for intra- and inter-species extrapolation, and 3 for database uncertainties) was applied, resulting in a proposed RfD of 0.3 µg/kg day.

58. The RIVM TDI for α-HCH was originally established by Slooff and Mathijsen, (1988). The TDI was based on a 90 day oral study in rats with a LOAEL for liver

changes (no further information given) equivalent to 0.1 mg/kg bw/day. Applying an UF of 100, the TDI was established at 1 µg/kg bw/day. No more information is provided on the original study or the rationale for applying a UF of 100 to a NOAEL. RIVM, (2001) re-evaluated the scientific evidence and confirmed the previously established TDI.

59. The RfD for β-HCH proposed by Integral Consulting, (2011b) was based on a study by Van Velsen et al, (1986a) on hepatotoxicity in rats exposed for 13 weeks, with a LOAEL of 0.18 mg/kg day (paragraph 29). The UF applied was 3,000 to account for inter- and intra-species differences, use of LOAEL, use of subchronic study, and database limitations. The RfD proposed was 0.06 µg/kg day.

60. The RIVM TDI for β-HCH was originally established by Slooff and Mathijsen, (1988). The TDI was based on a semi-chronic oral study on reproduction in rats reported in a PhD Thesis by Van Velsen (1986b) cited in WHO-IPCS (1992), with a NOAEL for infertility equivalent to 0.02 mg/kg bw/day (paragraph 38). Applying a UF of 1000. The TDI established was TDI 0.02 µg/kg bw/day. The basis for the UF of 1000 was not stated. RIVM, (2001) re-evaluated the scientific evidence and confirmed its previously established TDI.

61. The RfD for γ-HCH proposed by Integral Consulting, (2011c) was based on the study by Meera et al., (1992) on immunotoxicity in female rats exposed for 24 weeks with a LOAEL of 12 µg/kg bw/day (paragraph 36). An UF of 1,000 was applied (10 for intra-species extrapolation, 10 for inter-species extrapolation, and 10 for extrapolation from LOAEL to NOAEL) and the RfD proposed was 0.01 µg/kg bw per day.

62. The TDI for γ-HCH established by RIVM in 2001 was based on a study by Meera et al., (1992) on immunotoxicity in female rats exposed for 24 weeks, with a LOAEL of 12 µg/kg bw/day (paragraph 36). A UF of 300 was applied (10 each for intra- and inter-species variability and 3 to compensate for the use of a LOAEL rather than a NOAEL). This study was criticised by JMPR due to the purity of the preparation used (~ 97%). However RIVM concluded that the JMPR argument was invalid since there were no indications at the time for impurities that would cause such a substantial higher toxicity of the substance tested.

63. JMPR established an ADI of 5 µg/kg b.w. on the basis of the NOAEL for hepatotoxicity, equivalent to 0.47 mg/kg b.w./day from a long-term study of toxicity and carcinogenicity in rats (Amyes et al, 1990) (paragraph 30). Applying a UF of 100, the ADI established was 5 µg/kg bw/day (FAO/WHO, 2002).

64. In 1992 Health Canada set a group TDI for all HCH isomers of 0.3 µg/kg b.w. (Feeley, 2005, personal communication to EFSA, 2005). Details on the derivation of this group TDI are not available in the public domain.

Regulatory limits

65. The current maximum levels in force for pesticides are described 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 pesticide level for food products for human consumption and animal feedingstuffs is 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 specifically set for a product or product type. This is the case for infant and follow-on formula and processed cereal foods and baby foods for infant and young children. In relation to other food products for human consumption, several different MRLs apply depending on the HCH isomer and the food commodity although for the majority of them the default MRL applies. The MRLs for each specific HCH and food commodity are accessible in the European Union pesticides database provided by the Directorate General for Health and Consumers. In summary, for γ-HCH, the MRLs range from 0.001 mg/kg to 1 mg/kg. HCH isomers have MRLs ranging from 0.01 mg/kg to 0.02 mg/kg for the sum of the two isomers (α- and β-HCH) depending on the food commodity. Likewise, there are MRLs exclusively for α-HCH ranging from 0.004 mg/kg to 0.2 mg/kg and for β-HCH ranging from 0.1 mg/kg to 0.003 mg/kg depending on the food commodity.

Sources of HCHs and occurrence levels

Drinking water

66. Reports from water companies across the UK conveying the results of the samples analysis performed in 2011 are available in the public domain. For example, the following water companies, Wales, Trent-Severn, Bristol and Wessex, indicated that the 99th percentile for α-HCH in 1172 samples was < 0.002 µg/L. The reports from the water companies Wales and Trent-Severn indicated that the 99th percentile for β-HCH accounting for 566 samples in total was < 0.002 µg/L.

67. In 2011, 3565 samples of treated water were analysed for γ-HCH in the UK. Four samples were reported to contain detectable concentrations (typical limit of detection is 0,003 µg/L). None exceeded the regulatory limit established at 0.1µg/L (Drinking Water Inspectorate, personal communication, 2013).

Breast milk

68. A time-related decline in the levels of HCH isomers in breast milk is apparent from the scientific literature. Table 2 shows the concentrations of HCH isomers in breast milk from studies in UK populations published since 1965.

Table 2. UK studies measuring HCH isomers in breast milk published since 1965.

N	µg/kg milk fat mean (% samples with detectable residues)		Years of sample collection	Reference
	β-HCH	γ-HCH		
19	13 (100)	n/a (n/a)	1963-1964	Egan et al, 1965
102	7 (80)	7 (55)	1979-1980	Collins et al, 1982
-	5 (95)	< 1 (0)	1984	Ministry of Agriculture, Fisheries and food, 1998
193	2 (82)	< 1 (18)	1989-1991	Dwarka et al, 1995
156	1 (36)	< 1 (2)	1997-1998	Harris et al, 1999
54	15 (100)	0.8 (91)	2001-2003	Kalantzi et al, 2004

69. In a study that included 92 samples from 48 donors in the UK sampled in 2001-2002 , β-HCH was not detected in any sample at a limit of detection of 100 µg/kg fat and α- and γ-HCH were not detected either in any sample at a limit of detection of 10 µg/kg fat (Wooldridge et al, 2004).

70. In the context of the 3rd WHO human milk field study α-HCH, β-HCH and lindane were analysed in 16 human milk pools from 10 European countries (Bulgaria, Czech Republic, Germany, Ireland, Italy, Luxembourg, Norway, Russia, Spain and Ukraine) and 11 pools from 6 non-European countries (Brazil, Egypt, Fiji, Hong Kong, Philippines and USA) (Malisch et al., 2004). The pools from Bulgaria, Russia and Ukraine contained 2 to 6 µg α-HCH/kg fat. α-HCH was not detected in other European samples at a limit of detection of 1 µg/kg fat. In the pools from European countries the concentrations of β-HCH ranged from 11 to 279 µg/kg fat, and γ-HCH ranged from < 1 to 13 µg/kg fat. The highest concentration in the European samples was found in pools in Ukraine (α-HCH: 6 µg/kg fat, β-HCH: 153 µg/kg fat, γ-HCH: 1 µg/kg fat). Considerably higher concentrations were found in 2 pooled human milk samples from Hong Kong which contained β-HCH at 1,320 and 1,360 µg/kg fat, respectively.

71. The occurrence levels of HCH isomers in breast milk in studies on populations in the United States and Europe published since 1975 are shown in Table 3.

Table 3. US and European studies measuring HCH isomers in breast milk published since 1993 in chronological order of sample collection.

Country (City/Region)	µg/kg milk fat median/mean/level as indicated (high percentile as indicated) (time data provided)		Years samples collection	Reference
	β-HCH	γ-HCH		
Sweden		75 mean **(not indicated)** (1978) 27 mean **(not indicated)** (1990)	1975-1990	Vaz, 1995
Spain (Huelva / Andalucia)		80 mean **(highest sample, 200)** (after 1 month) 71 mean **(highest sample, 130)** (after 3 months)	1989-1990	Martinez Montero, 1993
Italy (average of Rome, Milan, Florence and Pavia)	130 mean **(not indicated)**		1987	Larsen et al, 1994
Germany (North)	200 median **(not indicated)** (1986) 50 median **(not indicated)** (1997)		1986-1997	Schade et al, 1998
Spain	240 unknown mean or median **(not indicated)**		1991	Hernandez et al. in Wong (2002)
Germany (Saxony)	40 median **(95th%, 7,970)**	5 median **(95%, 3,240)**	1992-1993	Raum et al, 1998
Germany (Saxony)	59 median **(not indicated)**	12 median **(not indicated)**	1992-1993	Schlaud et al, 1995
German (Saxony – Rural areas)	45 median **(not indicated)**	16 median **(not indicated)**	1992-1993	Schlaud et al, 1995
Russia (Murmansk)	853 mean **(not indicated)**		1993	Polder et al, 1998
Russia (Monchegorsk)	740 mean **(not indicated)**		1993	Polder et al, 1998
Ukraine	731 median **(90th%, 1,305)**		1993-1994	Gladen et al, 1999
Greece		58 mean	1995-	Schinas et al,

(South West)		In whole milk **(not indicated)**	1997	2000
Norway (Oslo)	14 mean **(not indicated)**	0.7 mean **(not indicated)**	2000-2001	Polder et al, 2008
Norway (Tromsø)	10 mean **(not indicated)**	0.3 mean **(not indicated)**	2000-2001	Polder et al, 2008
Germany (North Ryne-Westphalia)	130 mean **(not indicated)**	20 levels **(not indicated)**	1984	P Fürst, personal communication to EFSA, 2005.
	20 mean (**not indicated)**	< 1 mean **(not indicated)**	2001	
North Germany	11.6 median **(unknown)**		2006	Zietz et al, 2008
USA (California)	0.22 urban median **(75%, 0.24)**		2002-2007	Weldon et al, 2011
	0.44 rural median **(75%, 0.52)**			
Spain (Almeria, agricultural area and Granada, urban area / Andalucia)		(1-7 days) Almeria 0.31 mean **(not indicated)**	Not mentioned	Campoy et al, 2001
		(1-7 days) Granada 1.60 mean **(not indicated)**		
		(6-12 days) Almeria 0.28 mean **(not indicated)**		
		(6-12 days) Granada 1.90 mean **(not indicated)**		
		(13-35 days) Almeria 0.32 mean **(not indicated)**		
		(13-35 days) Granada 0.82 mean **(not indicated)**		

72. In a study on a German cohort, the median levels of β-HCH in breast milk were positively correlated with maternal age and negatively associated with parity and the total period of breast-feeding. Post-pregnancy body mass index (BMI) was a significant predictor of the likelihood of having higher concentrations of β-HCH in breast milk. Women who had followed a low-fat diet for at least 3 years had lower β-HCH levels in their breast milk than women whose diet included large quantities of meat (Schade, 1998).

Infant formula

73. Infant formulae are included in the UK national monitoring programme for pesticide residues in food, which is overseen by the Defra Expert Committee on Pesticide Residues in Food (PRiF). Infant formula was last surveyed in July-September 2009 (PRiF, 2010). γ-HCH, α-HCH and β-HCH were not detected at or above the reporting limits of 10 µg/kg each, i.e the current MRL.

74. A study from 2001 to 2006 on marketed food including infant formula in Barcelona (Catalonia, Spain) did not find any infant formula sample at or above the quantification limits out of the 1484 samples analysed (Fontcuberta et al., 2008). This indicated a reduction since in a previous monitoring study carried out from 1989 to 2000 in the same area, 17 samples out of 4330 analyzed had detectable levels. The quantification limits were 10 µg/kg in low fat food and 5 µg/kg in high fat food.

75. A study performed in Huelva (Andalucia, Spain) measured occurrence levels of γ-HCH and total HCH (sum of α-, β- and γ-HCH) in milk formula reconstituted as per manufacturers' instructions. The mean levels were 21 and 22 µg/kg respectively (Martínez Montero et al., 1993). No information was provided on range, median or percentiles, or on the levels of HCH in the water used for reconstitution.

76. A survey of the pesticide content of 25 infant formulae marketed in New Zealand was undertaken in 1996. It included a representative mixture of imported and New Zealand manufactured infant foods. Approximately 140 pesticides including γ-HCH were screened. γ-HCH was not detected with a limit of detection of 0.2 µg/kg (Cressey and Vannoort, 2003).

Weaning diet

77. Cereal-based, fruit and vegetables, and other products containing egg, fish, meat or cheese to be consumed by infants were last surveyed by PRiF in March (2011) (PRiF, 2011), August (2011) (PRiF, 2012) and February (2009) (PRiF, 2009) respectively. No α-, β- or γ-HCH was detected at or above the reporting limits of 10 µg/kg each.

78. The Food Safety Authority of Ireland published in 2004 a report on surveillance of infant food for pesticide residues (Food Safety Authority of Ireland, 2004). Of the 41 infant food samples tested for 366 pesticide compounds including γ-HCH, representing 15006 individual results, there were no positive results for the presence of γ-HCH. The limit of quantification was 1 µg/kg. The samples were biscuits for infants (2 samples), infant formula (6 samples), fruit-based infant food (11 samples), vegetable/meat infant food (12 samples), cereal-based infant food (6 samples) and juices for infant and young children (3 samples).

79. A survey of the pesticide content of 30 weaning food products available in New Zealand was undertaken in 1996. It included a representative mixture of imported and New Zealand manufactured infant foods. Approximately 140 pesticides including γ-HCH were screened. γ-HCH was not detected with a limit of detection of 0.2 µg/kg (Cressey and Vannoort, 2003).

Exposure

80. The consumptions used for the exposure calculation for breast milk and infant formula were 800 mL (average consumer) and 1200 mL (high consumer) as proposed by EFSA (2012) and applied in other COT papers. The mean bodyweights used for calculation of exposures were 5.9 kg, 7.7 kg, 8.9 kg and 9.8 kg for infants aged 0-3, 4-6, 7-9 and 10-12 months old respectively (Department of Health, 1991).

Breast milk

81. The occurrence values selected for the calculation of exposure to β-HCH and γ-HCH were the mean values from the most recent UK studies presented in Table 2, i.e. 15 µg/kg for β-HCH and 0.8 µg/kg for γ-HCH (Kalantzi et al., 2004). The occurrence value for α-HCH was selected based on the limit of detection (< 1 µg/kg fat) for most European countries within the 3rd WHO human milk field study. The exposures estimated are presented in Table 4, calculated on the assumption that the fat content of breast milk was 3.5 %. Due to the reported decreases in HCHs in breast milk over time, these could possibly overestimate current exposure.

Table 4. Estimated exposure of infants to HCHs for average and high consumption of breast milk.

		Exposure (µg/kg bw day)			
Chemical	**Consumption**	**0 – 3 months**	**4 – 6 months**	**7 – 9 months**	**10 – 12 months**
α-HCH	Average	< 0.004	< 0.004	< 0.003	< 0.003
	High level	< 0.007	< 0.005	< 0.005	< 0.004
β-HCH	Average	0.07	0.05	0.05	0.04
	High level	0.11	0.08	0.07	0.06
γ-HCH	Average	0.003	0.003	0.002	0.002
	High level	0.006	0.004	0.003	0.003

82. EFSA calculated, assuming an average intake of 800 ml breast milk with a fat content of 3.5 % that the concentration of 20 µg β-HCH/kg fat identified from a study in Western Germany in 1984 would result in a daily intake of 0.11 µg/kg b.w. for a fully breastfed infant weighing 5 kg (EFSA, 2005).

83. The exposure values provided in Table 5 are extracted from representative studies on populations in Canada and Europe published since 1990.

Table 5. Canadian and European studies with calculated exposures to HCH isomers levels in breast milk published since 1990 provided chronologically in order of data collection.

Country	Average or range (µg/kg b.w.)				Years sample collection	Citation
	α-HCH	β-HCH	γ-HCH	t-HCH		
Spain (Huelva / Andalucia)			0.27 (1 month old) – 0.23 (3 months old)	0.65 (1 month old) - 0.58 (3 months old)	1989-1990	Martinez Montero et al., 1993
Canada	0.0004	0.0004	0.001		1993-96	Health Canada, 2003
Czech republic	0.004	0.008	0.019		1994	Ruprich et al., 1995
Czech republic	0.002	0.002	0.006		2002	Ruprich et al., 2003

Infant formula

84. In the surveys carried out in the UK by PRiF on infant formula no samples were found at or above the MRL (10 µg/kg) for any of the HCHs. From the summary reports provided by the water companies in several regions in the UK the 99th percentiles for α- and β-HCH were < 0.002 µg/L and the limit of detection for γ-HCH, exceeded in 4 out of 3565 analyses, was 0.003 µg/L. If an HCH isomer was present at 0.003 µg/L in 1200 mL of water used to reconstitute infant formula, the exposure from the water would be 0.0036 µg, equivalent to 0.0006 µg/kg bw day for an infant of 0-3 months weighing 5.9kg. This would have a negligible impact on the total. Table 6 provides the exposure that would result from consumption of infant formula containing HCHs at the MRLs. It is likely that actual exposure would be much lower than this.

Table 6. Theoretical maximum exposure of infants to HCHs from average and high consumption of infant formula that is compliant with the legislation

	Maximum exposure to each HCH isomer (µg/kg bw day)			
Consumption	**0 – 3 months**	**4 – 6 months**	**7 – 9 months**	**10 – 12 months**
Average (800 ml)	0.18	0.14	0.12	0.11
High level (1200 ml)	0.27	0.21	0.18	0.17

Reconstitution has been performed on the assumption that that 0.135 kg of powder is used to reconstitute 1 L of formula recommended by the Center for the Evaluation of Risks to Human Reproduction CERHR. For reconstituted formulas, CERHR converted between mg/kg and mg/L because the density of prepared formula is similar to water. These recommendations are consistent with infant formula manufacturers' advice in the UK.

Weaning diet

85. Mean- and high-level consumption (97.5th percentile) data for infant foods were derived from the MAFF, (1986) infant study and published in Mills and Tyler (1992). The average total food consumption (solids and liquids) for 6 to 12 months old from the MAFF, (1986) survey (156 g/kg bw per day) was slightly higher than that derived by EFSA, (2012) from the comprehensive database (107 g/kg bw per day). The average and 97.5th percentile level of solids consumed by infants in the MAFF (1986) infant study was 300 and 500 grams respectively, corresponding to 46 and 77 g/kg bw per day for an infant aged 6-12 months with average weight of 6.5kg (MAFF, 1986).

86. No samples were found at or above the MRL (10 µg/kg) for any of the HCHs in the surveys carried out in the UK on cereal-based, fruit and vegetables, and other products containing egg, fish, meat or cheese to be consumed by infants, Table 7 provides the exposure that would result from consumption of infant foods containing HCHs at the MRLs. It is likely that actual exposure from infant foods would be much lower than this. Potential exposures from liquids are not taken into account in these calculations, since no data are currently available on the different types of liquid (e.g. milk, formula, water, soft drinks) that are consumed by this age group.

Table 7. Theoretical maximum exposure of infants to HCHs from average and high consumption of infant foods

Maximum exposure to each HCH isomer (µg/kg bw/ day) at age 6 to 12 months old	
Average	97.5 th percentile
0.46	0.77

Risk characterisation

87. The estimated exposures to α-, β- and γ-HCH from breast milk, infant formula and weaning diet are compared to the respective HBGVs in Table 8. The estimated exposures from breast milk to α- and γ-HCH are well below all of the proposed HBGVs, whereas some are exceeded by the estimated exposure to β-HCH. β-HCH is persistent in the environment, but has been decreasing since it was banned in the EU in 1978. These estimates are based on data for occurrence of breast milk sampled in the UK in 2001-2003, and it is possible that levels have decreased since that time.

88. No occurrence data were available for estimating exposure through infant formula, and therefore a worst-case calculation has been made, assuming that all infant formula is compliant with the maximum permitted level of 10 µg/L. These calculations show some potential exceedances of the most conservative HBGVs for all 3 isomers. However, actual exposures are likely to be much lower since it is highly unlikely that all infant formula would contain HCHs at the maximum permitted level. The available data indicate that exposure from water used to reconstitute infant formula would be negligible.

89. Similarly, no occurrence data were available for estimating exposure through infant food, and therefore a worst-case calculation has been made, assuming that all infant food is compliant with the maximum permitted level of 10 µg/kg. Such calculations all exceed the available HBGVs, but again actual exposures are likely to be much lower.

Table 8. Potential maximum exposure of infants to HCHs from average and high consumption breast milk, infant formula and infant foods

	Isomer	HBGV (µg/kg bw/day)	Consumption	Exposure (µg/kg bw/day)			
				0 – 3 months	4 – 6 months	7 – 9 months	10 – 12 months
Breast milk	α-HCH	0.1[a] 0.3[b] 0.3[c]	Average	< 0.004	< 0.004	< 0.003	< 0.003
			High level	< 0.007	< 0.005	< 0.005	< 0.004
	β-HCH	0.02[a] 0.3[b] 0.06[c]	Average	0.07	0.05	0.05	0.04
			High level	0.11	0.08	0.07	0.06
	γ-HCH	0.04[a] 0.3[b] 0.01[c] 0.5[d]	Average	0.003	0.003	0.002	0.002
			High level	0.006	0.004	0.003	0.003
Infant formula (assuming compliance with EU legislation)	α-HCH	0.1[a] 0.3[b] 0.3[c]	Average	< 0.18	< 0.14	< 0.12	< 0.11
			High level	< 0.27	< 0.21	< 0.18	< 0.17
	β-HCH	0.02[a] 0.3[b] 0.06[c]	Average	< 0.18	< 0.14	< 0.12	< 0.11
			High level	< 0.27	< 0.21	< 0.18	< 0.17
	γ-HCH	0.04[a] 0.3[b] 0.01[c] 0.5[d]	Average	< 0.18	< 0.14	< 0.12	< 0.11
			High level	< 0.27	< 0.21	< 0.18	< 0.17
Infant food (assuming compliance with EU legislation)	α-HCH	0.1[a] 0.3[b] 0.3[c]	Average	N/A	N/A	< 0.46	
			High level	N/A	N/A	< 0.77	
	β-HCH	0.02[a] 0.3[b] 0.06[c]	Average	N/A	N/A	< 0.46	
			High level	N/A	N/A	< 0.77	
	γ-HCH	0.04[a] 0.3[b] 0.01[c] 0.5[d]	Average	N/A	N/A	< 0.46	
			High level	N/A	N/A	< 0.77	

a. Slooff and Mathijsen, (1988) and/or RIVM (2001),
b. Health Canada (2003),
c. Integral Consulting (2011a, b, c),
d. JMPR (FAO/WHO, 2002)

Questions for the Committee:

90. Members are invited to comment on the information provided in this paper and to consider the following questions:

i. Are any of the HBGVs in Table 1 appropriate for use in risk characterisation for infants' exposure to HCHs?

ii. If the HBGVs are not considered appropriate due to the limitations in the data, which NOAELs or LOAELs should be used in a margin of exposure approach, and what size margins of exposure would indicate a low level of concern?

iii. Are members able to come to any conclusions on whether there is a toxicological concern for the health of infants from dietary exposure to HCHs?

iv. Given the available information, is there a need for more data on levels of HCH in infant formula and food?

Secretariat
January 2013

ABBREVIATIONS

ADI	Acceptable Daily Intake
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body Mass Index
CERHR	Center for the Evaluation of Risks to Human **Reproduction**
CNS	Central Nervous System
COC	Committee on carcinogenicity of chemicals in food, consumer products and the environment
COT	Committee on toxicity of chemicals in food, consumer products and the environment
CYP	Cytochrom P450
EC	European Commission
EFSA	European Food Standards Agency
EU	European Union
GABA	Gamma-amino butyric acid
HBGV	Health-based guidance value
HPRT	Hypoxanthine-guanyl phosporibosyl transferase
HCH	Hexachlorocyclohexane
IPCS	Intternational Program in Chemical Safetyl
JMPR	WHO/FAO Joint Meeting on Pesticide Residues
MAFF	Ministry of Agriculture, Forestry and Fisheries
MHRA	Medicines and Healthcare products Regulatory Agency
MRL	Maximum Residue Limit
LOAEL	Lowest observable adverse effect
NOAEL	Non observable adverse effect
PRiF	Defra Expert Committee on Pesticide Residues in Food
RfD	Reference dose
RIVM	Rijksinsituut Voor Volksgezondheid En Milieu
SACN	Scientific Advisory Committee on Nutrition International Unit
SD	Standard Deviation
TDI	Tolerable Daily Intake
US FDA	United States Food and Drug Administration
WHO	World health Organization

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Search strategy

Databases interrogated –

- Pubmed
- EFSA
- COT
- COC
- FSA
- IPCS-WHO
- JMPR
- ATSDR
- USFDA

Scientific publications literature search

Specific search terms:

HCHs/α-HCH/β-HCH/γ-HCH/lindane AND breast milk
Search Dates (From/To) - From 1965 to present

HCHs/α-HCH/β-HCH/γ-HCH/lindane AND infant formula
Search Dates (From/To) - From 1970 to present

HCHs/α-HCH/β-HCH/γ-HCH/lindane AND infant food
Search Dates (From/To) - From 1970 to present

HCHs/α-HCH/β-HCH/γ-HCH/lindane AND weaning
Search Dates (From/To) - From 1970 to present

Other sources:

- Medical and Healthcare products Regulatory Agency
- Drinking Water Inspectorate

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α- and β- HCH Part A and Part B page 43-139

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α- HCH (Integral Consulting, 2011)

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TOX/2013/04 Annex E

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Integral Consulting (2011c). Toxicity criterion for gamma-hexachlorocyclohexane. http://ndep.nv.gov/bmi/docs/gammahch_reportoffinalcriterion_08_23_2011.pdf. .

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