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

Second draft statement on endosulfan isomers, pentachlorobenzene and chlordecone in relation to infant diet.

Introduction

1. The Committee on Toxicity (COT) has been asked to consider the 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/2012/04), highlighting some of the areas for possible consideration was discussed by the COT in February, 2012, and Members concluded that number of persistent organic pollutants (POPs) included in the Stockholm convention since 2009 required further evaluation.

2. A brief overview of the toxicology and occurrence data available for endosulfan and its related isomers, and for pentachlorobenzene and chlordecone (TOX/2013/15) was presented to Members in March 2013. Members agreed that further details on more recent toxicity studies and data on residues in breast milk were needed. A first draft statement (TOX/2013/21) in May 2013 therefore focussed on the information available on the toxicity, levels of exposure and potential risks to health from newly designated POPs. Members requested further clarification and study details throughout the paper particularly with respect to information on the proportions of endosulfan isomers in the material tested in various studies and that each chemical section of the statement had a conclusion.

3. The second draft statement in Annex A has been revised taking into account the previous discussions and incorporating requested details. Additional editorial changes have also been made.

Questions on which the views of the Committee are sought

4. Members are invited to comment on the text of the second draft statement.

Secretariat
June 2013

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

Second draft statement on endosulfan isomers, pentachlorobenzene and chlordecone in relation to infant diet.

Background

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that bears on the Government's dietary recommendations for infants and young children. The review will identify new evidence that has emerged since the Government's current recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years, but will be considered in two stages focussing first on infants aged 0-12 months, and then on advice for children aged 1 to 5 years. SACN is examining the nutritional basis of the advice, and has asked that evidence on possible adverse effects of diet should be considered by other advisory committees with relevant expertise. In particular, SACN asked COT to review the risks of toxicity from chemicals in the infant diet.

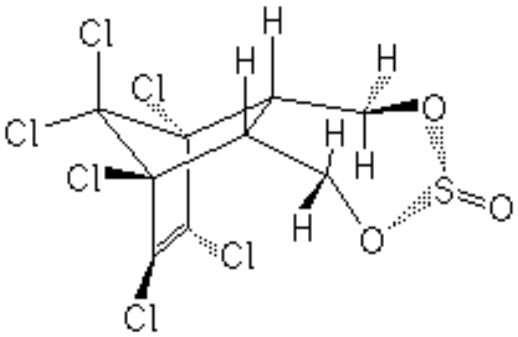
2. The COT considered that chemicals recently classed as persistent organic pollutants (POPs) under the Stockholm Convention[1] should be included in this series of evaluations, as such substances have the potential to accumulate in the food chain. This statement summarises the information that is available on the toxicity of four POPs - two endosulfan isomers, pentachlorobenzene and chlordecone, their occurrence in the infant diet, levels of exposure, and potential risks to health.

Endosulfan

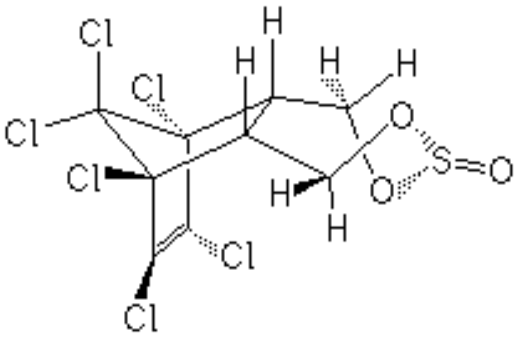
3. Endosulfan occurs as two biologically active isomers: α- and β-endosulfan (Figure 1). Technical endosulfan is a mixture of the two isomers (-) with a ratio of α:β of approximately 2:1 to 7:3, with small amounts of impurities and degradation products (UNEP, 2010).

[1] Available at: http://chm.pops.int/Implementation/NewPOPs/TheNewPOPs/tabid/672/Default.aspx

Figure 1. Structures of endosulfan isomers.



α – endosulfan



β – endosulfan

4. Endosulfan is an insecticide that has been used since the 1950s to control crop pests, tsetse flies and ectoparasites of cattle, and as a wood preservative. As a broad-spectrum insecticide, endosulfan is currently used to control a wide range of pests on a variety of crops including coffee, cotton, rice, sorghum and soy in some parts of the world. Endosulfan has not been authorised for use as a pesticide in the European Union since 2005 because of concerns about its environmental persistence, eco-toxicological profile and risks to operators from exposures during application, and it is now regulated as an undesirable substance in animal feed (EFSA, 2011). Endosulfan was included in a list of newly designated POPs in the Stockholm Convention in 2011 since it meets the criteria for long-range transport, bioaccumulation, persistence in the environment and toxicity. Currently, the use of endosulfan is banned or is being phased out in at least 60 countries where its usage has been estimated to account for 45 per cent of current global use. However, some of these countries have indicated that a temporary use of endosulfan in specific applications will be allowed for a specific length of time or until alternative products and methods are accessible (UNEP, 2011).

5. Technical endosulfan and its isomers have not been evaluated by the COT or its sister committees on Mutagenicity (COM) and Carcinogenicity (COC), or by the International Agency for Research on Cancer (IARC). It has, however, been evaluated by European Food Safety Authority (EFSA) as an undesirable substance in animal feed (EFSA, 2005), although health-based guidance values were not established. The latest evaluation of endosulfan undertaken by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Meeting on Pesticide Residues (JMPR) was in 1998 (FAO/WHO, 1998). The International Programme on Chemical Safety (IPCS) of the WHO also evaluated endosulfan in the Environmental Health Criteria series in 1984 (WHO-IPCS, 1984), and in the Health and Safety Guide in 1988 (WHO-IPCS, 1988). In the US, endosulfan was evaluated by the Agency for Toxic Substances and Disease Registry (ATSDR) in 2000, and the Environmental Protection Agency (EPA) in 2002. This statement draws on information from these authoritative reviews, supplemented by more recent relevant scientific publications where available.

Toxicokinetics

6. In experimental animals and humans, endosulfan isomers are readily absorbed from the gastrointestinal tract, and distributed to various tissues, with the highest accumulation occurring in the liver and kidney. Distribution patterns of the isomers differ between species tissues (ATSDR, 2000).

7. No information is available on the metabolism of endosulfan in humans. In animals, both isomers can be converted into endosulfan sulphate and endosulfan diol, which can be further metabolised to endosulfan lactone, hydroxyether and ether (WHO-IPCS, 1984; FAO/WHO, 1998).

8. In animals, elimination of endosulfan and its metabolites following oral exposure occurs mainly through faeces (72-82% of the dose), with lesser amount by renal excretion (12-22% of the dose). Estimated elimination half-lives of endosulfan isomers and their metabolites range between approximately 1 and 7 days in adult humans and animals, with the α-isomer being excreted faster than the β-isomer. Experiments in male rats showed a biphasic elimination curve with an initial half-life of 8 hours followed by a later half-life of 110 hours (FAO/WHO, 1998; ATSDR, 2000). Both isomers can be transported across the placenta (Cerrillo *et al*., 2005; Schaalan *et al*., 2012) and transferred into the breast milk of lactating women and animals (ATSDR, 2000; Schaalan *et al*., 2012).

Toxicity

9. Reports on effects of endosulfan do not always specify the grade of isomer of endosulfan that was tested. This statement provides information on the tested material when available.

10. The acute toxicity of endosulfan varies widely depending on the route of administration, species, vehicle, and sex of the animal. In rats, and possibly mice, females are more sensitive than males. The lowest oral LD50 value for technical endosulfan was 9.6 mg/kg bw in female Sprague-Dawley rats. The oral LD50 values of α-endosulfan are up to 3 times lower than those of β-endosulfan (ATSDR, 2000; FAO/WHO, 1998).

11. Neurotoxicity is the most prominent adverse effect of endosulfan. Other effects include liver and kidney toxicity (FAO/WHO, 1998; Choudhary *et al*., 2003). Some animal studies have indicated effects also on the immune system, such as depressed humoral and cellular immune responses (rats, daily oral dose of 0.45 – 4.5 mg/kg bw of endosulfan for 22 weeks), but no adverse effects on organs of the immune system were observed in chronic studies (ATSDR, 2000).

12. A number of studies have failed to find adverse effects of endosulfan on reproductive performance in animals; however, adverse effects on male reproductive organs such as reduced sperm count and increased testis weight have been observed in rats dosed by gavage with 2.5 mg technical endosulfan/kg bw/day 5 days/week for 70-90 days and mice (gavage, 3 mg technical endosulfan/kg bw/day for 35 days) (FAO/WHO, 1998; ATSDR, 2000; Sinha *et al*., 2001).

13. JMPR concluded that endosulfan was not genotoxic in an adequate battery of tests for mutagenicity and clastogenicity *in vitro* and *in vivo*, which included bacterial mutation assays in Salmonella typhymurium (Ames test) and Escherichia coli, the mouse lymphoma assay, and tests for chromosome aberrations in human lymphocytes and rat bone marrow, and for dominant lethal mutation in mice (FAO/WHO, 1998). Since the JMPR review, a number of studies have indicated that endosulfan can cause DNA damage, possibly by a mode of action involving reactive oxygen species (Antherieu *et al*., 2007; Ahmed *et al*., 2008; Ahmed *et al*., 2011; Bajpayee *et al*., 2006; Jamil *et al*., 2004; Lu *et al*., 2000; Li *et al*., 2011). Recent data have also shown evidence of mutagenicity in the Ames test (Bajpayee *et al*., 2006; Yaduvanshi *et al*., 2012). Bajpayee *et al*. reported that endosulfan (mixture of isomers) produced weak positive responses (twice the background) in Salmonella strains TA100 and TA102 at 1-20 µg/plate, In addition, both endosulfan isomers and their metabolites produced positive responses (three-times the background) in TA97a and TA98 strains, and in TA100 and TA102 strains (endosulfan diol only). The maximum response was observed for all compounds (with or without metabolic activation) at 10 µg/plate, with a smaller effect at 20 µg/plate (Bajpayee *et al*., 2006). The results of this study are difficult to interpret since the concentrations were 250 times lower than those reported to be negative in studies summarised by JMPR (FAO/WHO, 1998). When endosulfan (as a mixture of isomers) was tested by Yaduvanshi *et al*., mutagenic responses were observed only in TA98 strain and only at a high concentration (500 µg endosulfan/plate) and in the absence of metabolic activation (Yaduvanshi *et al*., 2012). Overall, the evidence for direct mutagenicity of endosulfan is inconsistent.

14. Chronic feeding studies with endosulfan in rats and mice did not produce carcinogenic effects (FAO/WHO, 1998).

15. Contradictory findings have been reported on the oestrogenic potential of endosulfan *in vitro,* whereas generally negative outcomes have been obtained *in vivo* (ATSDR, 2000; Ozen *et al*., 2012). Some more recent animal studies have suggested that endosulfan can mimic oestrogenic actions in tissues other than the uterus (Varayoud *et al*., 2008).

16. Information on the effects of endosulfan in humans relates mostly to accidental or intentional poisoning or to occupational exposure. In studies of occupational exposure, it has generally not been possible to ascribe effects specifically to endosulfan because of concomitant exposure to other chemicals, and this limits the interpretation of such studies for the purposes of risk assessment. Human data have not shown evidence of carcinogenicity for endosulfan (ATSDR, 2000).

Health-based guidance values

17. JMPR (FAO/WHO, 1998) established an acceptable daily intake (ADI) of 6 µg/kg b.w. for endosulfan on the basis of a no-observed adverse effect level (NOAEL) of 600 µg/kg b.w./day in a two-year dietary study of the toxicity of technical grade endosulfan in rats and a safety factor of 100. Reduced body weight and

pathological findings in the kidney and lymph nodes were observed at higher doses. The ADI was supported by similar NOAEL values in other studies and species. An acute reference dose (ARfD) of 20 µg/kg bw/day was established based on a NOAEL of 2000 µg/kg bw /day in a 90-day study of neurotoxicity in rats, with a safety factor of 100. Although mutagenicity of endosulfan has been suggested in some more recent studies, the Committee considered that the lack of consistency in the reported effects, together with the absence of carcinogenicity in animal studies, argues against the need for a lower ADI or ARfD.

Occurrence in food and breast milk

18. A survey of pesticide residues in animal feed ingredients was conducted in the UK in 1998, in which samples of cereals, fodder and beans were analyzed for 28 different pesticides including endosulfan. None of these samples contained endosulfan at concentrations above the detection limit (50 µg/kg) (MAFF-UK, 1998).

19. As part of the UK Pesticide Residues Monitoring Programme, cereal-based infant foods were surveyed in 2012; fruit- and vegetable-based infant foods were surveyed in 2011; and meat-, egg-, cheese- and fish-based infant foods were surveyed in 2012. Infant formula was surveyed in 2009, with dried samples reconstituted prior to analysis. Neither α-endosulfan, β-endosulfan nor their metabolite endosulfan sulphate were identified at or above reporting limits of 100 µg/kg each in any of the samples (PRiF, 2009, 2011).

20. Shen *et al*. (2008) detected α-endosulfan in all breast milk samples obtained between 1997 and 2001 from Finnish (4-8 weeks postpartum; n=65) and Danish (4-12 weeks postpartum; n=65) women, with median (range) concentrations of 6.40 (1.19 – 22.66) and 7.43 (1.92 – 18.05) µg/kg lipid, respectively. Levels of β-endosulfan were reported as undetectable (LOD was not specified). The respective median lipid content was 4.26 and 2.84 % w/w. From this, it can be estimated that median levels of α-endosulfan in the Finnish and Danish samples were approximately 0.27 and 0.21 µg/L breast milk, respectively. In Spain all of 23 breast milk samples collected between 2000 and 2002[2] (2-5 weeks postpartum,) contained endosulfan isomers: α-endosulfan was detected with a median value of 0.87 (max 1.00) and β-endosulfan: 7.29 (max 26.89) µg/L breast milk (Cerrillo *et al*., 2005). The reason for the higher proportion of β-endosulfan in the Spanish study is unclear.

Exposure

21. No data on exposure to endosulfan in the UK population have been identified. Exposures were estimated in Canada in a single location with maximum intake (0.03 µg total endosulfan/kg bw/day, 5-11 years old maximum exposure age group), the USA (0.05 µg total endosulfan/kg bw/day), Taiwan (0.01 µg α-endosulfan/kg bw) and the Czech Republic (0.015 µg sum of α-, β-endosulfan and endosulfan sulphate/kg bw/day) based on occurrence data from the 90s (EFSA, 2005).

[2] Information on sampling period was provided in personal communication from the author

22. The lowest (0.21 µg/L breast milk as α-endosulfan, estimated from Shen *et al*., 2008) and highest (8.16 µg/L breast milk as a sum of α- and β-endosulfan, from Cerrillo *et al*., 2005) reported median concentrations of endosulfan in breast milk in the EU were used to estimate potential exposure of breastfed infants, with average (800 mL per day) and high level (1200 mL per day) consumption of breast milk (Table 1). Bodyweight data from the recently published UK Dietary and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), with a mean of 7.8 kg for infants aged 4 – 6 months, were used to calculate potential intakes for this age group. Since DNSIYC did not include infants younger than 4 months, in this statement the value of 5.9 kg for infants aged 0 – 3 months from an earlier survey (DH, 1994), is applied to infants aged 0 – 4 months. Estimated intakes were in the range 0.02 – 1.11 µg/kg bw/day for average consumption of milk and 0.03 – 1.66 µg/kg bw/day for high level consumption. These are much lower than the ADI of 6 µg/kg bw/day set by JMPR in 1998. No data are available to allow estimation of possible dietary exposure of infants who are not exclusively breastfed.

Table 1. Endosulfan exposure (µg/kg bw/day) from exclusive breastfeeding estimated for average and high level consumption

Endosulfan concentration in breastmilk	Age in months (consumption volume)			
	0 – 4 (800 mL)	0 – 4 (1200 mL)	>4 – 6 (800 mL)	>4 – 6 (1200 mL)
	Body weight (kg)			
	5.9		7.8	
0.21 µg/L (Shen *et al*., 2008)	0.03	0.04	0.02	0.03
8.16 µg/L (Cerrillo *et al*., 2005)	1.11	1.66	0.83	1.25

Conclusions

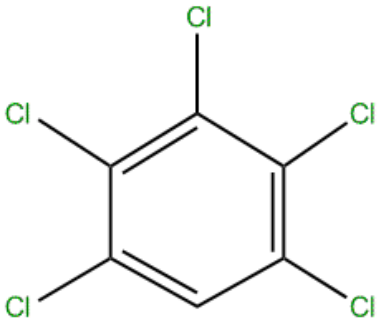
23. The use of endosulfan as a pesticide has been banned in the EU since 2005 and significant residues in food are not expected. The limited available data indicate that infant dietary exposure to endosulfan is well below the ADI at 6 µg/kg bw/day set by JMPR in 1998 and do not suggest a health risk.

Pentachlorobenzene

24. Pentachlorobenzene (PeCB) was used in the past as a flame retardant and dyestuff carrier[3] and can still be found at low levels as an impurity in several pesticides, including herbicides, insecticides and fungicides. It was used as a chemical intermediate in the production of the agricultural fungicide quintozene. It is also still present in the atmosphere, sediments and biota (mosses, fish, penguin eggs, seals and predatory animals in the arctic and Antarctic regions) (UNEP, 2007). The main sources of PeCB nowadays include combustion of solid wastes, biomass burning, and degradation of quintozene (Bailey *et al*., 2009).

[3] Hydrophobic chemical substance used in dyeing of polyester fibres.

Figure 2. Structure of pentachlorobenzene.



25. PeCB has not been evaluated by the COT, COM, COC, EFSA or IARC. It has been evaluated in the context of "chlorobenzenes other than hexachlorobenzenes" by the IPCS (WHO-IPCS, 1991). Other evaluations have been carried out by US EPA (EPA) (1998) and United Nations Environment Program (UNEP) (2007). This statement draws on the information in these authoritative reviews, supplemented by more recent relevant scientific publications where available.

26. JMPR has not evaluated PeCB on its own. However, quintozene, the toxicity of which is partly due to the presence of PeCB, was evaluated in 1998. Plant protection quintozene products containing more than 10 g/kg PeCB were banned in the European Union in 1990 and subsequently quintozene has been manufactured by a different process that does not use PeCB (UNEP, 2007). In 2000 in the EU, authorisations for plant protection products containing quintozene were withdrawn and its use had to cease within 18 months (EC, 2000).

27. In 2009, the Stockholm convention agreed to eliminate the use of PeCB because of its high toxicity and persistence in the environment, bioaccumulation, long-range environmental transport, moderate toxicity in laboratory mammals, and aquatic organisms. Regulation (EC) No 850/2004 was subsequently amended in 2010 to prohibit the production, use and marketing of PeCB in the EU.

Toxicokinetics

28. PeCB was readily absorbed and distributed in blood, liver, kidney and adipose tissue of rats and excreted in faeces (Umegaki *et al*, 1993). Similar observations have been reported in coyotes (Johnston *et al.,* 1997).

29. Analyses of serum in children at birth and again at four years of age showed decreases in concentration of PeCB and small body burden variation and were shown to be not correlated with the age of mother, maternal or formula feeding or duration of breastfeeding (Carrizo *et al*., 2006).

Toxicity

30. The oral LD50 values of PeCB are between 250 and 1125 mg/kg bw (rats) and 1175 – 1370 mg/kg bw (mice) (Allen *et al*., 1979, cited by Slooff *et al*., 1991,

UNEP, 2007). Sub-chronic and chronic studies gave consistent findings at doses of approximately 500 mg/kg, with increased liver weight, generally in conjunction with hypertrophy, increased kidney weight with occasional hyalinization, disruption of the thyroid function and increased weight of the adrenal glands. At higher doses (1000 mg/kg), the same effects were reported, though more severe. There was also a decrease in haemoglobin concentration and an increase in white blood cell count in both sexes of rats, and a decrease in red blood cells count and haematocrit in males (UNEP, 2007).

31. The UNEP (2007) evaluation noted contrasting outcomes in reproductive toxicity studies. Fetotoxicity has been reported in rats at doses that were non-toxic in mothers. In contrast, no embryotoxic, fetotoxic or teratogenic effects were observed in the offspring of mice at doses that were maternally toxic. The NOAELs and lowest observed adverse effect levels (LOAELs) varied between 17 and 200 mg/kg PeCB per day.

32. PeCB appears not to be genotoxic. It was negative in the Ames test, with and without activation, and in tests for various cytogenetic endpoints (Gustaffson *et al*., 2000, cited in UNEP, 2007). Formation of preneoplastic foci in rat liver has been described following initiation by diethylnitrosamine (Thomas *et al*., 1998; Ou *et al*., 2001). In assessing the toxicity of PeCB, the US EPA (1998) and UNEP (2007) stated that there was a lack of data in humans from which to determine its carcinogenicity.

Health-based guidance values

33. The US EPA established a reference dose (RfD) of 0.8 µg/kg bw/day based on a LOAEL for liver and kidney damage in a sub-chronic study by Linder et al., (1980) with an uncertainty factor of 10,000 to allow for inter- and intra-species and interhuman variation, extrapolation from subchronic to chronic exposure and from a LOAEL to a NOAEL (US EPA, 1998). Health Canada established a TDI of 0.5 µg/kg bw/day based on a sub-chronic study with a LOAEL for hepatocellular hypertrophy and necrosis of 5.2 mg/kg bw/day and an uncertainty factor of 10,000 (NTP, 1991). Whilst the use of uncertainty factors in these studies appears conservative, no more recent studies have been found to establish health-based guidance values on a more robust basis.

Occurrence in food and breast milk

34. PeCB is not a pesticide, and therefore it is not included in the UK pesticide monitoring programme. Nor does it have an MRL. No relevant data on levels of PeCB in food products are currently available. Results of a Food Standards Agency (FSA) survey of PeCB in food, including infant foods and formulae, are expected to be available in 2015.

35. Data on PeCB in human breast milk in the UK have not been identified. PeCB was detected in all breast milk sampled between 1997 and 2001 in Finland (4-8 weeks postpartum; n=65) and Denmark (4-12 weeks postpartum; n=65) with median

(range) concentrations of 0.25 (0.08 – 1.17) and 0.32 (0.13 – 1.41) µg/kg lipid, respectively. The respective median lipid contents were 4.26 (Finnish samples) and 2.84 (Danish samples) % w/w (Shen *et al*., 2008). Based on those values it can be estimated that the breast milk contained approximately 0.01 µg of PeCB/L.

Exposure

36. No data on exposure to PeCB in the UK population have been identified

37. The concentration of PeCB in breast milk estimated from the study by Shen *et al*., 2008 (0.01 µg/L) was used to estimate potential PeCB exposure for average (800 mL) and high level (1200 mL) consumption by exclusively breastfed infants. The bodyweights assumed for different age groups were as described in paragraph 20. The estimated exposure was approximately 0.001 µg/kg bw/day for average consumption and 0.002 µg/kg bw/day for high level consumption. These exposures are substantially lower than the TDI of 0.5 µg/kg bw/day established by Health Canada (1993).

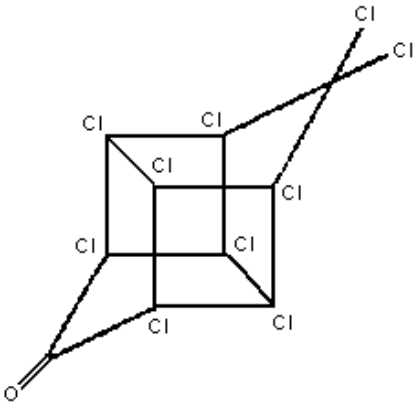
Conclusions

38. Available animal studies show some evidence for accumulation of PeCB Data on PeCB in food are currently not available. Reported levels of PeCB in breast milk samples would result in exposures to infants substantially less than the TDI of 0.5 µg/kg bw/day set by Health Canada, and do not indicate a health concern.

Chlordecone

39. Chlordecone is a synthetic chlorinated organic compound used as an agricultural insecticide, miticide and fungicide. It was marketed as Kepone®. In the UK, all Kepone® and Kepone® products had their licence for sale revoked in July 1977 (DEFRA, 2012). According to DEFRA, “Chlordecone may not have been used in the UK prior to its ban in 1977”.

Figure 1. Structure of chlordecone



40. In 2009, the Stockholm convention agreed to eliminate chlordecone because of its persistence in the environment, bioaccumulation, long-range transport and toxic effects. UNEP considered there was extensive data on occupational exposures, showing potential for adverse effects in humans including carcinogenicity and reproductive toxicity and also evidence of very high toxicity in aquatic organisms (UNEP, 2007). Regulation (EC) No 850/2004 was subsequently updated in 2010 to prohibit the production, use and marketing of chlordecone in the EU.

41. Chlordecone has not been evaluated by the COT, COM, COC, EFSA or JMPR. A number of international bodies have published reports on chlordecone, including IARC (1979, 1987), WHO-IPCS (1984 and 1990), ATSDR (1995), UNEP (2007) and US EPA (2009).

Toxicokinetics

42. Chlordecone is well absorbed following oral, dermal and inhalation exposure. It is widely distributed in the body, with accumulation in the liver and to a lesser extent in fat, brain and kidneys, both in experimental animals and in humans (ATSDR, 1995; IPCS-WHO, 1984). Chlordecone is metabolised to chlordecone alcohol in some species, including humans. Elimination is mainly via the bile, either as unmetabolised chlordecone or as the glucuronide conjugate of the alcohol (US EPA, 2009).

43. Workers occupationally exposed to chlordecone had high concentrations in the liver, whole blood and subcutaneous fat. The chlordecone serum half-life in chemical plant workers was estimated to be between 63 to 148 days and elimination was primarily in the bile at a mean daily rate of 0.075% of the estimated total body burden (US EPA, 2009).

Toxicity

44. Chlordecone has been shown to cause neurotoxicity, immunotoxicity, and reproductive, musculoskeletal and liver toxicity at doses between 1 and 10 mg/kg bw/day in experimental animals. Liver cancer was induced in rats at a dose of 1 mg/kg bw/day (UNEP, 2007).

45. Chlordecone has been evaluated under the EU-Strategy for Endocrine Disrupters[4] and placed in category 1 (evidence of endocrine-disrupting activity in at least one species using intact animals). This categorisation was based on evidence of endocrine disrupting activity in a number of experimental systems, including the mouse uterotropic assay, increased uterine weight in rats given multiple injections of chlordecone postnatally, and receptor binding assays, indicative of an oestrogenic effect (BKH, 2000).

46. Chlordecone was not genotoxic in microbial or *in vitro* mammalian cell gene mutation assays, in a clastogenicity test, or in the dominant lethal assay (ATSDR,

[4] http://europa.eu.int/comm/environment/endocrine/strategy/substances_en.htm

1995). It has been suggested that the hepatocarcinogenicity occurs through an epigenetic, tumour-promoting mechanism involving hepatic toxicity and hypertrophy, and cytochrome P-450 induction (UNEP, 2006).

47. In humans, neurotoxicity has been reported in workers exposed to chlordecone during its manufacture (ATSDR, 1995). A number of studies found oligospermia and decreased sperm motility, but not reduced fertility, in occupationally exposed workers (Guzelian, 1982; Taylor, 1982, 1985). No evidence of hepatic cancer was found in liver biopsy samples taken from workers with hepatomegaly resulting from intermediate or chronic exposures to high concentrations of chlordecone (Guzelian *et al*, 1980). Environmental contamination by chlordecone in the French West Indies led to a number of epidemiological studies in the affected area. In one recent study, higher plasma chlordecone concentration, as a consequence of environmental exposure (over a period of 30 years) was associated with increased risk of prostate cancer (Multigner *et al*, 2010).

Occurrence

48. No data have been identified on levels of chlordecone in human breast milk in the UK.

49. Chlordecone has not been monitored in the UK Pesticide Residues Monitoring Programme. In 2010, EFSA presented results of the monitoring of pesticide residues in food and reported that tests for chlordecone had been carried out in 5 European countries. However, it was found at quantifiable levels (levels not specified) in only 2 out of 9214 samples of fruit and vegetables (EFSA, 2010).

Exposure

50. No information has been identified on exposure to chlordecone from human breast milk or other dietary sources in the UK.

Conclusions

51. Available data show that even if chlordecone was historically used in the UK, the exposure would be expected to be decreasing and remain low. There are no data available on chlordecone levels in food or human breast milk and there is no reason to assume a health concern.

Overall Conclusions

52. The use of endosulfan as a pesticide has been banned in the EU since 2005 and significant residues in food are not expected. The limited available data on endosulfan levels in breast milk samples from Europe indicate that infant dietary exposure to endosulfan is well below the ADI at 6 µg/kg bw/day set by JMPR in 1998 and do not suggest a health risk.

53. Available animal studies have shown some evidence for accumulation of PeCB in tissues. Data on PeCB levels in food are currently not available. Reported levels of PeCB in human breast milk samples would result in exposures to infants substantially less than the TDI of 0.5 µg/kg bw/day set by Health Canada, and do not indicate a health concern.

54. Available data show that even if chlordecone was historically used in the UK, the exposure would be expected to be decreasing and remain low. There are no data available on chlordecone levels in food or human breast milk and therefore it is not possible to identify a health concern

55. The Committee concluded that, based on the available information, there appeared to be no toxicological concern about any of the three chemicals since exposures were below the ADI or the TDI, or if no ADI had been set, were low and decreasing.

June 2013

Abbreviations

ADI	acceptable daily intake
ARfD	acute reference dose
ATSDR	Agency for Toxic Substances and Disease Registry
COC	Committee on Carcinogenicity
COM	Committee on Mutagenicity
COT	Committee on Toxicity
DH	Department of Health
DNSIYC	Dietary and Nutrition Survey of Infants and Young Children
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
FAO/WHO	Food and Agriculture Organization/World Health Organization
FSA	Food Standards Agency
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD50	lethal dose, 50% kill
LOAEL	lowest observed adverse effect level
LOD	Limit of Detection
MAFF	Ministry of Agriculture, Forestry and Fisheries
MRL	maximum residue level
NOAEL	no-observed adverse effect level
NTP	National Toxicology Program
PeCB	pentachlorobenzene
POPs	persistent organic pollutants
PRiF	Pesticide Residues in Food
RfD	reference dose
SACN	Scientific Advisory Committee on Nutrition
TDI	tolerable daily intake
UNEP	United Nations Environment Program

References

Ahmed T, Tripathi AK, Ahmed RS, Das S, Suke SG, Pathak R, Chakraboti A, Banerjee BD (2008) Endosulfan-induced apoptosis and glutathione depletion in human peripheral blood mononuclear cells: Attenuation by N-acetylcysteine. J *Biochem Mol Toxicol* **22**(5):299-304

Ahmed T, Pathak R, Mustafa MD, Kar R, Tripathi AK, Ahmed RS, Banerjee BD (2011) Ameliorating effect of N-acetylcysteine and curcumin on pesticide-inducd oxidative DNA damage in human peripheral blood mononuclear cells. *Environ Monit Assess* **179**(1-4): 293-9

Antherieu S, Ledirac N, Luzy AP, Lenormand P, Caron JC, Rahmani R (2007) Endosulfan decreases cell growth and apoptosis in human HaCaT keratinocytes: partial ROS-dependent ERK1/2 mechanism. *J Cell Physiol* **213**(1):177-86

ATSDR. (1995). Toxicological profile for Mirex and Chlordecone. U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) (1995). http://www.atsdr.cdc.gov/toxprofiles/tp66-p.pdf

ATSDR (2000). Toxicological profile for endosulfan. http://www.atsdr.cdc.gov/toxprofiles/tp41.pdf

Bailey RE, Wijk D, Thomas PC (2009) Sources and prevalence of pentachlorobenzene in the environment. *Chemosphere* **75**:555-564

Bajpayee M, Pandey AK, Zaidi S, Musarrat J, Parmar D, Mathur N, Seth PK, Dhawan A (2006) DNA damage and mutagenicity induced by endosulfan and its metabolites. *Environ Mol Mutagen* **47**(9): 682-92

BKH Consulting Engineers Final Report (2000): Towards the Establishment of a Priority List of Substances for Further Evaluation of their Role in Endocrine Disruption. Prepared for the European Commission, DG Environment. http://europa.eu.int/comm/environment/docum/pdf/bkh_main.pdf

Carrizo D, Grimalt JO, Ribas-Fito N, Sunyer J, Torrent M (2006) Physical-chemical and maternal determinants of the accumulation of organochlorine compounds in four-year-old children. *Environ Sci Technol* **1**:40(5):1420-6

Cerrillo I, Granada A, Lopez-Espinosa MJ, Olmos B, Jimenez M, Cano A, Olea N, Olea-Serrano MF (2005) Endosulfan and its metabolites in fertile women, placenta, cord blood, and human milk. *Environ Research* **98**:233-239

Choudhary N, Sharma M, Verma P, Joshi SC (2003) Hepato and nephrotoxicity in rat exposed to endosulfan. *J Environ Biol* **24**(3):305-8

Damgaard IN, Skakkebaek NE, Toppari J, Virtanen HE, Shen H, Schramm KW, Petersen JH, Jensen TK, Main KM, and the Nordic Cryptorchidism Study Group (2006) Persistent Pesticides in Human Breast Milk and Cryptorchidism. *Environ Health Perspectives* **114**(7):1133-1138

DEFRA (2012). National Implementation Plan for the Stockholm Convention on Persistent Organic Pollutants. http://www.defra.gov.uk/consult/files/consult-nip-pop-doc-20121121.pdf. Page 14.

Devos S, Den Heuvel R, Hooghe R, Hooghe-Peters EL (2004) Limited effect of selected organic pollutants on cytokine production by peripheral blood leukocytes. *Eur. Cytokine Netw*. **15**(2):145-151

DH (Department of Health) (1994). Department of Health (DH) (1994). The COMA report on Weaning and the Weaning Diet. Report on Health and Social Subjects 45. The Stationary Office London

DH (Department of Health) (2013). Diet and nutrition survey of infants and young children, 2011. Available at: http://transparency.dh.gov.uk/2013/03/13/dnsiyc-2011/

European Commission (2000). 2000/816/EC: Commission Decision of 27 December 2000 concerning the non-inclusion of quintozene in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant-protection products containing this active substance. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32000D0816:EN:NOT

EFSA (2005). Opinion of the Scientific panel on contaminants in the food chain on a request from the commission related to endosulfan as undesirable substance in animal feed. *The EFSA Journal* (2005) **234**, 1 – 31 http://www.efsa.europa.eu/en/efsajournal/doc/234.pdf

EFSA (2010). 2008 Annual Report on Pesticide Residues according to Article 32 of Regulation (EC) No 396/2005. The EFSA Journal 2010; 8(7):1646 http://www.efsa.europa.eu/en/efsajournal/pub/1646.htm

EFSA (2011). Statement on oral toxicity of endosulfan in fish. *The EFSA Journal* 2011;**9**(4):2131 http://www.efsa.europa.eu/de/efsajournal/doc/2131.pdf

European Parliament Regulation No 850/2004 on persistent organic pollutants (2004). Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:158:0007:0049:EN:PDF

FAO/WHO (Food and Agriculture Organization/World Health Organization), 1998. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Endosulfan, part II, toxicology. http://www.inchem.org/documents/jmpr/jmpmono/v098pr08.htm.

Gaspari L, Paris F, Jeandel C, Sultan C (2011) peripheral precocious puberty in a 4-month-old girl: role of pesticides? *Gynecol Endocrinol* **27**(9):721-4

Guzelian PS, Vranian G, Boylan JJ, Cohn WJ, Blanke RV (1980). Liver structure and function in patients poisoned with chlordecone (Kepone). *Gastroenterology* **78**(2):206-13

Guzelian PS. 1982. Chlordecone poisoning: A case study in approaches for the detoxification of humans exposed to environmental chemicals. *Drug Metab Rev* **13**:663-679.

Health Canada (2007). Environment and work place. Pentachlorobenzene. http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/pentachlorobenzene/pentachlorobenzene_3-eng.php

IARC. 1979. Chlordecone. In *Some Halogenated Hydrocarbons*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. Lyon, France: International Agency for Research on Cancer. pp. 67-81. http://monographs.iarc.fr/ENG/Monographs/vol20/volume20.pdf

IPCS-WHO (1984). Environmental Health Criteria (EHC) 43: Chlordecone. IPCS International Programme on Chemical Safety. United Nations Environment Programme. International Labour Organisation. World Health Organization. Geneva 1990 (available at: http://www.inchem.org/documents/ehc/ehc/ehc43.htm)

IPCS (1984) Environmental Health Criteria Monographs 40. Endosulfan. World Health Organization.

IPCS (1988) Health and Safety Guide No. 17: Endosulfan. World Health Organization

IPCS-WHO (1990). Health and Safety Guide No. 41, 1990. IPCS International Programme on Chemical Safety. United Nations Environment Programme. International Labour Organisation. World Health Organization. Geneva. http://www.inchem.org/documents/hsg/hsg/hsg041.htm

Jamil K, Shaik AP, Mahboob M, Krishna D (2004) Effect of organophosphorus and organochlorine pesticides (monochrotophos, chlorpyriphos, dimethoate, and endosulfan) on human lymphocytes in vitro. *Drug Chem Toxicol* **27**(2): 133-44

Johnston JJ, Furcolow CA, Kimball BA. (1997). Identification of Metabolites of Pentachlorobenzene and 1,2,4,5-Tetrachlorobenzene in Coyote Feces: Development of Physiological Markers for Wildlife Damage Control. *Pestic. Sci*. **50**, 249-257

Li D, Liu J, Li J (2011) Genotoxic evaluation of the insecticide endosulfan based on the induced GADD153-GFP reporter gene expression. *Environ Monit Assess* **176**(1-4):251-8

Linder, R., T. Scotti, J. Goldstein, K. McElroy and D. Walsh. (*1980)*. Acute and subchronic toxicity of *pentachlorobenzene*. *J. Environ. Pathol. Toxicol*. **4**: 183-196.

Lu Y, Morimoto K, Takeshita T, Takeuchi T, Saito T (2000) Genotoxic effects of α-endosulfan and β-endosulfan on human HepG2 cells*. Environ Health Perspect* **108**:559-561

MAFF UK, (1998). Survey of retail products for ochratoxin. Food surveillance information sheet. Number 185.

Multigner L, Ndong JR, Giusti A, Romana M, Delacroix-Maillard H, Cordier S, Jégou B, Thome JP, Blanchet P. (2010). Chlordecone exposure and risk of prostate cancer. *Clin Oncol*. **28**(21):3457-62

NTP (National Toxicology Program). 1991. Toxicology Studies of pentachlorobenzene in F344/N Rats and B6C3F1 Mice (Feed Studies). U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, Research Triangle Park, NC.

Ou YC, Conolly RB, Thomas RS, Xu Y, Andersen ME, Chubb LS, Pitot HC, Yang RSH (2001) A clonal growth model: time-course simulations of liver foci growth following penta- or hexachlorobenzene treatment in a medium-term bioassay. *Cancer Research* **61**:1879-1889

Ozen S, Darcan S, Bayindir P, Karasulu E, Simsek DG, Gurler T (2012) Effects of pesticides used in agriculture on the development of precocious puberty. *Environ Monit Assess* **184**(7):4223-32

PRIF (2009).Infant food (meat/cheese/egg/fish). Pesticide Residues Monitoring Report. First Quarter Report. http://www.pesticides.gov.uk/Resources/CRD/Migrated-Resources/Documents/P/PRC_Q1_2009_report.pdf . Pages 18 and 77.

PRIF (2009). Infant formula. Pesticide Residues Monitoring Report. Third Quarter Report 2009. http://www.pesticides.gov.uk/Resources/CRD/Migrated-Resources/Documents/Other/2009_Q3_Report.pdf. Pages 18 and 71.

PRIF (2011). Infant food (cereals). Pesticide Residues Monitoring Programme for Quarter 12011.http://www.pesticides.gov.uk/Resources/CRD/PRiF/Documents/Results%20and%20Reports/2011/Q1_2011_Report.pdf Pages 19 and 82.

PRIF (2011). Infant food (fruit and vegetables). Pesticide Residues Monitoring Programme for Quarter 3 2011. http://www.pesticides.gov.uk/Resources/CRD/PRiF/Documents/Results%20and%20Reports/2011/Q3_2011.pdf Pages 18 and 94.

Schaalan MF, Abdelraouf SM, Mohamed WA, Hassanein FS (2012) Correlation between maternal milk and infant serum levels of chlorinated pesticides 9CP) and the impact of elevated CP on bleeding tendency and immune status in some infants in Egypt. *J Immunotoxicol*. **9**(1):15-24

Shen H, Main KM, Virtanen HE, Damgaard IN, Haavisto AM, Kaleva M, Boisen KA, Schmidt IM, Chellakooty M, Skakkebaek NE, Toppari J, Schramm KW (2007) From mother to child: investigation of prenatal and postnatal exposure to persistent bioaccumulating toxicants using breast milk and placenta biomonitoring. *Chemosphere* **67**:256-262

Shen H, Main KM, Andersson AM, Damgaard IN, Virtanen HE, Sjajjebaek NE, Toppari J, Schramm KW (2008) Concentrations of persistent organochlorine

compounds in human milk and placenta are higher in Denmark than in Finland. *Human Reprod* **23**(1):201-210

Sinha N, Adhikari N, Saxena DK (2001) Effect of endosulfan during fetal gonadal differentiation on spermatogenesis in rats. *Environ Toxicol Pharmacol* **10**(1-2):29-32

Slooff W, Bremer HJ, Hesse JM, Matthijsen AJCM (eds.), 1991. Integrated criteria document chlorobenzenes. Report no. 710401015. RIVM. Available at: http://www.rivm.nl/bibliotheek/rapporten/710401015.pdf

Taylor JR. 1982. Neurological manifestations in humans exposed to chlordecone and follow-up results. *Neurotoxicology* **3**(2):9-16.

Taylor JR. 1985. Neurological manifestations in humans exposed to chlordecone: Follow-up results. *Neurotoxicology* **6**(1):23 l-236.

Thomas RS, Gustafson DL, Pott WA, Long ME, Benjamin SA, Yang RSH (1998) Evidence for hepatocarcinogenic activity of pentachlorobenzene with intralobular variation in foci incidence. *Carcinogenesis* **19**(10):1855-1862

Umegaki, K, Ikegami, S., Ichikawa, T. (1993). Effects of restricted feeding on the absorption,metabolism, and accumulation of pentachlorobenzene in rats. *J. Nutr. Sci. Vitaminol*.**39**:11-22.

UNEP (2007). Draft risk profile for Pentachlorobenzene. Persistent Organic Pollutants Review Committee (POPRC). An introduction to the chemical added to the Stockholm Convention at the fifth meeting of the Conference of the Parties. http://www.pops.int/documents/meetings/poprc/drprofile/drp/DraftRiskProfile_PeCB.pdf

UNEP (2009). Draft risk profile: endosulfan. Stockholm Convention on Persistent Organic Pollutants (POPs) Review Committee (POPRC); July, 2009. Available at: http://chm.pops.int/tabid/592/Default.aspx

UNEP (2010). Endosulfan. Risk management evaluation. Report of the Persistent Organic Pollutants Review Committee on the work of its sixth meeting. Available at: http://www.thehindu.com/multimedia/archive/00556/Stockholm_Conventio_556512a.pdf

UNEP (2011). Endosulfan. An introduction to the chemical added to the Stockholm Convention at the fifth meeting of the Conference of the Parties. Available at: http://chm.pops.int/Convention/Publications/BrochuresandLeaflets/tabid/3013/Default.aspx

US EPA (1998). Memorandum 2/26/98 Assessment of the Dietary Cancer Risk of Hexachlorobenzene and Pentachlorobenzene as impurities in Chlorothalonil, PCNB, Picloram, and several other pesticides. DP Barcode D243499. Chemical codes 061001 (Hexachlorobenzene) & 081901 (Chlorothalonil).

US EPA. 2002. Reregistration Eligibility Decision for Endosulfan. EPA 738-R-02-013. Pollution, Pesticides and Toxic Substances (7508C), United States Environmental

protection Agency. Available at:
http://www.epa.gov/oppsrrd1/REDs/endosulfan_red.pdf

US EPA. (2009). Environmental Protection Agency. (2009). Toxicological review of chlordecone (Kepone). EPA/635/R-07/004F.
http://www.epa.gov/iris/toxreviews/1017tr.pdf

Varayoud J, Monje L, Bernhardt T, Munoz-de-Toro M, Lugue EH, Ramos JG (2008) Endosulfan modulates estrogen-dependent genes like a non-uterotrophic dose of 17beta-estradiol. *Reprod Toxicol* **26**(2):138-45

WHO (1984). Endosulfan. International Programme on Chemical Safety. Environmental Health Criteria 40. Geneva, Switzerland: World Health Organization, 1-62.

WHO-IPCS International Programme on Chemical Safety. (1991). Environmental Health Criteria (EHC) 128: Chlorobenzenes other than Hexachlorobenzene. United Nations Environment Programme. International Labour Organisation. World Health Organization. Geneva. Available at:
http://www.inchem.org/documents/ehc/ehc/ehc128.htm

Yaduvanshi SK, Srivastava N, Marotta F, Jain S, Yadav H (2012) Evaluation of micronuclei induction capacity and mutagenicity of organochlorine and organophosphate pesticides. *Drug Metab Lett* **1**;6(3):187-97

Search strategy
General POPs exposure search

Databases interrogated:
- EFSA
- COT
- FSA
- JECFA

Scientific publication literature search

Specific search terms:

Endosulfan/Pentachlorobenzene/Chlordecone and Toxicity
Search dates (from/to) – to present
Exclusion criteria:
- studies performed in plants and freshwater organisms
- studies involving occupational exposure
- freshwater and wastewater samples
- agricultural soil samples

Endosulfan/Pentachlorobenzene/Chlordecone and Neurotoxicity
Search dates (from/to) – to present
Exclusion criteria:
- studies performed in plants and freshwater organisms
- studies involving occupational exposure
- freshwater and wastewater samples
- agricultural soil samples

Endosulfan/Pentachlorobenzene/Chlordecone and Endocrine Disruptors
Search dates (from/to) – to present
Exclusion criteria:
- studies performed in plants and freshwater organisms
- studies involving occupational exposure
- freshwater and wastewater samples
- agricultural soil samples

Endosulfan/Pentachlorobenzene/Chlordecone AND Genotoxicity
Search dates (from/to) – to present
Exclusion criteria:
- studies performed in plants and freshwater organisms
- studies involving occupational exposure
- freshwater and wastewater samples
- agricultural soil samples

Endosulfan/Pentachlorobenzene/Chlordecone AND levels in Food
Search dates (from/to) – to present
Exclusion criteria:
- mixtures of pesticides
- contaminated land

Endosulfan/Pentachlorobenzene/Chlordecone AND breastmilk
Search dates (from/to) – to present
Exclusion criteria:

- studies from countries other than the UK and Europe

The above mentioned search terms were also used in Google. It identified latest government advice and opinions.