

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

### 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<sup>1</sup> 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:  $\alpha$ - and  $\beta$ -endosulfan (Figure 1). Technical endosulfan is a mixture of the two isomers with a ratio of  $\alpha$ : $\beta$  of approximately 2:1, and contains also small amounts of impurities and degradation products (UNEP, 2010).

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<sup>1</sup> Available at: <http://chm.pops.int/Implementation/NewPOPs/TheNewPOPs/tabid/672/Default.aspx>

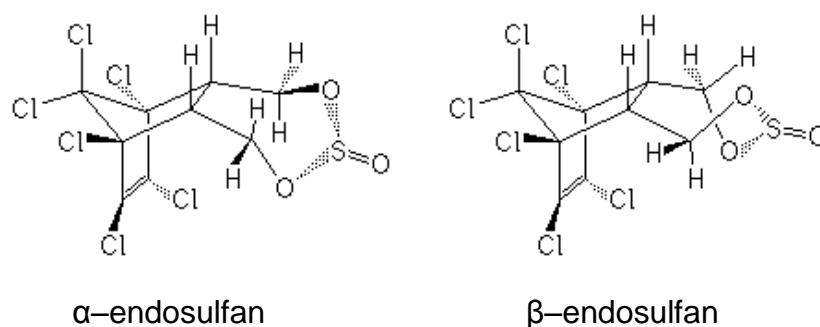


Figure 1. Structures of endosulfan isomers.

4. Endosulfan is a broad-spectrum insecticide that has been used since the 1950s to control crop pests, tsetse flies and ectoparasites of cattle, and as a wood preservative. Authorisations for its use as a pesticide in the European Union were withdrawn in 2005 (with a phase-out period of 18 months) 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). In 2011, endosulfan was included in a list of newly designated POPs in the Stockholm Convention, since it meets the criteria for long-range transport, bioaccumulation, persistence in the environment and toxicity, and its use is now banned or is being phased out in at least 60 countries. For example, in the United States, all uses are scheduled to be voluntarily cancelled and phased-out by 31st July, 2016 (US EPA, 2012). However, some countries have indicated that use of endosulfan for certain applications will be allowed to continue temporarily, either for a specified period, or until alternative products and methods of pest control are available (UNEP, 2011). Thus, it is still used in some parts of the world to control pests on various crops including coffee, cotton, rice, sorghum and soy.

5. Neither technical endosulfan nor the individual isomers have 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). Endosulfan 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 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 by 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.

### **Absorption, distribution, metabolism and excretion**

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. Studies with purified endosulfan isomers indicate that the  $\alpha$  isomer accumulates more than the  $\beta$  isomer (ATSDR, 2013).
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; ATSDR, 2013).
8. In animals, elimination of endosulfan and its metabolites following oral exposure occurs mainly through faeces (72-82% of the dose), with less by renal excretion (13-24% of the dose) (FAO/WHO, 1998). Estimated elimination half-lives of endosulfan isomers and their metabolites range between approximately 1 and 7 days in adult humans and animals (ATSDR, 2013). Experiments in male rats showed a biphasic elimination curve following oral exposure, with an initial half-life of 8 hours followed by a later half-life of 110 hours (FAO/WHO, 1998). Both isomers can be transported across the placenta (Cerrillo *et al.*, 2005; Schaalán *et al.*, 2012) and transferred into the breast milk of lactating women and animals (ATSDR, 2013; Schaalán *et al.*, 2012).

### **Toxicity**

9. Reports on effects of endosulfan do not always specify the isomeric composition of endosulfan that was tested. However, most of the studies in animals have been conducted on technical grade endosulfan (ATSDR, 2013). 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 values for technical endosulfan were 9.6 mg/kg bw in female Sprague-Dawley rats (FAO/WHO, 1998) and 7.4 mg/kg bw in male mice (ATSDR, 2013). In a group of rats fed exclusively with a protein-deficient diet prior to treatment, the LD50 was 5.1 mg/kg bw/day. In comparison, the LD50 in rats fed a standard laboratory diet was up to 121 mg/kg bw/day (ATSDR, 2013). The oral LD50 values of  $\beta$ -endosulfan are up to 3 times higher than those of  $\alpha$ -endosulfan (ATSDR, 2013; FAO/WHO, 1998).
11. Neurotoxicity is the most prominent adverse effect of endosulfan. Repeated exposure of immature rats by gavage to doses in the range of 2–6 mg/kg bw/day has induced changes in the levels of neurotransmitters in the brain and alterations in neurobehavioral tests. However, repeated dietary exposure of adult rats to doses near 30 mg/kg bw/day in one study, and near 46 mg/kg bw/day in another, did not significantly affect the results of a functional observational battery (FOB), which included examination of autonomic function, posture and gait, and behaviour. In

general, long-term studies have not found morphological alterations in tissues of the nervous system (ATSDR, 2013).

12. Other reported effects include liver and kidney toxicity, haematological effects, and alterations in the male reproductive organs. Of these, effects on the kidney are observed at the lowest doses (see paragraph 19) (FAO/WHO, 1998; Choudhary *et al.*, 2003; ATSDR, 2013).

13. Some animal studies have indicated effects also on the immune system. Studies in rats showed decreased serum antibody titre to tetanus toxin, and decreased levels of IgG, IgM and  $\gamma$ -globulin following 6-22 weeks dietary exposure to technical endosulfan at 0.9 to 4.5 mg/kg bw/day. Cell-mediated immune response was diminished in a dose-dependent manner at 1.8, 2.7, and 4.5 mg/kg bw/day. No effects were observed at 0.45 mg/kg bw/day (JMPR, 1998; ATSDR, 2013). In general, no adverse effects on organs of the immune system (lymph nodes and thymus) have been observed in chronic studies (doses of 1 to 48 mg/kg bw/day for up to 2 years) (ATSDR, 2013).

14. Adverse reproductive effects (e.g. implantation loss, reduction in litter size, sperm abnormalities, and altered spermatogenesis), have been reported in rats, mice and rabbits at endosulfan doses of 1 mg/kg bw/day or higher. Developmental effects have also been reported, mostly in studies conducted in rats with gavage dosing. It is not clear whether these developmental effects occur only in the presence of maternal toxicity (ATSDR, 2013).

15. 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 typhimurium* (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; Li *et al.*, 2011; Lu *et al.*, 2000). 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  $\mu$ g/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  $\mu$ g/plate, with a smaller effect at 20  $\mu$ g/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  $\mu$ g endosulfan/plate) and in the absence of metabolic activation (Yaduvanshi *et al.*, 2012). Overall, the evidence for direct mutagenicity of endosulfan is inconsistent.

16. Chronic feeding studies in which technical endosulfan was administered to rats (0.1 – 3.8 mg/kg bw/day) and mice (0.28 – 2.9 mg/kg bw/day) did not produce carcinogenic effects. However, decreased organ and body weights were observed at the highest doses (FAO/WHO, 1998; ATSDR, 2013).

17. Contradictory findings have been reported on the oestrogenic potential of endosulfan *in vitro*, whereas generally a lack of oestrogenic effects has been observed *in vivo* (ATSDR, 2013; 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).

18. Information on the effects of endosulfan in humans relates mostly to accidental or intentional poisoning. Acute poisoning following ingestion of endosulfan (often unknown amounts) by humans has been shown to result in various effects on the respiratory, cardiovascular, gastrointestinal, haematological, musculoskeletal, metabolic, hepatic and renal systems. In studies of occupational and environmental 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 (ATSDR, 2013).

### **Health-based guidance values**

19. JMPR established an acceptable daily intake (ADI) of 6 µg/kg bw for endosulfan on the basis of a no-observed adverse effect level (NOAEL) of 600 µg/kg bw/day in a two-year dietary study of the toxicity of technical grade endosulfan in rats, with 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. JMPR also established an acute reference dose (ARfD) of 20 µg/kg bw/day 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 (FAO/WHO, 1998). In contrast, ATSDR proposed an acute oral minimal risk level<sup>2</sup> of 7 µg/kg bw/day based on a NOAEL of 700 µg/kg bw/day for maternal toxicity in rabbits (clinical signs of toxicity such as noisy breathing, hyperactivity and convulsions were observed at 1800 µg/kg bw/day) (ATSDR, 2013). JMPR noted that the dose level of 1800 µg/kg bw/day resulted in maternal toxicity in this study, but did not use it as the basis for its ARfD (JMPR, 1998).

### **Occurrence in food and breast milk**

20. 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 the samples contained endosulfan at concentrations above the detection limit (50 µg/kg) (MAFF-UK, 1998).

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<sup>2</sup> An estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects over a period of 1-14 days

21. 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  $\alpha$ -endosulfan,  $\beta$ -endosulfan nor their metabolite endosulfan sulphate were identified in any of the samples at or above reporting limits of 10  $\mu\text{g}/\text{kg}$  (PRiF, 2009, 2011).

22. Shen *et al.* (2008) detected  $\alpha$ -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)  $\mu\text{g}/\text{kg}$  lipid, respectively. Levels of  $\beta$ -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  $\alpha$ -endosulfan in the Finnish and Danish samples were approximately 0.27 and 0.21  $\mu\text{g}/\text{L}$  breast milk, respectively. In Spain all of 23 breast milk samples collected between 2000 and 2002<sup>3</sup> (2-5 weeks postpartum,) contained endosulfan isomers:  $\alpha$ -endosulfan was detected with a median value of 0.87 (max 1.00) and  $\beta$ -endosulfan: 7.29 (max 26.89)  $\mu\text{g}/\text{L}$  breast milk (Cerrillo *et al.*, 2005). The reasons for the differing proportions of isomers in the Finnish and Danish as compared with the Spanish study are unclear.

## **Exposure**

23. No data on exposure to endosulfan in the UK population have been found. Exposures have been estimated for Canada (based on foods from a single location, with the highest intake of 0.03  $\mu\text{g}$  total endosulfan/kg bw/day reported for the 5-11 years old age group), the USA (0.05  $\mu\text{g}$  total endosulfan/kg bw/day), Taiwan (mean of 0.01  $\mu\text{g}$   $\alpha$ -endosulfan/kg bw) and the Czech Republic (median of 0.015  $\mu\text{g}/\text{kg}$  bw/day expressed as the sum of  $\alpha$ -,  $\beta$ -endosulfan and endosulfan sulphate) based on occurrence data from the 90s (EFSA, 2005).

24. The lowest reported median concentration of endosulfan in breast milk in the EU (0.21  $\mu\text{g}/\text{L}$  breast milk as  $\alpha$ -endosulfan, estimated from Shen *et al.*, 2008) and the highest (8.16  $\mu\text{g}/\text{L}$  breast milk as a sum of  $\alpha$ - and  $\beta$ -endosulfan, from Cerrillo *et al.*, 2005) were used to estimate potential exposures of breastfed infants, with average (800 mL per day) and high level (1200 mL per day) consumption of breast milk (Table 1). The mean bodyweight of 7.8 kg for infants aged 4 – 6 months in the recently published UK Dietary and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013) was used to calculate potential intakes for this age group. Since DNSIYC did not include infants younger than 4 months, the mean value of 5.9 kg for infants aged 0 – 3 months from an earlier survey (DH, 1994), was assumed for infants aged 0 – 4 months. Estimated intakes were in the range 0.02 – 1.11  $\mu\text{g}/\text{kg}$  bw/day for average consumption of milk and 0.03 – 1.66  $\mu\text{g}/\text{kg}$  bw/day for high level consumption. The highest measured concentration of endosulfan in breast milk (27.89  $\mu\text{g}/\text{L}$  breast milk as a sum of  $\alpha$ - and  $\beta$ -endosulfan, from Cerillo *et al.*, 2005),

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<sup>3</sup> Information on sampling period was provided in personal communication from the author

would give estimated intakes of 2.86 to 5.67 µg/kg bw/day. These estimates are all lower than the ARfD of 20 µg/kg bw/day and the ADI of 6 µg/kg bw/day set by JMPR in 1998, and the acute oral minimal risk level of 7 µg/kg bw/day derived by ATSDR. No relevant data are available from which to estimate possible dietary exposures 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 of milk

Endosulfan concentration in breastmilk (µg/L)	Age in months (consumption volume)			
	0 – 4 (800 mL)	0 – 4 (1200 mL)	>4 – 6 (800 mL)	>4 – 6 (1200 mL)
Median - 0.21 (Shen <i>et al.</i> , 2008)	0.03	0.04	0.02	0.03
Median - 8.16 (Cerrillo <i>et al.</i> , 2005)	1.11	1.66	0.83	1.25
Maximum – 27.89 (Cerrillo <i>et al.</i> , 2005)	3.78	5.67	2.86	4.29

## Conclusions

25. 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 below the ADI of 6 µg/kg bw/day that was set by JMPR in 1998, and thus do not suggest a health risk.

## Pentachlorobenzene

26. Pentachlorobenzene (PeCB) was used in the past as a flame retardant and dyestuff carrier<sup>4</sup> 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).

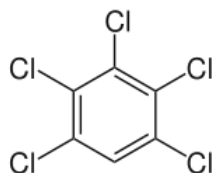


Figure 2. Structure of pentachlorobenzene.

<sup>4</sup> Hydrophobic chemical substance used in dyeing of polyester fibres.

27. 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.

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

29. 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, and 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.

### ***Absorption, distribution, metabolism and excretion***

30. Following oral administration to rats, PeCB was readily absorbed, detected in the blood, liver, kidney and adipose tissue, and excreted in faeces (Umegaki *et al.*, 1993). Similar observations have been reported in coyotes (Johnston *et al.*, 1997).

31. Analyses of serum in children at birth and again at four years of age showed decreases in the concentration of PeCB, and little variation in body burden, which did not correlate with mother’s age, whether breastfed or formula fed, or duration of breastfeeding (Carrizo *et al.*, 2006).

### ***Toxicity***

32. Oral LD50 values for PeCB are between 250 and 1125 mg/kg bw in rats, and between 1175 and 1370 mg/kg bw in mice (Allen *et al.*, 1979, cited by Slooff *et al.*, 1991, UNEP, 2007). Sub-chronic and chronic rat studies gave consistent findings at feed concentrations of approximately 500 ppm (reported by UNEP to be equivalent to approximately 37.5 mg/kg bw/day), with increased liver weight, generally in conjunction with hypertrophy, increased kidney weight with occasional hyalinization, disruption of thyroid function, and increased weight of the adrenal glands. At 1000 ppm in feed (reported by UNEP to be equivalent to approximately 80 mg/kg bw/day), these effects were more severe, and there was also a reduction in haemoglobin concentration and an increase in white blood cell count in both sexes of rats, and a decrease in red blood cell count and haematocrit in males (UNEP, 2007).

33. The UNEP (2007) evaluation noted contrasting outcomes in reproductive toxicity studies. In rats, an increased incidence of extra ribs and sternal defects,



indicating fetotoxicity has been reported at a dose not resulting in maternal toxicity (50 mg/kg bw per day). In contrast, no embryotoxic, fetotoxic or teratogenic effects were observed in the offspring of mice at doses that were maternally toxic (50 mg/kg bw per day and higher). The NOAELs and lowest observed adverse effect levels (LOAELs) varied between 17 and 200 mg/kg PeCB per day.

34. 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***

35. The US EPA established a reference dose (RfD) of 0.8 µg/kg bw/day based on a LOAEL of 8.3 mg/kg bw/day for liver and kidney damage in rats given PeCB in the diet for 100 days in a study by Linder *et al.* (1980). They applied an uncertainty factor of 10,000 to allow for inter- and intra-species variation, extrapolation from subchronic to chronic exposure, and extrapolation 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, with 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***

36. 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.

37. Data on PeCB in human breast milk in the UK have not been found. 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 PeCB/L.

### ***Exposure***

38. No data on exposure to PeCB in the UK population have been found.

39. 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 exposures for average (800 mL) and high level (1200 mL) consumption of milk by exclusively breastfed infants. The bodyweights assumed for different age groups were as described in paragraph 22. The estimated exposures were approximately 0.001 µg/kg bw/day for average consumption and 0.002 µg/kg bw/day for high level consumption. These estimates are substantially lower than the TDI of 0.5 µg/kg bw/day established by Health Canada (1993).

## Conclusions

38. Animal studies provide evidence that PeCB accumulates in tissues. Data on PeCB levels in food are not available currently, but are being obtained as part of an on-going FSA survey. 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<sup>®</sup>. In the UK, all Kepone<sup>®</sup> and Kepone<sup>®</sup> products had their licence for sale revoked in July 1977 (DEFRA, 2012). According to the Department for Environment, Food and Rural Affairs (DEFRA), "Chlordecone may not have been used in the UK prior to its ban in 1977".

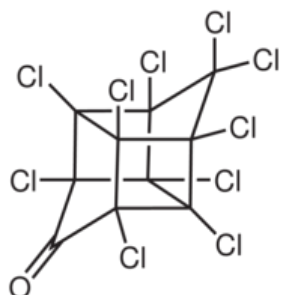


Figure 3. Structure of chlordecone

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 were extensive data on occupational exposures, showing potential for adverse effects in humans, including carcinogenicity and reproductive toxicity, and there was 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).

### ***Absorption, distribution, metabolism and excretion***

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 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. In experimental animals, studies of 10 days to 2 years duration using doses between 1 and 10 mg/kg bw/day, have shown that chlordecone causes neurotoxicity, immunotoxicity, and reproductive, musculoskeletal and liver toxicity. 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<sup>5</sup> and placed in category 1 (evidence of endocrine-disrupting activity in at least one species using intact animals). This categorisation was based on findings indicative of an oestrogenic effect from a number of experimental systems, including the mouse uterotrophic assay, receptor binding assays, and measurement of uterine weight in rats given multiple injections of chlordecone postnatally (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, 1995). It has been suggested that its 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 in occupationally exposed workers, but not reduced fertility (Guzelian, 1982; Taylor, 1982, 1985). No evidence of hepatic cancer was found in liver biopsy samples taken from workers with hepatomegaly resulting from occasional or chronic exposures to high concentrations of chlordecone

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<sup>5</sup> [http://europa.eu.int/comm/environment/endocrine/strategy/substances\\_en.htm](http://europa.eu.int/comm/environment/endocrine/strategy/substances_en.htm)

(Guzelian *et al*, 1980). Environmental contamination by chlordane in the French West Indies led to a number of epidemiological studies in the affected area. In one recent study, higher plasma chlordane 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 found on levels of chlordane in human breast milk in the UK.

49. Chlordane 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 chlordane had been carried out in five European countries. However, it was found at quantifiable levels (levels not specified) in only two out of 9214 samples of fruit and vegetables (EFSA, 2010).

### **Exposure**

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

### **Conclusions**

51. Available information indicates that even if chlordane was used historically in the UK, any current exposures are likely to be extremely low and decreasing. Thus, despite its known toxicity and the absence of measurements of chlordane in food or breast milk in the UK, the Committee consider that adverse effects in infants from dietary exposures are unlikely.

### **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 below the ADI of 6 µg/kg bw/day that was set by JMPR in 1998, and thus do not suggest a health risk.

53. Animal studies provide evidence that PeCB accumulates in tissues. Data on PeCB levels in food are currently not available but are being obtained as part of an on-going FSA survey. 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.

54. Available information indicates that even if chlordane was used historically in the UK, any current exposures are likely to be extremely low and decreasing.

Thus, despite its known toxicity and the absence of measurements of chlordecone in food or breast milk in the UK, the Committee consider that adverse effects in infants from dietary exposures are unlikely.

55. The Committee concluded that the available information did not indicate a toxicological concern regarding dietary exposures to any of the three chemicals. since exposures were below the ADI or the TDI, or if no ADI or TDI had been set, were low and decreasing. Although data on dietary exposures are limited, further research is unlikely to alter this view and is therefore not a priority.

COT Statement 2014/04

June 2014

## Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
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
DEFRA	Department for Environment, Food and Rural Affairs
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, Fisheries and Food
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

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## Search strategy

General POPs exposure search

Interrogated websites:

- EFSA
- COT
- FSA
- JECFA

Scientific publication literature search in PubMed from 1980 to March 2013

Specific search terms:

Endosulfan/Pentachlorobenzene/Chlordecone and Toxicity

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

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

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

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

Exclusion criteria:

- mixtures of pesticides
- contaminated land

Endosulfan/Pentachlorobenzene/Chlordecone AND breastmilk

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.