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

Statement on Chlorinated Paraffins in Food

Introduction

1. The Committee was asked for advice on possible risks associated with the levels of chlorinated paraffins (CPs) in foodstuffs that had been found in a Food Standards Agency (FSA) investigation.

2. The available toxicity data on chlorinated paraffins had previously been reviewed under the EU Existing Substances Regulation, with the UK Health and Safety Executive (HSE) as rapporteur for these risk assessments by the European Chemicals Bureau (ECB). This statement summarises the relevant data from the risk assessment reports[1,2] and details relevant papers published since the EU risk assessments were completed (1999 for short chain compounds and 2004 for medium chain compounds). The search strategy used to identify papers subsequent to the EU risk assessments is provided in Annex A. The statement also takes into account an update of the EU risk assessment for short chain CPs, which was published in 2008. Changes in the updated risk assessment related mainly to the section on environmental risk, but the section on human health was augmented to include consideration of human infants exposed via milk[3].

Background

3. CPs are a large group of several thousand individual chemicals. They are chlorinated linear hydrocarbons with between 10 and 30 carbon atoms and varying numbers of chlorine atoms, with a maximum of one chlorine atom per carbon atom. Depending on the length of the carbon skeleton, CPs are classified as short (SCCPs: C10-13), medium (MCCPs: C14-17) and long chain (LCCPs: C18-26). CPs are manufactured by the chlorination of liquid paraffin. The industrial applications of CPs vary depending on the chain length, and include use as industrial lubricants in metal manufacturing and as additives in plastics, paints and sealants. In addition, a common current use is as flame retardants[1,2,4].

4. CPs may be released into the environment during product use and through improper disposal. While they are expected to distribute mainly to soil and sediment following release to the environment, a small fraction will be present in water, and (in the case of SCCPs) also in air, and thus may be transported away from the source of release[1,5]. There is also potential for contamination of the food chain[4]. CPs have occasionally been detected in fish in other countries, with SCCPs being shown to

bioconcentrate in fish and molluscs to a large extent (with bioconcentration factors of 200-8000 for fish and 100,000-200,000 for molluscs)[1], and MCCPs to bioconcentrate in fish (with bioconcentration factors of 30-900) and to a lesser extent in earthworms (with bioconcentration factors of 1-6)[5]. The FSA investigation was carried out as there were no UK data on CP occurrence in food. Samples were assessed for SCCP and MCCP levels and, therefore, this risk assessment focuses on these two groups of compounds.

Toxicokinetics

SCCPs

5. Studies in animals have shown that approximately 60% of orally ingested SCCPs are absorbed. Following a single dose, distribution occurs in mice principally to the liver, intestinal mucosa, bone marrow, brown fat, salivary glands and thymus, with some evidence of greater accumulation with increasing chlorine content; and in rats to liver, kidney, adipose tissue and ovaries. No studies to identify metabolites have been performed, though metabolism to carbon dioxide has been demonstrated as excretion occurs via carbon dioxide in exhaled air, urine and faeces. In a mouse study using single doses of ^{14}C labelled polychlorododecane with 55.9% or 68.5% chlorine, 33% of the lower chlorinated compound dose was found in exhaled air, 29% was in urine and 5% in faeces by 12 hours. Only 8% of the higher chlorinated compound was recovered in exhaled air, 4% in urine and 21% in faeces. In rats, given a ^{14}C labelled $C_{10\text{-}12}$, 58% chlorinated paraffin, faecal elimination was predominant with 54-66% of the dose recovered by 7 days, as compared with 14% in urine and less than 1% in exhaled air[1]. Thus the degree of chlorination of the SCCPs has been shown to affect their absorption, distribution and excretion[1,6].

6. Day-old Lohmann meat broiler chickens were fed diets containing SCCPs with 60% chlorine content at 0 (n=48), 2 (n=8), 20 (n=8), 45 (n=8), 70 (n=8) or 100 (n=48) mg/kg feed for 31 days. At the end of the study, there was a linear relationship between concentration in feed and that in the tissues, with the highest concentrations found in the abdominal fat. In the meat, there was a direct correlation between the fat content and the CP concentration. Less than 5% of the ingested CPs remained in the tissues excluding the head, gut, feet and feathers[7].

7. Groups of laying Lohmann selected Leghorn hens aged 24 weeks were fed diets containing SCCPs with 60% chlorine content at 0 (n=21), 2 (n=9), 20 (n=9), 45 (n=9), 70 (n=9) or 100 (n=36) mg/kg feed for 8 weeks (equivalent to 0, 0.25, 2.5, 5.6, 8.8 or 12.5 mg/kg b.w./day). Ten eggs from different birds were collected on 9 occasions during the experiment for analysis of CP content. Nine animals from each group were killed when dosing finished and tissue samples were assessed for CP content. Concentrations of the CPs in feed had a linear relationship with the concentrations found in the tissues and blood, but not with those found in bile. Highest concentrations were found in the abdominal fat, yolk and liver. No residues were found in egg albumen[8].

8. From this study, two thirds of the high dose group were kept for a withdrawal study. Animals were killed at intervals between day 1 and 42 after cessation of dosing, with animals from the control group being killed on days 14, 28 and 42. Yolk

and albumen from 6 to 10 eggs were sampled at each interval. Concentrations in yolk showed a rapid drop following cessation of dosing and then a slow phase of elimination. All tissues showed a rapid and a slow phase of decrease in tissue concentrations, with the rapid phase being particularly distinct for the yolk, blood and liver. Rapid phase half-life was approximately 42 minutes in blood, 4-10 minutes in liver, kidney and leg muscle, and approximately 2.9 days in yolk. Terminal half-lives in all tissues were some 20-30 days. This was suggested to be related to equilibrium partitioning between blood and slowly perfused adipose tissue. About 30% of the ingested CPs were excreted in the urine and faeces, and an estimated 1.5% in egg yolk, with approximately 1% remaining in the body. The remainder of the mass balance was considered to be in tissues that were either not analysed, excreted by an unmeasured route, or were errors made in the final estimation[8].

9. One study has analysed human milk samples for SCCPs and MCCPs. Samples were obtained from women in Lancaster (n=5) and London (n=20) in 2001 and 2002. The median concentration of SCCPs was 180 µg/kg fat (range 49 to 820 µg/kg fat), with no significant differences between the two locations[9].

MCCPs

10. MCCPs are absorbed following oral administration to laboratory animals. A study in rats showed distribution to the liver, kidneys and ovaries occurs over the first 7 days after a single dose of radiolabelled MCCP, and subsequently there was an increase in the levels of MCCPs in adipose tissue. In a study where MCCPs were administered for 10 weeks, levels of MCCPs reached a plateau in the liver after one week, and in adipose tissue after 7 weeks. A limited study assessed metabolites in urine, and bile from rats, administered a single radiolabelled MCCP intravenously, and indicated that metabolism of MCCP probably involves glutathione conjugation in addition to metabolism to carbon dioxide. Seven days after a single radiolabelled dose of 10 mg/kg b.w., 30% and 40-48% of the total dose was recovered in the faeces in females and males respectively. With a higher single dose of 625 mg/kg b.w., increased recovery from faeces occurred with 62-74% in females and 53-61% in males. Over the same time period, urinary excretion was 0.8-3%, and 0.1-0.3% of the dose was recovered in expired air in both sexes after either dose. In another study, the elimination half-life from abdominal fat following cessation of 10 weeks treatment with 0.4 ppm (0.03 mg/kg b.w./day) radiolabelled MCCP was 8 weeks, and no radioactivity was detectable in the liver 1 week after cessation of treatment[2].

11. MCCPs have been detected in human breast milk at levels in the range 6.2-320 µg MCCP/kg fat, indicating that excretion can occur via this route[2,9].

Toxicity

SCCPs

12. This section provides a summary of the mammalian and avian studies conducted on SCCPs. Table 1 summarises the repeat dose, reproductive and developmental studies using oral administration with more than one treatment group, as described in the EU report on SCCPs.

Table 1: Summary of selected repeat dose, reproductive and developmental studies on SCCPs (based on the EU report[1]).

Type of study	Substance and dose	Most sensitive endpoint	LOAEL	NOAEL
Subchronic toxicity				
12 day oral gavage study in male and female mice (n=5 per sex per dose)	C_{12}, 60% Cl 0, 938, 1875, 3750, 7500 or 15000 mg/kg b.w./day	Liver enlargement	938 mg/kg b.w./day	-
12 day oral gavage study in male and female rats (n=5 per sex per dose)	C_{12}, 60% Cl 0, 469, 938, 1875, 3750 or 7500 mg/kg b.w./day	Liver enlargement	Males – 469 mg/kg b.w./day Females – 938 mg/kg b.w./day	Males – none Females – 469 mg/kg b.w./day
14 day oral gavage study in male mice focussing on liver effects (group size not specified)	$C_{10\text{-}13}$, 58% Cl 0, 10, 50, 100, 250, 500 or 1000 mg/kg b.w./day	Statistically significant increase in relative liver weight, and peroxisomal fatty acid β-oxidation activity	250 mg/kg b.w./day	100 mg/kg b.w./day
14 day oral gavage study in male mice focussing on liver effects (group size not specified)	$C_{10\text{-}13}$, 56% Cl 0, 10, 50, 100, 250, 500 or 1000 mg/kg b.w./day	Statistically significant increase in absolute and relative liver weight	100 mg/kg b.w./day	50 mg/kg b.w./day
14 day oral gavage study in male and female rats (n=5 per sex per dose)	$C_{10\text{-}12}$, 58% Cl 0, 30, 100, 300, 1000 or 3000 mg/kg b.w./day	Increase in absolute and relative liver weight	100 mg/kg b.w./day in both sexes	30 mg/kg b.w./day
14 day dietary study in male and female rats (n=5 per sex per dose)	$C_{10\text{-}12}$, 58% Cl 0, 100, 300, 1000 or 3000 mg/kg b.w./day	Increase in absolute and relative liver weight, increase in incidence and degree of hepatocellular hypertrophy	100 mg/kg b.w./day in both sexes	-
14 day oral gavage study in male rats focussing on liver effects (group size not specified)	$C_{10\text{-}13}$, 58% Cl 0, 10, 50, 100, 250, 500 or 1000 mg/kg b.w./day	Statistically significant increase in absolute and relative liver weight, and in peroxisomal fatty acid β-oxidation	250 mg/kg b.w./day	100 mg/kg b.w./day
14 day oral gavage study in male rats focussing on liver effects (group size not specified)	$C_{10\text{-}13}$, 56% Cl 0, 10, 50, 100, 250, 500 or 1000 mg/kg b.w./day	Statistically significant increase in absolute and relative liver weight	100 mg/kg b.w./day	50 mg/kg b.w./day
14 day oral gavage study in male guinea pigs (group size not specified)	58% Cl 0, 500 or 1000 mg/kg b.w./day	None determined. *Study assessed for effects on thyroid homeostasis, evidence of hepatic peroxisome proliferation and renal changes*	-	1000 mg/kg b.w./day
14 day oral gavage study in guinea pigs (group size not specified)	58% Cl 0, 500 or 1000 mg/kg b.w./day	Statistically significant decrease in body weight gain and in relative liver weight	500 mg/kg b.w./day	-
Oral gavage study in male and female rats with animals from each dose being autopsied on day 15, 29, 57 or 91 (group size not specified)	58% Cl 0, 313, 625, 1000 mg/kg b.w./day	Statistically significant increases in liver weight, peroxisomal β-oxidation, UDPGT activity, thyroid follicular hypertrophy and hyperplasia. Renal tubular eosinophilia in males	313 mg/kg b.w./day	-
13 week oral gavage study in male and female mice (n=10 per sex per dose)	C_{12}, 60% Cl 0, 125, 250, 500, 1000 or 2000 mg/kg b.w./day	Increases in relative liver weight Heptatocellular hypertrophy	250 mg/kg b.w./day	125 mg/kg b.w./day

Type of study	Substance and dose	Most sensitive endpoint	LOAEL	NOAEL
13 week oral gavage study in male and female rats (n=10 per sex per dose)	C_{12}, 60% Cl 0, 313, 625, 1250, 2500 or 5000 mg/kg b.w./day	Increase in relative liver weight	313 mg/kg b.w./day in both sexes	-
90 day dietary study in male and female rats (group size not specified)	$C_{10\text{-}12}$, 58% Cl 0, 10, 100 or 625 mg/kg b.w./day	Increase in relative and absolute liver and kidney weight. Hepatocellular hypertrophy, mild nephritis (males), brown pigmentation in renal tubules (females) and thyroid hypertrophy	100 mg/kg b.w./day in both sexes	10 mg/kg b.w./day
90 day oral gavage study in male and female rats (group size not specified)	$C_{10\text{-}12}$, 58% Cl 0, 10, 100 or 625 mg/kg b.w./day	Increases in liver and kidney weights Hepatocellular hypertrophy, thyroid hyperplasia and hypertrophy (males only at 100 mg/kg b.w./day), mild nephritis (males)	100 mg/kg b.w./day in both sexes	10 mg/kg b.w./day
6 or 12 month oral gavage study in F344/N rats (n=20 per sex per dose per timepoint) *NB this study was poorly conducted according to the EU risk assessment report*[1]	C_{12}, 60% Cl 0, 312 or 625 mg/kg b.w./day	Statistically significant increases in absolute and relative liver and kidney weights. Hepatocyte hypertrophy, damage to renal tubules and interstitial inflammation	312 mg/kg b.w./day	-
Chronic toxicity and Carcinogenicity				
2 year oral gavage study in $B6C3F_1$ mice (n=50 per sex per dose)	C_{12}, 60% Cl 0, 125 or 250 mg/kg b.w. 5 days per week	Statistically significant increases in incidence of hepatocellular adenomas and carcinomas, thyroid follicular cell adenomas and carcinomas in females, thyroid follicular cell lesions in both sexes	125 mg/kg b.w./day	-
2 year oral gavage study in F344/N rats (n=50 per sex per dsoe) *NB this study was poorly conducted with low survival rates according to the EU risk assessment report*[1]	C_{12}, 60% Cl 0, 312 or 625 mg/kg b.w. 5 days per week	Statistically significant increase in hepatocellular carcinoma in males and of liver neoplastic nodules in both sexes. Statistically significant increase in thyroid follicular cell adenomas in females and in kidney tubular cell adenomas in males Non-neoplastic changes in the kidney, liver and stomach	312 mg/kg b.w./day	-
Reproductive and Developmental toxicity				
14 day study in female rats (group size not specified)	$C_{10\text{-}12}$, 58% Cl 1000 or 3000 mg/kg b.w./day	Decrease in absolute and relative ovary weight, suggested to be secondary to 20% decrease in body weight gain	3000 mg/kg b.w./day	1000 mg/kg b.w./day
13 week study in mice (group size not specified)	C_{12}, 60% Cl Up to 2000 mg/kg b.w./day	None determined. *Study assessed for effects in seminal vesicles, prostate, testes, ovaries or uteri*	-	2000 mg/kg b.w./day
13 week study in rats (group size not specified)	C_{12}, 60% Cl Up to 5000 mg/kg b.w./day	None determined. *Study assessed for effects in seminal vesicles, prostate, testes, ovaries or uteri*	-	5000 mg/kg b.w./day
Oral gavage study in rats from GD 6-19 with Caesarian section on GD 20 (n=25 per dose)	$C_{10\text{-}13}$, 58% Cl 0, 100, 500 or 2000 mg/kg b.w./day	Signs of maternal toxicity	500 mg/kg b.w./day	100 mg/kg b.w./day

Type of study	Substance and dose	Most sensitive endpoint	LOAEL	NOAEL
Oral gavage study in rabbits from GD 6-27 with Caesarian section on GD 28 (n=16 per dose)	C_{10-12}, 58% Cl 0, 10, 30 or 100 mg/kg b.w./day	None determined. *Study assessed for maternal death and signs of toxicity*	-	100 mg/kg b.w./day

GD – gestation day

13. Oral dosing studies in rats and mice have shown liver and thyroid to be the major target organs for SCCP-mediated effects. Effects in the liver were increased weight, hepatocellular hypertrophy and peroxisome proliferation. Guinea pigs treated with SCCPs showed changes in relative liver weight but no associated peroxisome proliferation. Thyroid effects observed in rats and mice include hypertrophy followed by hyperplasia with associated increase in thyroid weight. Hepatic uridine diphosphate glucuronosyltransferase (UDPGT) activity showed a dose-related increase along with plasma thyroid stimulating hormone (TSH), while total and free thyroxine in plasma decreased. These thyroid effects were not observed in guinea pigs. Other effects observed in animal studies have been decreased body weight gain and increases in kidney weight, with mild nephritis in males and brown pigmentation of the renal tubules in females[1].

14. The mechanism of nephrotoxicity has been investigated in a number of studies where male and female rats have been administered SCCPs by oral gavage. One study, where 1000 mg/kg b.w./day C_{10-12}, 58% chlorinated paraffin was given for 28 days, showed moderate proximal tubule hypertrophy and eosinophilia in male rats. Decreased staining of α2u globulin in the pars convoluta and a decrease in bromodeoxyuridine incorporation in the pars convoluta and pars recta were observed following treatment. In contrast, in a similar study in which rats received 625 mg/kg b.w./day, increased α2u globulin staining in the pars convoluta and pars recta was seen, along with increased bromodeoxyuridine incorporation and marked proximal tubular hypertrophy and eosinophilia. Further investigations have shown that there is a marked decrease in hepatic α2u globulin content and inhibition of α2u globulin synthesis in the liver of males but not in females treated with SCCPs. An assay using radiolabelled chemical has shown that SCCP binds to three isoforms of α2u globulin in the kidney of male rats only[2].

15. Genotoxicity has been assessed in a number of studies. Mutation in bacteria and other *in vitro* genotoxicity assays have been largely negative. There was no increase in chromosome aberrations in the bone marrow of male rats treated with up to 2500 mg/kg b.w./day by gavage for 5 days. A dominant lethal assay was negative when male rats were treated with up to 2500 mg/kg b.w./day by gavage for 5 days. Overall, this evidence was considered by the EU to indicate that SCCPs are not mutagenic[1].

16. Carcinogenicity studies in rats and mice show dose-related tumours of the liver, thyroid and kidney. In the rat study, there was significant lethality in both groups receiving chloroparaffin (C_{12}, 60% Cl) at doses of 312 or 625 mg/kg b.w./day. There was a slight increase in hepatocellular carcinoma in males with overall rates of 0/50 for control, 3/50 for low dose and 2/48 for high dose animals. Liver neoplastic nodules were increased with treatment in both sexes with incidence rates of 0/50, 10/50 and 16/48 in control, low dose and high dose male rats respectively and 0/50,

4/50 and 7/50 for females. Thyroid follicular cell adenomas showed a significant increase in female rats at the low dose (0/50 in controls, 6/50 in the low dose group and 3/50 in the high dose group) and follicular cell carcinomas showed a non-statistically significant increase in the high dose (0/50 in controls, 0/50 in low dose and 3/50 in the high dose). Male rats also showed an increase in kidney tubular cell adenomas at the low dose with overall rates of 0/50 for control, 7/50 for low dose and 3/49 for high dose animals. Kidney tubular cell adenocarcinomas were found in 2/50 low dose males but were not present in controls or in the high dose group[1].

17. The mouse oncogenicity study showed increases in hepatocellular carcinoma in both sexes which reached statistical significance in the high dose females. Rates were 3/50, 4/50 and 9/50 for control, low dose (125 mg/kg b.w./day) and high dose (250 mg/kg b.w./day) females respectively and 11/50, 15/50 and 17/50 for control, low dose and high dose males respectively. The incidence of hepatocellular adenomas showed statistically significant increases with rates of 11/50, 20/50 and 29/50 for control, low and high dose male mice respectively, and 0/50, 18/50 and 22/50 for control, low and high dose females respectively. Thyroid adenomas and carcinomas were increased in female mice. For thyroid adenomas the incidence rates were 8/50, 12/49 and 13/49 for control, low and high dose animals respectively while thyroid carcinomas were seen in 0/50 controls, 0/49 low dose,and 2/49 high dose females. Non-neoplastic thyroid lesions, indicative of a chemical related toxicity, were seen in both male and female mice[1].

18. The International Agency for Research on Cancer (IARC) considered there to be sufficient evidence for carcinogenicity of a SCCP (C_{12}, 60% Cl) in experimental animals. No human data on carcinogenicity were available. SCCPs of an average length of 12 carbon atoms, and with an average degree of chlorination of 60%, were classified to Group 2B, “possibly carcinogenic to humans”[10].

19. A reduction in relative and absolute ovary weight was observed in a 14 day study in female rats at a dose causing a 20% decrease in body weight gain. No changes in the reproductive organs were observed in a 13 week study in rats and mice of both sexes. Developmental studies have been carried out in which pregnant rats were dosed from gestation day 6 to 19, and in pregnant rabbits dosed from gestation day 6 to 27. The rat study showed fetal effects only at maternally toxic doses, and while the rabbit study showed whole litter resorptions at the mid and high dose, this was at a similar level to the historical control incidence for the laboratory carrying out the studies[1].

20. The EU report identified no observed adverse effect levels (NOAELs) of 100 mg/kg b.w./day for general toxicity and kidney toxicity/carcinogenicity and 500 mg/kg b.w./day for developmental effects. The effects seen in the liver and thyroid of rats and mice were determined to be not relevant to human health as most of the liver effects were due to peroxisome proliferation, to which humans are known to be insensitive. Thyroid effects were considered to be secondary to the liver effects, with the increase in hepatic UDPGT activity arising as a result of, or from a similar mechanism to, peroxisome proliferation. Rats and mice are considered particularly sensitive to thyroid effects due to their lack of thyroxine binding globulin, which in humans binds thyroxine in the plasma, making it unavailable to UDPGT and therefore less likely to be rapidly metabolised and excreted[1]. As part of the EU

review, a group of specialised experts assessed the carcinogenicity data. Only the liver, thyroid and kidney tumours were statistically significantly increased, and of these the liver and thyroid tumours were considered not relevant to humans. Kidney tubular cell adenomas were found in male rats only, for which the experts considered that no plausible mechanism was suggested. Additional studies failed to show significant levels of α2u globulin protein in the kidney and there was some evidence that a treatment-related enhancement of chronic nephropathy might be a contributing factor in tumour development. Therefore, the specialised experts considered there to be insufficient evidence to conclude that the kidney carcinogenicity was specific to male rats and thus consequences for humans could not be ruled out. As the kidney tumours were considered unlikely to arise at doses lower than those causing chronic kidney toxicity, a NOAEL of 100 mg/kg b.w./day was identified for this effect. Developmental effects were not observed at 500 mg/kg b.w./day although this dose was associated with maternal toxicity[1]

21. The EC Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) reviewed the final draft of the EU report and agreed with the conclusions of the human risk characterisation[11]. Subsequently, in 2002 the CSTEE assessed the new data which had become available since the initial EU Risk Assessment Report. It concluded that these new data did not alter the conclusions drawn in the 1999 report[12].

22. As part of a study of the effects on thyroid hormone levels of various chlorinated compounds, singly and as mixtures, female Sprague Dawley rats were given Witaclor 171P (an SCCP with 71% chlorine content) orally once a day for 14 days. Animals were killed 24 hours after the final dose. Blood samples were taken, liver and thyroid glands were weighed, and a liver sample taken for enzyme analysis. There were no statistically significant differences between the Witaclor treated animals and controls. Increases in relative liver weight and liver enzyme activity, and decreases in free and total plasma thyroxine and protein-bound thyroxine were seen when Witaclor was combined with DE-47 (a polybrominated diphenyl ether congener) and/or Aroclor 1254 (a technical preparation of polychlorinated biphenyls)[13].

MCCPs

23. No further studies have been carried out on MCCPs since the EU report. Table 2 summarises the repeat dose, reproductive and developmental studies using oral administration with more than one treatment group, as described in the EU report on MCCPs.

Table 2: Summary of selected repeat dose, reproductive and developmental studies on MCCPs (based on the EU report[2]).

Type of study	Substance and dose	Most sensitive endpoint	LOAEL	NOAEL
Subchronic toxicity				
5 day oral gavage study in rats (group size not specified)	C_{14-17}, 52% Cl 0, 1000, 2500 or 5000 mg/kg b.w./day	None determined. *Study assessed animals for macroscopic findings*	-	5000 mg/kg b.w./day

Type of study	Substance and dose	Most sensitive endpoint	LOAEL	NOAEL
14 day dietary study in male and female F344 rats (n=5 per sex per dose)	$C_{14\text{-}17}$, 52% Cl Males: 0, 18, 58, 170, 550 or 1540 mg/kg b.w./day Females: 0, 18, 58, 180, 580 or 1290 mg/kg b.w./day	Statistically significant elevation in absolute and relative liver weight Diffuse mild hypertrophy of the liver	Males: 550 mg/kg b.w./day Females: 580 mg/kg b.w./day	58 mg/kg b.w./day
14 day oral gavage study in male F344 rats (n=5 per dose)	$C_{14\text{-}17}$, 40% Cl 0, 10, 50, 100, 250, 500 or 1000 mg/kg b.w./day	Statistically significant increase in absolute and relative liver weight	100 mg/kg b.w./day	50 mg/kg b.w./day
14 day oral gavage study in male Alderley Park CD-1 mice (n=5 per dose)	$C_{14\text{-}17}$, 40% Cl 0, 10, 50, 100, 250, 500 or 1000 mg/kg b.w./day	Significant increases in peroxisomal fatty acid β-oxidation	500 mg/kg b.w./day	250 mg/kg b.w./day
15, 29, 57 or 91 day oral gavage study in male and female F344 rats (n=10 per sex per dose per dose duration)	$C_{14\text{-}17}$, 40% Cl 0, 312 or 625 mg/kg b.w./day	Statistically significant increase in relative liver weight, peroxisomal β-oxidation and UDPGT activity. Statistically significant decrease in free and total plasma T_3 and increase in TSH. Thyroid follicular cell hypertrophy and increase in thyroid cell replicative DNA synthesis Renal tubular eosinophilia in males with focal or multifocal areas of basophilia	312 mg/kg b.w./day	-
90 day dietary study in male and female Sprague Dawley rats (n=10 per sex per dose)	$C_{14\text{-}17}$, 52% Cl Males: 0, 0.4, 4, 36 or 360 mg/kg b.w./day Females: 0, 0.4, 4, 42 or 420 mg/kg b.w./day	Minimal severity inner medullary tubular dilation of the kidney in females Minimal to mild morphological changes in the thyroid in females (seen in males at higher doses) *NB increased hyaline droplet-like cytoplasmic inclusions were observed in males at all doses* **The COT considered the most sensitive endpoint to be hepatic and renal changes**[a]	4 mg/kg b.w./day The COT identified 36 mg/kg b.w./day	0.4 mg/kg b.w./day The COT identified 4 mg/kg b.w./day
90 day dietary study in male and female F344 rats (n=15 per sex per dose)	$C_{14\text{-}17}$, 52% Cl 0, 10, 100 or 625 mg/kg b.w./day	Increased incidence of "chronic nephritis" (mixed population of interstitial inflammatory cells, tubular regeneration and/or minimal degenerative changes in tubular epithelium) *NB mild to moderate thyroid hypertrophy and hyperplasia were observed in all males including controls though increasing severity was observed with increasing dose* **The COT considered the most sensitive endpoint to be increased liver and kidney weight**[b]	10 mg/kg b.w./day The COT identified 100 mg/kg b.w./day	- The COT identified 10 mg/kg b.w./day
90 day dietary study in male and female Wistar-derived rats (n=24 per sex per dose)	$C_{14\text{-}17}$, 52% Cl (with epoxidised vegetable oil stabilizer) Males: 0, 33, 167 or 333 mg/kg b.w./day Females: 0, 32, 160 or 320 mg/kg b.w./day *At 6 weeks an additional 16 mg/kg b.w./day group of male and female rats and 12 additional controls of each sex were introduced*	Statistically significant increase in relative liver weight Proliferation of liver smooth endoplasmic reticulum	Males: 33 mg/kg b.w./day Females 32 mg/kg b.w./day	16 mg/kg b.w./day *NB this group was introduced 6 weeks after study initiation*

Type of study	Substance and dose	Most sensitive endpoint	LOAEL	NOAEL
90 day dietary study in Beagle dogs (n=4 per sex per dose)	MCCP, 52% Cl 0, 10, 30 or 100 mg/kg b.w./day	Cloudy, pale and enlarged hepatocytes and increase in smooth endoplasmic reticulum in hepatocytes **The COT considered the most sensitive endpoint to be increased alkaline phosphatase and relative liver weight[c]**	30 mg/kg b.w./day The COT identified 100 mg/kg b.w./day	10 mg/kg b.w./day The COT identified 30 mg/kg b.w./day
Reproductive and Developmental toxicity				
Dietary study in Wistar rats from 28 days before mating to PND 21 (n=5m, 10f per dose) with 5m and 10f F_1 pups kept on the same diet as their parents from weaning to PND 70	C_{14-17}, 52% Cl 0, 100, 1000 or 6250 ppm Males: 0, 6, 62 or 384 mg/kg b.w./day Females: 0, 8, 74 or 463 mg/kg b.w./day	Reduced pup survival (11% but not statistically significant) Increase in occurrence and severity in F_1 pups of haematoma; pallor; blood around the orifices; pale liver, kidneys, lungs and spleen; and blood in cranial cavity and brain. **The COT considered the most sensitive endpoint to be decreased pup body weight[d]**	1000 ppm diet Male F_0 dose: 62 mg/kg b.w./day Female F_0 dose: 74 mg/kg b.w./day The COT identified 100 ppm diet Female F_0 dose: 8 mg/kg b.w./day	100 ppm diet Male F_0 dose: 6 mg/kg b.w./day Female F_0 dose: 8 mg/kg b.w./day
Oral gavage study in rats from GD 6-19 with sacrifice on GD 20 (n=25 per dose)	C_{14-17}, 52% Cl 0, 500, 2000 or 5000 mg/kg b.w./day maternal dose	No developmental effects determined *NB Clinical signs of maternal toxicity were observed at 2000 and 5000 mg/kg b.w./day*	-	5000 mg/kg b.w./day
Oral gavage study in rabbits from GD 6-27 with sacrifice on GD 28 (n=16 per dose)	C_{14-17}, 52% Cl 0, 10, 30 or 100 mg/kg b.w./day	None determined. *Study assessed for treatment related developmental effects (mortalities, malformations) or toxicity in the dams*	-	100 mg/kg b.w./day

PND – post-natal day
GD – gestation day

[a] The COT considered the renal changes identified by the authors of this study and the EU in this study to be inconsistent and not significant. The NOAEL identified by the COT is based on hepatic and renal changes which are of equivocal toxicological significance.
[b] The COT did not consider the changes identified by the EU in this study to be relevant for the NOAEL.
[c] The COT did not consider the occurrence of cloudy, pale and enlarged hepatocytes relevant for identification of a NOAEL for this study.
[d] The COT considered the reduction in pup body weight at 8 mg/kg b.w./day maternal dose to be significant in this study.

24. MCCPs have been shown to cause effects in the liver, thyroid and kidney of rats and mice. Liver effects include increased absolute and relative liver weight, centrilobular hypertrophy and proliferation of the smooth endoplasmic reticulum and peroxisomes. Significant increases in peroxisomal β-oxidation and UDPGT activity in the liver were detected. Guinea pigs treated with MCCPs showed no treatment-related morphologic changes in the liver, but a 35% increase in β-oxidation was observed along with a 35% increase in relative liver weight. Thyroid hypertrophy and hyperplasia were seen in association with an increase in thyroid weight. Plasma thyroxine and triiodothyronine were decreased while TSH was increased. Kidney lesions included increased hyaline droplet inclusions in the cytoplasm and chronic nephritis in male rats, and inner medullary tubular dilation and renal tubular pigmentation in females along with increased kidney weight. A study in dogs showed a significant increase in liver weight with cloudy, pale and enlarged hepatocytes and an increase in smooth endoplasmic reticulum[2].

25. A number of studies have assessed the genotoxicity of MCCPs. Ames tests in *S. typhimurium* have shown negative results. No increase in chromosomal aberrations was observed in male rat bone marrow following administration of up to 5000 mg/kg b.w./day C_{14-17}, 52% chlorinated paraffin by oral gavage for 5 days. Two mouse bone marrow micronucleus studies have been reported which showed no increase in micronucleus formation following administration of a single dose of up to 5000 mg/kg b.w. C_{14-17}, 42 or 45% chlorinated paraffin. No carcinogenicity studies have been carried out on MCCPs[2].

26. Developmental studies in which rats and rabbits were given MCCP from gestation day 6 to 19 and 6 to 27 respectively showed no adverse developmental effects[2]. One study has been carried out to assess fertility, which showed that, while there was no effect on fertility, pup survival from birth to weaning was reduced with treatment. In this study, the F_0 generation received MCCPs in the diet from 28 days prior to mating until weaning at post-natal day 21 when the pups were transferred onto the same diet until post-natal day 70. Antemortem observations in the pups included subcutaneous haematoma; pallor; blood around the orifices; while necropsy showed pale liver, kidneys, lungs and spleen; and blood in the cranial cavity and brain. The NOAEL from this study was identified by the EU to be a maternal dose of 8 mg/kg b.w./day based on reduced pup survival, and necropsy findings indicative of internal haemorrhaging at the next dose (74 mg/kg b.w./day). However, the COT considered 8 mg/kg b.w./day to be a lowest observed adverse effect level (LOAEL) as reduced pup body weight during lactation and post-weaning was observed at this dose level. The COT also noted that over the time course of dosing, MCCPs would be approaching steady state in the adipose tissue of the dams. The pup intake causing haemorrhagic effects was calculated to be 93 mg/kg b.w./day resulting from levels in the dam milk of 504 mg/kg milk. Further work has been carried out to determine a possible mechanism by which internal haemorrhages develop post-natally in pups: This has indicated that lactational transfer is responsible for the effect. Adult females on day 12 of lactation showed reduced plasma vitamin K and clotting factors VII and X but without any effect on prothrombin time. After birth, the pup no longer receives these factors via the placenta but becomes reliant on factors in the breast milk. In addition to the likely decrease in transfer of vitamin K and clotting factors from the dam into the milk, MCCPs can also be detected in the milk and these may further reduce blood levels of vitamin K in the pups[2].

27. The EU identified a NOAEL of 0.4 mg/kg b.w./day for repeated dose toxicity on the basis of inner medullary tubular dilatation in the female rat kidney. A NOAEL of 8 mg/kg b.w./day maternal dose was identified from reproductive studies which found internal haemorrhage in rat pups during weaning. As with SCCPs, the liver and thyroid changes seen in rodents were considered not to be relevant to human health. While carcinogenicity of MCCPs had not been tested experimentally, their structural relationship to SCCPs and similar physicochemical and toxicological properties suggest that the carcinogenic potential of MCCPs could be comparable to SCCPs. Therefore, in the absence of direct evidence the carcinogenic potential of MCCPs was considered to be similar to that of SCCPs[2].

Estimates of dietary exposure

28. The WHO considered that food was the principal source of exposure to CPs for the general population[4]. In a market basket study carried out in Japan in 2003, the highest concentrations of SCCPs were found in fats (140 µg/kg), followed by fish and shellfish (16-18 µg/kg) and meat (7.0 µg/kg). The milk category, comprising milk, cream and yoghurt, had the lowest concentration. Total daily intakes were estimated for different age groups with highest exposure occurring in 1 year old females at 0.68 µg/kg b.w./day, which the authors considered was not a risk to human health[14]. No data on analysis of MCCPs in food were identified.

29. Using the predictive model, European Union System for the Evaluation of Substances (EUSES), the EU risk assessment estimated that dietary exposure resulting from release of SCCPs to the environment could be 20 µg/kg b.w./day[1]. For MCCPs, the EUSES predictions were 4 µg/kg b.w./day for regional[i] exposure using measured water and soil concentration data[2].

30. Infants consuming milk have been considered as a separate group by the EU for both SCCPs and MCCPs. The 95th percentile level of SCCPs in human milk sampled in 2001-2002 from the Thomas *et al.* (2006)[9] study was 680 µg/kg fat, and for cows' milk, a worst case estimate of SCCP content was 16 µg/kg fat[3]. The resulting infant intake of SCCPs has been estimated to be 3.17 µg/kg b.w./day from breast milk and 0.075 µg/kg b.w./day from cows' milk. For MCCPs, the corresponding levels were 127.5 µg/kg fat and 63 µg/kg fat respectively, and resulting intake of MCCPs by infants has been estimated as 0.60 µg/kg b.w./day from breast milk and 0.29 µg/kg b.w./day from cows' milk[2].

Results of the FSA investigation

31. Forty five samples of various food types were sampled in 2007 and analysed to ascertain the level at which CPs are present in food on sale in the UK. Edible portions of each sample were homogenised, extracted and purified. High resolution gas chromatography coupled with high resolution mass spectrometry was used to determine levels of SCCPs and MCCPs in each sample[15].

32. SCCPs and MCCPs were detected in fish at concentrations of <1.0-6.0 and <1.0-31.9 µg/kg respectively. SCCPs and/or MCCPs were also detected in butter (1.23 and 2.84 µg/kg respectively), pork sausage (3.9 and 7.5 µg/kg respectively), bread (2.1 and 4.0 µg/kg respectively), fruit (2.0 and <1.0 µg/kg respectively), beef (<1.0-1.2 and <1.0-8.3 µg/kg respectively) and lamb (<1.0-2.4 and <1.0-12.6 µg/kg respectively) samples, but very seldom or not at all in the milk products, eggs and poultry samples. The highest concentrations were in the cod liver oil sample (25 µg SCCPs/kg and 72 µg MCCPs/kg) and the highest concentrations in a foodstuff were in a freshwater eel sample (6.0 µg SCCPs/kg and 31.9 µg MCCPs/kg), both of which are consistent with the concentrations found in fish in other studies. Where both groups of compounds are detected, MCCPs were usually at a higher concentration than SCCPs[15]. The SCCP results are similar to those of the Japanese market basket survey[14].

[i] The regional environment used in EUSES comprises an area of 40,000 square kilometres with 20 million inhabitants and assumes that 10% of European production of the chemical in question takes place within that area.

33. Since the concentrations were measured and reported in a small number of samples, they may not be representative of these foods and it is not possible to calculate a reliable estimate of UK dietary exposure. However, on an extreme worst case basis, if all solid food consumed by an adult (1.5 kg/day for the 97.5th percentile consumer[16]) contained SCCPs at the level of 6.0 µg/kg as determined in freshwater eel, the exposure would be 0.12 µg/kg b.w./day for the 97.5th percentile consumer. The highest food consumption on the basis of body weight is by 4-6 year olds (1.0 kg solid food/day by the 97.5th percentile consumer[17]) and using the same assumptions, their exposure to SCCPs would be 0.29 µg/kg b.w./day for the 97.5th percentile consumer. Similarly, if all solid food contained MCCPs at the level of 31.9 µg/kg as determined for freshwater eels, the 97.5th percentile adult consumer would be exposed to 0.63 µg/kg b.w./day and the 97.5th percentile 4-6 year old consumer would be exposed to 1.6 µg/kg b.w./day.

Other Risk Assessments

34. Tolerable daily intakes (TDIs) for short, medium and long chain CPs were derived by the World Health Organization (WHO) in its 1996 review of CPs. For SCCPs, the lowest reported NOAEL of 10 mg/kg b.w./day for increases in liver and kidney weight and hypertrophy of the liver and thyroid from a 13 week study in rats was used with an uncertainty factor of 100 to derive a TDI of 100 µg/kg b.w./day. Similarly for MCCPs, a TDI of 100 µg/kg b.w./day was derived from a NOAEL of 10 mg/kg b.w./day for increases in liver and kidney weights in a 13 week study in rats with an uncertainty factor of 100[4].

35. In addition, the WHO derived a maximum daily dose on the basis of neoplastic effects of SCCPs. Multistage modelling of the hepatocellular adenomas and carcinomas in male mice, the tumours with the highest incidence, estimated that a dose of 11 mg/kg b.w./day would be associated with a 5% increase in the tumour. An uncertainty factor of 1000 for a non-genotoxic carcinogen was used to derive the recommended maximum daily dose of 11 µg/kg b.w./day on the basis of neoplastic effects[4].

36. A review of SCCPs on behalf of the Organisation for Economic Co-operation and Development (OECD) published in 2000 concluded that effects observed in liver and thyroid were not relevant to humans. NOAELs were identified for decreased bodyweight gain and increased kidney weight of 100 mg/kg b.w./day and 1000 mg/kg b.w./day for rats and mice respectively. A NOAEL of 100 mg/kg b.w./day was considered relevant for kidney carcinogenicity as, although this effect could not be concluded to be a male rat specific phenomenon, it was thought unlikely that carcinogenicity would occur below the level causing chronic kidney toxicity[18].

37. In 2001, the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) review of SCCPs concluded that the main hazard of SCCPs was general non-specific toxicity following repeated exposure. The NOAELs identified for this effect were 100 mg/kg b.w./day in rats and 1000 mg/kg b.w./day in mice[6].

COT Evaluation

SCCPs

38. The most reliable NOAEL of 10 mg SCCPs/kg b.w./day, for increased kidney weight, mild nephritis in males and brown pigmentation in renal tubules in females, was identified in a 90 day oral gavage and dietary study in rats. Longer term studies have been carried out but effects were observed at all tested doses (from 125 mg/kg b.w./day in mice and 312 mg/kg b.w./day in rats).

39. The Committee considered the liver tumours observed in rats and mice to arise as a result of peroxisome proliferation. As humans are known to be insensitive to hepatic peroxisome proliferation, the Committee considered the liver tumours were not relevant to human carcinogenesis. The thyroid tumours also observed in rats and mice were similarly considered not to be relevant to humans as they are likely to be secondary to the liver changes and to depend on the lower level of thyroxine-binding globulin present in rodents as compared with humans.

40. The increased incidence of kidney tumours was found only in male rats, so it is possible that a male rat specific mechanism could be responsible. Investigations of kidney α2u globulin have not shown an accumulation of the protein similar to that seen with other chemicals acting through this mechanism, such as 1,4-dichlorobenzene, which is known to bind to and subsequently cause α2u globulin deposition in the kidney. It was noted that this lack of protein accumulation could be related to a demonstrated inhibition in α2u globulin synthesis in the liver, since the second step in the mechanism, binding of SCCP to α2u globulin in the kidney, has been demonstrated to occur. As a consequence, the Committee felt unable to exclude the possibility that humans might be susceptible to the effects observed in the kidney.

41. As the genotoxicity data were negative, the Committee considered that tumours observed in the carcinogenicity studies on SCCPs were likely to arise by a non-genotoxic mechanism and would show a threshold phenomenon that would be secondary to kidney damage. Therefore, it would be appropriate to derive a TDI.

42. Using the NOAEL of 10 mg/kg b.w./day from the 90 day study, the Committee considered that an additional uncertainty factor of 3 was sufficient to take into account that the NOAEL was not from a long term study. This was because the response observed in the 90 day study at a 10-fold higher dose (100 mg/kg b.w./day) was modest, approximately a 10% increase in kidney weight. Additionally, when animals were dosed at 125 mg/kg b.w./day (NTP study), there was little evidence for progression of kidney weight changes from 3 months up to 12 months, the periods for which data were available. Therefore, with uncertainty factors of 10 for inter-, 10 for intra-species variation, and the additional factor of 3 for a non-chronic study, the Committee established a TDI of 30 µg/kg b.w. for SCCPs.

43. While exposure assessments as such cannot be made on the basis of the data from the FSA investigation, if all solid food consumed contained SCCPs at the level of 6.0 µg/kg, as determined in freshwater eel, the 97.5th percentile adult consumer would be exposed to 0.12 µg/kg b.w./day, a concentration that is considerably lower than the TDI. The highest food consumption relative to body

weight is by 4-6 year olds and, using the same assumptions, exposure of the 97.5th percentile 4-6 year old consumer would be 0.29 µg/kg b.w./day, which is two orders of magnitude lower than the TDI. Whilst these highly conservative assumptions form an unlikely scenario, the large margin between the TDI and the exposure estimates indicates that there is at present no cause for concern over dietary exposure to SCCPs.

MCCPs

44. The Committee identified a NOAEL of 4 mg MCCPs/kg b.w./day for changes in relative liver weight and minimal changes in the inner cortex of the kidney in female rats from a 90 day dietary study. Both these effects were thought to be of equivocal toxicological significance. However, liver and kidney changes were observed in other studies at higher doses and therefore this NOAEL was considered relevant, if somewhat conservative, for 90 day studies.

45. No carcinogenicity data were available for MCCPs. However, tumour formation has been observed following SCCP administration and, given the structural relationship and similar physicochemical and toxicological properties of the two groups of compounds, it is plausible that MCCPs also have the potential to be carcinogenic. Mechanistic studies, and the negative genotoxicity data, suggest that were such an effect to occur following MCCP administration, it is likely that it would be through a non-genotoxic mechanism mediated via sustained toxicity in the kidney and liver. Therefore, a TDI can be proposed for MCCPs and if it is adequately protective against liver and kidney toxicity it should also be protective against any potential carcinogenic effects. In addition, the Committee considered that if indeed MCCPs are carcinogenic, they would be highly unlikely to be potent carcinogens.

46. The data from the reproductive and developmental study showing haemorrhagic effects in pups also showed reduced pup body weight gain at a maternal dose of 8 mg/kg b.w./day. The Committee considered this to be the LOAEL for developmental effects and evidence from other studies indicated that lactational transfer was most likely route of exposure and to be responsible for the observed effects.

47. While the NOAEL of 4 mg/kg b.w./day from the 90 day study was considered the most appropriate basis for setting a TDI, the Committee raised doubt over whether it would adequately reflect possible toxic effects of long term exposure. An additional uncertainty factor of 10 was considered appropriate to allow for the absence of longer term studies and the lack of a NOAEL for reproductive and developmental effects. Using uncertainty factors of 10 for inter- and 10 for intra-species variation and the additional factor of 10 for the lack of appropriate animal data, the Committee established a TDI of 4 µg/kg b.w. for MCCPs.

48. While exposure assessments as such cannot be made on the basis of the data from the FSA investigation, if all solid food consumed contained MCCPs at the level of 31.9 µg/kg as determined for freshwater eels, the food source containing the highest levels, the 97.5th percentile adult consumer would be exposed to 0.63 µg/kg b.w./day, which is well below the calculated TDI. The highest food consumption relative to body weight is by 4-6 year olds and, using the same assumptions, exposure of the 97.5th percentile 4-6 year old consumer would be 1.6 µg/kg b.w./day,

which is also below the TDI. This latter scenario is considered unlikely based upon the highly conservative assumptions made, but the still considerable margin between the TDI and the exposure estimates indicates that at present there is no cause for concern over dietary exposure to MCCPs.

49. The levels of SCCPs and MCCPs determined in the FSA investigation give rise to no immediate concern for human health. Any further considerations of these compounds should, if possible, include a more reliable dietary exposure assessment, such as would be obtained by a Total Diet Study.

COT Conclusions

50. For SCCPs, we considered that the modes of action for liver and thyroid tumours observed in rodents are unlikely to be relevant to humans. The available evidence is currently insufficient to conclude that the tumours seen in the kidney of male rats are not relevant to humans, but it is highly likely that the tumours caused by SCCPs arise through a non-genotoxic, threshold, mechanism based upon chronic toxicity that occurs at lower dose levels than the carcinogenic effects. While there are gaps in the toxicological database on SCCPs, the available data are sufficient to derive a TDI. The long term studies carried out on SCCPs were at high doses, and there were effects at all tested doses. Therefore, the most reliable NOAEL (10 mg/kg b.w./day) was for effects on the kidney observed in 90 day oral gavage and dietary studies in rats. We agreed that an additional uncertainty factor of 3 would allow for extrapolating from this NOAEL in a 90 day study to long term exposure. This was considered sufficient as the response in the 90 day study at a 10-fold higher dose was modest and there was little evidence for progression of the response from 3 months to 6 months to 12 months. Together with the uncertainty factors of 10 for inter-species and 10 for intra-species variation, a TDI of 30 µg/kg b.w. is established for SCCPs.

51. For MCCPs, we identified a NOAEL of 4 mg/kg b.w./day for effects on liver and kidney in female rats in a 90 day dietary study as an appropriate basis for deriving a TDI for MCCPs. Despite the absence of carcinogenicity data, we considered that, were such effects to occur, they would arise through a non-genotoxic mechanism mediated via toxicity in the kidney and liver. Therefore a TDI set to protect against toxicity in the liver and kidney would also give adequate protection against any potential carcinogenicity. To take into account the lack of long term studies on toxicity of MCCPs, and to protect against reproductive and developmental effects, an extra uncertainty factor of 10 was required, in addition to 10 for inter-species and 10 for intra-species variation. On this basis, we conclude that a TDI of 4 µg/kg b.w. for MCCPs is appropriate.

52. Using these TDIs and highly conservative assumptions about dietary exposure, we conclude that the results of the FSA investigation of occurrence of SCCPs and MCCPs in food do not give rise to concern for human health.

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Annex A

Search Strategy

General Chlorinated Paraffins Search September 2006

Databases interrogated –

- Food Science and Technology Abstracts (FSTA)
- FoodlineWeb
- British Library Direct Plus

Search Terms – (chlorinated-paraffin* OR chloroparaffin*) AND (toxicolog* OR risk-assessment OR food* OR TEF*)

Search Dates (From/To) – 1999 to September 2006

Exclusion Criteria – Abstracts where reviewed and papers excluded if they:

- Were literature reviews of existing papers
- Focussed on temporal trends
- Were exposure assessments or contained mainly survey data
- Focussed on environmental contamination and/or bioaccumulation
- Concentrated on sampling, measurement, analysis and screening methods
- Did not consider Chlorinated Paraffins (CPs) in any detail
- Were not concerned with toxicity

General Chlorinated Paraffins Update Search

Databases interrogated –

- ISI Web of Knowledge Current Contents database
- Food Science and Technology Abstracts (FSTA)
- FoodlineWeb
- IngentaConnect
- British Library Direct Plus

Search Terms – (chlorinated-paraffin* OR chloroparaffin*) AND (toxicolog* OR risk-assessment OR food* OR TEF*)

Search Dates (From/To) – From September 2006 to April 2009

Exclusion Criteria – Abstracts where reviewed and papers excluded if they:

- Were literature reviews of existing papers
- Focussed on temporal trends
- Were exposure assessments or contained mainly survey data
- Focussed on environmental contamination and/or bioaccumulation
- Concentrated on sampling, measurement, analysis and screening methods
- Did not consider Chlorinated Paraffins (CPs) in any detail
- Were not concerned with toxicity
- Were duplicated papers or ones already held

Additional Chlorinated Paraffins Search

Databases interrogated –

- PubMed

Search Terms – (chlorinated-paraffin* OR chloroparaffin*) AND (toxicolog* OR risk-assessment OR food* OR TEF*)

Search Dates (From/To) – From Sept 2006 to April 2009

Exclusion Criteria – Abstracts where reviewed and papers excluded if they:

- Were literature reviews of existing papers
- Focussed on temporal trends

- Were exposure assessments or contained mainly survey data
- Focussed on environmental contamination and/or bioaccumulation
- Concentrated on sampling, measurement, analysis and screening methods
- Did not consider Chlorinated Paraffins (CPs) in any detail
- Were not concerned with toxicity
- Were duplicated papers or ones already held

Analysis of review papers

A number of review papers were identified during these searches. Any papers cited in relevant sections of these reviews but were obtained as relevant.