Canadian Environmental Protection Act, 1999

Follow-up Report on a PSL1 Substance for Which Data Were Insufficient to Conclude Whether the Substance Was "Toxic" to Human Health

Chlorinated Paraffins

October 2003

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List of Acronyms and Abbreviations

CEPA 1988	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CoA	coenzyme A
CYP	cytochrome P-450
DNA	deoxyribonucleic acid
ECNI	electron capture negative ion
GC	gas chromatography
HRGC	high-resolution gas chromatography
HRMS	high-resolution mass spectrometry
kg-bw	kilogram body weight
K_{ow}	octanol/water partition coefficient
LCCP	long-chain chlorinated paraffins
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEL	Lowest-Observed-Effect Level
LRMS	low-resolution mass spectromety
MCCP	medium-chain chlorinated paraffins
MS	mass spectrometry
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
NTP	National Toxicology Program (U.S.A.)
PPARα	peroxisome proliferator activated receptor, α isoform
PSL1	first Priority Substances List
SCCP	short-chain chlorinated paraffins
T_3	triiodothyronine
T_4	thyroxine
TD_{05}	Tumorigenic $Dose_{05}$, the dose associated with a 5% increase in tumour incidence
TDI	Tolerable Daily Intake
TSH	thyroid stimulating hormone
UDP	uridine diphosphate
UDPG	uridine diphosphoglucose
UDPGGT	uridine diphosphoglucose glucuronosyl transferase
UDPGT	uridine diphosphate glucuronosyl transferase

PREFACE

For very few of the substances on the first Priority Substances List (PSL1) for which data were considered insufficient to conclude whether they were "toxic" under Section 11 of the 1988 *Canadian Environmental Protection Act* (CEPA 1988) did this conclusion apply to both the environment (under Paragraphs 11(a) and 11(b) of CEPA 1988) and human health (under Paragraph 11(c) of CEPA 1988). Medium-chain and long-chain chlorinated paraffins are two of these substances. While information on the environmental effects of short-chain chlorinated paraffins was considered insufficient to conclude whether they were "toxic" under Paragraph 11(b) of CEPA 1988, this group of substances was considered "toxic" to human health under Paragraph 11(c) of CEPA 1988. In updating the assessments of medium and long chain chlorinated paraffins, included herein, more recent data on the effects of short-chain chlorinated paraffins on human health were also examined.

In the documentation that follows, the impact of critical new data on the initial assessment under CEPA 1988 is considered. These data are presented separately for the environmental and health effects, but cross-referenced, where appropriate. Information relevant to assessment of effects on the environment (i.e., determination of "toxic" under Paragraphs 64(a) and 64(b) of the *Canadian Environmental Protection Act, 1999* [CEPA 1999]) is presented initially, followed by information relevant to assessment of effects on human health (determination of "toxic" under Paragraph 64(c) of CEPA 1999).

SYNOPSIS

Short-chain chlorinated paraffins (SCCP) are imported into Canada for use as additives in extreme-pressure lubricants, plasticizers and flame retardants. Medium- and long-chain chlorinated paraffins (MCCP and LCCP, respectively) are produced in, and imported into, Canada for similar uses.

Chlorinated paraffins were included on the first Priority Substances List (PSL1) under the 1988 *Canadian Environmental Protection Act* (CEPA 1988) for assessment of potential risks to the environment and human health. As outlined in the Assessment Report released in 1993, relevant data identified before August 1992 were considered insufficient to conclude whether MCCP and LCCP were "toxic" to human health as defined in Paragraph 11(c) of CEPA 1988. As also outlined in the Assessment Report released in 1993, SCCP were considered to be "toxic" as defined under Paragraph 11(c) of CEPA 1998. This conclusion was based principally on the observed carcinogenicity of these compounds, for which available information on mode of action could not preclude it being the result of direct interaction with genetic material. To set context for the update on MCCP and LCCP, more recent data on the effects of SCCP on human health have also been considered here.

For SCCP, critical data relevant to both estimation of exposure of the general population in Canada and assessment of the weight of evidence for the mode of induction of specific tumours were identified following release of the PSL1 assessment and prior to February 2001, although most of this information has been reported in incomplete published summary accounts or abstracts. These data suggest that several tumours observed in carcinogenicity bioassays in rats and mice exposed to SCCP are induced by modes of action either not relevant to humans (kidney tumours in male rats) or for which humans are likely less sensitive (in rats, liver tumours related to peroxisome proliferation and thyroid tumours related to thyroid–pituitary disruption). Additional documentation of available studies and consideration in additional investigations of the reversibility of precursor lesions in the absence of continued exposure is desirable. However, reported data on mode of induction of tumours in addition to the weight of evidence that SCCP are not DNA reactive are at least sufficient as a basis for consideration of a Tolerable Daily Intake (TDI) for non-cancer effects as protective for carcinogenicity for observed tumours.

Upper-bounding estimates of daily intake of SCCP approach or exceed the TDI for these compounds, which, on the basis of available information, is likely also protective for potential carcinogenicity.

Therefore, it is proposed that there is no reason to revise the conclusion for PSL1 that short-chain chlorinated paraffins are "toxic" as defined under Paragraph 64(c) of the *Canadian Environmental Protection Act, 1999*.

For MCCP and LCCP, critical data relevant to both estimation of exposure of the general population in Canada and assessment of effects were identified following release of the PSL1

assessment and prior to December 2000. Based upon these semi-quantitative data, upper-bounding estimates of daily intake for MCCP and LCCP are within the same order of magnitude of, or exceed, the TDIs for these substances.

Therefore, it is proposed that there is reason to suspect that medium- and long-chain chlorinated paraffins are "toxic" to human health as defined in Paragraph 64(c) of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

Acquisition of data on levels of these compounds (SCCP, MCCP and LCCP) within foodstuffs in Canada continues to be considered a high priority.

1.0 INTRODUCTION

A common Introduction, which describes the process for the preparation of the updates of the Assessment Reports for the seven substances (including medium-chain and long-chain chlorinated paraffins [MCCP and LCCP, respectively]) on the first Priority Substances List (PSL1) for which data were considered insufficient to conclude whether the substances were "toxic" to human health under the 1988 *Canadian Environmental Protection Act* (CEPA 1988) is posted on all web sites where the Assessment Reports appear.[1]

The strategy for the literature search to identify critical new data (including commercial activity in Canada, human exposure and effects) on short-chain chlorinated paraffins (SCCP), MCCP and LCCP is presented in Appendix A of this report. Only relevant data acquired prior to February 2001 and December 2000 were considered in the re-examination of whether SCCP and MCCP/LCCP, respectively, are "toxic" to human health under Paragraph 64(c) of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

2.0 SUMMARY OF THE HUMAN HEALTH RISK ASSESSMENT FOR CHLORINATED PARAFFINS CONDUCTED UNDER CEPA 1988 (BASED UPON INFORMATION IDENTIFIED UP TO AUGUST 1992 (GOVERNMENT OF CANADA, 1993)

The PSL1 assessment addressed the short-chain ($C_{10–13}$), medium-chain ($C_{14–17}$) and long-chain ($C_{18–28}$) chlorinated paraffins. At the time of release of the PSL1 assessment, SCCP, MCCP and LCCP were produced in, and imported into, Canada for use as plasticizers and flame retardants, as well as extreme-pressure additives in lubrication oils. Quantitative data on amounts produced or used were not reported.

Relevant data were insufficient to derive quantitative estimates of exposure to chlorinated paraffins for the general population in Canada. Identified information was limited principally to the lack of detection of chlorinated paraffins in edible shellfish in a survey in Atlantic Canada (Environment Canada, 1989) and levels in a limited range of foodstuffs in the United Kingdom for which identified information was insufficient to permit evaluation of the validity of the results (Campbell and McConnell, 1980a). Environmental fate modelling (e.g., fugacity model;

[1] See "Introduction to Assessment Reports for Reconsideration of PSL1 Substances for Which Data Were Insufficient to Conclude Whether the Substances Were 'Toxic' to Human Health (Paragraph 11(c), CEPA 1988; Paragraph 64(c), CEPA 1999)" at the following web site: <http://www.hc-sc.gc.ca/hecs-sesc/exsd/psl1.htm>.

Mackay *et al*., 1985) was considered unsuitable for predicting levels in the Canadian environment, due to the paucity of information on transformation and release rates, complexity of composition (chlorinated paraffins are mixtures of compounds of varying chain lengths) and very high octanol/water partition coefficients (log K_{ow}).

Epidemiological studies of populations exposed to chlorinated paraffins were not available, and data on effects in humans were restricted to poorly documented clinical studies of the potential to induce irritation or sensitization of the skin following dermal application (Dover Chemical Corporation, 1975; Howard *et al*., 1975; English *et al*., 1986).

In a well-documented carcinogenesis bioassay for which there were some, but not critical, limitations, there was clear evidence of the carcinogenicity of SCCP (C_{12}, 60% chlorine content) in B6C3F1 mice and F344/N rats. Based on these considerations, the SCCP were considered to be probably carcinogenic to humans. Moreover, available data were insufficient to support a mode of induction of tumours other than through direct interaction with genetic material. As a result, **short-chain chlorinated paraffins were considered to be "toxic" under Paragraph 11(c) of CEPA 1988.** It was not possible to estimate exposure of the general population in Canada to SCCP. Hence, it was not possible to compare quantitative estimates of cancer potency with estimated exposure, as a basis for providing guidance on the priority for investigating options to reduce exposure, as part of the risk management strategy.

Data were adequate to derive a Tolerable Daily Intake (TDI) for MCCP and LCCP (see below). However, since it was not possible to quantitatively estimate exposure of the general population in Canada to either group of substances, the calculated TDIs could not be compared with estimated daily intake of these compounds. Based primarily on limitations of information to serve as a basis for estimation of exposure, therefore, **available data were considered inadequate to determine whether medium-chain or long-chain chlorinated paraffins were "toxic" to human health as defined in Paragraph 11(c) of CEPA 1988.**

2.1 Short-chain chlorinated paraffins

In the well-documented bioassay in which there was clear evidence of the carcinogenicity of SCCP (C_{12}, 60% chlorine) in B6C3F1 mice and F344/N rats, it was further specified that the maximum tolerated dose may have been exceeded in male and female rats (NTP, 1986a; Bucher *et al*., 1987). In the PSL1 Assessment Report, it was noted, however, that increases in tumour incidence were observed in rats in the absence of histopathological damage in at least one organ (i.e., the thyroid). Moreover, most of the mortality in exposed male rats occurred after 80 weeks, whereas overall survival in exposed female rats was reasonable compared with that in vehicle controls.

At the time of release of the PSL1 assessment, data available on the mode of induction of tumours were restricted to the results of two studies (one for which the published account was an abstract), which indicated that SCCP may act as peroxisome proliferators in the induction of liver adenomas in rats, based upon their lack of effect on unscheduled DNA synthesis but their

positive response on cell proliferation following exposure of rats to single doses of a SCCP up to 2000 mg/kg-bw (Elcombe *et al*., 1989; Ashby *et al*., 1990). In addition to the very limited data available on mode of induction of the observed tumours, the pattern of tumour development in the National Toxicology Program (NTP) bioassay for SCCP was dissimilar to that of identified epigenetic carcinogens, in that tumours were observed at multiple sites and sometimes in the absence of tissue damage. In addition, SCCP were clastogenic and induced cell transformation in *in vitro* studies, although they had not been clastogenic or mutagenic in a limited number of *in vivo* assays.

2.2 Medium-chain chlorinated paraffins

At the time of release of the PSL1 assessment, information was not identified on the chronic toxicity or carcinogenicity of MCCP in studies in experimental animals. MCCP were not mutagenic in *in vitro* assays with or without metabolic activation and were negative in an *in vitro* assay for cell transformation (Birtley *et al*., 1980). In an inadequately reported *in vivo* study, oral administration of MCCP to rats did not increase the frequency of chromosomal aberrations in bone marrow (Serrone *et al*., 1987).

The lowest effect level in the longer-term studies of the effects of MCCP identified in the PSL1 report was that in a reproductive bioassay in which rats were exposed to one of three doses of a $C_{14–17}$ (52% chlorine) chlorinated paraffin in the diet for 28 days before mating, during mating and, for females, continuously up to postnatal day 21. Pups were also exposed from weaning to 70 days of age (IRDC, 1985). At 100 ppm in the diet (5.7 mg/kg-bw per day in males and 7.2 mg/kg-bw per day in females), there was a decrease in body weight gain in exposed pups by day 21 of lactation, an effect that continued after weaning but became less pronounced in males. Histopathological effects were not observed at this concentration. These effects appeared to be attributable to lactational rather than to *in utero* exposure.

The lowest reported effect levels in subchronic studies identified in the PSL1 report were similar to those observed in the reproductive study. In three subchronic studies in which MCCP were administered in the diet to rats and dogs (Birtley *et al*., 1980; Serrone *et al*., 1987), the No-Observed-(Adverse-)Effect Levels (NO(A)ELs) ranged from 10 to 13 mg/kg-bw per day; effects observed at the next highest doses included increases in organ weights (liver and kidney), in serum hepatic enzymes and in the smooth endoplasmic reticulum of the hepatocytes.

A TDI (i.e., the level of intake to which it is believed that a person may be exposed daily over a lifetime without deleterious effects) of 6 µg/kg-bw per day was derived, therefore, for non-neoplastic effects. This value was based on the lowest dose of MCCP (Lowest-Observed-Effect Level [LOEL] = 5.7 mg/kg-bw per day) at which adverse effects (decrease in body weight gain in male rats by day 21 of lactation, which continued after weaning) were observed, in a reproductive animal study in which an adequate range of endpoints had been examined (IRDC, 1985), divided by an uncertainty factor of 1000 (×10 for intraspecies variation; ×10 for interspecies variation; ×10 for lack of data on carcinogenicity and less than chronic study). No uncertainty factor was incorporated for use of a LOEL rather than a NO(A)EL owing to the

minor nature of the effects observed at this concentration.

2.3 Long-chain chlorinated paraffins

Although the available information at the time of release of the PSL1 report was inadequate to assess the carcinogenicity of LCCP in humans, in a well-documented carcinogenesis bioassay in rats and mice, there was no evidence of carcinogenicity for male F344/N rats, equivocal evidence of carcinogenicity for female F344/N rats and female B6C3F1 mice and clear evidence of carcinogenicity for male B6C3F1 mice (NTP, 1986b). For female mice, 60–70% of the early deaths in each group were attributed to utero-ovarian infection, and it was noted that this may have decreased the sensitivity of the study to detect a carcinogenic effect. LCCP were not mutagenic in bacterial assays with or without metabolic activation (Birtley *et al*., 1980; NTP, 1986b). They were negative in an *in vitro* assay for cell transformation (ICI, 1982). In an *in vivo* study, the complete report of which was not available, LCCP did not increase the frequency of chromosomal aberrations in bone marrow cells of rats (Serrone *et al*., 1987).

The lowest dose at which non-neoplastic effects were observed in the longest-term bioassay following exposure to LCCP identified in the PSL1 report was 100 mg/kg-bw per day (NTP, 1986b; Bucher *et al*., 1987). At this dose, there was a diffuse lymphohistiocytic inflammation in the liver and in the pancreatic and mesenteric lymph nodes in female rats. Splenic congestion was a secondary effect. In subchronic studies, the lowest reported effect level was 100 mg/kg-bw per day, which induced increases in liver weight and multifocal granulomatous hepatitis (characterized by inflammatory changes) and necrosis in female rats (Serrone *et al*., 1987).

A TDI (i.e., the level of intake to which it is believed that a person may be exposed daily over a lifetime without deleterious effects) of 71 µg/kg-bw per day was derived, therefore, for non-neoplastic effects. This value was based on the lowest dose of LCCP (Lowest-Observed-Adverse-Effect Level [LOAEL] = 100 mg/kg-bw per day) at which adverse effects (diffuse lymphohistiocytic inflammation in the liver and in the pancreatic and mesenteric lymph nodes in female rats) were observed, in a carcinogenicity bioassay in which an adequate range of endpoints had been examined (NTP, 1986b; Bucher *et al*., 1987), divided by an uncertainty factor of 1000 (×10 for intraspecies variation; ×10 for interspecies variation; ×10 for use of a LOAEL rather than a NOAEL) and multiplied by 5/7 (for conversion of 5 days/week administration to daily exposure). An additional factor for limited evidence of carcinogenicity was not incorporated, since there was no increase in tumour incidence in female rats in the target organ for the non-neoplastic effect upon which the LOAEL is based.

3.0 POST-PSL1 ANALYSIS (BASED UPON INFORMATION IDENTIFIED BETWEEN AUGUST 1992 AND DECEMBER 2000 (MCCP/LCCP) OR FEBRUARY 2001 (SCCP)

3.1 Production, importation, use and release

Canadian producers of SCCP have not been identified. Most SCCP used in Canada are imported from the United States (Camford Information Services, 2001).

PCI Canada (formerly ICI Canada), Cornwall, Ontario, produces MCCP and LCCP with a chlorine content of up to 56% (Camford Information Services, 2001). The capacity for production was 5.0, 5.0, 8.5 and 8.5 kilotonnes in 1997, 1998, 1999 and 2000, respectively; the corresponding imports were 2.0, 2.0, 1.7 and 1.8 kilotonnes. Chlorinated paraffins are used primarily as plasticizers and high-pressure lubricant additives.

3.2 Population exposure

The following presentation is limited to identified recent data considered critical to quantitative estimation of exposure of the general population in Canada to chlorinated paraffins and, hence, to assessment of "toxic" under Paragraph 64(c) of CEPA 1999. Other sources of data that were also identified but were not directly relevant to estimation of exposure in Canada include Peters *et al*. (2000), Borgen *et al*. (2000, 2002) and Lahaniatis *et al*. (2000).

The degree of confidence in data on the concentrations of chlorinated paraffins in various media varies considerably, depending upon the nature of the analysis. To the extent possible, estimates of intake have been based on higher-confidence analyses by high-resolution gas chromatography (HRGC)/electron capture negative ion high-resolution mass spectrometry (ECNI-HRMS), due to its higher mass resolving power and selectivity. However, such information is limited solely to determination of SCCP in human breast milk (Tomy, 1997), fish (Muir *et al*., 1999) and media that contribute less to human exposure, including ambient air (Tomy, 1997), surface water (Tomy, 1997) and sediment (Muir *et al*., 2001). For all chlorinated paraffins, either concentrations in surface water and sediment, or the limits of detection for these media, were used as surrogates for concentrations in drinking water and soil, respectively, in estimating intake.

Indeed, data on concentrations of chlorinated paraffins in foodstuffs are extremely limited. While additional data on the concentrations of SCCP, MCCP and LCCP in foods in the United Kingdom (Campbell and McConnell, 1980b) reported in an early investigation reviewed in the PSL1 assessment (Campbell and McConnell, 1980a) were acquired and are presented in Table 1, they are considered, at best, to be semi-quantitative, owing to limitations of the methodology available at that time. Analysis was based on liquid–solid adsorption chromatography, which has now largely been replaced by micro-analytical techniques, and quantification by visual reference to spots appearing on thin-layer chromatographic plates.

3.2.1 Short-chain chlorinated paraffins

Tomy (1997) determined SCCP ($C_{10–13}$, 60–70% chlorine) in 24-hour air samples collected daily

during a 4-month period in the summer of 1990 in Egbert, Ontario, a "rural site northwest of Toronto," by HRGC/ECNI-HRMS (Muir *et al*., 1999). Concentrations ranged from 65 to 924 pg/m^3. Although a summary statistic of 543 pg/m^3 was reported, it was not specified whether this was a mean or median value. Egbert has also been reported to be near an "industrialized area" (Muir *et al*., 2000). Lower concentrations of SCCP have been identified at other sites in Canada (Halsall *et al*., 1998; Stern *et al*., 1998; Bidleman *et al*., 1999, 2000, 2001; Muir *et al*., 2001).

Concentrations of SCCP ($C_{10–13}$, 52% chlorine) ranged from 11 to 17 µg/kg in human breast milk in Canada (Tomy, 1997). Analyses were carried out by HRGC/ECNI-HRMS. No additional details were reported.[2]

Muir *et al*. (1999) analysed whole fish samples for SCCP ($C_{10–13}$) and detected 2630 ng/g (wet weight) in carp from Hamilton Harbour, 58.8 ng/g (wet weight) in lake trout from Niagara-on-the-Lake and 72.6 ng/g (wet weight) in lake trout from Port Credit. The quantification was by GC/ECNI-HRMS. Lower concentrations were reported in an earlier study (Muir *et al*., 1996).

In a market basket survey (KAN-DO Office and Pesticides Team, 1995)[3] of 234 ready-to-eat foods, which represented approximately 5000 food types in American diets, "Chlorowax 500C"[4] was detected once, in enriched white bread, at a concentration of 0.13 µg/g. Food items were screened by gas or liquid chromatography using ion-selective detectors. Findings were confirmed by unspecified analysis.

Concentrations of SCCP have been identified in blubber of aquatic mammals such as ringed seal, beluga and walrus (Tomy *et al*., 2000[5]; Bennie *et al*., 2000[6]). The samples were from animals in Greenland, the Canadian Arctic and the St. Lawrence River. A mean concentration of 46 100 ng/g (n = 15) was reported for beluga from the St. Lawrence River/Gulf of St. Lawrence. Concentrations in ringed seals from Ellesmere Island ranged from 370 to 770 ng/g. Jansson *et al*. (1993) detected SCCP in biota in Sweden, including fish and both terrestrial and marine mammals. Analysis was by GC/MS.

Data on concentrations of SCCP in drinking water in Canada or elsewhere were not identified. The maximum concentration of SCCP ($C_{10–13}$, 50–70% chlorine) in the Red River, at a site remote from industrialized areas, was 0.05 µg/L (Tomy, 1997).[7] Analyses were by

[2] These data were identified in a secondary source and were originally reported in a Ph.D. thesis.

[3] Reported as a summary of results from 1982 to 1991.

[4] The average molecular formula for Chlorowax 500C is $C_{12}H_{19}Cl_7$, with 60–65% chlorine content (w/w) (IPCS, 1996).

[5] Analysis by HRGC/ECNI-HRMS.

[6] Analysis by GC/low-resolution negative chemical ionization mass spectrometry.

[7] These data were identified in a secondary source and were originally reported in a Ph.D. thesis.

HRGC/ECNI-HRMS. A lower concentration was reported in surface water from Lake Ontario (Muir *et al*., 2001).

Concentrations of SCCP in soil in Canada or elsewhere were not identified. The concentrations in surface sediment in harbours in Lake Ontario ranged from 5.9 to 290 ng/g dry weight (Muir *et al*., 2001). Analyses were by HRGC/ECNI-HRMS.

Upper-bound estimates of intake of SCCP for the general Canadian population and the assumptions upon which they are based are presented in Table 2. For each age group in the Canadian population, virtually all of the estimated intake is from food. The upper-bound estimated intake of breast-fed infants was 1.7 µg/kg-bw per day, and that of formula-fed infants was 0.01 µg/kg-bw per day. For the remaining age groups, intakes ranged from 5.1 µg/kg bw per day for adults over 60 years of age to 26.0 µg/kg-bw per day for infants who were not formula fed (i.e., those being introduced to solid foods[8]).

Canadian data incorporated within this estimate include high-confidence values in fish (whole carp determined by GC/ECNI-HRMS) and data on breast milk, for which details of sampling and analysis were not reported. Estimated intake of SCCP in fish represents up to 58% of the total daily intake. The intake from dairy products, which accounts for 89.9% of the intake of infants not formula fed, is based upon limited sampling and analysis — considered semi-quantitative only — of dairy products in the United Kingdom, reported in 1980. Probably the most representative estimates of intake are those from cereals, which are based upon data reported in an American market basket survey, carried out from 1982 to 1991; however, intake from this foodstuff constitutes <0.1% of total estimated intake, and analytical methods were not specified.

Intake of SCCP by a potentially higher-exposure subgroup of Inuit for whom the primary source of food is subsistence hunting and fishing (Kuhnlein, 1989; Kinloch *et al*., 1992) was also estimated, based on data on concentrations of SCCP in blubber from marine mammals in Canada (Tomy *et al*. 2000) and less specific data (including both SCCP and MCCP) for terrestrial and marine mammals from Sweden (Jansson *et al*., 1993). On the basis of these data, the estimated intake of an Inuit adult, namely 1.47 µg/kg-bw per day, is well within the range of values estimated above for the general population (see supporting documentation).

[8] Solid foods are introduced to approximately 50% of infants by 4 months of age and to 90% by 6 months of age (NHW, 1990).

3.2.2 Medium-chain chlorinated paraffins

MCCP were detected by HRGC/low-resolution mass spectrometry (LRMS) in effluent (13 µg/L) from a chlorinated paraffin manufacturing plant in Canada in 1993, but not in surface water or sediment (Metcalfe-Smith *et al*., 1995). MCCP were detected in three samples of carp from Hamilton Harbour in 1996 by low-resolution GC/MS (mean 0.393 µg/g; range 0.276–0.563 µg/g) (Bennie *et al*., 2000). Similarly, MCCP were detected in the homogenized (whole) samples of 10 trout collected from western Lake Ontario in 1996 (mean 1.23 µg/g; range 0.257–4.39 µg/g) (Bennie *et al*., 2000).

Upper-bounding estimates of intake for MCCP and the assumptions on which they are based are presented in Table 3. For each age group, virtually all of the estimated intake is from food, which, in turn, is based almost entirely upon the limited data reported by Campbell and McConnell (1980a,b). The highest intake estimated (25.5 µg/kg-bw per day) was for infants not formula fed.

3.2.3 Long-chain chlorinated paraffins

Upper-bounding estimates of total intake of LCCP and associated assumptions are presented in Table 4. As for SCCP and MCCP, for each age group, virtually all of the estimated intake is from food. The highest intake estimated (16.8 µg/kg-bw per day) was for infants not formula fed. In addition to the limitations of the analytical methodology noted previously, these estimates are further limited in that estimates for five of the eight food groups are based upon the limit of detection in that survey (Campbell and McConnell, 1980a,b).

3.3 Hazard characterization and dose–response analyses

A limited number of studies on the toxicity of SCCP have been reported in the period following release of the PSL1 assessment. Most of these studies were conducted to investigate the mode of action of carcinogenicity for the tumours observed in the NTP (1986a) bioassay, which were liver tumours in both sexes of rats and mice, kidney tumours in male, but not female, rats and thyroid tumours in rats and mice (females only). For several of these more recent studies, results have been reported in abstracts or summaries only: Elcombe *et al*. (1994) (abstract), Elcombe *et al*. (2000) (summary) and Warnasuriya *et al*. (2000) (abstract). For only one of the relevant investigations has a full published account been identified (Wyatt *et al*., 1993). While secondary accounts of (possibly) other studies investigating mode of action of tumour induction in assessments have been reported by the European Commission (2000), the U.S. National Research Council (U.S. NRC, 2000) and the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2001), they are not further considered here, owing to lack of availability or confirmation of subsequent publication (Jackson, 2001).

Few data relevant to the assessment of the toxicity of either MCCP or LCCP were identified for the period to the release of the PSL1 assessment report. The following presentation is limited to those considered critical to hazard characterization or dose–response

analyses for effects in the general population and, hence, to assessment of "toxic" under Paragraph 64(c) of CEPA 1999. Other sources of non-critical data identified but not included were DuPont (1995), Kato and Kenne (1996) and Warngard (1996).

In view of the absence of recent toxicological data that impact on critical aspects, the dose–response analyses for MCCP and LCCP presented here reflect primarily those developed in the PSL1 Assessment Report released under CEPA 1988.

3.3.1 Short-chain chlorinated paraffins

3.3.1.1 Liver

Increased liver weight, hepatocellular hypertrophy, peroxisomal proliferation and increased S-phase activity in hepatocytes were reported in Fischer 344 rats administered SCCP for up to 90 days (presumably by gavage) at dose levels up to 1000 mg/kg-bw per day (Elcombe *et al*., 1994; abstract). Lower doses administered were not specified, and quantitative dose- or sex-specific data and analyses were not presented.

Elcombe *et al*. (2000) administered Chlorowax 500C ($C_{10–13}$; 58% chlorine) to male and female Fischer 344 rats by gavage in corn oil for up to 90 days, at dose levels of 0, 312 or 625 mg/kg-bw per day. In both sexes, liver weight was increased, accompanied by peroxisomal proliferation (as indicated by an increase in cyanide-insensitive palmitoyl coenzyme A [CoA] oxidation) and increased thyroxine (T_4)–uridine diphosphoglucose glucuronosyl transferase (UDPGGT). (The effects were, presumably, observed at both dose levels.) These effects were not observed in male Dunkin Hartley guinea pigs similarly administered 0, 500 or 1000 mg/kg-bw per day for 14 consecutive days. The numbers of animals exposed were not specified, and quantitative dose- or sex-specific data and analyses were not presented in this summary account.

Wyatt *et al*. (1993) exposed groups of five male rats (Alpk:APfSD strain) each by gavage for 14 days to 0, 10, 50, 100, 250, 500 or 1000 mg/kg-bw per day to two SCCP (Chlorowax 500C: $C_{10–13}$, 58% chlorine; or Cereclor 56L, $C_{10–13}$: 56% chlorine). For the 58% chlorine SCCP, both absolute and relative liver weights were significantly increased in a dose-related manner, at doses of 100 mg/kg-bw per day or greater. Peroxisomal fatty acid β-oxidation activity (indicated by palmitoyl CoA oxidation) was significantly increased at 250 mg/kg-bw per day and greater (irregular dose–response). For the 56% chlorine SCCP, the pattern of response for absolute liver weight was irregular; however, relative liver weight was increased in a dose-related manner, significantly at 50 mg/kg-bw per day and greater. Palmitoyl CoA oxidation was significantly increased only at the highest dose.

In similarly exposed male mice (Alpk:APfCD-1 strain), for the 58% chlorine SCCP, there was a dose-related increase in relative liver weight and palmitoyl CoA oxidation, both significant at 250 mg/kg-bw per day and greater (Wyatt *et al*., 1993). For the 56% chlorine SCCP, both absolute and relative liver weights were significantly increased in a dose-related manner at doses of 100 mg/kg-bw per day or greater. Palmitoyl CoA oxidation was significantly

increased in a dose-related manner at 250 mg/kg-bw per day and greater.

The only other relevant investigation identified was an *in vitro* study in which SCCP inhibited gap junction intercellular communication in rat liver cells (Kato and Kenne, 1996; Warngard *et al*., 1996).

3.3.1.2 Kidney

Increased proximal tubular cell eosinophilia (suggestive of a protein overload, but not necessarily α_{2u} globulin) and regenerative focal basophilic tubules, as well as increased S-phase activity in the proximal tubular cells, were reported in male, but not female, rats administered up to 1000 mg SCCP/kg-bw per day for up to 90 days (other dose levels were not specified) (Elcombe *et al*., 1994). These observations were reported in an abstract; neither quantitative data nor statistical analyses were presented.

Elcombe *et al*. (2000) also investigated renal effects in F344 rats and guinea pigs administered 0, 312 or 625 mg SCCP/kg-bw per day for up to 90 days. In the male rats only, there was chronic protein nephropathy, associated with regenerative hyperplasia and increased DNA synthesis (S-phase activity), presumably at both dose levels. There was "some limited evidence" for an involvement of α_{2u} globulin. These changes were not observed in the guinea pigs. Again, neither quantitative data nor statistical analyses were presented in this summary account.

Warnasuriya *et al*. (2000) exposed male and female rats by gavage for 28 days to 625 mg SCCP (C_{12}; 60% chlorine)/kg-bw per day. There was an increase in α_{2u} globulin and cell proliferation in the kidney of males only. Data from individual rats indicated that increased cell proliferation was directly correlated with the increase in α_{2u} globulin. Five different isoelectric isoforms of α_{2u} globulin were identified by Western blotting in the control male kidney, and all five were increased in the treated males. These observations were reported in an abstract; neither quantitative data nor statistical analyses were presented.

3.3.1.3 Thyroid

Elcombe *et al*. (1994) reported that exposure of rats to SCCP for up to 90 days resulted in induction of T_4–glucuronosyl transferase activity, accompanied by a decrease in plasma T_4 and an increase in thyroid stimulating hormone (TSH). Thyroid follicular cell hypertrophy and hyperplasia were also observed. Increased S-phase activity in the thyroid follicular cells was also reported. The maximum dose was 1000 mg/kg-bw per day; other dose levels were not specified. This study was reported as an abstract; neither quantitative data nor statistical analyses were presented.

In male and female Fischer 344 rats exposed by gavage in corn oil to 0, 312 or 625 mg/kg-bw per day for up to 90 days, there were decreases in plasma T_4, increases in plasma TSH and thyroid follicular cell hypertrophy and hyperplasia in both sexes, changes that were not

observed in male guinea pigs (Elcombe *et al*., 2000). Quantitative data and statistical analyses were not presented in this summary account.

Gavage administration of 6.8 mg/kg-bw per day commercial $C_{10–13}$ (71% chlorine) to female Sprague-Dawley rats for 14 days had no effect upon thyroid hormonal T_4 levels or microsomal enzyme activity (Hallgren and Darnerud, 1998).

In male rats (Alpk:APfSD strain) exposed by gavage for 14 days to two SCCP (Chlorowax 500C: $C_{10–13}$, 58% chlorine; or Cereclor 56L, $C_{10–13}$: 56% chlorine), for which examination of thyroid function was restricted to the control and high-dose groups (1000 mg/kg-bw per day), both free and total T_4 were significantly reduced, TSH was significantly increased and the capability of liver microsomes to glucuronidate T_4 was significantly increased in exposed animals (Wyatt *et al*., 1993). No differences in levels of free or total triiodothyronine (T_3) were observed for either SCCP. A significant increase in glucuronosyl transferase activity with p-nitrophenol was observed only from microsomes from rats exposed to the $C_{10–13}$ (58% chlorine) compound.

3.3.2 Medium-chain chlorinated paraffins

A subchronic dietary study with MCCP in rats (Poon *et al*., 1995) was initiated by Health Canada in response to the research needs identified in the PSL1 assessment of chlorinated paraffins (Government of Canada, 1993). Sprague-Dawley rats (10 per sex per group) were fed diets containing 0, 5, 50, 500 or 5000 ppm for 13 weeks. The dose levels calculated by the authors on the basis of weekly food consumption were 0, 0.4, 3.6, 36 and 363 mg/kg-bw per day for males and 0, 0.4, 4.2, 42 and 419 mg/kg-bw per day for females. The protocol included serum biochemistry, hematology, hepatic enzyme activities, urinary enzyme activity, organ weights and histopathology. Mild, adaptive histological changes were detected in the liver of rats of both sexes at the two highest doses (LOEL = 36 mg/kg-bw per day) and in the thyroid of males at 36 mg/kg-bw per day and greater and of females at 4.2 mg/kg-bw per day and greater (NOAEL = 0.4 mg/kg-bw per day). Minimal changes were observed in the renal proximal tubules of males at the highest dose and in the inner medulla of females at the two highest doses.

3.3.3 Long-chain chlorinated paraffins

No critical data relevant to the assessment of the toxicity of LCCP were identified for the period since the PSL1 assessment was released.

3.4 Human health risk characterization and conclusions

3.4.1 Short-chain chlorinated paraffins

3.4.1.1 Hazard characterization

Genotoxicity

Requisite criteria for assessing the weight of evidence for hypothesized modes of induction of tumours addressed below include the criterion that SCCP are not DNA-reactive. Recent data on genotoxicity reported since the PSL1 assessment was released have not been identified. Limited available data reviewed within the PSL1 assessment indicated that SCCP were clastogenic in *in vitro* assays, although they had not been clastogenic or mutagenic in a limited number of *in vivo* assays.

Based on review of the available data, including two additional unpublished studies in which no increases in revertant colonies in five strains of *Salmonella*[9] and no increases in mutant colonies in Chinese hamster V79 cells[10] were reported in the secondary account, it was concluded that "as a group, SCCP are not mutagenic" (European Commission, 2000).

Liver

It has been hypothesized that SCCP cause liver tumours in rodents secondary to peroxisome proliferation. Peroxisome proliferation involves activation of a nuclear receptor in rodent liver, the peroxisome proliferator activated receptor, α isoform (PPARα). The activated PPARα interacts with regulatory elements of the DNA to initiate transcription of genes for increased peroxisomal enzyme activity and cell proliferation characterized by morphological and biochemical changes in the liver. These changes include increased liver weight through both hepatocyte hypertrophy and hyperplasia, increased number and size of peroxisomes, increased activity (up to 40-fold) of peroxisomal enzymes (especially those involved in peroxisomal fatty acid oxidation) and induction of microsomal fatty acid oxidation through the CYP4A subfamily of cytochrome P-450 isozymes. Minimum criteria for characterizing peroxisome proliferation are considered to include hepatomegaly, enhanced cell proliferation and an increase in hepatic acyl-CoA oxidase and/or palmitoyl-CoA oxidation levels.

In the NTP bioassay (NTP, 1986a; Bucher *et al*., 1987) reported in the PSL1 assessment, increases in benign liver tumours were observed in both SCCP-exposed rats (312 and 625 mg/kg-bw per day) and mice (125 and 250 mg/kg-bw per day), with males of both species being

[9] Cited by the European Commission (2000) as: Unpublished Report 86, Hoechst AG, Unpublished study, 88.0099, 1988.

[10] Cited by the European Commission (2000) as: Unpublished Report 92, Hoechst AG, Unpublished study, 87.1719, 1987.

considerably more sensitive. This pattern of induction of liver tumours by SCCP is consistent with that for other peroxisome proliferating hepatocarcinogens, such as di(2-ethylhexyl)phthalate.

Available data on the role of peroxisome proliferation in the etiology of hepatic effects and liver tumours induced by SCCP are restricted to one study for which there is a published manuscript (Wyatt *et al*., 1993) and two investigations reported only in summary (Elcombe *et al*., 2000) or abstract form (Elcombe *et al*., 1994). Significant, dose-related increases in both absolute and relative liver weights accompanied at higher doses by increases in palmitoyl CoA oxidation in male Alpk:APfSD rats and Alpk:APfCD-1 mice exposed to two SCCP, reported by Wyatt *et al*. (1993), are consistent with the observations in rats of Elcombe *et al*. (1994, 2000). Also, to the extent to which the more recent and better-documented study of Wyatt *et al*. (1993), with more extensive characterization of dose–response, can be compared with the earlier investigations of Elcombe *et al*. (1994, 2000), for which only summary reports are available, observations on dose–response for increases in liver weight and palmitoyl CoA oxidation in rats in these investigations are also consistent (increases in relative liver weight in rats were significant at ≥50 mg/kg-bw per day and palmitoyl CoA oxidation at ≥250 mg/kg-bw per day; comparable values for mice were 100 mg/kg-bw per day and 250 mg/kg-bw per day).

Therefore, although characterization of exposure–response was limited in the NTP bioassay to only two dose levels, evidence to date indicates that tumours in both rats and mice occur only at doses at which peroxisome proliferation and associated morphological and biochemical effects have been observed in shorter-term studies (Wyatt *et al*., 1993; Elcombe *et al*., 1994, 2000).

Additional weight of evidence for concordance might have been afforded through consideration of sex-related differences in peroxisome proliferation in shorter-term mechanistic studies. Unfortunately, this aspect was not investigated in the well-reported study by Wyatt *et al*. (1993) in which only male rats and mice were exposed; moreover, the limited extent of reporting in Elcombe *et al*. (1994, 2000) precludes consideration of relevant data in this context, if such data were, indeed, collected. Recovery studies would also have been informative, since peroxisome proliferation is initiated rapidly after treatment with a proliferator begins, attains a maximal response in a few weeks and is maintained only in the continued presence of the proliferator. Consistent with a receptor-mediated response, the process is reversible.

While there have been no carcinogenesis bioassays for SCCP in species other than rats and mice, the variation in species sensitivity to peroxisome proliferation reported by Elcombe *et al*. (2000) is consistent with that observed for other peroxisome proliferators. Rats and mice are uniquely responsive to the morphological and biochemical effects of peroxisome proliferators, while Syrian hamsters exhibit intermediate responsiveness. This is consistent with marked interspecies variations in the expression of PPARα.

Additional published documentation of existing relevant studies is desirable. Also, investigation of additional aspects of concordance would strengthen the weight of evidence for

causality for the purported association between peroxisome proliferation and liver tumours induced by SCCP. However, although there are limitations of the identified information, data are strongly suggestive that peroxisome proliferation plays a role in the etiology of liver damage and hepatic tumours associated with exposure to SCCP. Although additional evidence for the weight of causality for liver tumours is desirable, a TDI based on hepatic effects in experimental animals is considered to be protective for carcinogenicity.

Kidney

It has been hypothesized that the kidney tumours observed following exposure of male rats to SCCP are a species- and sex-specific response attributable to α_{2u} globulin nephropathy and hence not relevant to humans. This mode of induction of renal tumours, which is relatively well characterized, involves binding to α_{2u} globulin, a protein specific to male rats. This binding renders the protein more resistant to proteolytic degradation, which causes its accumulation in renal proximal tubule cells (manifested as hyaline droplets on histopathological examination), resulting in cell death and regenerative proliferation. Sustained cell proliferation leads to a low but significant incidence of renal tubular tumours.

Minimum criteria for establishment of α_{2u} globulin nephropathy as a basis for tumour development include lack of genotoxicity and observation of requisite precursor lesions and tumours in male rats only. Confirmation of requisite precursor lesions is based not only on histopathological observations such as excessive accumulation of hyaline droplets in renal proximal tubule cells, subsequent cytotoxicity and single-cell necrosis of the tubular epithelium and sustained regenerative tubular cell proliferation in the presence of continued exposure, but also on explicit identification of the protein accumulating in tubule cells as α_{2u} globulin, along with demonstrated reversible binding of the relevant chemical or metabolite to α_{2u} globulin (U.S. EPA, 1991; IARC, 1999).

In the NTP bioassay (NTP, 1986a; Bucher *et al*., 1987) reported in the PSL1 assessment, renal tubular cell adenomas were observed in male rats at both doses (312 and 625 mg/kg-bw per day), although the increase was significant ($p < 0.05$) only at the lower dose. Characterization of exposure–response was limited, therefore, in the NTP bioassay to only two dose levels.

Available data on the mode of induction of kidney tumours in male rats by SCCP are restricted to three investigations reported only in summary or abstract format (Elcombe *et al*., 1994, 2000; Warnasuriya *et al*., 2000). In Elcombe *et al*. (1994, 2000), regenerative focal basophilic tubules and increased S-phase activity in the proximal tubular renal cells were observed in male, but not female rats and considered by the authors to constitute "limited evidence" of the role of α_{2u} globulin. More recently, the presence of α_{2u} globulin was confirmed using immunohistochemical techniques, although no details of methodology were provided (Warnasuriya *et al*., 2000).

Owing to the inadequate characterization in abstracts of even administered doses, in some cases with quantitative data on effects and analyses not being reported, there is very

limited documentation to serve as a basis for conclusion that renal tumours occur only at doses at which either chronic protein nephropathy associated with regenerative hyperplasia and increased DNA synthesis (Elcombe *et al*., 2000) or α_{2u} globulin is observed (Warnasuriya *et al*., 2000).

While information is strongly suggestive that the kidney tumours observed in male rats are attributable to hyaline droplet formation, a male rat-specific phenomenon not relevant to humans, additional published documentation of available studies is clearly desirable as a basis for consideration of the weight of evidence of mode of induction of kidney tumours. Although additional confirmation is desirable, a TDI based on renal effects in experimental animals is considered to be protective for carcinogenicity.

Thyroid

There are a variety of non-DNA-reactive compounds that cause thyroid tumours in rats associated with decreased circulating thyroid hormone levels due to increased hepatic metabolism (particularly Phase II conjugating enzymes such as uridine diphosphate (UDP) glucuronosyl transferases [UDPGTs] and glutathione S-transferases) and clearance. These compounds induce hepatic glucuronidation of thyroid hormones and increase biliary excretion of the conjugated hormones, resulting in decreased circulating T_3 and T_4 levels. As a result of the hypothyroid state, TSH levels increase and cause sustained thyroid follicular cell hyperplasia, leading to tumour formation.

While the basic physiology and feedback mechanisms of the hypothalamic–pituitary–thyroid axis are qualitatively similar across species, quantitative differences make rodents more sensitive than humans to development of thyroid cancer for which the sole mode of action is thyroid–pituitary disruption (U.S. EPA, 1998). These include the lack of a high-affinity thyroid binding globulin in rats relative to humans (Dohler *et al*., 1979), which likely affects the turnover of the hormone. With a more rapid turnover of T_4, there is a generalized increased activity of the pituitary–thyroid axis in rats compared with humans, which correlates with increased susceptibility to thyroid gland neoplasia.

Minimum criteria for establishment of this mode of action as a basis for tumour development include evidence of increases in thyroid growth and hormonal changes (the latter including reduction in circulating serum T_4 and T_3 and an increase in TSH levels within days or a few weeks of exposure). Evidence of increases in thyroid growth is provided by measured increases in absolute or relative thyroid weight, histological indication of cellular hypertrophy and hyperplasia, morphometric determination of alteration in thyroid cellular components and changes in proliferation of follicular cells detected by DNA labelling or mitotic indices (U.S. EPA, 1998).

In the NTP bioassay (NTP, 1986a; Bucher *et al*., 1987) reported in the PSL1 assessment, increases in follicular cell adenomas and carcinomas (combined) were observed in female rats only, at 312 and 625 mg/kg-bw per day, and in female mice only, at 250 mg/kg-bw per day.

Available data relevant to assessment of the weight of evidence of induction of thyroid tumours in rats by SCCP are limited to one study for which there is a published manuscript (Wyatt *et al*., 1993) and two investigations for which only a published summary report (Elcombe *et al*., 2000) or abstract (Elcombe *et al*., 1994) is available. In the study for which a complete account was published, effects on the thyroid were considered only in the control and highest dose groups; the administered dose for the latter was considerably greater than those in the NTP bioassay associated with thyroid tumours (i.e., 1000 mg/kg-bw per day versus 312 and 625 mg/kg-bw per day). In addition, in the abstract and summary accounts, quantitative data on effects or analyses were not presented. For example, Elcombe *et al*. (2000) reported only that male and female Fischer 344 rats were exposed by gavage in corn oil for up to 90 days at dose levels of 0, 312 or 625 mg/kg-bw per day and that "there were decreases in plasma thyroxine, increases in plasma TSH concentration and thyroid follicular cell hypertrophy and hyperplasia in both sexes." There are extremely limited data, therefore, to serve as a basis for consideration of concordance of dose–response between thyroid tumour induction and precursor effects in shorter-term studies, such as thyroid growth and hormonal changes. In a single additional study for which a full account is available (Hallgren and Darnerud, 1998), the dose level at which effects on thyroid hormonal T_4 levels or microsomal enzyme activity were not observed were much less than those administered in the NTP bioassay; as a result, these are not additionally meaningful in this context.

As a result, although data from the studies reported by Elcombe *et al*. (1994, 2000) and Wyatt *et al*. (1993) fulfil the criteria for tumour induction by thyroid disruption in part, it should be noted that these data are insufficient as a basis for analysis of dose–response for concordance with that for thyroid tumours. Also, recovery in the absence of continued exposure has not been investigated. In view of the limitations of both reporting and dose–response analyses, therefore, there is considerable uncertainty in attributing observed thyroid tumours to thyroid–pituitary disruption, to which rodents are more sensitive than humans.

3.4.1.2 Risk characterization

Available data relevant to consideration of the weight of evidence for proposed modes of induction of liver, kidney and thyroid tumours associated with exposure to SCCP, although limited, are suggestive that tolerable intakes that protect for non-neoplastic precursor effects will likely also be protective for cancer. However, owing principally to limited investigation of aspects such as recovery and inadequate documentation of relevant studies, there is considerable uncertainty in drawing this conclusion, particularly for the thyroid tumours. In recognition of this uncertainty, both neoplastic and non-neoplastic effects are considered here.

IPCS (1996) derived a TDI of 100 µg/kg-bw per day for non-neoplastic effects of SCCP on the basis of the lowest reported No-Observed-Effect Level (NOEL) of 10 mg/kg-bw per day in a 13-week study in rats (IRDC, 1984). At the next higher dose in the critical study (100 mg/kg-bw per day), there were increases in liver and kidney weight and hypertrophy of the liver and thyroid. In IPCS (1996), an uncertainty factor of 100 was applied in the development of the TDI to account for interspecies variation (×10) and intraspecies variation (×10). The potential for

progression of lesions following longer-term exposure was not explicitly addressed in the development of the TDI. This is balanced to some degree by the relatively large margin between the NOEL and the LOEL (10-fold) in the critical study and the minimal severity of the effects at the next higher concentration; however, there is some justification for considering a somewhat lower value for the TDI.

On the basis of multistage modelling of the tumours with highest incidence (hepatocellular adenomas or carcinomas [combined] in male mice) in the carcinogenesis bioassay with SCCP, IPCS (1996) also estimated the dose associated with a 5% increase in tumour incidence (Tumorigenic $Dose_{05}$ [TD_{05}]) to be 11 mg/kg-bw per day (amortized for period of administration).

The upper-bound estimate of exposure for the age group with greatest exposure to SCCP (i.e., 26 µg/kg-bw per day) is within the range of the IPCS (1996) TDI, for which there is some justification for considering a somewhat lower value, to take into account potential progression of the lesions in longer-term studies.

The margin between the upper-bound estimate of exposure for the age group with greatest exposure to SCCP and the Tumorigenic Dose (TD_{05}) (i.e., 440) is also considered inadequate in view of the uncertainty concerning mode of induction of tumours.

Therefore, it is proposed that there is no reason to revise the conclusion for PSL1 that short-chain chlorinated paraffins are "toxic" as defined previously under Paragraph 11© of the *Canadian Environmental Protection Act, 1988* and currently under Paragraph 64(c) of the *Canadian Environmental Protection Act, 1999*.

3.4.2 Medium-chain chlorinated paraffins

A TDI developed on the basis of the NOAEL (0.4 mg/kg-bw per day) in the more recent subchronic study conducted by Health Canada (Poon *et al*., 1995) would be similar to that derived for the PSL1 assessment (i.e., 6 µg/kg-bw per day).

Several of the highly uncertain bounding estimates of total daily intake of MCCP from drinking water, food and soil for the general population of Canada exceed the TDI (6 µg/kg-bw per day) for non-neoplastic effects. Indeed, for infants not formula fed, the total daily intake of MCCP (i.e., 25.5 µg/kg-bw per day) exceeds the TDI by up to 4-fold.

Based on the limited available data, therefore, there is reason to suspect that medium-chain chlorinated paraffins are "toxic" to human health, as defined in Paragraph 64(c) of the *Canadian Environmental Protection Act, 1999*.

3.4.3 Long-chain chlorinated paraffins

None of the highly uncertain bounding estimates of total daily intake of LCCP from drinking water, food and soil for the general population of Canada exceeds the TDI (71 µg/kg-bw per day) for non-neoplastic effects. However, for infants not formula fed, the total daily intake of LCCP (16.8 µg/kg-bw per day) is within the same order of magnitude as the TDI.

Based on the limited available data, therefore, there is reason to suspect that long-chain chlorinated paraffins are "toxic" to human health, as defined in Paragraph 64(c) of the *Canadian Environmental Protection Act, 1999.*

3.5 Uncertainties and degree of confidence in human health risk characterization

There is low confidence in the upper-bounding estimates of exposure to all chlorinated paraffins. The estimates of intake for most age groups in the general Canadian population are based almost entirely upon limited sampling of foodstuffs in the United Kingdom, which were published in 1980. Methodology for analysis in this study is considered inadequate by present-day standards, and, as such, the data can be regarded at best as semi-quantitative. Reported concentrations represented both SCCP and MCCP, and, as a result, intake of the individual groups of chlorinated paraffins (SCCP, MCCP and LCCP) from these sources has been overestimated.

The estimates of intake for SCCP are based in part upon the results of more recent surveys, for which methods of analysis were more reliable (i.e., quantification by GC/ECNI-HRMS). Concentrations of SCCP determined by HRMS were available for ambient air, water and samples of carp from Hamilton Harbour (intake from fish represented 38–58% of estimated total intake of SCCP, although fish accounts for, at most, 4% of the total daily intake of food across the six age groups).

However, it is not possible to quantify the extent of overestimation of exposure based on the earlier, likely less selective analytical methodology, owing to lack of comparable data. Moreover, results based on analysis of the same samples by LRMS versus HRMS have been inconsistent, with levels of SCCP being 1–2 orders of magnitude less for the latter in samples of whale blubber (Bennie *et al*., 2000; Tomy *et al*., 2000) and trout (Muir *et al*., 1999; Bennie *et al*., 2000) but slightly greater for the high-resolution analysis in carp (Muir *et al*., 1999; Bennie *et al*., 2000).

There is minimal confidence in the upper-bounding estimates of exposure to MCCP. These estimates are based in large part upon concentrations reported in a limited number of foodstuffs in the United Kingdom, which were published in 1980. More recent, although limited, data on concentrations in trout analysed by LRMS were included in the calculation of upper-bounding estimates.

There is minimal confidence in the upper-bounding estimates of exposure to LCCP. These estimates are based entirely upon concentrations reported in a limited number of foodstuffs in the United Kingdom, which were published in 1980. Furthermore, concentrations in foods were represented by the limits of detection for five of eight food groups in the calculations

of daily intake.

There is a low degree of confidence in the database of toxicological studies that serves as the basis for the assessment of the weight of evidence for mode of induction of tumours by SCCP, for which only one published complete report (Wyatt *et al*., 1993) is available and for which it has not been possible to identify published accounts for reported pre-publication manuscripts reviewed in previous assessments. Results in the only fully documented study provide most meaningful support for the purported role of peroxisome proliferation in induction of liver tumours in rats and mice.

There is a moderate degree of confidence in the database of toxicological studies upon which the TDI for MCCP is based, for which studies on chronic toxicity or carcinogenicity are lacking. The database for LCCP is more complete, including a well-documented carcinogenicity bioassay in rats and mice.

3.6 Considerations for follow-up

Acquisition of higher-confidence data on levels of, particularly, MCCP and LCCP in environmental media to which the general population is exposed, particularly foodstuffs, is desirable. Since, on the basis of limited available data, there is reason to suspect that MCCP and LCCP are toxic, additional information is being requested as a basis for concluding whether the compounds can be considered to be "toxic" under CEPA 1999. If no relevant information is received, it is proposed that the Ministers of the Environment and of Health consider the substances to be "toxic" under CEPA 1999.

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Table 1. Concentrations of short-chain, medium-chain and long-chain chlorinated paraffins in foodstuffs

Food group	Concentration used to represent food group	
	Short- and medium-chain chlorinated paraffins	**Long-chain chlorinated paraffins**
Dairy	0.3 µg/g mean of 13 samples of dairy products in U.K. $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)	0.19 µg/g 1 sample of cheese in U.K. $C_{20–30}$ (Campbell and McConnell, 1980a)
Fats	0.15 µg/g mean of 6 samples of vegetable oils and derivatives $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)	0.05 µg/g detection limit in analysis of 1 sample of lard in U.K. $C_{20–30}$ (Campbell and McConnell, 1980b)
Fruits	0.025 µg/g mean of 16 samples of fruits and vegetables in U.K. $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)	0.025 µg/g 1 sample of peach fruit in U.K. $C_{20–30}$ (Campbell and McConnell, 1980a)
Vegetables	0.025 µg/g mean of 16 samples of fruits and vegetables in U.K. $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)	0.025 µg/g 1 sample of potato crisps in U.K. $C_{20–30}$ (Campbell and McConnell, 1980a)
Cereal products	SCCP 0.13 µg/g one reported concentration for "Chlorowax 500C" in enriched white bread in market basket survey carried out by U.S. Food and Drug Administration (KAN-DO Office and Pesticides Team, 1995); average molecular formula is $C_{12}H_{19}Cl_7$, with 60–65% chlorine content (w/w) (IPCS, 1996)	0.05 µg/g detection limit in analyses of corn flakes in U.K. $C_{20–30}$ (Campbell and McConnell, 1980b)
	SCCP/MCCP 0.05 µg/g detection limit in analysis of 1 sample of corn flakes in U.K. $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980b)	
Meat and poultry	0.099 µg/g 1 sample of bacon in U.K. $C_{10–20}$ (SCCP and MCCP)	0.05 µg/g detection limit in analysis of 1 sample each of ox liver and beef in U.K.

Food group	Concentration used to represent food group	
	Short- and medium-chain chlorinated paraffins	**Long-chain chlorinated paraffins**
	(Campbell and McConnell, 1980b)	$C_{20–30}$ (Campbell and McConnell, 1980b)
Fish	Note: Campbell and McConnell (1980b) presented data for combined SCCP and MCCP. Data for fish identified in Bennie *et al*. (2000), Muir *et al*. (1999) and Tomy and Stern (1999) were presented as separate analyses.	no data identified
	SCCP 2.630 µg/g (wet weight); analysis of whole samples of carp from Hamilton Harbour; C_{10}–C_{13} (Muir *et al*., 1999) 0.0588 µg/g; lake trout, Niagara-on-the-Lake (Muir *et al*., 1999) 0.0726 µg/g; lake trout, Port Credit (Muir *et al*., 1999) 0.502 µg/g; carp (n = 3) (Bennie *et al*., 2000) 1.47 µg/g; trout (n = 10) (Bennie *et al*., 2000) 1.8 µg/g (estimated); perch, Detroit River (Tomy and Stern, 2000)	
	MCCP 1.23 µg/g; mean of 10 samples of whole trout from western Lake Ontario (Bennie *et al*., 2000) 0.393 µg/g; carp (n = 3) (Bennie *et al*., 2000) 82 ng/g in perch; 904 ng/g in catfish (Tomy and Stern, 1999) 0.008 µg/g (estimated); perch, Detroit River (Tomy and Stern, 2000)	
Eggs	no data identified	no data identified
Foods primarily sugar	0.025 µg/g 1 sample of strawberry jam in U.K. $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980b)	0.05 µg/g detection limit in 1 sample of strawberry jam in U.K. $C_{20–30}$ (Campbell and McConnell, 1980b)
Mixed dishes	no data identified	no data identified
Nuts and seeds	no data identified	no data identified

Food group	Concentration used to represent food group	
	Short- and medium-chain chlorinated paraffins	**Long-chain chlorinated paraffins**
Soft drinks, alcohol, coffee, tea	0.05 µg/g detection limit in analyses of beverages in U.K. (Campbell and McConnell, 1980a)	0.05 µg/g detection limit in analysis of 1 sample each of beer and tea in U.K. $C_{20–30}$ (Campbell and McConnell, 1980b)

Table 2. Upper-bounding estimated average daily intake of short-chain chlorinated paraffins by the population of Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of short-chain chlorinated paraffins by various age groups							
	0–6 months[1]			0.5–4 years[5]	5–11 years[6]	12–19 years[7]	20–59 years[8]	60+ years[9]
	breast fed[2]	formula fed[3]	not formula fed[4]					
Ambient air[10]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Indoor air[11]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Drinking water[12]	1.7	0.005	0.001	0.001	0.001	<0.001	<0.001	<0.001
Food[13]			25.96	24.26	16.44	9.02	7.18	5.14
Soil[14]	0.001	0.001	0.001	0.002	0.001	<0.001	<0.001	<0.001
Total intake[15]	**1.7**	**0.01**	**25.97**	**24.26**	**16.44**	**9.02**	**7.18**	**5.14**

1 Assumed to weigh 7.5 kg and to breathe 2.1 m^3 per day (21 hours indoors, 3 hours outdoors) (EHD, 1998).

2 Concentrations of SCCP ($C_{10–13}$, 52% chlorine) ranged from 11 to 17 µg/kg in human breast milk in Canada (Tomy, 1997). No additional details were reported. These data were identified in a secondary source and were originally reported in a Ph.D. thesis. Assumed to consume 0.75 kg breast milk per day (EHD, 1998).

3 For formula-fed infants, intake from water is synonymous with intake from food. Assumed to consume 0.8 L reconstituted formula daily (EHD, 1998).

4 Assumed to drink 0.2 L of water per day. Consumption of food groups reported by Health Canada (EHD, 1998).

5 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 per day (21 hours indoors, 3 hours outdoors) and to drink 0.2 L of water per day. Consumption of food groups reported by Health Canada (EHD, 1998).

6 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 per day (21 hours indoors, 3 hours outdoors) and to drink 0.4 L of water per day. Consumption of food groups reported by Health Canada (EHD, 1998).

7 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 per day (21 hours indoors, 3 hours outdoors) and to drink 0.4 L of water per day. Consumption of food groups reported by Health Canada (EHD, 1998).

8 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 per day (21 hours indoors, 3 hours outdoors) and to drink 0.4 L of water per day. Consumption of food groups reported by Health Canada (EHD, 1998).

9 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 per day (21 hours indoors, 3 hours outdoors) and to drink 0.4 L of water per day. Consumption of food groups reported by Health Canada (EHD, 1998).

10 The maximum concentration of C_{10}–C_{13} (60–70% chlorine) in gas-phase air samples collected every day over a 4-month period in the summer of 1990 at Egbert, a rural site northwest of Toronto, was 924 pg/m^3 (Muir *et al*., 1999).

11 Concentrations of SCCP in indoor air in Canada or elsewhere were not identified. The value used for calculating intake here is the above concentration identified for ambient air (Muir *et al*., 1999).

12 Concentrations of SCCP in drinking water were not identified. The maximum concentration of SCCP ($C_{10–13}$, 50–70% chlorine) identified in the Red River, at a site remote from industrialized areas, was 0.05 µg/L (Tomy, 1997).

13 Estimates of intake from food are based upon concentrations in foods that are selected to represent the food groups addressed in calculating exposure to Priority Substances (EHD, 1998):

Dairy: 0.3 µg/g; mean of 13 samples of dairy products in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)
Fats: 0.15 µg/g; mean of 6 samples of vegetable oils and derivatives; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)
Fruits: 0.025 µg/g; mean of 16 samples of fruits and vegetables in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)
Vegetables: 0.025 µg/g; mean of 16 samples of fruits and vegetables in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)
Cereal products: 0.13 µg/g; one reported concentration for "Chlorowax 500C" in enriched white bread in market basket survey carried out by U.S. Food and Drug Administration (KAN-DO Office and Pesticides Team, 1995); average molecular formula is $C_{12}H_{19}Cl_7$, with 60–65% chlorine content (w/w) (IPCS, 1996)
Meat and poultry: 0.099 µg/g; 1 sample of bacon in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980b)
Fish: 2.630 µg/g (wet weight); analysis of whole samples of carp from Hamilton Harbour; C_{10}–C_{13} (Muir *et al*., 1999)

Eggs: no data identified
Foods primarily sugar: 0.025 µg/g; 1 sample of strawberry jam in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980b)
Mixed dishes: no data identified
Nuts and seeds: no data identified
Soft drinks, alcohol, coffee, tea: 0.05 µg/g; detection limit in analyses of beverages in U.K. (Campbell and McConnell, 1980a)

Amounts of foods consumed on a daily basis by each age group are described by Health Canada (EHD, 1998).

[14] No data were identified on concentrations of SCCP in soil in Canada. The maximum concentration in surface sediment in harbours in Lake Ontario was 290 ng/g dry weight (Muir *et al*., 2001).

[15] Medium-specific and total intakes were calculated on a Microsoft Excel spreadsheet. Only significant numbers have been presented, which accounts for seemingly inaccurate totals.

Table 3. Upper-bounding estimated average daily intake of medium-chain chlorinated paraffins by the population of Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of medium-chain chlorinated paraffins by various age groups						
	0–6 months[1]		6 months–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	formula fed[2]	not formula fed[3]					
Ambient air[9]	–	–	–	–	–	–	–
Indoor air[10]	–	–	–	–	–	–	–
Drinking water[11]	0.05	0.01	0.01	0.01	<0.01	<0.01	<0.01
Food[12]		25.48	18.48	11.64	6.3	4.69	3.47
Soil[13]	0.01	0.01	0.02	0.01	<0.01	<0.01	<0.01
Total intake[14]	**0.07**	**25.51**	**18.51**	**11.65**	**6.3**	**4.69**	**3.47**

1 Assumed to weigh 7.5 kg and to breathe 2.1 m^3 per day (21 hours indoors, 3 hours outdoors) (EHD, 1998).

2 For formula-fed infants, intake from water is synonymous with intake from food. Assumed to consume 0.8 L reconstituted formula daily. No data on concentrations of MCCP in formula were identified for Canada.

3 Assumed to drink 0.2 L of water per day. Consumption of food groups reported by Health Canada (EHD, 1998).

4 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 100 mg of soil per day and to drink 0.2 L of water per day. Consumption of food groups reported in EHD (1998).

5 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 65 mg of soil per day and to drink 0.4 L of water per day. Consumption of food groups reported in EHD (1998).

6 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 30 mg of soil per day and to drink 0.4 L of water per day. Consumption of food groups reported in EHD (1998).

7 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 30 mg of soil per day and to drink 0.4 L of water per day. Consumption of food groups reported in EHD (1998).

8 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 30 mg of soil per day and to drink 0.4 L of water per day. Consumption of food groups reported in EHD (1998).

9 Concentrations of MCCP in ambient air in Canada or elsewhere were not identified.

10 Concentrations of MCCP in indoor air in Canada or elsewhere were not identified.

11 Concentrations of MCCP in Canadian drinking water were not identified. Intakes are based upon the limit of detection (0.5 µg/L) in a survey of drinking water in reservoirs in the U.K. (Campbell and McConnell, 1980a).

12 Estimates of intake from food are based upon concentrations in foods that are selected to represent the food groups addressed in calculating exposure to Priority Substances (EHD, 1998):

Dairy: 0.3 µg/g; mean of 13 samples of dairy products in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)
Fats: 0.15 µg/g; mean of 6 samples of vegetable oils and derivatives; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)
Fruits: 0.025 µg/g; mean of 16 samples of fruits and vegetables in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)
Vegetables: 0.025 µg/g; mean of 16 samples of fruits and vegetables in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980a)
Cereal products: 0.05 µg/g, detection limit in analyses of corn flakes in U.K. (Campbell and McConnell, 1980b)
Meat and poultry: 0.099 µg/g; 1 sample of bacon in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980b)
Fish: 1.23 µg/g (wet weight); mean of 10 samples of whole trout from western Lake Ontario (Bennie *et al*., 2000)
Eggs: no data identified
Foods primarily sugar: 0.025 µg/g; 1 sample of strawberry jam in U.K.; $C_{10–20}$ (SCCP and MCCP) (Campbell and McConnell, 1980b)
Mixed dishes: no data identified
Nuts and seeds: no data identified
Soft drinks, alcohol, coffee, tea: 0.05 µg/g; detection limit in analyses of beverages in U.K. (Campbell and McConnell, 1980a)

Amounts of foods consumed on a daily basis by each age group are described by Health Canada (EHD, 1998).

[13] The value used for calculating intake from soil is the limit of quantification (3.5 µg/g) in a survey of sediment from the St. Lawrence River (Metcalfe-Smith *et al*., 1995).

[14] Medium-specific and total intakes were calculated on a Microsoft Excel spreadsheet. Only significant numbers have been presented, which accounts for seemingly inaccurate totals.

Table 4. Upper-bounding estimated average daily intake of long-chain chlorinated paraffins by the population of Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of long-chain chlorinated paraffins by various age groups						
	0–6 months[1]		6 months–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	formula fed[2]	not formula fed[3]					
Ambient air[9]	–	–	–	–	–	–	–
Indoor air[10]	–	–	–	–	–	–	–
Drinking water[11]	0.05	0.01	0.01	0.01	<0.01	<0.01	<0.01
Food[12]		16.81	9.66	5.61	3.04	2.12	1.73
Soil[13]	0.01	0.01	0.02	0.01	<0.01	<0.01	<0.01
Total intake[14]	**0.07**	**16.83**	**9.69**	**5.63**	**3.04**	**2.12**	**1.73**

1 Assumed to weigh 7.5 kg and to breathe 2.1 m^3 per day (21 hours indoors, 3 hours outdoors) (EHD, 1998).

2 For formula-fed infants, intake from water is synonymous with intake from food. Assumed to consume 0.8 L reconstituted formula daily. No data on concentrations of LCCP in formula were identified for Canada.

3 Assumed to drink 0.2 L of water per day. Consumption of food groups reported in EHD (1998).

4 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 100 mg of soil per day and to drink 0.2 L of water per day. Consumption of food groups reported in EHD (1998).

5 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 65 mg of soil per day and to drink 0.4 L of water per day. Consumption of food groups reported in EHD (1998).

6 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 30 mg of soil per day and to drink 0.4 L of water per day. Consumption of food groups reported in EHD (1998).

7 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 30 mg of soil per day and to drink 0.4 L of water per day. Consumption of food groups reported in EHD (1998).

8 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 per day (21 hours indoors, 3 hours outdoors), to ingest 30 mg of soil per day and to drink 0.4 L of water per day. Consumption of food groups reported in EHD (1998).

9 Concentrations of LCCP in ambient air in Canada or elsewhere were not identified.

10 Concentrations of LCCP in indoor air in Canada or elsewhere were not identified.

11 Concentrations of LCCP in Canadian drinking water were not identified. Intakes are based upon the limit of detection (0.5 µg/L) in a survey of drinking water in reservoirs in U.K. (Campbell and McConnell, 1980a).

12 Estimates of intake from food are based upon concentrations in foods that are selected to represent the food groups addressed in calculating exposure to Priority Substances (EHD, 1998):

Dairy: 0.19 µg/g; 1 sample of cheese in U.K.; $C_{20–30}$ (Campbell and McConnell, 1980a)
Fats: 0.05 µg/g; detection limit in analysis of 1 sample of lard in U.K.; $C_{20–30}$ (Campbell and McConnell, 1980a)
Fruits: 0.025 µg/g; 1 sample of peach fruit in U.K.; $C_{20–30}$ (Campbell and McConnell, 1980a)
Vegetables: 0.025 µg/g; 1 sample of potato crisps in U.K.; $C_{20–30}$ (Campbell and McConnell, 1980a)
Cereal products: 0.05 µg/g, detection limit in analysis of corn flakes in U.K. (Campbell and McConnell, 1980b)
Meat and poultry: 0.05 µg/g; detection limit in analysis of 1 sample each of ox liver and beef in U.K.; $C_{20–30}$ (Campbell and McConnell, 1980b)
Fish: no data identified
Eggs: no data identified
Foods primarily sugar: 0.05 µg/g; detection limit in analysis of 1 sample of strawberry jam in U.K.; $C_{20–30}$ (Campbell and McConnell, 1980b)
Mixed dishes: no data identified
Nuts and seeds: no data identified
Soft drinks, alcohol, coffee, tea: 0.05 µg/g; detection limit in analysis of 1 sample each of beer and tea in U.K.; $C_{20–30}$ (Campbell and McConnell, 1980b)

Amounts of foods consumed on a daily basis by each age group are described by Health Canada (EHD, 1998).

13 The value used for calculating intake from soil is the maximum concentration (3.2 µg/g) reported in a survey of sediment in the U.K. (Campbell and McConnell, 1980a).

[14] Medium-specific and total intakes were calculated on a Microsoft Excel spreadsheet. Only significant numbers have been presented, which accounts for seemingly inaccurate totals.

APPENDIX A: SEARCH STRATEGY — NEW INFORMATION FOR THE ASSESSMENT OF "TOXIC" TO HUMAN HEALTH UNDER PARAGRAPH 64(C) OF CEPA 1999

A comprehensive literature search was conducted (SCCP, up to February 2001; MCCP and LCCP, up to September 2000) of monitoring data in Canada (or elsewhere) and toxicological studies in animals and humans to identify critical new data for the assessment of human health risk under Paragraph 64(c) of CEPA 1999. To identify critical new exposure and toxicological data, a search was conducted in the following databases: CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Library of Medicine), Current Contents (Institute for Scientific Information), DART (Development and Reproductive Toxicology, Environmental Teratology Information Centre), GENE-TOX (Genetic Toxicology, Office of Toxic Substances, U.S. Environmental Protection Agency), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine), IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency), Medline (U.S. National Library of Medicine; 1994–2000), Toxline (U.S. National Library of Medicine; 1994–2000) and Toxline Plus — including BIOSIS (Biological Abstracts), CA (Chemical Abstracts, Chemical Abstracts Service), CIS (CIS Abstracts, International Labour Office), CRISP (Computer Retrieval of Information on Scientific Projects, National Institutes of Health), DART, EPIDEM (Epidemiology Information System, Toxicology Information Response Centre), FEDRIP (Federal Research in Progress, National Technical Information Service), HMTC (HMTC Abstracts Bulletin, Hazardous Material Technical Centre), IPA (International Pharmaceutical Abstracts, American Society of Hospital Pharmacists), NTIS (Government Reports Announcements and Index, National Technical Information Service), PESTAB (Pesticide Abstracts, U.S. Environmental Protection Agency), PPBIB (Poisonous Plants Bibliography), RISKLINE (Swedish National Chemicals Inspectorate), TOXBIB (Medline, National Library of Medicine) and TSCATS (Toxic Substances Control Act Test Submissions to U.S. Environmental Protection Agency). A search of the following web sites was also conducted (up to December 2000): Centers for Disease Control and Prevention (U.S. Department of Health and Human Services), Health Canada, National Pollutant Release Inventory, U.S. Consumer Product Safety Commission, U.S. Environmental Protection Agency and U.S. Food and Drug Administration.