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of Ministers

Human exposure to Legacy and Current- use Chlorinated Paraffins in Scandinavia

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Association between human biomonitoring and external exposures to SCCPs, MCCPs, and LCCPs in a Norwegian cohort

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This publication is also available online in a web-accessible version at <https://pub.norden.org/temanord2023-509>.

Foreword

Chlorinated paraffins (CPs) are popular industrial chemicals. As a group of global contaminants, their pollution has been ongoing for over 40 years. The magnitude of CP usage is enormous. At present, the annual production volume of CPs is approximately as high as the total cumulative historical production of polychlorinated biphenyls. SCCPs are newly defined as POPs, the use of which is restricted. Consequently, the use of the other CPs is expected to increase. The current-use MCCPs have been registered under the REACH Regulation and are included on the ECHA candidate list as PBT and vPvB substances¹ and on the EU endocrine disruptor candidates list as well as SCCPs². They have received global attention by both chemical and environmental agencies, and by the industries involved in producing or using CPs.

This project will comprehensively assess human exposure pathways for both legacy and current-use CPs in the Nordic countries. It will determine their presence using multiple biomonitoring approaches using the following matrices:

- Indoor air and personal air
- Settled dust and floor dust
- Duplicate diet
- Hand wipe
- Human plasma

and will answer how and to what extent they enter humans. The project will evaluate and compare human exposure to the legacy CPs versus the extensively used CPs. This will touch upon potential risks for the in-use CPs at an early stage before their presence in humans reaches levels of concern.

By delivering effective biomonitoring approaches for widespread and extensively used CPs within the Nordic countries, the project will benefit public health and associated regulators, as it can result in improved risk assessment of recent, current, and newly developed chemicals. Eventually, effective biomonitoring can lead to more sustainable approaches to the use of chemicals and enhancement of our ability to design strategies to reduce human exposure to chemicals.

The results will benefit public health and those tasked with regulating CPs, in particular chemical agencies and environment agencies. By identifying the relative importance of different exposure pathways to overall human exposure, the project will generate information useful to regulators to develop effective methods to reduce exposure.

The project will generate substantially enhanced scientific understanding of how humans are exposed to CPs used in consumer products, and how best to monitor this exposure. This knowledge will be highly valuable to regulatory authorities involved in exposure and risk assessment of these chemicals all over the world.

1. ECHA.
2. EC

Summary

In late 2017, a group of new POPs, short chain chlorinated paraffins (SCCPs), and replacement chlorinated paraffins (CPs) were found in both Norwegian and Swedish mothers' milk, and later in mothers' milk from over 50 countries across five continents. Only SCCPs have been regulated as POPs, while the majority of CPs are still currently produced and used in large quantities globally (c.a. 1 million metric tons per year). It is unclear to what extent human beings are exposed to chlorinated paraffins and from what exposure pathways. It is also unclear if the current-use CPs are safe alternatives to the legacy CPs.

A Norwegian cohort with 61 participants was recruited in 2013, with the purpose of comprehensive investigation of human exposure to a wide variety of consumer chemicals, which provided a rare opportunity of exploring human exposure to chlorinated paraffins and comparing with the other consumer chemical contaminants.

This project focused on a comprehensive understanding of body burden and multiple human exposure pathways to both legacy CPs and current-use CPs in the Norwegian cohort. The chemical body burden of CPs was determined in their plasma samples. Human inhalation, dust ingestion, dermal, and dietary exposures to CPs were assessed using exposure medium samples of indoor air, living room dust, hand wipe, and duplicate diet collected from each participant. Combining both internal and external information, we studied for the first time: (1) how much and to what extent people are exposed to the chemicals via different pathways, and (2) what the differences are between the legacy CPs and the current CPs in human exposure and accumulation. Eventually, the project will contribute to the development of approaches to use chemicals in consumer products in ways that minimize adverse health impacts.

Complex mixtures of CPs were found in the exposure media of the cohort. The CPs covered a wide range of paraffin carbon chain lengths from C_6 to C_{48} and thus consisted of the legacy SCCPs (C_{10-13}), current-use MCCPs (C_{14-17}) and LCCPs ($C_{>17}$), as well as very-short chain impurities (vSCCPs, C_{6-9}). The high detection frequencies of CPs in all the exposure media (>98%) suggested a ubiquitous human exposure. The concentrations of CPs in most cases were higher than other flame retardants in the exposure media. Nevertheless, the 95th percentile exposure for CPs did not exceed the reference dose. MCCPs were the most abundant CP category (contributing on average >56% of the total CP concentrations) in most exposure media except for air, in which SCCPs dominated (on average 82% of the CP concentrations).

CPs, from vSCCPs to LCCPs, were found in the human plasma of 86% of the cohort participants with a median concentration of 4200 ng/g lipid. The plasma concentrations of SCCPs were predicted well based on the external exposure data, while those MCCPs and LCCPs were underpredicted. Dietary exposure contributed the most to CP body burden in the cohort, accounting for a median of 60-88% of the total daily intakes. The contribution from dust ingestion and dermal exposure was greater for the intake of the current-use MCCPs and LCCPs than the legacy SCCPs. Some exposure sources were correlated to plasma levels of CPs, including residence construction parameters such as the construction year ($p < 0.05$).

1. Background

Chemical products bring benefits to society, but may emit to the environment during their lifecycle and possibly harm humans and ecosystems.³ Some organic chemicals are of particular environmental concern when they are persistent, bioaccumulative, toxic, and capable of transporting long distances to remote areas. To protect human health and the environment from these chemicals, the Stockholm Convention on Persistent Organic Pollutants (POPs) was adopted by the United Nations Environment Programme (UNEP) in 2001.

A list of 30 chemicals have been regulated under the Stockholm Convention.⁴ In 2017, short-chain chlorinated paraffins (SCCPs) were added to the list of POPs. SCCPs belong to a high-volume production and use industrial chemical category chlorinated paraffins (CPs). They are popular industrial chemicals used as plasticizers, as extreme-pressure additives in metal-machining fluids, as additives to paints, coatings and sealants, and as flame retardants.⁵ Globally, CP production is approximately 1.3 million metric tons per year currently, about 30% of which were SCCPs.⁶ The major share of global CP production has been from medium-chain chlorinated paraffins (MCCPs) and long-chain chlorinated paraffins (LCCPs). SCCPs, MCCPs, and LCCPs are produced in the form of complex mixtures of polychlorinated *n*-alkanes (chemical formula: $C_nH_{2n+2-m}Cl_m$; for selected chemical structures see Figure 1) with carbon chain lengths ranges of 10 – 13, 14 – 17, and > 17, respectively. Occasionally, CP products may contain impurities with very-short chain CPs (vSCCPs), the carbon chain lengths of which are shorter than 10. The chlorine number varies, and thus there are 600 – 700 CP homologues, each of which consist of CP molecules of the same numbers of carbons and chlorines. The estimated physical-chemical properties and bioavailability data are given Table 1.

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3. Wang, Z.; Walker, G. W.; Muir, D. C. G.; Nagatani-Yoshida, K.
 4. Fernandes, A.; Mortimer, D.; Rose, M.; Smith, F.; Steel, Z.; Panton, S.
 5. Cancer, I. A. f. R. o.
 6. Chen, C.; Chen, A.; Zhan, F.; Wania, F.; Zhang, S.; Li, L.; Liu, J.

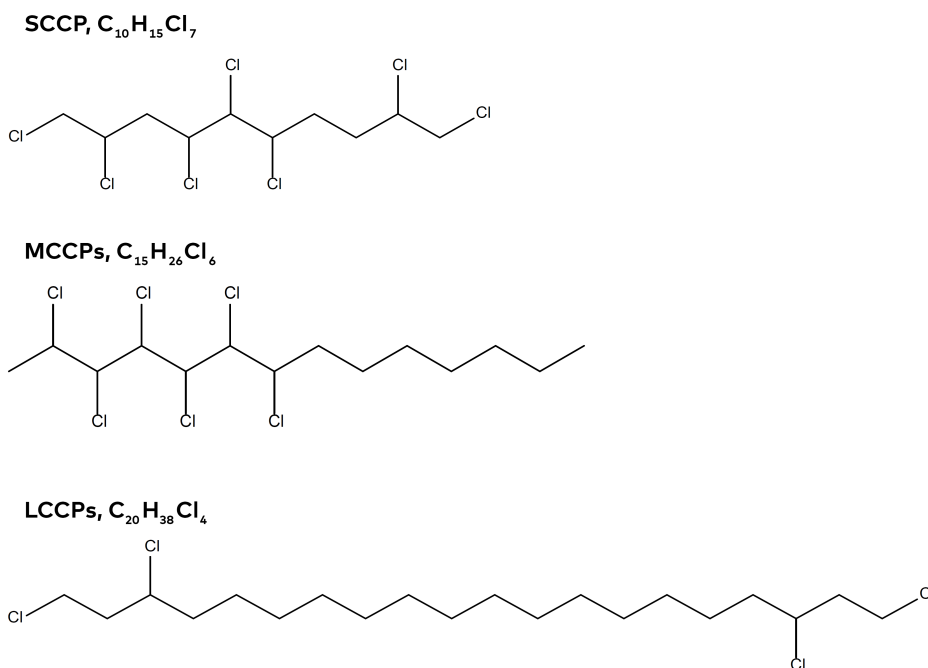


Figure 1. Selected chemical structures of three chlorinated paraffin isomers.

Due to the complexity of CPs, they are produced, used, studied, and regulated on the basis of mixtures, i.e., SCCPs, MCCPs, and LCCPs. SCCPs are legacy CPs, which are under regulation as POPs,⁷ while MCCPs and LCCPs are currently used in large quantities and are being considered for listing under the Stockholm Convention.⁸ So far, all the three CP classes have been found to be persistent^{9, 10}, bioaccumulative,^{11, 12, 13} and have long-range transport potential.¹⁴ They have been detected in multiple environmental matrices in different regions worldwide including Nordic countries.¹⁵ Developmental toxicity was shown to be a sensitive endpoint for the mammalian toxicity of CPs.¹⁶ Endocrine disruption effects have been found for all the three CP classes.^{17, 18}

Nordic countries were the earliest countries working on regulation of CPs. For example, emissions and discharges of SCCPs were reduced in Denmark as early as 1991, which was 26 years earlier before they were defined as global POPs in 2017. Following the ban of some formulations, alternative chemicals have been introduced in consumer products as replacements. There is a need to continue to take a long-term approach and work methodically to protect human health and the environment. The enormous production of the current-use CPs together with their POP-like properties have made them a regulatory top priority. At present Sweden is

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7. POPRC.
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 9. Yuan, B.; Brüchert, V.; Sobek, A.; de Wit, C. A.
 10. Zhang, C.; Chang, H.; Wang, H.; Zhu, Y.; Zhao, X.; He, Y.; Sun, F.; Wu, F.
 11. Yuan, B.; Vorkamp, K.; Roos, A. M.; Faxneld, S.; Sonne, C.; Garbus, S. E.; Lind, Y.; Eulaers, I.; Hellström, P.; Dietz, R.; et al.
 12. de Wit, C. A.; Bossi, R.; Dietz, R.; Dreyer, A.; Faxneld, S.; Garbus, S. E.; Hellström, P.; Koschorreck, J.; Lohmann, N.; Roos, A.
 13. Wang, H.; Chang, H.; Zhang, C.; Feng, C.; Wu, F.
 14. Yuan, B.; McLachlan, M. S.; Roos, A. M.; Simon, M.; Strid, A.; de Wit, C. A.
 15. Schlabach, M.; Røsrud Borgen, A.; Bæk, K.; Kringstad, A.
 16. Ali, T. E.; Legler, J.
 17. Ren, X.; Geng, N.; Zhang, H.; Wang, F.; Gong, Y.; Song, X.; Luo, Y.; Zhang, B.; Chen, J.
 18. Sprengel, J.; Behnisch, P. A.; Besselink, H.; Brouwer, A.; Vetter, W.

considering a regulatory initiative of its own within the European Union, namely nominating MCCPs for a ban under the RoHS-directive which regulates chemicals in electronics. Relevant regulation is also being pursued under REACH in Europe,¹⁹ in the United States,²⁰ and in Canada²¹. A comprehensive assessment on the current-use CPs is urgently needed for chemical regulation and contributes to the development of approaches to use chemicals in consumer products in ways that minimize adverse health impacts.

Table 1. Estimated physical-chemical properties and bioavailability data of CPs.

	Example molecular weight	Log KOW	Log KOA	Bioavailability data	Estimated absorption fraction	Estimated half-life (year)
vSCCPs	335 (C ₉ H ₁₄ Cl ₆)	5.99 ²²	7.24 ²²	–	0.33	–
SCCPs	363 (C ₁₁ H ₁₈ Cl ₆)	4.10-8.67 ²³	9-11 ²⁴	0.21 ²⁵	–	5.1 ²⁶
MCCPs	405 (C ₁₄ H ₂₄ Cl ₆) 516 (C ₁₇ H ₂₈ Cl ₈)	5.56-8.38 ²³	11-15 ²⁴	0.079 ²⁵	–	1.2 ²⁶
LCCPs	461 (C ₁₈ H ₃₂ Cl ₆) 545 (C ₂₄ H ₄₄ Cl ₆) 713 (C ₃₆ H ₆₈ Cl ₆)	6.58-11.34 ²³	–	–	0.03*	0.6 ²⁶

* predicted on the basis of the regression model²⁵ that the bioaccessibility of homologue C₁₈Cl₇ was ~33% of C₁₄Cl₇.

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CPs have been found to be the dominant flame retardants in indoor environments. These chemicals can be absorbed by human skin, accumulate in the dust we inhale, or attach to the food we eat. They resist degradation and accumulate in the bodies of human beings. In recent years, CPs have been detected in mothers' milk from several countries worldwide.^{27 28} Their levels in human milk of Scandinavian mothers have been found to exceed several legacy POPs such as PCBs and PBDEs. To minimize adverse health impacts, it is essential to understand how and to what extent humans are exposed to these chemicals.

Such an assessment requires highly developed interdisciplinary teams and collaborative work groups, which is usually beyond the national level. This was achieved in an EU project, Advanced Tools for Exposure Assessment and Biomonitoring (ATEAM). Human dietary, hand-to-mouth/dermal, dust and inhalation exposures for a wide variety of consumer chemicals were characterized and compared to internal concentrations from biomonitoring samples in a Norwegian cohort with 61 participants. However, human exposure to CPs was not included as the analysis of CPs was technically too challenging at the beginning of the project in 2013. To date, human exposure pathways for CPs are still unclear.

In this project, we comprehensively assessed body burden and multiple human

19. ECHA

20. USEPA

21. Canada, E. a. C. C.

22. Xia, D.; Gao, L.; Zheng, M.; Sun, Y.; Qiao, L.; Huang, H.; Zhang, H.; Fu, J.; Wu, Y.; Li, J.; et al

23. Hilger, B.; Fromme, H.; Volk, W.; Coelhan, M.

24. Muir, D.; Stern, G.; Tomy, G.

25. Du, X.; Zhou, Y.; Li, J.; Wu, Y.; Zheng, Z.; Yin, G.; Qiu, Y.; Zhao, J.; Yuan, G.

26. Dong, Z.; Li, T.; Wan, Y.; Sun, Y.; Hu, J.

27. Zhou, Y.; Yuan, B.; Nyberg, E.; Yin, G.; Bignert, A.; Glynn, A.; Odland, J. Ø.; Qiu, Y.; Sun, Y.; Wu, Y.; et al.

28. Krätschmer, K.; Malisch, R.; Vetter, W.

exposure pathways to both legacy (SCCPs) and current-use CPs (MCCPs and LCCPs) in a Norwegian cohort. The cohort consists of 61 adult participants who were recruited in ATEAM from Oslo in 2013. CPs in their plasma samples were measured to determine the chemical body burden. Samples of indoor air, living room dust, hand wipe, and duplicate diet were collected from each participant and used for assessing inhalation, dust ingestion, dermal, and dietary exposures to CPs. In each sample, a total number of up to 675 CP homologues were analyzed. The main aims are to explore (1) how much and to what extent people are exposed to the chemicals, and (2) what are the differences between the legacy CPs and the current CPs in human exposure and accumulation.

2. Methods

2.1 Sampling

A cohort of 61 participants were recruited in Oslo, Norway, between November 2013 and April 2014.²⁹ The recruited participants were the staff of the Norwegian Institute of Public Health (NIPH). Duplicate dietary, hand-to-mouth/dermal, dust and inhalation exposures for a wide variety of consumer chemicals had been characterized and compared to internal concentrations from biomonitoring samples in the cohort. The participants consist of 45 females and 16 males aging between 20 and 66.

Table 2. Overview of samples analyzed for CPs in the Norwegian cohort study.

Exposure pathways	Sample type	Sample size*
Dietary exposure	Duplicate diet	59
Dermal exposure	Hand wipe	60
Dust ingestion exposure	Settled dust	61
	Floor dust	5
Inhalation exposure	Stationary air	61
	Personal air	13
Internal exposure	Human plasma	59

* Plasma samples from 59 out of the 61 participants and personal air samples from 13 out of the 61 participants were available for this study; the diet samples from 2 out of the 61 participants had been used up in the previous tasks of the cohort study; one hand wipe sample was lost in the analytical process.

An overview of samples that were included in this study is shown in Table 2. Duplicate diet was collected and used for assessing dietary exposure. Participants collected weighed duplicate food portions prepared as for consumption over 2 consecutive days. Hand wipe samples were collected for assessing dermal exposure. The participants were advised to avoid hand washing for at least 60 min before the collection of the hand wipes. Each participant wiped the palm and the back from wrist to fingertips using two sterile gauze pads (3 in. × 3 in., Swift First Aid Inc., Valencia, CA), one for each hand. Two wipes were stored together as one sample. Stationary air was collected for 24 h using a low-volume active air pump (Leland Legacy, SKC Inc., Eighty Four, PA) with the sampling train containing two polyurethane foam (PUF) plugs and one glass fiber filter (GFF). The sampling volume was approximate 17 m³ per sample. Personal air was collected for 24 h with a low-volume active air pump (SKC pump 224-PCMTX4, SKC Inc., Eighty Four, PA) with one sampling train containing two PUF plugs and a GFF. The sampling volume of air

29. Papadopoulou, E.; Padilla-Sanchez, J. A.; Collins, C. D.; Cousins, I. T.; Covaci, A.; de Wit, C. A.; Leonards, P. E. G.; Voorspoels, S.; Thomsen, C.; Harrad, S.; et al.

was c.a. 1.4 m³ per participant. Thirteen personal air samples were available for the present CP study, as the other personal air samples went to studies of other consumer chemicals elsewhere. Settled dust was collected from all elevated surfaces at least 0.5 m above the floor such as tables, bookshelves, windowsills, while floor dust was collected from the entire floor surface of the living room. A venous blood sample was collected from each participant by a research nurse at the NIPH during a scheduled appointment. Whole blood was collected in 10 mL plastic BD Vacutainer® whole blood tube with EDTA, to provide whole blood and plasma. Whole blood was centrifuged at 2200–2500 rpm and plasma was transferred to a 10 mL tube.

The participants also answered a questionnaire regarding the characteristics of their diet frequency, home, such as information on building and consumer goods. Each participant completed a questionnaire regarding her or his age, gender, weight and height, type and number of home appliances, and other characteristics of the indoor home environment.

2.2 Chemical analysis

A method overview is shown in Figure 2. Each matrix was prepared following respective methods. Afterwards, an ultra-high-resolution mass spectrometer (HRMS) was used for sample analysis. Quantification of CPs were on a mixture basis, i.e., the concentrations of CPs were reported in the form of total concentration of vSCCPs, SCCPs, MCCPs, or LCCPs.

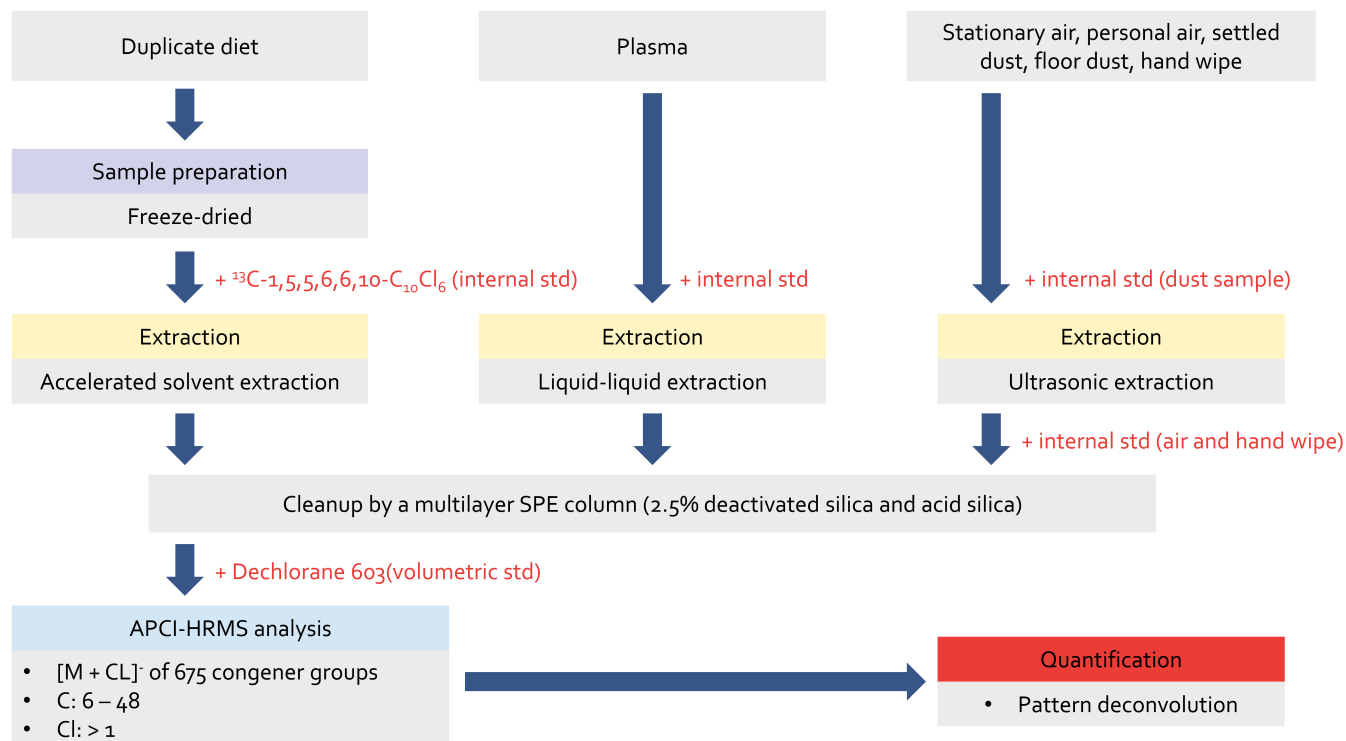


Figure 2. Method overview of chlorinated paraffin analysis.

2.2.1 Sample treatment: diet

Sample treatment of food samples was adopted from Yuan et al. (2017)³⁰. The duplicate diet samples of two consecutive days were first mixed based on the food portions. Then the samples were freeze-dried, and the water content of the sample was determined gravimetrically after freeze-drying. About 2 – 3 grams sample was spiked with $^{13}\text{C}_{10}$ -1,5,5,6,6,10-hexachlorodecane ($^{13}\text{C}_{10}$ -HCD, Cambridge Isotope Laboratories, Andover, MA) as the internal standard and extracted using accelerated solvent extraction (ASE 300; Dionex Europe, Leeds, UK). The extract was gently nitrogen-blow dried, and the lipid content was determined gravimetrically. Crude extracts were then cleaned-up on a multilayer SPE column. The eluent was reconstituted in dichloromethane with 20 ng of Dechlorane-603 (Occidental Chemical Corp.) used as volumetric standard.

2.2.2 Sample treatment: hand wipe

The extraction and cleanup methods were introduced in previous studies.^{31,32} In brief, hand wipe samples were ultrasonic extracted three times with 8 mL of a mixture of hexane and acetone (1:1, v:v). The extracts were reanalyzed for CPs. The extract was spiked with 10 ng of $^{13}\text{C}_{10}$ -HCD and then cleaned up on a multilayer SPE column. Twenty nanograms of Dechlorane 603 (Occidental Chemical Corp.) was added to the eluent as the volumetric standard before instrumental analysis.

2.2.3 Sample treatment: stationary air and personal air

Stationary air and personal air samples were ultrasonic extracted twice with dichloromethane (DCM) for 30 min. The extracts were spiked with 10 ng of $^{13}\text{C}_{10}$ -HCD and then cleaned-up on a multilayer SPE column. The eluents of air samples were reconstituted in ~40 μL acetone. Twenty ng of Dechlorane 603 was added into the eluent as volumetric standard.

2.2.4 Sample treatment: settled dust and floor dust

About 50 mg dust sample was spiked with 10 ng of $^{13}\text{C}_{10}$ -HCD and ultrasonic extracted twice with dichloromethane (DCM) for 30 min. The extracts were cleaned-up on a multilayer SPE column. The eluents of dust samples were reconstituted in ~300 μL acetone. The volumetric standard Dechlorane 603 was added into the eluent as before instrumental analysis.

2.2.5 Sample treatment: plasma

The internal standard $^{13}\text{C}_{10}$ -HCD was added to samples of 1 – 2 g human plasma. The samples were extracted with a mixture of 2-propanol, *n*-hexane, and MTBE according to the modified Jensen II extraction.^{33,34} The plasma extract was then cleaned with a solution of potassium chloride. The aqueous phase was re-extracted

30. Yuan, B.; Strid, A.; Darnerud, P. O.; de Wit, C. A.; Nyström, J.; Bergman, Å.

31. Tay, J. H.; Sellström, U.; Papadopoulou, E.; Padilla-Sánchez, J. A.; Haug, L. S.; de Wit, C. A.

32. Yuan, B.; Benskin, J. P.; Chen, C.-E. L.; Bergman, Å.

33. Jensen, S.; Häggberg, L.; Jörundsdóttir, H.; Odham, G.

34. Sahlström, L. M. O.; Sellström, U.; de Wit, C. A.; Lignell, S.; Darnerud, P. O.

with *n*-hexane and the combined organic phases were evaporated to dryness in beakers. The lipid content was determined gravimetrically. The lipids were dissolved in isooctane and treated with a multilayer SPE column. The elute was collected, spiked with Dechlorane 603, and condensed for the analysis of CPs.

2.2.6 Instrument method

All the samples were analyzed using an Ultra-High-Performance Liquid Chromatograph (UPLC) with Quadrupole-Orbitrap ultra-high resolution mass spectrometer (Orbitrap-MS) except for the hand wipe samples, which were analyzed using direct-injection Orbitrap-MS. The ion source was atmospheric-pressure chemical ionization (APCI) enhanced with chloride anion.

Table 3. CP reference mixture list.

Category	Product	Manufacturer	Country	Ingredients*
SCCPs	C ₁₀ 50.18%Cl	Ehrenstorfer GmbH	Germany	C ₁₀ 50.18% Cl
	C ₁₀ 55.00%Cl	Ehrenstorfer GmbH	Germany	C ₁₀ 55.00% Cl
	C ₁₀ 60.09%Cl	Ehrenstorfer GmbH	Germany	C ₁₀ 60.09% Cl
	C ₁₁ 50.21%Cl	Ehrenstorfer GmbH	Germany	C ₁₁ 50.21% Cl
	Witaclor 149	Dynamit Nobel AG	Germany	C ₁₀₋₁₃ 49% Cl
	SCCP 51.5%Cl	Ehrenstorfer GmbH	Germany	C ₁₀₋₁₃ 51.5% Cl
	SCCP 55.5%Cl	Ehrenstorfer GmbH	Germany	C ₁₀₋₁₃ 55.5% Cl
	SCCP 63.0%Cl	Ehrenstorfer GmbH	Germany	C ₁₀₋₁₃ 63.0% Cl
	Hüls 70C	Hüls AG	Germany	C ₁₀₋₁₃ 70% Cl
MCCPs	MCCP 42.0%Cl	Ehrenstorfer GmbH	Germany	C ₁₄₋₁₇ 42.0% Cl
	MCCP 52.0%Cl	Ehrenstorfer GmbH	Germany	C ₁₄₋₁₇ 52.0% Cl
	MCCP 57.0%Cl	Ehrenstorfer GmbH	Germany	C ₁₄₋₁₇ 57.0% Cl
	Cloparin 49st	Caffaro	Italy	C ₁₄₋₁₇ 49% Cl
	Cloparin 50	Caffaro	Italy	C ₁₄₋₁₇ 50% Cl
	Cereclor S52	INEOS Chlor Ltd.	UK	C ₁₄₋₁₇ 52% Cl
LCCPs	Hüls 40N	Hüls AG	Germany	C ₁₈₋₂₆ 40% Cl
	Witaclor 549	Dynamit Nobel AG	Germany	C ₁₈₋₂₅ 49% Cl
	Uniclor40	Neville Chemical Co	USA	C ₂₂₋₂₇ 40% Cl
	LCCP 36.0%Cl	Ehrenstorfer GmbH	Germany	C ₁₈₋₂₀ 36.0% Cl
	LCCP 49.0%Cl	Ehrenstorfer GmbH	Germany	C ₁₈₋₂₀ 49.0% Cl
Unknown	CP-52	Unknown	China	C ₆₋₂₉ 52% Cl†

* specifications from the manufacturer.

† determined using an APCI-QTOF; not specified by the manufacturer.

The UPLC-APCI-Orbitrap-HRMS (Q Exactive, Thermo Fisher Scientific, San Jose, USA) was operated in full-scan mode (m/z 250–2000) with a resolution of 120 000 full width at half-maximum (FWHM).³⁵ An ACQUITY UPLC BEH C18 column (1.7 μ m, 2.1 $\times$ 50 mm², Waters, Manchester, U.K.) was maintained at 40 °C. Three μ L of sample solution was injected, and the flow rate was 0.4 mL/min. The mobile phases were water (A) and methanol (B). The gradient elution started from 10% B for 0.5 min, ramped to 100% by 2.5 min, held for 2.5 min, ramped to 10% by 5.1 min, and finally held for 1 min. Dichloromethane (DCM) was introduced using a syringe pump into the mobile phase using a T-connector between the UPLC column and the ion source. The MS instrumental settings were optimized using a SCCP mixture (51.5% Cl) and a LCCP mixture (Witacolor 549) as follows: DCM flow rate 0.028 mL/min, capillary temperature 250 °C, auxiliary (Aux) gas heater temperature 250 °C, spray current 5.7 μ A, maximum IT (ion time) 250 ms, automatic gain control (AGC) target 5e6, sheath gas flow rate 17 arbs, and Aux gas flow rate 1 arb.

The direct injection method APCI-Orbitrap-HRMS was operated in full-scan mode (m/z 250–2000) with a resolution of 120 000 FWHM. The instrumental settings were optimized as follows: injection volume 3 μ L, mobile phase flow rate 0.100 mL/min, DCM flow rate 0.010 mL/min, capillary temperature 250 °C, Aux gas heater temperature 250 °C, spray current 5.7 μ A, maximum IT (ion time) 250 ms, AGC target 5e6, sheath gas flow rate 17 arbs, and Aux gas flow rate 1 arb.

2.2.7 Quantification

Detailed quantification methods were introduced in Du et al. (2020)³⁶. S/M/LCCPs in the samples were quantified using a C_nCl_m -profile deconvolution method³⁷ with 9 SCCP, 7 MCCP, and 5 LCCP reference mixtures, respectively (Table 3). The C_nCl_m -profile of each sample was linearly superimposed using the reference mixtures, and the response factors of the deconvolved/superimposed reference mixtures were used for quantifying the CP mixtures in the samples. The concentrations of SCCPs were quantified based on a Chinese CP mixture (CP-52).³⁸

2.2.8 QA/QC

The resolution of MS was 120,000 FWHM to resolve C_nCl_m from the mass interference of the other homologues³⁹ and unsaturated CPs⁴⁰. The single-chain-length standards (Table 3) were used to improve the performance of profile deconvolution, which was evaluated with the goodness-of-fit R^2 between the measured C_nCl_m profile and the deconvolved one. Quantification of S/M/LCCPs of most samples fulfilled the criterion of $R^2 \geq 0.50$, while those results with $R^2 < 0.5$ were reported as tentative values.⁴¹ For quantification of vSCCPs, the median R^2 in all matrices were above 0.50. The mean recoveries of ¹³C-labeled CP internal standard (¹³C₁₀-HCD) in individual matrix categories were all higher than 75%.

Sampling tools, containers, and glasswares were carefully pre-washed and rinsed using ultrapure solvents, and for those which are high temperature resistance, heat-

35. uan, B.; Tay, J. H.; Padilla-Sánchez, J. A.; Papadopoulou, E.; Haug, L. S.; de Wit, C. A.

36. Du, X.; Yuan, B.; Zhou, Y.; de Wit, C. A.; Zheng, Z.; Yin, G.

37. Bogdal, C.; Alsberg, T.; Diefenbacher, P. S.; MacLeod, M.; Berger, U.

38. Zhou, Y.; de Wit, C. A.; Yin, G.; Du, X.; Yuan, B.

39. Yuan, B.; Alsberg, T.; Bogdal, C.; MacLeod, M.; Berger, U.; Gao, W.; Wang, Y.; de Wit, C. A.

40. Schinkel, L.; Lehner, S.; Heeb, N. V.; Marchand, P.; Cariou, R.; McNeill, K.; Bogdal, C.

41. randsma, S. H.; van Mourik, L.; O'Brien, J. W.; Eaglesham, G.; Leonards, P. E. G.; de Boer, J.; Gallen, C.; Mueller, J.; Gaus, C.; Bogdal, C.

cleaning in a furnace at 450 °C for 24 h before use. Field blanks were collected and analyzed together with the samples. Method detection limits (MDLs) were defined as mean field blank values plus 3 times the standard deviation (SD).

2.3 Exposure calculation

The external exposure pathways were assessed based on the respective equations adopted from the U.S. EPA Exposure Handbook.⁴²

2.3.1 Dietary exposure calculation

The diet samples were duplicates of everything that was consumed by the participants over a 24-h period. The body weight (BW, kg) of the individual participants were used for dietary assessment. The total intake of CPs was calculated using the concentrations times the weight of duplicate diet in 24-h period. The dietary exposure was reported in the unit of ng/kg BW/day(d).

2.3.2 Dermal exposure calculation

Hand skin surface area (SA, cm²) was first estimated using an equation adopted from the U.S. EPA Exposure Handbook⁴³ based on BW (kg) and height (cm) of the participants:

$$SA = a \times BW^b \times height^c \quad (1)$$

where a, b, and c are gender-specific constants (Table 4).⁴⁴

Table 4. Gender-specific constants used for the estimation of hand surface area.

	a	b	c
male	0.0257	0.573	-0.128
female	0.0131	0.412	0.0274

(Source: U.S. EPA Exposure Factors Handbook⁴⁴)

Dermal exposure to CPs via hand contact (ng/kg bw/d) was then estimated for each participant:

$$Dermal\ exposure = \frac{C_h \times SA \times AF \times ED \times EF}{BW} \quad (2)$$

42. USEPA

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where C_{hw} (ng/cm²) is the surface-area normalized mass of CPs in hand wipes, AF is the absorption fraction (unitless) and is referred to the values in Table 1, ED is the exposure duration of 24 h, EF is the exposure frequency and is assumed to be 1 event/day.

2.3.3 Inhalation exposure calculation

The calculation of daily intake [ng/kg BW/d] was performed individually for each participant according to eq 3 from the U.S. EPA *Exposure Factors Handbook*.⁴⁵

$$inhalation \ exposure = \frac{C_{air} \times IR \times ED \times AF_{inhalation}}{BW} \quad (3)$$

where C_{air} is the concentration of CPs in air (ng/m³). IR is the inhalation rate (m³/day) which was assigned on the basis of body weight (BW, range: 52 – 125 kg), gender, and age of each participant (Table 5) according to the U.S. EPA *Exposure Factors Handbook*.⁴⁶ Here, the assigned IRs ranged from 11.93 to 20.39 m³/day. ED is the exposure duration and is given as a time fraction of 24 h. When assessing exposure via stationary air, the ED is calculated based on average hours spent indoors per day, the range of which is 18 – 23.8 h as assessed by questionnaires, which ranges from 0.75 to 0.99. When assessing exposure using personal air, the ED is 24 h/24 h = 1. $AF_{inhalation}$ is the absorption fraction of inhalation (assumed to be 100% bioavailable).

Table 5. Inhalation rate used for exposure assessment.

Inhalation rate (m ³ /d)				
Age	Female		Male	
	normal weight	overweight	normal weight	overweight
18.1-40.1	13.37	15.66	17.41	20.39
40.1-70.1	11.93	13.01	15.60	17.96

Source: Table 6-6 in U.S. EPA *Exposure Factors Handbook*;⁴⁴

Normal weight: body mass index (BMI) between 18.5 and 24.9;

Overweight: BMI between 25 and 29.9 (Source: U.S. Department of Health & Human Services; see: https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm).

2.3.4 Dust ingestion exposure calculation

The calculation of daily intake [ng/kg body weight (bw)/d] was performed individually for each participant according to eq 4 from the U.S. EPA *Exposure Factors Handbook*.⁴⁷

$$dust \ ingestion \ exposure = \frac{C_{dust} \times DI \times AF_{ingestion}}{BW} \quad (4)$$

where C_{dust} is the concentrations of CPs in dust (ng/g). $AF_{ingestion}$ is the absorption

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fraction of ingestion (Table 1). DI is the mean daily dust intake, which is empirically set as 30 mg/d for adults⁴⁸. $AF_{\text{ingestion}}$ values were estimated to be 33%, 21%, 7.9%, and 3% bioavailable for vSCCPs, SCCPs, MCCPs, and LCCPs, respectively.

2.3.5 Estimation of plasma concentrations from intake data

A simple one-compartment, first order PK model⁴⁹ was applied to calculate the mass of CPs in the lipids based on the intake values from all the above external exposure pathways. The steady state condition is assumed using the model, which is an inherent uncertainty with this approach.⁵⁰

$$\text{estimated plasma concentration} = \frac{I_{CPS} \times AF_{CPS}}{BL \times K_{CPS}} \quad (5)$$

where the unit of estimated plasma concentration is ng/g lipid; I_{CPS} is the daily intake of CPs (ng/d); AF_{CPS} is the absorption fraction (Table 1, and the inhalation fraction was assumed to be 100% bioavailable). The term $I_{CPS} \times AF_{CPS}$ was the total daily exposure (ng/kg bw/d) to CPs for the Norwegian cohort calculated as the sum of exposure through inhalation, dust ingestion, diet, and dermal uptake estimated above $\times$ body weight (kg) since AF_{CPS} was included in the calculations. BL is the body lipid mass estimated from each individual participant's height and body weight (g) using eq 6:

$$\text{Adult body fat (\%)} = (1.20 \times BMI) + (0.23 \times Age) - (10.8 \times sex) - 5.4 \quad (6)$$

where Body mass index (BMI) for each participant was calculated based on height and weight provided during questionnaires, sex is 1 for males and 0 for females, the source of which is BMI Calories (<http://bmi-calories.com/body-fat-percentage-calculator.html>). k_{CPS} is the compound specific first order dissipation rate (day^{-1}), which was calculated as $0.693/t_{0.5}$, where $t_{0.5}$ is the half-life of CPs in the body lipid compartment (Table 1).

2.4 Statistical analysis

Masses below the MDL were replaced with $MDL/\sqrt{2}$. The distribution of CPs in the samples of each matrix was highly skewed. Therefore, the Mann-Whitney U and Kruskal-Wallis tests were used to explore differences between CP amounts in samples (with >75% detection frequency) and categorical indoor environment variables, while the Spearman's rank correlation was used for continuous variables. The level of significance was set to $p=0.05$.

48. USEPA

49. Lorber, M.

50. Tay, J. H.; Sellström, U.; Papadopoulou, E.; Padilla-Sánchez, J. A.; Haug, L. S.; de Wit, C. A.

3. Results

3.1 CPs in food and dietary exposure

Concentrations of CPs were above the MDLs in 98% of the diet samples (Table 6). MCCPs were the dominant CPs in the food samples. The mean proportion of MCCPs were 64% of the total concentrations of CPs, followed by SCCPs (29%) and LCCPs (5%).

Table 6. CP levels and detection frequencies in duplicate diets (unit: ng/g lipid).

CP category	vSCCPs	SCCPs	MCCPs	LCCPs
median	3.7	58	130	11
max	18	240	400	170
Detection Frequency (DF)	58%	98%	98%	92%

The dietary exposure to CPs in the Norwegian cohort (Table 7) was assessed using the concentrations of CPs in the food items. The median exposure levels of SCCPs (42 ng/kg BW/d), MCCPs (96 ng/kg BW/d), and LCCPs (8.5 ng/kg BW/d) were generally comparable to the other European countries such as Germany. The mean dietary intake of SCCPs and MCCPs in 2018–2019 based on ready-made meals were 57 ng/kg BW/d and 35 ng/kg BW/d, respectively.⁵¹ The mean dietary intake levels of SCCPs, MCCPs, and LCCPs in Sweden in 2015 based on a market basket study⁵² were 18 ng/kg BW/d, 39 ng/g BW/d, and 2 ng/kg BW/d, respectively, which was lower than the results in the Norwegian cohort. The dietary exposure to CPs in the Norwegian cohort is about one to two orders of magnitude lower than those in China. For example, the mean dietary intake of SCCPs and MCCPs in nine provinces in China in 2017–2018 based on a total diet study⁵³ ranged 260–1300 ng/kg BW/d and 190–940 ng/kg BW/d, respectively.

Table 7. Dietary exposure to CPs in the Norwegian cohort (unit: ng/kg BW/d).

CP category	vSCCPs	SCCPs	MCCPs	LCCPs
5 th percentile	N.A.	14	36	2.3
50 th percentile	2.9	42	96	8.5
95 th percentile	8.8	120	250	38

51. rätschmer, K.; Schächtele, A.; Vetter, W.

52. Yuan, B.; Strid, A.; Darnerud, P. O.; de Wit, C. A.; Nyström, J.; Bergman, Å.

53. Cui, L.; Gao, L.; Zheng, M.; Li, J.; Zhang, L.; Wu, Y.; Qiao, L.; Xu, C.; Wang, K.; Huang, D.

3.2 CPs in hand wipe and dermal exposure

Complex mixtures of vSCCPs, SCCPs, MCCPs, and LCCPs were found in hand wipes of the participants in the Norwegian cohort. The highest concentration of total CPs was 18,000 ng per participant (Table 8). The most abundant CP class was MCCPs (mean 58% of the total concentration), followed by LCCPs (22%) and SCCPs (20%). The dermal exposure to CPs was assessed based on the hand wipe data (Table 8). This is so far the first and currently the only assessment of dermal exposure to CPs using hand wipes, and thus no comparison with other studies is made here.

Table 8. Descriptive statistics for CPs measured in hand wipe samples (n = 60) and estimated daily dermal exposure to CPs for adults based on these data.

CP category	vSCCPs	SCCPs	MCCPs	LCCPs	sumCP
DF	40%	97%	100%	100%	
Mass (ng/participant)					
geometric mean	<0.70	170	490	150	870
median	<0.70	160	490	150	950
range	<0.70-13	22-2400	33-7400	10-8500	43-18000
Mass per hand surface area (pg/cm²)					
geometric mean	<0.53	160	460	150	830
median	<0.53	160	520	120	830
range	0.16-17	11-3400	16-11000	7.4-12000	35-26000
Chlorine content (w/w)					
geometric mean	63% Cl	58% Cl	52% Cl	46% Cl	51% Cl
median	63% Cl	58% Cl	52% Cl	46% Cl	51% Cl
range	59-65% Cl	56-60% Cl	47-55% Cl	40-52% Cl	40-56% Cl
Estimated daily dermal exposure (ng/kg bw/d)					
5 th percentile	N.A.	0.12	0.55	0.038	0.71
50 th percentile	N.A.	0.62	2.4	0.3	3.8
95 th percentile	0.045	3.6	11	5.5	17

3.3 CPs in indoor air and inhalation exposure

The vSCCPs and SCCPs were detected in all the air samples, both the stationary indoor air and the personal air samples (Table 9). The concentrations of vSCCPs, SCCPs, MCCPs, and LCCPs were significantly higher in personal air (medians of 2.1, 33, 4.5, and 0.58 ng/m³, respectively) compared to the corresponding stationary air samples (medians of 0.46, 11, 2.0, and 0.020 ng/m³, respectively) (Wilcoxon signed rank test, $p < 0.05$). One possible reason could be due to high levels of CPs in office and other indoor environment, the air of which were collected by personal air sampler but not by stationary air sampler at home. Another possible reason could be personal cloud effect.⁵⁴ The semi volatile organic pollutants tend to partition to particles and can be resuspended to a higher degree by human activities, which thus may contribute to higher concentrations of CPs near the body.

Most results of CPs in indoor air worldwide are from China. The concentrations were summarized in Yuan et al. (2021).⁵⁵ The mean concentration of vSCCPs in the Norwegian cohort (0.37 ng/m³) was lower than that found in indoor air from Beijing, China (C₉ CPs only, 47.4 ng/m³). The mean SCCP concentration (8.9 ng/m³) was lower than that found in China, the means of which ranges 13.4–368 ng/m³. Means of MCCPs (1.4 ng/m³) were also lower than reported MCCPs, the means of which ranges 3.36 and 30.9 ng/m³ in China. To date, there is a lack of data for LCCP concentrations in indoor air. Therefore, no comparison was made here.

Table 9. Descriptive Statistics for CPs Measured in Stationary Air and Personal Air Samples.

CP category	vSCCPs	SCCPs	MCCPs	LCCPs	sumCP
Stationary air concentration (ng/m³, n = 61)					
geometric mean	0.37	8.9	1.4	0.031	11
median	0.42	9.6	1.2	0.020	13
range	0.044–7.1	1.7–54	<0.35–13	<0.0063–1.1	2.0–61
chlorine content	60% Cl	55% Cl	48% Cl	45% Cl	52% Cl
DF	100%	100%	95%	79%	100%
Personal air concentration (ng/m³, n = 13)					
geometric mean	2.2	38	6.7	0.58	50
median	2.1	33	4.5	0.58	50
range	0.37–11	8.3–97	<1.8–59	<0.087–4.1	10–170
chlorine content	59% Cl	54% Cl	48% Cl	43% Cl	52% Cl
DF	100%	100%	92%	85%	100%

54. Allen, J. G.; McClean, M. D.; Stapleton, H. M.; Nelson, J. W.; Webster, T. F.

55. Yuan, B.; Tay, J. H.; Padilla-Sánchez, J. A.; Papadopoulou, E.; Haug, L. S.; de Wit, C. A.

Inhalation exposure to CPs was assessed based on stationary air and personal air results (Table 10). The inhalation exposure was a significant pathway for relative volatile CP classes, in particular SCCPs. The median inhalation intake of SCCPs contributes to 81% and 84% of the total CP intake via inhalation based on stationary air results and personal air results, respectively. The inhalation exposure was the least significant for LCCPs, which contributed about 1% of the total CP intake via inhalation in both cases.

Table 10. Estimated Daily Inhalation Exposure to CPs for Adults Based on Stationary Air and Personal Air Data, respectively.

CP category	vSCCPs	SCCPs	MCCPs	LCCPs	sumCP
Estimated Air Inhalation Exposure for Adults (ng/kg bw/d, stationary air, n = 61)					
5P	0.0094	0.36	0.075	not available	0.43
median	0.073	1.6	0.23	0.0046	2.0
95P	0.41	6.8	1.1	0.078	7.6
Estimated Air Inhalation Exposure for Adults (ng/kg bw/d, personal air, n = 13)					
5 th percentile	0.090	2.4	not available	not available	3.3
50 th percentile	0.46	8.8	1.1	0.12	13
95 th percentile	2.2	21	7.2	0.65	30

3.4 CPs in indoor dust and ingestion exposure

All CP classes except for vSCCPs were detected in all of the 61 settled indoor dust samples (Table 11). The total CP concentrations ranged from 4.7 to 1400 µg/g dust. Mean percentage compositions were 0.052%, 19%, 56%, and 25% for vSCCPs, SCCPs, MCCPs, and LCCPs, respectively. Concentrations of SCCPs, MCCPs, and LCCPs in house dust from international studies are summarized in Yuan et al. (2021).⁵⁶ Since this is the first study including the concentrations of vSCCPs, there is no data to compare with. The median concentration of SCCPs (5.8 µg/g) found in the Norwegian cohort was comparable to those in house dust samples from 13 cities in Canada between 2007 and 2010 (6.2 µg/g) and Munich, Germany (6.0 µg/g),^{57,58} and lower than from Beijing, China (98.7 µg/g), and Pretoria, South Africa (16 µg/g). The median concentration of MCCPs (21 µg/g) in the present study was comparable with those from the 13 Canadian cities (19 µg/g) (67) and lower than from Beijing in 2014–2015 (89.8 µg/g),⁵⁹ Munich (176 µg/g),⁶⁰ and Pretoria, South Africa in 2018 (46 µg/g).⁶¹ The median concentration of LCCPs in the Norwegian cohort (8.1 µg/g) was lower than from Pretoria, South Africa in 2018 (11 µg/g).⁶²

56. Yuan, B.; Tay, J. H.; Padilla-Sánchez, J. A.; Papadopoulou, E.; Haug, L. S.; de Wit, C. A.

57. Shang, H.; Fan, X.; Kubwabo, C.; Rasmussen, P. E.

58. Hilger, B.; Fromme, H.; Völkel, W.; Coelhan, M.

59. ao, W.; Cao, D.; Wang, Y.; Wu, J.; Wang, Y.; Wang, Y.; Jiang, G.

60. Hilger, B.; Fromme, H.; Völkel, W.; Coelhan, M.

61. Brits, M.; de Boer, J.; Rohwer, E. R.; De Vos, J.; Weiss, J. M.; Brandsma, S. H.

62. Brits, M.; de Boer, J.; Rohwer, E. R.; De Vos, J.; Weiss, J. M.; Brandsma, S. H.

Table 11. Descriptive Statistics for CPs Measured in Settled Dust (unit: $\mu\text{g/g}$ dust).

CP category	vSCCPs	SCCPs	MCCPs	LCCPs	sumCP
geometric mean	0.0085	6.7	22	8.5	40
median	0.0040	5.8	21	8.1	37
range	<0.0038–0.19	0.76–460	2.3–840	0.66–340	4.7–1400
chlorine content	61% CI	58% CI	54% CI	47% CI	53% CI
DF	56%	100%	100%	100%	100%

The dust can be collected from different places in indoor environment, such as from floor (floor dust) or from elevated surfaces (settled dust). To investigate possible differences in exposure assessment using different dust types, five paired floor dust and settled dust samples from the same households were analyzed, and the concentrations and chlorine contents of CPs are shown Table 12. The median total CP concentration in the five floor dust samples ($51 \mu\text{g/g}$) was slightly higher compared to the paired settled dust samples ($49 \mu\text{g/g}$), but the differences were not significant, i.e., $p > 0.05$. The chlorine contents of CPs in the floor dust samples were approximately 1% CI higher than those in the settled dust samples. However, the difference was not statistically significant either ($p > 0.05$).

Table 12. Descriptive statistics for CPs measured in five paired settled dust and floor dust samples.

CP category	vSCCPs	SCCPs	MCCPs	LCCPs	sumCP
Settled dust concentrations ($\mu\text{g/g}$, n = 5)					
geometric mean	0.087	5.0	20	15	44
median	0.074	5.7	21	12	49
range	0.048–0.19	1.9–12	12–31	5.0–75	19–110
chlorine content	63% CI	57% CI	52% CI	47% CI	52% CI
Floor dust concentrations ($\mu\text{g/g}$, n = 5)					
geometric mean	0.14	4.1	17	16	49
median	0.13	3.3	22	12	51
range	<0.0038–0.26	2.9–9.8	4.6–34	4.5–130	19–140
chlorine content	65% CI	58% CI	53% CI	48% CI	53% CI

Given that no significant differences were found between CPs in the settled dust and in the floor dust, the settled dust results were used for calculating dust ingestion exposure to CPs (Table 13). Compared with the inhalation exposure, which was a significant pathway for relative volatile CP classes, dust ingestion exposure (median 1.1 ng/kg bw/d) was similar to the inhalation exposure to SCCPs (1.6 ng/kg bw/d). For relatively less volatile MCCPs and LCCPs, dust ingestion exposures (0.70 and 0.090 ng/kg bw/d, respectively) were ~3 and ~20 times higher than inhalation exposures (0.23 and 0.0046 ng/kg bw/d, respectively). This was probably due to the partitioning tendencies of vSCCPs, SCCPs, MCCPs, and LCCPs in indoor air and dust, which led to different exposures from inhalation and dust ingestion for different CP classes.

Table 13. Estimated Daily Dust Ingestion Exposure to CPs for Adults based on Settled Dust Data (unit: ng/kg BW/d).

CP category	vSCCPs	SCCPs	MCCPs	LCCPs	sumCP
5 th percentile	not available	0.19	0.15	0.015	1.1
50 th percentile	0.00069	1.1	0.70	0.090	5.7
95 th percentile	0.012	7.9	4.1	0.60	40

3.5 CPs in human plasma

In the plasma samples, vSCCPs, SCCPs, MCCPs, and LCCPs were above method detection limits in 58%, 86%, 76%, and 75% participants, respectively. The concentrations of SCCPs, MCCPs, and LCCPs were in the range (median) of <520–10 000 (2500), <590–9800 (1100), and <51–700 (120) ng/g lipid, respectively (Table 14). SCCP levels were lower than those reported in China (Shenzhen and Beijing, 2012–2013, median: 3500–16100 ng/g lipid), while MCCP and LCCP levels were comparable (median: 740–1340 and 150 ng/g lipid, respectively).

Table 14. CP levels in human plasma of the Norwegian cohort (unit: ng/g lipid).

CP category	vSCCPs	SCCPs	MCCPs	LCCPs
median (ng/g lipid)	68	2500	1100	120
max (ng/g lipid)	360	10000	9800	700
DF	58%	86%	76%	75%

3.6 Estimated CP levels using external exposure results

Comparability between external exposures to CPs and body burdens was assessed using a one-compartment, first order PK model. The predicted plasma concentrations of SCCPs were comparable to the measured concentrations, with a median (mean) ratio of 1.0 (1.5). The concentrations of MCCPs, and LCCPs were under-predicted by a factor of 0.48 (0.70) and 0.15 (0.67) for MCCPs and LCCPs, respectively (Table 15). The performance of the predicted values is comparable to or better than those applied for PBDEs in the same cohort, the factors of which varied from 1.7 – 13. Here vSCCPs were not included in the model calculation due to the relatively low detection frequencies in several matrices.

Table 15. Predicted levels using external exposure data vs. observed levels (predicted levels ÷ observed levels; vSCCPs were not calculated due to a low detection frequency).

CP category	SCCPs	MCCPs	LCCPs
median of individual pairs	1.0	0.48	0.15
mean of individual pairs	1.5	0.70	0.67

4. Discussion

4.1 CPs were the dominant flame retardants in the Norwegian cohort

The samples used for exposure assessment were from the EU project ATEAM. The samples have been applied for assessing exposures to a large group of organic chemicals which included perfluoroalkyl substances (PFASs),⁶³ polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDDs), emerging brominated flame retardants (EBFRs) such as tetrabromobisphenol A (TBBPA),⁶⁴ organophosphate esters (OPEs), and phthalate diesters.^{65,66} In this report, human exposure to the high-volume-use chemicals chlorinated paraffins (CPs) was included, which were ubiquitous in four external exposure samples sets. This enables comparisons among several different pollutants. The hand wipe mass levels are compared in Table 16, which shows that CPs were the most abundant flame retardants in the hand wipes in the studied cohort. This is also the case for indoor dust (Table 17) and duplicate diet (Table 18). However, in the stationary air samples, OPEs were much more abundant than CPs, which may be due to different volatilities of the two chemical categories.

Table 16. Comparisons of concentrations of flame retardants in the hand wipes of the Norwegian cohort.

FRs	CPs	PBDEs	HBCDDs	EBFRs	OPEs
Median / ng	950	2.9	180	570	192
Range / ng	43–18000	0.44–64	49–8900	31–11000	20–14100

Table 17. Comparisons of concentrations of flame retardants in the the settled dust and stationary air of the Norwegian cohort.

FRs	CPs	PBDEs	HBCDDs	EBFRs	OPEs
Median / µg/g dust	37	1.2	0.19	0.73	33.1
Median / ng/m³ air	13	0.018	0.0004	0.22	163

63. Poonthong, S.; Padilla-Sánchez, J. A.; Papadopoulou, E.; Giovanoulis, G.; Thomsen, C.; Haug, L. S.

64. Tay, J. H.; Sellström, U.; Papadopoulou, E.; Padilla-Sánchez, J. A.; Haug, L. S.; de Wit, C. A.

65. Xu, F.; Giovanoulis, G.; van Waes, S.; Padilla-Sanchez, J. A.; Papadopoulou, E.; Magnér, J.; Haug, L. S.; Neels, H.; Covaci, A.

66. Giovanoulis, G.; Bui, T.; Xu, F.; Papadopoulou, E.; Padilla-Sanchez, J. A.; Covaci, A.; Haug, L. S.; Cousins, A. P.; Magnér, J.; Cousins, I. T.; et al.

Table 18. Comparisons of concentrations of flame retardants in the duplicate diets of the Norwegian cohort.

FRs	CPs	PBDEs	EBFRs	OPEs
Median / ng/g ww	23	0.055	<MQL	3.0
Range / ng/g ww	4.5–55	<MQL–1.05	<MQL–0.103	<MQL–188

Table 19. Comparisons of concentrations of organic pollutants in the human blood of the Norwegian cohort.

FRs	CPs	PBDEs	TBBPA	PFOS*	PFOA*
Median / ng/g ww	22	–	–	6.16	2.02
Range / ng/g ww	<MQL–76	–	–	1.00–23.8	0.32–20.0
Median / ng/g lipid	3800	6.7	<0.28	–	–
Range / ng/g lipid	<MQL–21000	<MQL–160	<0.28–74	–	–

*assuming that the plasma has a density of 1.025 g/mL

For internal exposure (plasma/serum), comparisons were made between CPs and a selected EBFR, TBBPA, and perfluorinated alkyl substances (Table 19), due to the low detection frequencies of many flame retardants⁶⁷. OPEs were not compared with because only the OPE metabolites were analyzed.⁶⁸ the median levels of CPs (3800 ng/g lipid) were several orders of magnitude higher than those of other halogenated flame retardants such as PBDEs (6.7 ng/g lipid) and TBBPA (<0.28 ng/g lipid).⁶⁹ In addition, the levels of CPs (median: 22 ng/g wet weight) were higher than those of PFAS such as PFOS (median: 6.16 ng/g wet weight) and PFOA (median: 2.02 ng/g wet weight).⁷⁰

4.2 Legacy vs current-use CPs

In diet, dust, and hand wipe samples in the cohort, the current-use MCCPs were the dominant CPs, and contributed 64%, 56%, and 58% of the total CP concentrations, respectively. Another current-use CP, LCCPs, were the second most abundant CPs in dust and hand wipes, and contributed 25% and 22% of the total CP concentrations, respectively, and were comparable to those of the legacy SCCPs (19% and 20%, respectively). In diet samples, the legacy SCCPs were much more abundant (median: 29% of the total concentration) than LCCPs (median: 5% of the total

67. Tay, J. H.; Sellström, U.; Papadopoulou, E.; Padilla-Sánchez, J. A.; Haug, L. S.; de Wit, C. A.

68. u, F.; Eulaers, I.; Alves, A.; Papadopoulou, E.; Padilla-Sanchez, J. A.; Lai, F. Y.; Haug, L. S.; Voorspoels, S.; Neels, H.; Covaci, A.

69. Tay, J. H.; Sellström, U.; Papadopoulou, E.; Padilla-Sánchez, J. A.; Haug, L. S.; de Wit, C. A.

70. Poonthong, S.; Thomsen, C.; Padilla-Sanchez, J. A.; Papadopoulou, E.; Haug, L. S.

concentration). This is possibly due to the relative low accumulation capability of LCCPs in food items compared with SCCPs. The legacy SCCPs are more volatile than the current-use MCCPs and LCCPs (Table 1), which may explain the predominance of SCCPs in the air (median 82% of the total CP concentration).

SCCPs were the dominant CP class in human plasma of participants of the cohort, which contributed 67% of the total CP concentration (median), followed by MCCPs (30%). Although MCCPs were the dominant CPs in all the four external exposure matrices, they have relatively lower bioaccessibility, which is estimated to be 37% of SCCPs (Table 1). In addition, the half-life of MCCPs in mammals is estimated to be much shorter than that of SCCPs (24% of the half-life of SCCPs). However, due to the ban of SCCPs, the use of MCCPs (and LCCPs) as alternatives is expected to increase.⁷¹⁷² This may both increase the amount of emissions as well as the exposure frequencies to MCCPs, and thus lead to an increase in exposure and human body burdens of the current-use MCCPs. With regard to this, it should be noted that regulatory measures are ongoing for MCCPs and other substances that contain chloroalkanes with carbon chain lengths within the range from C14 to C17 both in the European Union under REACH and globally under the Stockholm Convention.⁷³

CPs have received global attention by both chemical and environmental agencies, and by the industries and companies involved in producing or using CPs. The focus of the debate is whether MCCPs and LCCPs are safe replacements for SCCPs. The enormous production of CPs together with their POP-like properties has made them a regulatory top priority. Not only are they included or being considered for the Stockholm Convention, their regulation is also being pursued in different jurisdictions around the world. Sweden for example is considering a regulatory initiative of its own within the European Union, namely nominating MCCPs for a ban under the RoHS-directive, which regulates chemicals in electronics. The regulators in Europe and in North America have recognized the need for assessment of these extensively used chemicals. The exposure results of the present project provides an "early-warning" via which current-use CPs may be identified before their presence in the environment and humans reaches levels of concern.

4.3 Dietary Intake Contributed the Most to Body Burden of CPs

The sum of the medians of all the exposures to SCCPs, MCCPs, and LCCPs were 61, 69, and 2.8 ng/kg bw/d, respectively. The sum of the 95th percentiles of all the exposures to SCCPs, MCCPs, and LCCPs were 190, 190, and 16 ng/kg bw/d, respectively. These were still far lower than the oral reference doses (RfDs) of 2300, 6000, 71000 ng/kg bw/d for SCCPs, MCCPs, and LCCPs, respectively.⁷⁴⁷⁵

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73. ECHA

74. EFSA

75. Environment Canada

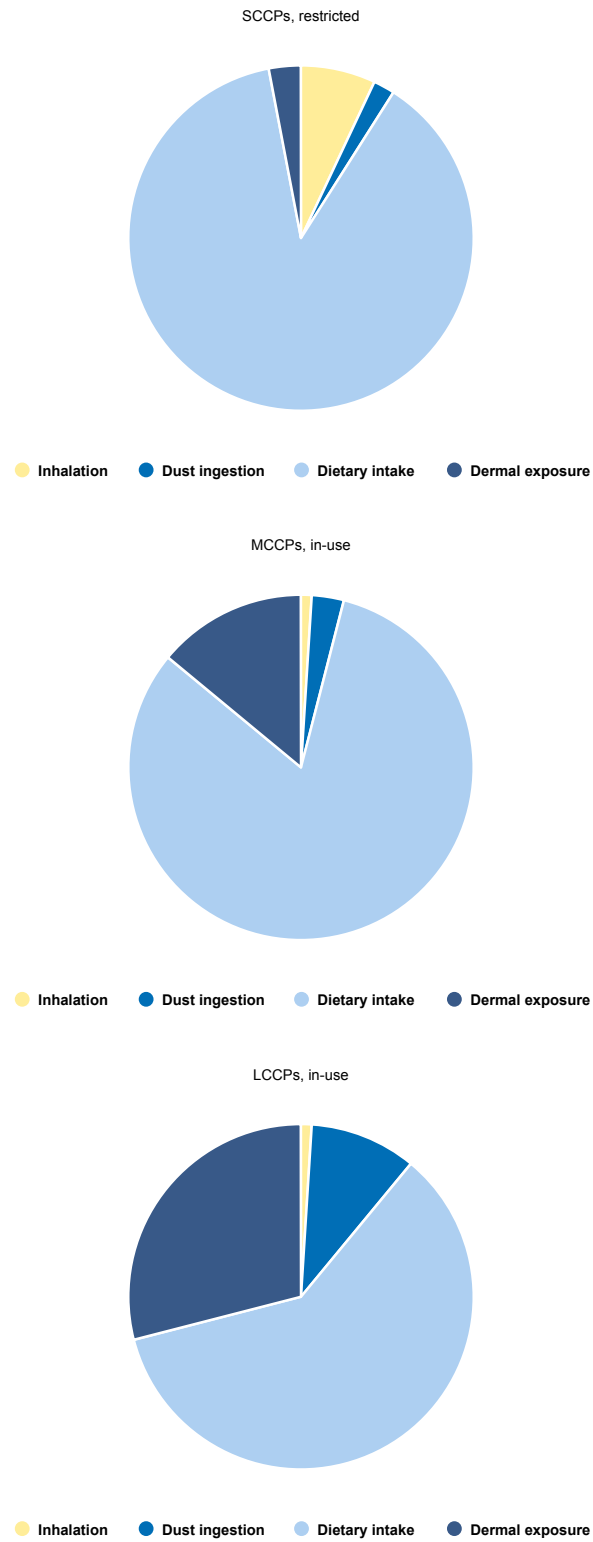


Figure 3. Median percentage contributions of four exposure pathways to legacy SCCPs and current-use MCCPs and LCCPs in the studied cohort.

Percentage contributions of the four exposure pathways were estimated on the basis of medians (Figure 3). Dietary exposure contributed the most to the body burden of CPs in the cohort, accounting for 60–88% of the total intake. The restricted SCCPs are relatively volatile CPs, and inhalation was found to be the second most important exposure pathway to SCCPs, accounting for 7% of the total intake. The increasing chain lengths of CPs decrease the volatility and increase the hydrophobicity of CPs. Relative to the legacy SCCPs, the current-use MCCPs and LCCPs tend to adhere to surfaces and dust. The dermal exposure was found to be the second most important exposure pathway to MCCPs (14%) and LCCPs (29%). Relative to inhalation, dust ingestion turns out to be a more significant exposure pathway to MCCPs (3%) and LCCPs (10%).

4.4 Potential sources

CPs have been popularly used chemicals and are found in multiple items in indoor environments. High contents of CPs have been found in window sealing materials in Germany⁷⁶ and recently found in spray polyurethane foams in the Netherlands,⁷⁷ in kitchen tools such as ovens⁷⁸ and hand blenders⁷⁹. CPs have also been found in plastic and rubber products including synthetic sports courts⁸⁰, plastic food packaging,⁸¹ car tyres,⁸² and toys⁸³. In the human diet, CPs have been reported in various food items sold on the European market.^{84,85,86} Detection of CPs in food could be due to bioaccumulation from the environment⁸⁷ and from the animal feed⁸⁸, migration from food packaging into the food,⁸⁹ or contamination during food processing.⁹⁰

It is not clear how much each such potential source contributes to human exposure, and how many potential sources that have not been identified. This may explain that most associations were not statistically significant between CP concentrations in the cohort and the personal characteristics or indoor environment Information. However, we found that participants living in buildings built between 1963 – 2002 have higher levels of SCCPs than those living in older or newer buildings (Kruskal–Wallis tests, $p < 0.05$). The peak use of CPs in Scandinavia was within this period of time, and the use of SCCPs was banned since 2002 in Norway. Similar trends were also found in the indoor dust and hand wipe results, which may suggest successful enforcement of the regulation of SCCPs in Norway. Nordic countries exercise strict control over production, use and discharges of consumer chemicals, which is supported and motivated by relevant scientific research. Newly banned SCCPs and their replacement CPs in the Nordic countries pose a need to take further actions on these chemicals.

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4.5 Strengths and Limitations

Personalized sampling is one of the future sampling strategies for complex environmental mixtures in human exposure studies.⁹¹ One advantage of a cohort study like the present one is that it contains personal exposure information and thus estimated body burden from external exposures with actual internal exposure measurements can be corroborated in the same individuals, and individual variation can be studied. It is thus possible to explore potential sources of exposure, as discussed in Section 4.4, by associations with food frequency questionnaires, food diary, and questionnaires on housing characteristics of individual participants.

The underprediction of the plasma concentrations of the current-use MCCPs and LCCPs is likely due to that not all exposure pathways were identified and included in the prediction calculation. This might be improved through research into the diverse uses and sources of CPs. There was relatively large underestimation of LCCP plasma concentrations in the present study. LCCPs consisted of a wide range of homologues from C₁₈ to C_{>40}, which could result in high uncertainties in the estimated absorption fraction of LCCPs and/or the estimated half-life (Table 1) and thus lead to large deviation in the predicted plasma concentrations. The uncertainties in the prediction of the complex mixture could be reduced if there is increased precision in the measurement of the mixture to individual formula (in the scenario of CPs, that is homologue⁹²), which, however, requires advances in synthesizing more specific reference standards⁹³.

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5. Conclusions

This Norwegian cohort study revealed the ubiquitous presence of CPs in multiple human exposure pathways. The levels of CPs surpassed those of many other flame retardants in both external and internal exposure matrices. Dietary exposure was identified as the main contributor of human exposure to CPs, which contributed over 56% of total CP intake in the cohort. A preliminary exposure assessment is thus assumed to be possible with a prompt calculation of CP intake based on the major CP contributor. Although the Nordic countries started restriction and regulation on the production and use of CPs as early as the 1990s, the legacy CPs, SCCPs, were still the most abundant CP class found in human plasma. However, significantly lower levels were found in the samples from the participants living in buildings built after the year when SCCPs started to be regulated, indicating the important role of chemical regulation on reduction of human exposure. The current-use MCCPs and LCCPs were also found to accumulate in human beings via the studied exposure pathways with slight differences from the legacy SCCPs. These current-use CPs are less volatile and the dust ingestion and dermal exposure pathways contributed more significantly to human exposure than for SCCPs. The detection frequencies of vSCCPs were low in most media except for air. Their correlations with the other three CP classes indicate that vSCCPs may be present as impurities in the CP products and/or are degradation products of longer chain CPs⁹⁴. The ban of SCCPs may result in a further increase in the use of MCCPs and LCCPs, which may eventually lead to an increase in human exposure and body burden of these persistent and bioaccumulative chemicals. For the time being, regulatory measures have been ongoing for MCCPs and other substances that contain CPs with carbon chain lengths within the range of MCCPs both in the EU and the Stockholm Convention. Together with the recent advances in toxicological studies on MCCPs and LCCPs, the present cohort study supports regulating and handling all CPs as one class of chemicals.

The results of the present cohort study have been published in peer-reviewed journals. For details in assessments of (1) dermal exposure,⁹⁵ (2) inhalation and dust ingestion,⁹⁶ (3) dietary exposure and comparability between external exposures and body burdens⁹⁷ see respective articles cited.

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Association between human biomonitoring and external exposures to SCCPs, MCCPs, and LCCPs in a Norwegian cohort

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