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Temporal Trends and Age-Dependent Sex Differences in Chlorinated Paraffin Accumulation in Moose

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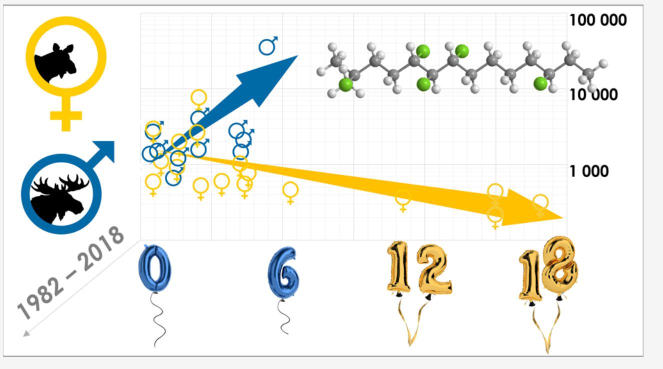
ABSTRACT: Previous studies have found relatively high chlorinated paraffin (CP) concentrations in moose (*Alces alces*) compared with other wildlife from Scandinavia. To explore CP accumulation behaviors in this long-lived terrestrial mammal, temporal trends of muscle concentrations of CPs were first measured in samples collected over the past 40 years from moose calves from Grimsö, Sweden. The four CP classes, i.e., very-short-chain, short-chain, medium-chain, and long-chain (LCCPs) classes, showed similar temporal trends, with increasing concentrations from 1982 to the 1990s, relatively high levels in two time periods around 1993 and 2008, and decreasing concentrations after 2012. A concentration plateau period was identified, and moose samples of both sexes and different ages from the median year (1993) of the concentration plateau period were selected for further analysis. CP levels increased exponentially with age in the male moose, while CP levels were found to exponentially decrease with age in females. LCCPs showed the slowest decreasing tendency with age in females compared with the other three classes, resulting in a general increase of the LCCP proportions with age. The sex-biased accumulation of CPs indicates additional stresses from these POP-like chemicals toward males of the largest and one of the most widespread terrestrial mammals in northern hemisphere forests.



KEYWORDS: *retrospective trend, terrestrial mammal, sex difference, bioaccumulation, chlorinated paraffins*

INTRODUCTION

Wild mammals are subject to strong human pressure, leading to global biodiversity losses.[1] Large-bodied mammal species show generally higher extinction risk than small-bodied species.[2] Environmentally driven mortality could select against frail individuals[3] and biases are also seen based on sex[4] and age,[5] which thus impacts the population dynamics.[6] Chemical pollution is one of the greatest global threats to biodiversity.[7] Among multiple anthropogenic stressors, "forever chemicals" such as persistent organic pollutants (POPs) pose long-lasting exposure and harmful effects on global wildlife, due to their persistence in the environment, bioaccumulation in animals to high concentrations, and toxicity to organisms.[8] The global health impacts of, e.g., polychlorinated biphenyls (PCBs) on large-bodied mammals have been seen across their lifespans and are still significant after decades since the bans on production and use.[9]

New chemical entities have replaced PCBs[10] for industrial uses such as metal-working fluids, plasticizers, and flame retardants, and the primary replacement is chlorinated paraffins (CPs).[11] Today, the annual global production of CPs exceeds 1.3 million metric tons, which is equivalent to the total cumulative historical production of PCBs.[12] CPs are polychlorinated straight-chain alkanes. They are produced in the form of mixtures of $C_nH_{2n+2-m}Cl_m$ homologues (C_nCl_m) of varying chain lengths (n) and different numbers of chlorines (m) with limited substitution selectivity.[13] The products are classified based on the range of raw paraffin materials: short-chain (n = 10−13, SCCPs), medium-chain (n = 14−17, MCCPs), and long-chain CPs (n > 17, LCCPs), as well as very-short-chain impurities (n < 10, vSCCPs).[14]

CPs have been used, studied, and regulated at a resolution of the four mixture classes, i.e., vS/S/M/LCCPs. In 2017, SCCPs became the first class of CPs regulated as POPs under the UN Stockholm Convention on POPs.[15] MCCPs and LCCPs, as substitutes for SCCPs, have potentially growing usage and are being evaluated as potential POPs.[15] All the CP classes have been found to induce endocrine[16] and oxidative stress effects[17] which indicate potentially chronic mammalian and environmental toxicities.[18] Sex differences in CP toxicities were shown in rats and mice. Exposure to SCCPs caused kidney tumors,[19]

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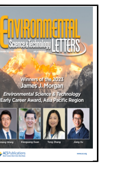

adenocarcinomas, and an increase in mononuclear cell leukemia in male rats, and thyroid follicular cell neoplasms in female rats and mice.[20] The corresponding health risks from CP exposure could possibly become significant if the accumulation of CPs were sex-biased and negatively impact population dynamics.[7]

Large-scale industrial production of CPs started in the 1930s,[21] as did their releases and emissions to the environment.[22] Recently, CP global pollution has been highlighted by findings of CPs in marine mammals from remote regions[23] and as dominant POPs (accounting for 18−46% of the summed POPs) in human mothers' milk in 53 countries across five continents.[24] CPs are ubiquitous in wildlife at both low and high trophic levels.[25] Male-biased accumulation of CPs has been found in amphibians, with males having concentrations 3.3−7.6 times higher than females.[26] Maternal transfer from female to egg was given as a possible explanation for the lower CP concentrations found in female muscle.[26] Significant knowledge gaps exist in sex differences in CP accumulation in most animal classes, especially those with relatively long lifespans.

CPs were previously screened for their presence and concentrations in a total of 23 terrestrial and marine wildlife species from Scandinavia collected in the 1980s[27] and in the 2010s.[28] Both studies found the highest concentrations in the muscle tissue of adult moose (*Alces alces*). Moose belong to the largest and one of the most widespread terrestrial mammals in northern hemisphere forests.[29] In Sweden, moose have been sampled by Grimsö Wildlife Research Station and samples have been stored in the Swedish Environmental Specimen Bank (Miljöprovbanken, MPB) at the Swedish Museum of Natural History since the 1960s.[30] The availability of retrospective samples over decades and the high body levels of CPs made moose a potential model species to explore CP accumulation behaviors in a long-lived, large-bodied terrestrial mammal.

First, we scanned the levels of vSCCPs, SCCPs, MCCPs, and LCCPs in muscle samples from moose calves collected from the same sampling site over the past 40 years, in order to select a time window for CP accumulation behavior studies. Next, the variability of CP accumulation in moose was explored using individual moose of both sexes and different ages from the same site and from the same sampling year. For the first time, temporal trends of all CP classes were determined in a terrestrial species, and age-dependent sex differences were found in the mammalian accumulation of CPs.

■ MATERIALS AND METHODS

Samples. The moose muscle samples are collected annually within the Swedish National Environmental Monitoring Programme and stored in the MPB at −25 °C before subsampling for chemical analyses. All the moose were from the central forest district of Sweden (Grimsö, Västmanland) (Figure S1), and muscle tissues were used, consistent with the previous studies.[27,28] Calves that were less than one year old were used for the temporal trend study. CPs were assumed to have reached equilibrium levels in calves based on previous *in vivo* tests in rats.[31] Therefore, CP concentrations in calves were presumed to reflect the chemical pollutant status of the year when the calves were sampled. The samples were collected between 1982 and 2018, with intervals of 1−3 years. Eighty-three individuals were pooled into 18 samples. For most of the sampling years, 2−8 individuals collected in the same year were pooled with equal numbers of both sexes. There was only one calf sample collected in the years of 2013, 2015, and 2018, and thus, the individual samples were used. In a second step, individual moose of both sexes and different ages collected in the year 1993 were then selected, consisting of 33 individuals. Female moose ranged from calf to 17 years old, while the age of male moose samples ranged from calf to 5 years old. For detailed sample information, see Table S1.

Chemical Analysis. The analytical method has been described in detail previously.[23] In brief, 5−8 g of wet sample was solvent-extracted, and the lipid weight was determined gravimetrically. Ten ng of ^{13}C-1,5,5,6,6,10-hexachlorodecane (Cambridge Isotope Laboratories, Andover, MA U.S.A.) was added as an internal standard. The extract was then cleaned up on a multilayer SPE column. The eluent was reconstituted in dichloromethane, and 10 ng of ^{13}C-1,1,1,3,10,12,12,12-octachlorododecane (Cambridge Isotope Laboratories, Andover, MA, U.S.A.) was added as an injection standard prior to instrumental analysis. C_nCl_m homologues (n = 6−36 and $m \geq 2$) were analyzed using a chloride-enhanced UPLC-APCI-Orbitrap-MS (Q Exactive, Thermo Fisher Scientific, San Jose). Quantification of vSCCPs, SCCPs, MCCPs, and LCCPs was based on homologue profile reconstruction. For detailed chemical analysis and the reference CPs, see Supporting Information (SI) and Table S2.

Quality Assurance and Quality Control. The recovery of the internal standard was 83 ± 21%. The CP homologue profiles were satisfactorily reconstructed (R^2 > 0.50) in all the samples (SI and Table S1). A procedural blank was included with each batch of samples prepared. The method detection limit (MDL) of each CP class was defined as the mean procedural blank plus 3 times the standard deviation, divided by sample lipid mass. The average MDLs were 0.33, 64, 51, and 13 ng/g lipid for vSCCPs, SCCPs, MCCPs, and LCCPs, respectively, while the specific MDLs of individual samples can be found in Table S1 and on the Geological Survey of Sweden database for national environmental monitoring.[32]

Statistical Analysis. Statistical analysis was performed using Past 4.10.[33] LOESS-Trend Version 1.1 (the German Environment Agency) was used for statistical analysis of temporal trends for CPs. The significance of nonlinear trends was tested using ANOVA following the approach of Fryer and Nicholson,[34] and for details, see the SI. The significance level was set to p = 0.05.

■ RESULTS AND DISCUSSION

Temporal Trends of CPs. The concentrations of four CP classes in moose calves from Grimsö between 1982 and 2018 are plotted in Figure 1. The four CP classes show similar temporal trends (Figure S2a), with concentrations increasing from 1982 to the 1990s, relatively higher levels in two time periods around 1993 and 2008 with fluctuations between, and decreasing levels after 2012. The peak concentration of SCCPs (280 ng/g lipid) was in the year 1993, which mirrors the peak import of CPs in Sweden and peak concentrations of SCCPs in Swedish Baltic Sea coastal sediment core sections representing the early 1990s.[22]

The concentrations of MCCPs in calves from Grimsö had relatively high levels between 1989 and 1996, which fluctuated around 530 ng/g lipid. The peak concentration was found in the year 2013 (950 ng/g lipid). The peak concentrations of LCCPs were found between the years 1989 and 1993 (∼70

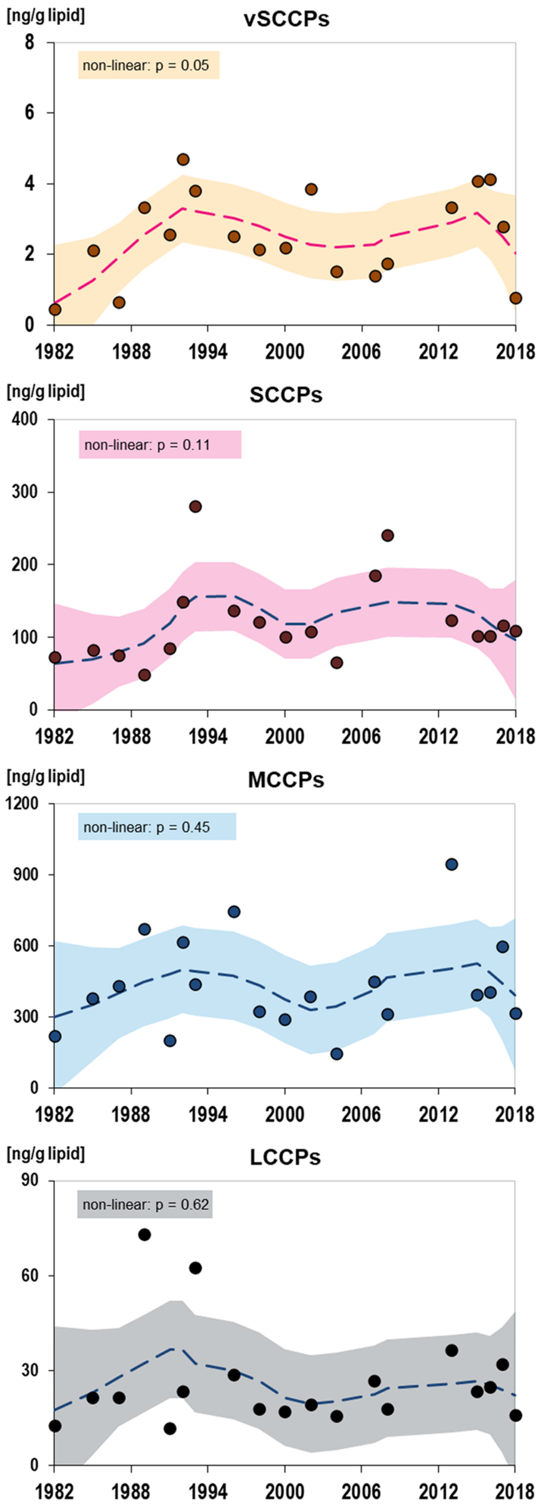

Figure 1. Temporal trends of the concentrations of four CP classes in moose calves collected from Grimsö between 1982 and 2018. For raw data, see Table S1.

ng/g lipid), with another peak concentration in the year 2013 (36 ng/g lipid). The fluctuation in concentrations indicates the impacts from multiple emission sources that have different temporal trends, which was seen in a study of several Swedish coastal sediment cores.[22] In a sediment core close to a municipal wastewater treatment plant (Himmerfjärden), the peak concentrations of MCCPs and LCCPs were found in the 1990s, but in the sediment core collected in proximity to steelworks (Oxelösund), the peak concentrations were found in the 2010s. In the sediment core from a wood-related industrial area (Rundvik), the peak concentration of MCCPs was in the 2010s, while the peak concentration of LCCPs was in the 1990s. The sediment core records may reflect that MCCPs and LCCPs are still being used for different industrial purposes in Sweden in recent years. As SCCPs are now banned for use, MCCPs and LCCPs are expected to replace SCCPs in their applications,[35] which may explain why concentrations of MCCPs and LCCPs in the environment remain high compared with the trend of SCCPs. Different trends of M/LCCPs from municipal and industrial sources may explain why the nonlinear temporal trends in moose were not statistically significant ($p > 0.05$, Figure 1).

The proportions of the four CP categories in the moose samples were relatively constant throughout the sampling years (Table S1). MCCPs were the predominant CPs in the moose and accounted for a mean of 75% of the total CP concentrations. The concentrations of vSCCPs were positively correlated to the other CPs ($r = 0.22-0.36$, $p < 0.05$, Table S3), indicating that vSCCPs are present as impurities in the CP products[14] and/or are degradation products of longer chain CPs.[36] No significant correlations were found between regulated SCCPs and current-use M/LCCPs, which may indicate that these CPs had been used individually.

The total concentrations of the four CP classes in moose showed two plateaus over the past 40 years (Figure S2b), which can be a result of the overall usage and emissions as reflected by the Swedish sediment core records.[22] The concentrations in moose collected during the first plateau period (the early 1990s) were relatively more constant than the second period (the 2010s). Therefore, moose samples collected from the median year of the first period (1993) were selected for further studies on variability of CP accumulation based on age and sex. Moreover, the concentrations of LCCPs were the highest in the early 1990s, which maximizes the chance that the concentrations could still be detectable for individuals with low accumulation potential.

Sex and Age Variability of CP Accumulation in Moose. Statistically significant exponentially increasing CP concentrations with age were found in male moose ($r^2 = 0.42$, $p < 0.05$, Figure 2). In contrast, statistically significant exponentially decreasing CP concentrations with age were found for female moose ($r^2 = 0.14$, $p < 0.05$). The highest SCCP concentration was found in the oldest male that was 5 years old, which may have strongly influenced the regression for total CPs. If the statistical analysis was performed without the 5-year-old male (Table S4), the exponentially increasing trend remains statistically significant only for LCCPs ($r^2 = 0.38$, $p < 0.05$). Instead of elimination of data points, the regression could be improved with a wider age range and/or more 5-year-old males, which, however, was severely limited by the availability of older male samples.

The decreasing trend of CPs in female moose may indicate that female adults enhance elimination of these organic pollutants via, e.g., giving birth and lactation, as has been seen for other POPs.[37] The decreased body burden of CPs in female moose mirrors the age-specific observed parturition rates found in another study.[38] The parturition rates in female moose ≥4 years old increased 75% on average, and in the current study, CPs decreased to a relatively constant low level

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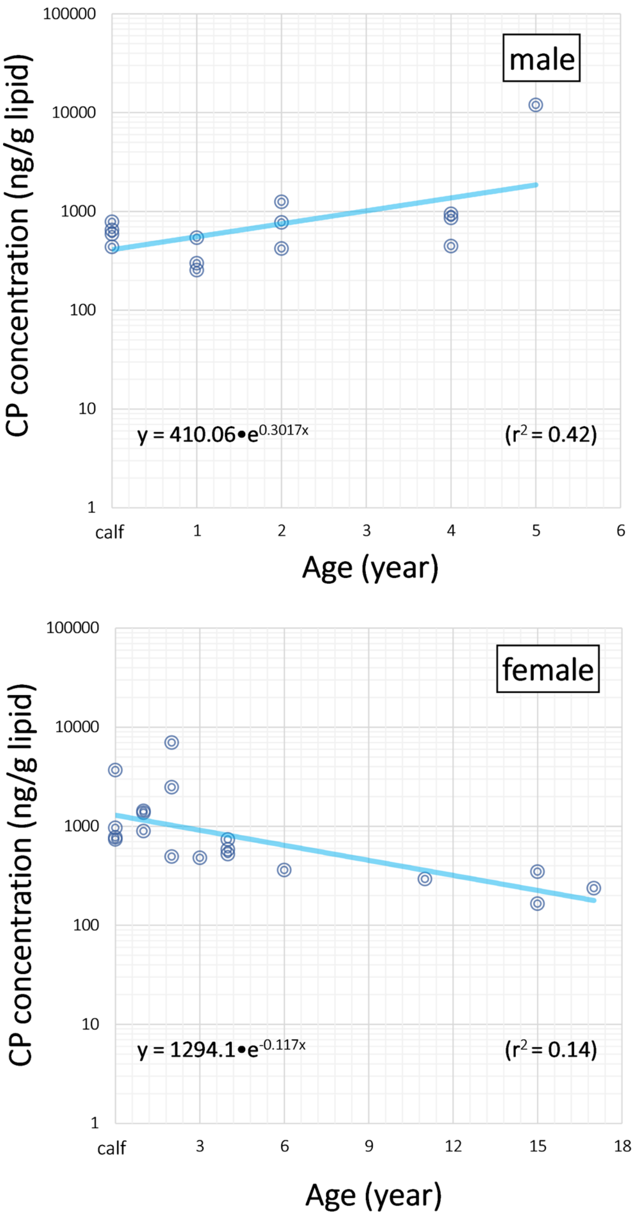

Figure 2. Correlations between total CP concentrations and the age of female and male moose collected in the year 1993. The *y* axis is the logarithmic scale of CP concentrations. The age of calves was set to zero when fitting exponential functions. For raw data, see Table S1.

for the female moose ≥4 years old. Another possible excretion route of CPs in female is via lactation. This was indicated in a human breast milk study in which CP concentrations in human milk from first-time mothers were generally higher than those from second-time mothers.[39]

The age-dependent accumulation of four CP classes varied (Figure S3, Table S4). The increasing tendency of SCCP concentration in male moose seems to be faster than the other three CP classes, resulting in generally increasing proportions of SCCPs in the total CPs with age (Figure 3). In female moose, the decreasing tendency of LCCP concentrations was the slowest, and thus, the proportions of LCCPs were found generally to increase with age, and in particular from 4 years of age. This may be due to more efficient elimination of SCCPs and MCCPs than LCCPs via parturition and lactation in older females.

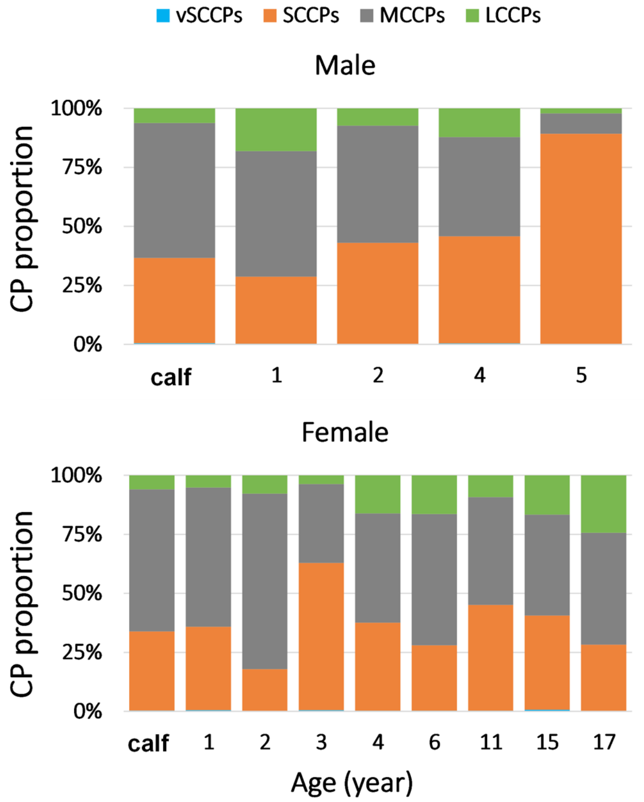

Figure 3. Median CP class compositions in female and male moose of different ages collected in the year 1993.

Environmental Implications. The dose makes the poison.[40] The dramatic age-dependent increase of CP concentrations in adult male moose indicates elevated risks of adverse effects including carcinogenic[19] and endocrine-disrupting effects.[16] In particular, the significant age-dependent accumulation tendency of SCCPs in male moose is perhaps of high concern. Recent studies revealed oxidative stress effects of SCCPs,[17] and SCCPs showed activation of NRF2 with cross-model comparison of transcriptomic dose−response.[41] These indicate possible testicular dysfunction induced by SCCPs via, e.g., Nrf2-mediated oxidative stress.[42]

The age-dependent accumulation potential of CPs does not necessarily mean that adult male moose are currently in danger, especially since CP concentrations were within no observed effect levels. However, CPs are unfortunately not the only organic pollutants that show sex-biased accumulation. Similar accumulation behaviors have been found in other POPs such as polychlorinated biphenyls[43] and perfluorooctanesulfonic acid.[44] Cumulative exposure to a cocktail of organic pollutants with similar toxic effects (e.g., endocrine disrupting chemicals) could lead to adverse health outcomes even if the concentrations of individual chemicals were below the regulatory dose,[45] especially if these tend to increase with age.

Male mammals typically have shorter lifespans than females partly due to higher mortality rates and aging rates in males.[46] For example, the males of red deer (*Cervus elaphus*, Isle of Rum population) showed an exponential rate of increase of mortality risk with increasing age.[2] The decreased proportion and mean age of male moose in some populations have been associated with inadequate number of males for timely reproduction.[47] If sex ratio imbalance is aggravated, it could endanger the population.[48] It is important to determine if

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multiple chemical stressors may be contributing to these adverse impacts and which species other than moose may be facing these ubiquitous pressures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.2c00672.

> Sampling site map (Figure S1), temporal trend of total CP concentrations (Figure S2), correlations between CP concentrations and moose age (Figures S3), raw data (Table S1), CP reference (Table S2), correlations among CP classes (Table S3), fitting functions (Table S4), LOESS-Trend analysis, and chemical analysis (PDF)

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Notes

The authors declare no competing financial interest.

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